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Review

Rhubarb in renal fibrosis: from traditional ethnopharmacology to mechanistic therapeutic development

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ABSTRACT

Rhubarb (*Rheum* spp.), a traditional herbal medicine, has attracted growing interest due to its anti-renal fibrosis effects in chronic kidney disease (CKD). This review systematically evaluates Rhubarb's botanical features, global distribution, and diverse processing methods, which influence its chemical composition and bioactivity. Major bioactive constituents, including anthraquinones, stilbenes, and polyphenols, are cataloged, and their potential roles in renal protection are elucidated. Traditional applications in nephropathy management are critically assessed alongside contemporary pharmacological evidence demonstrating Rhubarb's ability to attenuate renal fibrosis. Notably, this review highlights that multiple bioactive components in Rhubarb exert potent anti-fibrotic effects through complex, interactive modulation of multiple signaling pathways. Despite promising preclinical data, clinical translation remains limited by insufficient understanding of pharmacokinetics and potential herb-drug interactions. This synthesis identifies key research gaps, advocating for interdisciplinary studies to decipher multi-target mechanisms, refine pharmacokinetic profiles to enhance bioavailability, and translate preclinical findings into randomized controlled trials (RCTs). By integrating ethnopharmacological knowledge with modern drug discovery frameworks, this review underscores Rhubarb's potential as a multifaceted anti-fibrotic agent while calling for methodologically rigorous research to validate its therapeutic integration into CKD management protocols.

1. Introduction

Chronic kidney disease (CKD), characterized by progressive renal fibrosis, constitutes a significant global health burden with limited therapeutic options [1]. Renal fibrosis, defined by excessive extracellular matrix (ECM) deposition, tubular atrophy, and inflammatory infiltration, represents the final common pathway of CKD progression, irrespective of etiology, such as diabetes, hypertension, or glomerulonephritis [2]. Despite advances in renin-angiotensin system inhibitors and sodium-glucose cotransporter-2 inhibitors, these therapies often fail to halt fibrosis progression, highlighting the urgent need for novel anti-fibrotic agents [3]. In recent decades, natural products have re-emerged as promising candidates due to their multi-target mechanisms and long-standing use in traditional medicine [4]. Among these, Rhubarb (*Rheum* spp.), a perennial herb from the Polygonaceae family, has attracted increasing attention for its potential to mitigate renal injury and fibrosis through diverse bioactive constituents.

Rhubarb, native to temperate regions of Asia and Europe, has been cultivated for millennia in China (*Da huang*), where its roots and rhizomes are processed into various formulations, such as raw, wine-fried, or carbonized forms, to modulate therapeutic effects. Traditionally, it has been prescribed in East Asian medicine for constipation, inflammation, and blood purification. Modern pharmacological studies attribute its bioactivity to a rich array of phytochemicals, including anthraquinones, flavonoids, stilbenes, and tannins, which collectively exhibit antioxidant, anti-inflammatory, and anti-fibrotic properties [5]. Notably, emerging evidence indicates that Rhubarb extracts and isolated compounds ameliorate renal fibrosis by targeting key signaling pathways, such as the transforming growth factor-beta (TGF-β)/Smad cascade, oxidative stress responses, and epithelial-mesenchymal transition (EMT). For instance, Emodin, a primary anthraquinone, improves renal dysfunction by activating autophagy and inhibiting EMT in rodent models of renal fibrosis, whereas Resveratrol derivatives attenuate mitochondrial dysfunction in glomerular mesangial cells [6]. These findings position Rhubarb as a multifaceted phytotherapeutic agent with substantial translational potential.

This review systematically consolidates current evidence on Rhubarb's anti-renal fibrotic properties, addressing its botanical background, functional constituents, and mechanistic insights. We further evaluate the roles of specific phytochemicals, such as

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anthraquinones and flavonoids, in modulating fibrotic pathways and propose strategies to bridge phytochemistry with translational nephrology. By elucidating Rhubarb's potential as a cost-effective adjuvant therapy, this work aims to inspire targeted research into its clinical validation and sustainable application in CKD management.

2. Botany and geographical distribution of Rhubarb

2.1. Botanical characteristics

Rheum palmatum L., commonly known as Chinese Rhubarb or Dahuang, belongs to the Polygonaceae family within the genus Rheum. This perennial herbaceous plant exhibits distinct morphological features that facilitate identification [7]. It develops a robust, fleshy rhizome system with characteristic yellow-orange transverse markings when cut longitudinally, a key diagnostic trait in traditional Chinese medicine (TCM) authentication. Mature plants typically reach 1–3 meters in height, bearing large palmately lobed leaves (15–40 cm in diameter) with 5–7 deeply divided segments and prominent venation. Reddish-green flowering stalks emerge in early summer, producing panicles of small hermaphroditic flowers, each with six tepals and nine stamens. Three primary medicinal species are recognized: R. palmatum, R. officinale, and R. tanguticum, distinguishable by leaf morphology and microscopic features of root cross-sections (Fig. 1). The bioactive compounds, particularly anthraquinones (e.g., Emodin, Chrysophanol) and tannins, accumulate in the parenchyma cells of the thickened roots and rhizomes, with optimal concentrations achieved after 3–5 years of growth.

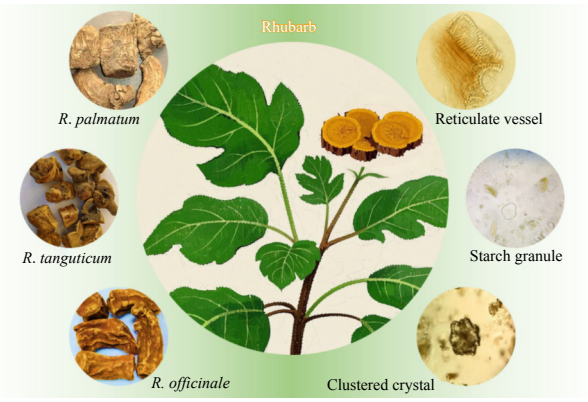


Fig. 1 Botanical characteristics of Rhubarb. Three primary medicinal varieties are recognized: *R. palmatum*, *R. officinale*, and *R. tanguticum* (left). The microstructure of Rhubarb is characterized by clustered crystals, reticulate vessels, and starch granules (right).

2.2. Geographical distribution

Native to temperate regions of East Asia, *Rheum palmatum* thrives at altitudes between 1500 and 4000 meters across specific biogeographical zones. Its natural habitat extends along the eastern Qinghai-Tibet Plateau, spanning western China (Gansu, Sichuan, Qinghai, Tibet), northern Nepal, and Bhutan. Commercial cultivation is concentrated in China's "Rhubarb Belt", a 1200 km corridor from southern Gansu to northwestern Yunnan, where well-drained sandy loam soils and diurnal temperature fluctuations (15–25 °C daytime; 5–12 °C nighttime) optimize secondary metabolite production. *R. palmatum* is primarily produced in Gansu, Qinghai, Tibet, Sichuan, and Yunnan provinces. *R. tanguticum* is mainly cultivated in Qinghai, Gansu, Tibet, and Sichuan provinces, while *R. officinale* is predominantly grown in Sichuan, Guizhou, Yunnan, Hubei, and Shaanxi provinces (Fig. S2). Historical trade routes facilitated its spread to Central Asia, with wild populations persisting in Mongolia's Khangai Mountains and Russia's Altai region. Modern introductions to Europe (Germany, Poland) and North America have established limited cultivation, although these non-native populations exhibit reduced concentrations of bioactive compounds compared to indigenous Chinese varieties.

3. Processing methods of Rhubarb

The processing of medicine represents a critical pharmaceutical technique in TCM that directly influences its clinical applications [8]. Through distinct preparation methods, practitioners can modulate the herb's chemical composition and therapeutic properties to suit specific therapeutic needs [9]. The primary processed forms include raw Rhubarb (Sheng Dahuang), steamed Rhubarb (Shu Dahuang), wine-processed Rhubarb (Jiu Dahuang), and charred Rhubarb (Dahuang Tan), each demonstrating unique processing protocols and pharmacological outcomes (Fig. 2).

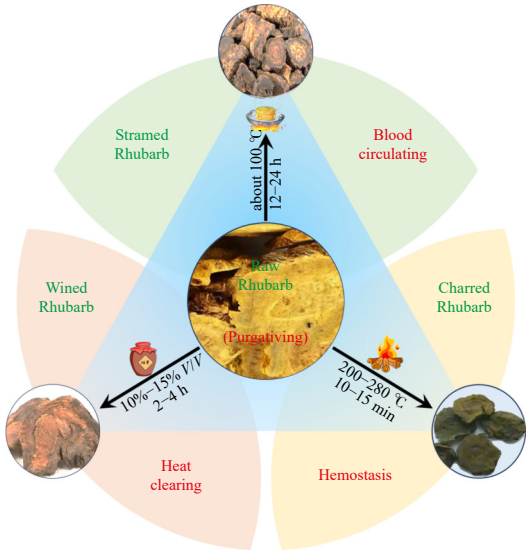


Fig. 2 Main processed products and effects of Rhubarb. The primary processed forms include raw Rhubarb (Sheng Dahuang), steamed Rhubarb (Shu Dahuang), wine-processed Rhubarb (Jiu Dahuang), and charred Rhubarb (Dahuang Tan), each demonstrating unique processing protocols and pharmacological outcomes.

3.1. Raw Rhubarb (Sheng Dahuang)

The simplest form involves cleaning fresh rhizomes with running water to remove soil impurities, followed by slicing into 2–3 mm thick pieces. These slices undergo natural sun-drying or low-temperature oven drying (40–50 °C) to preserve bioactive components [10]. Raw Rhubarb contains the highest concentration of anthraquinone glycosides, making it the most potent form for purgative effects [11]. However, its strong cathartic properties and potential gastric irritation limit its use in patients with deficient spleen/stomach conditions.

3.2. Steamed Rhubarb (Shu Dahuang)

This method modifies the herb's action through prolonged moist-heat treatment [12]. Sliced Rhubarb is layered with or without black bean soup (30%, *W/W*) in a bamboo steamer and processed for 12–24 hours at 100 °C. The extended steaming converts bitter naphthodianthrones into more palatable forms while preserving emodin and chrysophanol [13]. The processed herb demonstrates milder purgative effects with enhanced blood-nourishing capabilities, often prescribed for chronic constipation in debilitated patients [14].

3.3. Wine-processed Rhubarb (Jiu Dahuang)

This preparation employs yellow rice wine (10%–15% *W/W*) as a processing medium. The cleaned Rhubarb slices are moistened with wine and allowed to marinate for 2–4 hours until complete absorption. The impregnated material is then stir-fried in a copper wok at 160–180 °C until achieving a dark brown color with slight scorch spots [15]. Wine processing enhances the herb's ability to clear upper-jiao heat while reducing its drastic purgative effects through partial decomposition of anthraquinones. The alcohol-soluble components improve blood-activating properties, making it suitable for treating blood stasis syndromes [16].

3.4. Charred Rhubarb (Dahuang Tan)

Prepared through controlled carbonization, raw slices are stir-fried in an iron wok at 220–280 °C until surfaces turn charcoal-black while maintaining reddish-brown interiors [17]. This high-temperature processing (approximately 10–15 minutes) significantly increases tannin content through Maillard reactions while reducing anthraquinones by 40%–60% [18]. The resultant product exhibits enhanced hemostatic and astringent properties, particularly effective for treating hematemesis and hemorrhagic disorders [19].

3.5. The Rhubarb processing and chemical compositions

The complex chemical components of TCM are the main material basis for its clinical therapeutic effects. Through various processing and preparation methods, TCM can induce changes in its chemical components, thereby enhancing therapeutic effects or reducing toxicity. Based on this, researchers [15, 20] used different methods such as UHPLC-Q-TOF-MS to detect changes in the main chemical components of processed Rhubarb, revealing the internal logic of TCM processing (Table 1). It should be noted that numerous factors influence processing, including different excipients, processing time, and temperature, all of which can cause varying degrees of change in chemical composition. This variability constitutes both the complexity of TCM processing and a key challenge in its standardization.

3.6. The Rhubarb processing and pharmacokinetics

In addition, the pharmacokinetics of chemical components in different processed products also change, which is an important factor affecting pharmacodynamics. Prof. Xiao Yongqing's team established a rapid and efficient UPC-MS/MS method to determine pharmacokinetic changes of the main chemical components in rat plasma after oral administration of raw and steamed Rhubarb [12, 14]. The results show that wine steaming alters the pharmacokinetic behavior of Rhubarb components, providing a theoretical basis for the differences in pharmacological activities among processed forms (Table 2).

3.7. The Rhubarb processing and pharmacodynamics

After processing, the efficacy of various Rhubarb preparations varies to some extent. For instance, the purgative effect of wine-processed and steamed Rhubarb is slightly milder. Wine-processed Rhubarb is particularly effective at clearing heat from the "upper jiao" and resolving "heat toxins," while steamed Rhubarb exhibits enhanced effects in promoting blood circulation and resolving blood stasis. Charred Rhubarb has a weak purgative effect but excels in cooling the blood and stopping bleeding. According to TCM theory, "blood stasis" is one of the key pathogeneses of CKD. Compared with other processed forms, steamed Rhubarb is advantageous due to its ability to "promote blood circulation and resolve blood stasis," a property supported by modern pharmacological evidence [21]. Additionally, anthraquinone glycosides in raw Rhubarb can cause certain renal toxicity, whereas in steamed Rhubarb, these compounds decompose into free anthraquinones, thereby reducing nephrotoxicity [22]. Therefore, in the treatment of CKD, steamed Rhubarb is generally preferred. It should be noted that TCM emphasizes "syndrome differentiation and treatment." Drug selection is closely tied to the patient's constitution and syndrome type, and various TCM diagnostic frameworks exist. Thus, drug use is not fixed. For example, in chronic kidney failure, if a patient is highly sensitive to Rhubarb, steamed Rhubarb should be prioritized. If steamed Rhubarb proves ineffective, raw Rhubarb may be considered. Conversely, if the patient presents with an "excess syndrome (Shi Zheng)" requiring "purging the fu-organs and descending turbidity", raw Rhubarb is indicated. For physically weak patients, wine-processed Rhubarb may be selected to achieve both purgation and tonification.

4. The traditional applications of Rhubarb

Rhubarb's traditional applications reveal a multifaceted adaptogen-like profile, modulating diverse physiological pathways across cultures (Fig. 3). Its prominence in digestive, hepatic, inflammatory, gynecological, and topical therapies stems from empirical observations of its dose-dependent, preparation-specific actions. While modern pharmacology has clarified mechanisms, such as anthraquinones for constipation and rhein for inflammation, these historical uses underscore Rhubarb's enduring role as a versatile "regulator" of systemic homeostasis in pre-scientific medical systems.

4.1. Gastrointestinal disorders

Rhubarb has been a cornerstone in managing gastrointestinal ailments across TCM, Ayurveda, and European herbalism [23]. Its primary application centers on constipation and dyspepsia, attributed to anthraquinone compounds (e.g., sennosides) that stimulate intestinal peristalsis [24]. In TCM, raw Rhubarb root is prescribed for acute "excess heat" conditions, such as abdominal distention and fecal impaction, often combined with bitter herbs like Mangxiao (mirabilite) in formulations such as Dachengqi Tang [25]. Conversely, processed Rhubarb (e.g., wine-fried or charcoal-baked) is used for chronic constipation in frail patients, reflecting TCM's emphasis on tailoring preparations to individual vitality. In addition to its laxative effects, Rhubarb has also been used in the treatment of dysentery. At low doses, its astringent tannins may help counteract diarrhea, highlighting its bidirectional regulatory role in gastrointestinal health [26].

4.2. Hepato-biliary system

Traditional systems have leveraged Rhubarb's purported detoxifying properties to address liver and gallbladder disorders [27]. In TCM, it is integral to formulas targeting jaundice and hepatitis, believed to clear "damp-heat" pathogens obstructing bile flow. Classical texts such as Shanghan Lun describe Rhubarb paired with Yinchenhao (Artemisia capillaris) in Yinchenhao decoction to resolve yellowing of the skin and dark urine by relieving cholestasis [28, 29]. Similarly, Tibetan medicine employs Rhubarb for liver congestion and gallstones, often blending it with gentian and chebulic myrobalan. Its choleretic effects are thought to enhance bile secretion, while antioxidant components (e.g., rhein) may mitigate hepatic inflammation, a rationale later corroborated by modern studies [30, 31].

4.3. Inflammatory and febrile conditions

As a "cold" herb in TCM energetics, rhubarb is a key remedy for inflammatory and febrile diseases [32]. It is prescribed to clear

Table 1 The influence of different processing methods of Rhubarb on its main chemical components.

Chemical composition	Raw Rhubarb	Steamed Rhubarb	Wine-Processed Rhubarb	Charred Rhubarb	References
Rhein		**		**	15, 20
Emodin		**	*	**	15, 20
Aloe-emodin		**		**	20
Chrysophanol		**	**	**	20
Physcion		**	*	**	20
Gallic acid		**	**	**	20
Catechin		*	**		15, 20
Polydatin		**	**	**	20
Frambione		**	**	**	20
Sennoside A		**	**	**	15
Sennoside B		*		**	15
Rhein-8-*O*-*β*-*D*-glucopyranoside		**	**	**	20
Chrysophanol-8-*O*-*β*-*D*-glucopyranoside				**	20
Emodin-8-*O*-*β*-*D*-glucopyranoside		*		/	15, 20
Physcion-8-*O*-*β*-*D*- glucopyranoside		**	**	**	20
Aloe-emodin-8-*O*-*β*-*D*-glucopyranoside		**	**	**	20
Dimer of catechin		/	**	/	15
Cassialoin		/	**	/	15
Sennoside C/D		/	*	/	15
Gallic acid 3-*O*-*β*-*D*-(6'-*O*-galloyl)-glucopyranoside		/	*	/	15
Epicatechin-(4*β*-8)-epicatechin-(4*β*-8)-catechin		/	*	/	15
(−)Epicatechin-3-*O*-gallate		/	**	/	15
2-*O*-p-coumaroyl-1-*O*-galloy-*β*-*D*-glucose		/	**	/	15
2-*O*-cinnamoyl-1-*O*-galloy-*β*-*D*-glucose		/	**	/	15
Emodin-8-*O*-(6'-*O*-malonyl)-glucopyranoside		/	**	/	15
6-Methyl-aloe-emodin		/	**	/	15

Note: The red block indicates an increase in content compared with raw Rhubarb, the blue block indicates a decrease in content compared with raw Rhubarb, and the gray block indicates no significant difference in content compared with raw Rhubarb. * indicates $P < 0.05$ *vs* raw Rhubarb, ** indicates $P < 0.01$ *vs* raw Rhubarb. "/" indicates that the relevant data not available.

"heat-toxins" manifesting as high fever, sore throat, or skin eruptions, frequently combined with antipyretic herbs like Huangqin (Scutellaria) in Xiexin Tang. Topically, poultices of rhubarb paste treat burns, abscesses, and infected wounds, capitalizing on its anti-microbial and astringent properties [33]. In Ayurveda, Rhubarb root (called Revandchini) is used for inflammatory joint disorders, though less prominently than in East Asian traditions. Notably, its dual role as both purgative and anti-inflammatory agent aligns with the ancient concept of "expelling pathogenic fire through the bowels."

4.4. Gynecological and circulatory disorders

Rhubarb's ability to "invigorate blood and resolve stagnation" makes it a unique agent for gynecological conditions [34]. TCM practitioners prescribe it for amenorrhea, postpartum abdominal pain, and dysmenorrhea linked to blood stasis, often processing it with wine to enhance circulation. Formulas like TaoHeChengQi Tang combine Rhubarb with peach kernels to dissolve pelvic static blood. Additionally, its hemostatic effects are exploited for hematemesis or epistaxis caused by "heat in the blood," typically using charred Rhubarb. This paradoxical capacity, both promoting blood flow and arresting bleeding, underscores its context-dependent applications guided by TCM diagnostics [19].

4.5. Renal support

Rhubarb has a long history of clinical use in the treatment of kidney diseases, particularly [35]. According to TCM theory, the kidneys and intestines are interconnected through the function of Qi transformation. CKD is often associated with damp-heat, blood stasis, and toxin accumulation [36]. Its main pathogenesis is "internal accumulation of turbid toxins", so "unblocking the bowels and eliminating turbid toxins" is the treatment strategy. Rhubarb exerts purgative, heat-clearing, detoxifying, and accumulation-attacking effects, and is regarded as a key medicine for "unblocking the bowels and eliminating turbidity" [37, 38]. Thus, the pathogenesis of CKD aligns with the pharmacological mechanism of Rhubarb in TCM. A meta-analysis involving 34 studies and 2 786 patients indicated that Rhubarb use in chronic renal failure significantly reduces serum creatinine (Scr), blood urea nitrogen (BUN), and uric acid (UA), increases creatinine clearance rate (Ccr), and enhances the total effective rate of symptom and sign improvement [39]. Research based on modern biotechnology shows that the

Table 2 The influence of steamed Rhubarb on the pharmacokinetics of its main chemical components

Pharmacokinetic parameters	$AUC_{(0\text{-}t)}$ ($mg{\cdot}L^{-1}{\cdot}h^{-1}$)	$AUC_{(0\text{-}\infty)}$ ($mg{\cdot}L^{-1}{\cdot}h^{-1}$)	$MRT_{(0\text{-}t)}$ (h)	$MRT_{(0\text{-}\infty)}$ (h)	$T_{1/2z}$ (h)	T_{max} (h)	$V_z{\cdot}F$ ($L{\cdot}kg^{-1}$)	$CL_z{\cdot}F$ ($L{\cdot}h{\cdot}kg^{-1}$)	C_{max} ($\mu g{\cdot}L^{-1}$)	References
Rhein	*	*	**	*	**	**	**	**	**	12, 14
Rhein glucuronide	**	**	**	*			*	**	*	14
Rhein-8-*O*-*β*-*D*-glucoside	**	**	**	**	*	*	**	**	**	12, 14
Emodin	**	**	*	**	**	**		*	*	12, 14
Emodin glucuronide	**	**	**	**	**			**	**	14
Aloe-emodin	**	*	*	**	**	**	**	**	*	12, 14
Aloe-emodin glucuronide	**	**					**	**	**	14
Chrysophanol	*	*					**	*	**	12, 14
Chrysophanol glucuronide	**	**					**	**	**	14
Physcion	**		**	**	**		**	**		12, 14

Note: The red block indicates an increase in value compared with raw Rhubarb, the blue block indicates a decrease in value compared with raw Rhubarb, and the gray block indicates no significant difference in value compared with raw Rhubarb. * represents $P < 0.05$ *vs* raw Rhubarb, ** represents $P < 0.01$ *vs* raw Rhubarb.

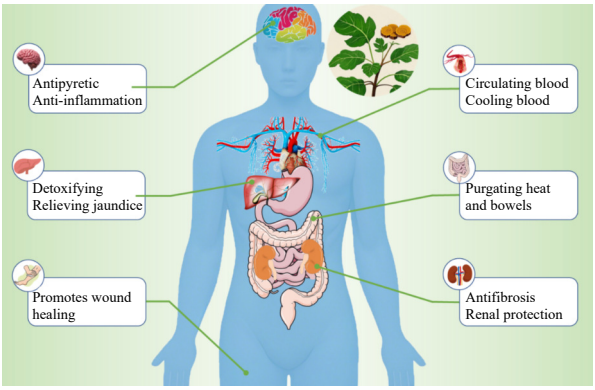


Fig. 3 Traditional applications of Rhubarb. Rhubarb has been widely used in traditional medicine. Its typical applications include promoting blood circulation, cooling the blood, purging heat and relieving constipation, exerting antifibrotic and renoprotective effects, providing antipyretic and anti-inflammatory activities, detoxifying and relieving jaundice, and promoting wound healing.

main active components of Rhubarb exert a synergistic anti-renal fibrosis effect by regulating abnormal ECM accumulation, controlling inflammatory factor release, and maintaining coagulation-fibrinolysis balance [40]. Additionally, Rhubarb and Astragalus are often used together to treat various types of CKD [41-43]. These reports further validate the traditional therapeutic value of Rhubarb in kidney diseases.

4.6. Topical applications

Externally, Rhubarb-based liniments address traumatic injuries and dermatitis; its anthraquinones inhibit microbial growth, while tannins reduce exudation in eczema [44, 45]. In medieval Europe, Rhubarb root was a prized ingredient in wound salves, paralleling its Eastern uses despite differing theoretical frameworks.

5. The main mechanism of Rhubarb against CKD

The multi-target therapeutic potential of Rhubarb in CKD stems from its synergistic modulation of inflammation, oxidative stress, autophagy, fibrosis, and gut-kidney interactions. These mechanisms collectively preserve renal architecture, delay functional deterioration, and interrupt the vicious cycle driving fibrosis. While clinical validation is ongoing, Rhubarb's pleiotropic actions position it as a promising adjunctive strategy for managing CKD progression.

5.1. Anti-inflammatory effects

Chronic inflammation is a hallmark of CKD progression, driving renal fibrosis and functional decline [46, 47]. Rhubarb contains bioactive compounds such as emodin and rhein that suppress pro-inflammatory signaling pathways, including nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) cascades [48]. By inhibiting the release of cytokines like TNF-α, interleukin-6 (IL-6), and IL-1β, Rhubarb mitigates tubulointerstitial inflammation and reduces immune cell infiltration. This anti-inflammatory action alleviates endothelial dysfunction and glomerular damage, thereby slowing the transition from renal injury to fibrosis [22]. Its ability to modulate macrophage polarization toward an anti-inflammatory phenotype further underscores its role in disrupting the inflammatory microenvironment of diseased kidneys [49].

5.2. Antioxidant stress modulation

Oxidative stress exacerbates renal injury by promoting cellular apoptosis, mitochondrial dysfunction, and ECM deposition [50]. Rhubarb-derived anthraquinones and polyphenols scavenge reactive oxygen species (ROS) while enhancing endogenous antioxidant defenses *via* nuclear factor erythroid 2-related factor 2 (Nrf2)/ARE pathway activation [51, 52]. This dual action reduces lipid peroxidation, deoxyribonucleic acid (DNA) damage, and protein carbonylation in renal tubular cells. By preserving redox homeostasis, Rhubarb attenuates oxidative stress-mediated podocyte loss and glomerulosclerosis, key contributors to CKD progression.

5.3. Autophagy regulation

Dysregulated autophagy in CKD leads to the accumulation of damaged organelles and protein aggregates, accelerating tubular atrophy and interstitial fibrosis [53, 54]. Rhubarb compounds modulate autophagy flux by balancing mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) signaling pathways [55]. Enhanced autophagy clearance removes cytotoxic debris, mitigates endoplasmic reticulum stress, and inhibits apoptosis in renal parenchymal cells [56]. This mechanism is particularly critical in diabetic nephropathy, where autophagic impairment drives hyperglycemia-induced renal injury.

5.4. Anti-fibrotic actions

Renal fibrosis, characterized by ECM deposition, represents the terminal pathway of CKD. Rhubarb targets TGF-β/Smad3 signaling, a central axis in fibroblast activation and ECM synthesis [57].

Emodin suppresses myofibroblast differentiation by downregulating α-smooth muscle actin (α-SMA) and collagen I/III expression, while rhein inhibits EMT in tubular cells [58]. Additionally, Rhubarb disrupts crosstalk between angiotensin II and profibrotic mediators, preventing glomerular basement membrane thickening and peritubular capillary rarefaction [59].

5.5. Gut-kidney axis modulation

The core view of the "gut-kidney axis" theory holds that during CKD progression, intestinal microecosystem disorders occur, which aggravate the accumulation of enterogenic uremic toxins in the blood, further decrease renal function, and eventually form a vicious cycle between the intestine and kidney [60]. Emerging evidence highlights Rhubarb's role in reshaping gut microbiota composition, which influences uremic toxin production and systemic inflammation in CKD [61]. By promoting the growth of short-chain fatty acid (SCFA)-producing bacteria and reducing indoxyl sulfate and p-cresol levels, Rhubarb alleviates enteric dysbiosis-induced renal oxidative stress [62]. Its mild laxative properties also mitigate nitrogenous waste retention, indirectly lowering the metabolic burden on compromised kidneys [63].

6. Core signaling pathways involved in renal fibrosis

Renal fibrosis is a common mechanism leading to the progression of kidney disease from various etiologies to end-stage renal disease. In pathological conditions, the interaction between renal cells and matrix is disrupted, and inflammatory cell infiltration and intrinsic cell transformation lead to increased expression of pro-fibrotic cytokines [64]. Abundant ECM deposition in the renal interstitium is the main cause of renal fibrosis. Multiple signaling pathways contribute to fibrogenesis, with the following being central players (Fig. 4).

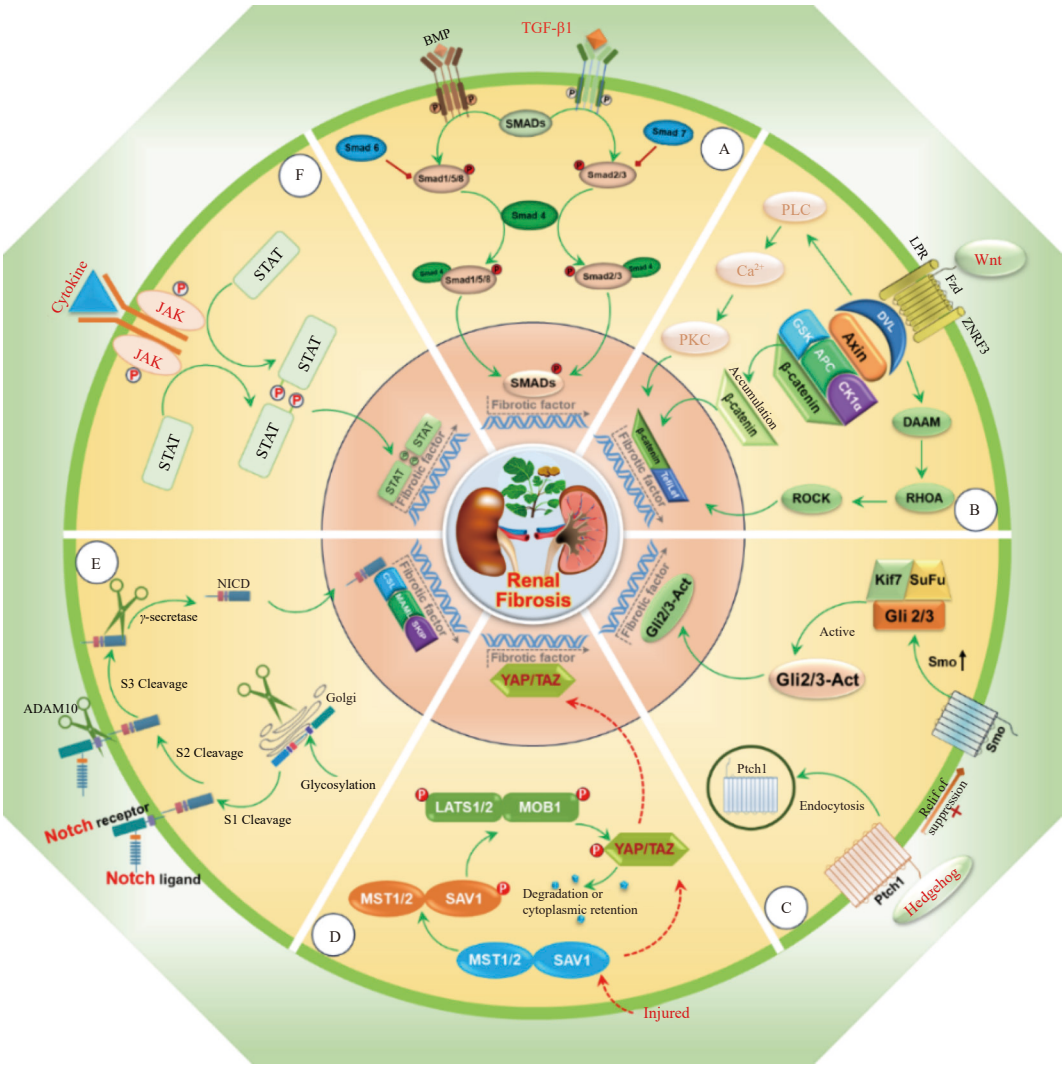


Fig. 4 Core signaling pathways involved in renal fibrosis. Multiple signaling pathways contribute to fibrogenesis, the central players including: TGF-β/Smad signaling (A), Wnt/β-catenin signaling (B), Hedgehog signaling (C), Hippo/YAP signaling (D), Notch signaling (E), and JAK/STAT signaling (F).

6.1. TGF-β/Smad signaling

The TGF-β signaling pathway consists of TGF-β1, TGF-β2, and TGF-β3, among which TGF-β1 is the core molecule. The inactive form of TGF-β1 is the TGF-β1/leucine aminopeptidase (LAP) complex. Upon stimulation by injury, LAP dissociates, releasing active TGF-β1 [65]. TGF-β ligands then bind to type II receptors, which phosphorylate type I receptors, activating downstream Smad2/3 proteins. Phosphorylated Smad2/3 complexes with Smad4 translocate to the nucleus, driving transcription of profibrotic genes (e.g., collagen, α-SMA) [66]. Non-canonical pathways, including MAPK and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), further amplify ECM production. In renal fibrosis, TGF-β promotes EMT, fibroblast activation, and sustained inflammation, creating a vicious cycle of tissue scarring [67]. Recent research has found that Taohe Chengqi Decoction, with Rhubarb as its core ingredient, significantly alleviates chronic renal failure in a 5/6 nephrectomy model by regulating the TGF-β

pathway. Further studies suggest that rhein is one of the main active components responsible for this effect [68].

6.2. Wnt/β-catenin signaling

The Wnt signaling pathway is widely present in invertebrates and vertebrates and is highly conserved during species evolution. The canonical pathway begins when Wnt proteins bind to the cysteine-rich domain of frizzled (Fz) family receptors [69]. This binding inhibits β-catenin degradation, leading to its accumulation [70]. Stabilized β-catenin enters the nucleus and activates target genes such as fibronectin (FN) and matrix metalloproteinases (MMPs). In damaged kidneys, aberrant Wnt/β-catenin signaling enhances fibroblast proliferation, disrupts tubular repair, and exacerbates ECM deposition [71]. Studies have shown that the Wnt/β-catenin pathway is activated in the db/db mouse model of diabetic nephropathy. After 12 weeks of treatment with rhein, renal function is significantly improved through inhibition of this pathway [72].

6.3. Notch signaling

The Notch signaling pathway comprises Notch receptors, ligands, CBF-1-suppressor of hairless-Lag (CSL) DNA-binding proteins, and regulatory molecules. Signaling is initiated by ligand-receptor interaction between adjacent cells. The Notch protein undergoes three proteolytic cleavages, releasing the Notch intracellular domain (NICD), which translocates to the nucleus and binds to the CSL transcription factor [73]. In renal fibrosis, Notch hyperactivation in tubular cells induces EMT and inflammation while suppressing regeneration [74]. Dysregulated Notch also promotes pericyte-to-myofibroblast differentiation, directly fueling interstitial fibrosis [75]. Many compounds in Rhubarb, such as emodin and resveratrol, have been confirmed to regulate the Notch signaling pathway [76, 77], indicating Rhubarb's potential to ameliorate renal fibrosis *via* this pathway.

6.4. Hedgehog (Hh) signaling

There are three homologous Hh genes in mammals: Sonic Hh (SHH), Indian Hh (IHH), and Desert Hh (DHH), which encode SHH, IHH, and DHH proteins, respectively. Hh signaling is controlled by two receptors, Patched (Ptc) and Smoothened (Smo), on the target cell membrane. Hh ligands bind to Ptc, relieving its suppression on Smo [78]. This activates Gli transcription factors, which regulate genes involved in fibroblast activation and ECM synthesis [79]. In fibrotic kidneys, Hh signaling is upregulated in interstitial fibroblasts, driving myofibroblast differentiation and collagen accumulation [80]. In unilateral ureteral obstruction (UUO) rats, treatment with resveratrol, an active component of Rhubarb, significantly antagonizes excessive activation of the Hh pathway, resulting in reduced cell proliferation, EMT, and ECM accumulation [81].

6.5. Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling

The JAK/STAT signaling pathway is a key cytokine-mediated signal transduction mechanism [82]. Its molecular conduction process includes four stages: ligand-receptor binding, JAK kinase activation, STAT phosphorylation and dimerization, and nuclear translocation for transcriptional regulation of target genes. When cytokines such as interferon and interleukin bind to receptors, receptor dimerization triggers self-phosphorylation of JAK family kinases [83]. Activated JAK recruits and phosphorylates STATs, forming homodimers or heterodimers. These activated STATs translocate to the nucleus to regulate transcription of pro-inflammatory and ECM-related genes, ultimately accelerating fibrosis [84]. It has been reported that emodin-8-*β*-*D*-glucoside binds to JAK1/2, thereby inhibiting STAT activation and the associated inflammatory response [85].

6.6. Hippo/YAP signaling

The Hippo/YAP pathway is one of the core regulators of organ fibrosis. Under physiological conditions, mammalian sterile 20-like kinases 1/2 (MST1/2) and salvador homolog 1 (SAV1) form a complex that phosphorylates large tumor suppressors 1/2 (LATS1/2) and MOB kinase activator 1 (MOB1) [86]. The latter further phosphorylates the downstream effectors YAP/TAZ. Phosphorylated YAP/TAZ are either ubiquitinated and degraded or bind to 14-3-3 proteins and remain in the cytoplasm [87]. Conversely, under inflammatory or injurious stimuli, the upstream kinase cascade is disrupted, leading to YAP/TAZ dephosphorylation and nuclear translocation, which induces expression of fibrotic factors [88]. Research suggests that oral administration of emodin activates YAP phosphorylation and promotes its intracellular degradation, thereby reducing oxidative stress damage mediated by nuclear entry [89]. This provides evidence for Rhubarb's regulation of the Hippo/YAP pathway.

6.7. Other Pathways

Additional pathways include MAPK/ERK signaling (activated by oxidative stress or cytokines, promoting fibroblast proliferation) and peroxisome proliferator-activated receptor (PPAR) signaling (its downregulation exacerbates lipid metabolism dysfunction, linked to fibrosis progression). These interconnected pathways form a complex network driving renal fibrosis [90]. Targeting key nodes or their crosstalk holds therapeutic potential. However, pathway-specific modulation remains challenging due to context-dependent roles in tissue repair versus fibrosis.

7. Major chemical constituents of Rhubarb and their effects on renal fibrosis

The chemical diversity of Rhubarb underpins its multifaceted pharmacological profile. Modern pharmacological studies have shown that Rhubarb contains various chemical components, including anthraquinones, flavonoids, anthrones, chromones, tannins, stilbenes, and others (Fig. 5). These components exhibit

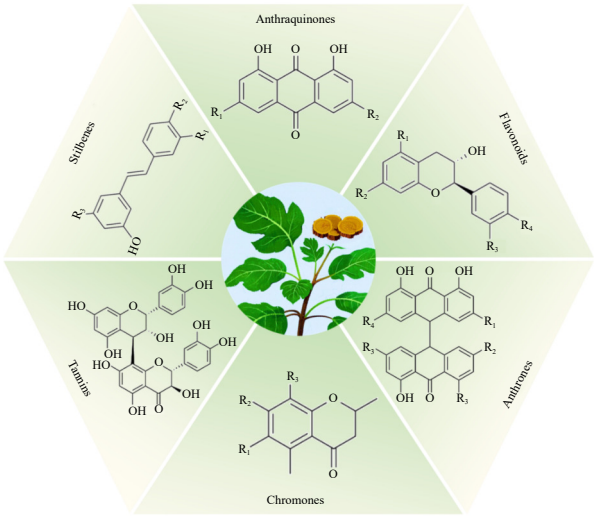


Fig. 5 Major chemical constituents of Rhubarb. The main chemical components of Rhubarb include: anthraquinones, flavonoids, anthrones, chromones, tannins, stilbenes, and so on. This figure lists the basic skeleton structure or representative compound of each class of compounds.

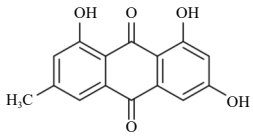
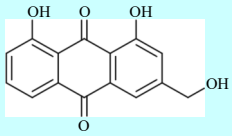
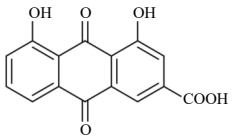
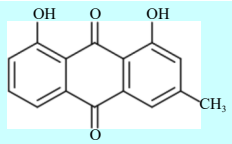
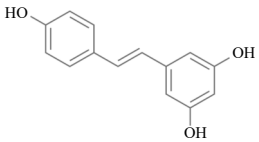
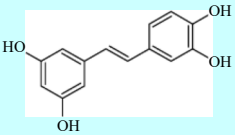
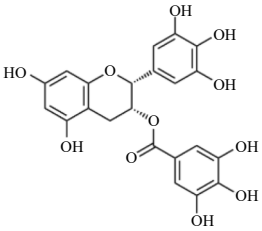
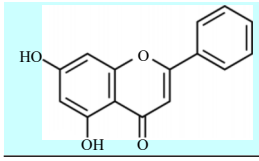
strong therapeutic effects in the treatment of CKD and renal fibrosis (Table 3).

7.1. Anthraquinone derivatives

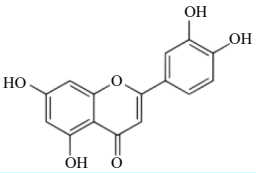
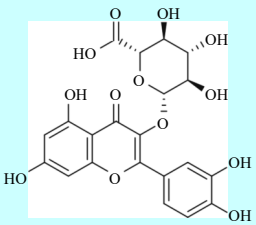
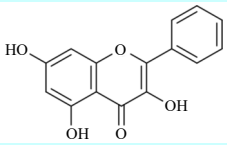
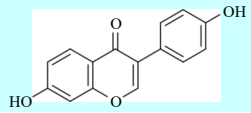
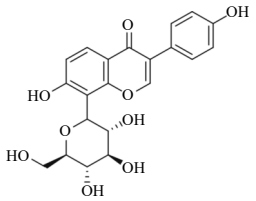
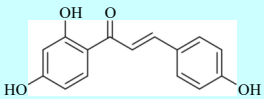
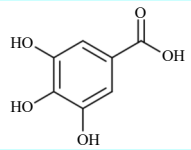
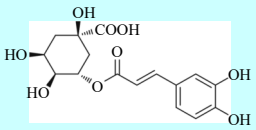
Anthraquinones are the most prominent and pharmacologically active compounds in Rhubarb, responsible for its characteristic laxative effects [91]. These compounds exist in both free forms (aglycones, e.g., emodin, rhein, aloe-emodin) and conjugated forms (glycosides, e.g., sennosides A–D). Structurally, they feature a 9,10-anthracenedione core with hydroxyl, methyl, or carboxyl substitutions [92]. Sennosides act as prodrugs metabolized by gut microbiota into active anthrones, stimulating colonic motility [93]. Beyond their purgative properties, anthraquinones exhibit anti-microbial [94], anti-inflammatory [95], and anti-tumor activities [96].

Emodin ($C_{15}H_{10}O_5$, 1,3,8-trihydroxy-6-methylanthraquinone) is a lipophilic anthraquinone compound isolated from Rhubarb,

Table 3 The chemical composition of Rhubarb and its effect on renal fibrosis.

Chemical structure	Name	Model	Mechanisms	Ref
	Emodin	*In vivo*: UUO rats *In vitro*: TGF-β-induced NRK-52E	Regulating PGC-1α-mediated mitochondria function and energy homeostasis	97
		In vivo: adriamycin-induced rat RF with unilateral nephrectomy *In vitro*: TGF-β-induced HK-2 cells	Alleviating EMT by actuating autophagy through BMP-7/TGF-β signaling	98
		In vivo: 5/6 renal mass reduction	Down-regulating expressions of TGF-β and Smurf 2 and up-regulating Smad7 expression	99
		In vivo: UUO mouse *In vitro*: TGF-β-induced HK-2 cells	Regulating HGF and TGF-β/Smad Signaling Pathway.	100
	Aloe-emodin	*In vivo*: UUO mouse *In vitro*: TGF-β-induced NRK-49F cells	Inhibiting PI3K/Akt/mTOR pathway	101
	Rhein	*In vivo*: UIRI rats *In vitro*: TGF-β-induced HK-2 cells	Regulating the expression of MAPK and AKT in the NF-κB and MAPK signaling pathways	102
		In vivo: UIRI rats *In vitro*: TGF-β and oleic acid induced HK-2 and NRK-52E cells	Activating the PPARα-CPT1A axis	103
		In vivo: UUO rats *In vitro*: TGF-β-induced primary rat renal tubular epithelial (RTE) cells	Regulating the SirT1/STAT3/Twist1 pathway	104
		In vivo: UUO rats *In vitro*: SHH-activated NRK-49F cells	Regulating the SHH-Gli1-Snail signal pathway	105
		In vivo: UUO rats	Inhibiting p-STAT3-mediated apoptosis	106
		In vivo: UUO mouce *In vitro*: TGF-β induced HK2 and HEK293 cells	Regulating aberrant methyltransferase 1/3a expressions in preventing Klotho loss	107
	Chrysophanol	*In vivo*: UUO mouse *In vitro*: TGF-β-induced HK-2 cells	Inhibiting the TGF-β/Smad signaling pathway	108
		In vivo: UUO mouse *In vitro*: TGF-β-induced HK-2 cells	Suppressing NKD2/NF-κB pathway	109
	Resveratrol	*In vivo*: UUO rats *In vitro*: TGF-β-induced HK-2 cells	Inactivating of Smad2/3 signaling	117
		In vivo: 5/6Nx rats	Inhibiting TGF-β and CTGF	118
		In vivo: db/db mice *In vitro*: high glucose-induced NRK-49F cells	Regulating of AMPK/NOX4/ROS signaling	119
		In vivo: UUO mouse *In vitro*: aristolochic acid or TGF-β-induced HK-2 cells	Deacetylation of Smad4 and inhibition of MMP	120
		In vivo: UUO mouse *In vitro*: TGF-β-induced HK-2 cells	Decreased EMT *via* Sirt1-dependent deacetylation of Smad3/Smad4	121
	Picetannol	*In vivo*: UUO mouse	Inhibiting HDAC4/5 and the p38 MAPK signaling	122
	Epigallocatechin-3-gallate (EGCG)	*In vitro*: arsenic-induced Caki-1 and HK-2 cells	Antioxidant and epigenetic regulatory abilities	126
		In vitro: high glucose induced HPC	Inhibiting the NF-κB pathway	127
		In vitro: pcDNA6.2-SNAI1 cells transfected with renal TEPs	Inhibiting SNAI1 overexpression and promoting the process from MET to EMT	128
		In vitro: TGF-β induced HK-2 cells	Deactivating the GSK-3β/β-catenin/Snail1 pathway and activating the Nrf2 pathway	129
		In vitro: TGF-β induced NRK-52E cells	Inhibiting EMT and fibrotic proteins expression by Nrf2 activation	130
		In vivo: UUO mouse	Inhibiting of TGF-β/Smad signaling pathway	131
	Chrysin (5,7-dihydroxyflavone)	*In vivo*: Cyclosporin A induced rats *In vitro*: TGF-β or CsA induced LLC-PK1 cells	Inhibiting the activation of TGF-β/Smad 3/Snail and Akt/GSK-3β pathways	133
		In vivo: db/db mice *In vitro*: High glucose induced RPTECs	Inhibiting renal tubular EMT	134

Continued

Chemical structure	Name	Model	Mechanisms	Ref
	Luteolin	*In vivo*: Aristolochic acid induced mice *In vitro*: Hypoxia/TGF-β or CsA induced NRK49F cells	Activating the SIRT1/FOXO3 pathway	136
	Quercetin	*In vivo*: UUO rats *In vitro*: TGF-β-induced HK-2 cells	Inhibiting the activation of AREG/EGFR pathway	137
		In vivo: UUO rats *In vitro*: TGF-β-induced HK-2 cells	Inhibiting the activation of NLRP3 inflammatory bodies	138
		In vivo: MRL/lpr mice *In vitro*: IL-33 induced HK-2 cells	Inhibiting IL-33/ST2 pathway	139
		In vivo: db/db mice *In vitro*: High glucose induced TECs	Inhibiting FAO pathway by upregulating PPARα	140
		In vivo: adenine induced CRF rats	Inhibiting the PI3k/Akt pathway	142
		In vivo: UUO rats *In vitro*: AngII-treated RTECs	Activating the SIRT1/PINK1/Parkin-mediated mitophagy	143
	Rutin	*In vivo*: 5/6 Nx rats	Inhibiting of TGF-β/Smad signaling pathway	144
	Daidzein	*In vivo*: VOX + UUO rats	Regulating the expression of miR-33a and miR-27a	147
	Puerarin	*In vivo*: Ⅱ DN rats *In vitro*: High glucose induced GMCs	Regulating iron homeostasis and alleviating iron deprivation anemia	148
		In vivo: renal I/R rats *In vitro*: HR induced HK-2 cells	Inhibiting TLR4/Nox4 pathway	149
		In vivo: db/db mice *In vitro*: High glucose induced podocytes	Inhibiting the cAMP/PKA/CREB pathway in podocytes activated via Gnai1	150
		In vivo: Adenine induced CRF rats *In vitro*: LPS induced HK-2 cells	Reducing renal injury and pyroptosis by targeting the miR-342-3p/TGF-β/SMAD axis	151
		In vivo: UUO mice	Inhibiting the NF-κB p65/STAT3 and TGF-β/Smads pathways	152
		In vivo: UUO mice *In vitro*: H_2O_2 induced HK-2 cells	Inhibiting oxidative stress induced-epithelial cell apoptosis through MAPK signaling	153
	Isoliquiritigenin	*In vivo*: UUO mice *In vitro*: LPS/TGF-β-induced bone marrow-derived macrophages (BMDM)	Inhibiting the Mincle/Syk/NF-κB signaling pathway	154
		In vivo: Adenine induced CKD rats	Activating sGC, increasing cGMP and its downstream PKG	155
		In vitro: glycation end-products (AGEs) induced HK-2 cells	Inhibiting the EMT and suppressing the TGF-β/STAT3 signaling	156
		In vivo: STZ-induced diabetes nephropathy rats *In vitro*: High glucose induced HK-2 cells	Inhibiting the JAK2/STAT3 signaling pathway	157
		In vivo: STZ-induced type 1 DN *In vitro*: high glucose-induced NRK-52E cells	Direct binding to SIRT1, the inhibition of MAPK activation, and the induction of Nrf-2 signaling	158
	Gallic acid	*In vivo*: glyoxal induced renal fibrosis rats	ROS quenching and anti-glycation activity	162
	Chlorogenic acid	*In vivo*: Kidney ischemic/reperfusion (I/R) injury rats	Reducing inflammation, tubular injury, and myofibroblast formation	163
		In vivo: hyperuricemia nephropathy rats	Inhibiting the PI3K/AKT/mTOR signaling	164

which has been shown to alleviate fibrosis in multiple organs. Administration of emodin in renal fibrosis models significantly inhibits PGC-1α-mediated lipid accumulation and mitochondrial biogenesis, indicating that emodin regulates mitochondrial function and energy homeostasis through PGC-1α, thereby inhibiting renal fibrosis [97]. Studies have also found that in renal fibrosis rats and cell models treated with emodin, upregulation of BMP-7 is observed, accompanied by activation of autophagy and inhibition of EMT. This suggests that emodin activates autophagy *via* the BMP-7 pathway, thereby reducing EMT in renal fibrosis [98]. Emodin significantly improves pathological abnormalities and renal function in renal fibrosis, and its mechanism may involve upregulation of Smad7 and inhibition of TGF-β/Smad signaling-related Smurf2 and ECM components [99]. Additionally, another study found that the combination of emodin and HGF exhibits better anti-fibrotic effects than HGF alone, and this mechanism is related to the regulation of the TGF-β/Smad signaling pathway [100].

Aloe-emodin ($C_{15}H_{10}O_5$, 1,8-dihydroxy-3-hydroxymethylanthraquinone) is another common anthraquinone in Rhubarb, which alleviates histopathological and renal dysfunction in UUO mice by inhibiting the PI3K/Akt/mTOR pathway. Administration of the PI3K inhibitor wortmannin or siRNA-PI3K counteracts the renal protective effect of aloe-emodin [101].

Rhein ($C_{15}H_8O_6$, 1,8-dihydroxy-3-carboxy anthraquinone) is

often used as a raw material for synthesizing the arthritis drug diacerhein. A metabolomics-based study found that rhein's alleviation of renal fibrosis is closely associated with sphingolipid, arachidonic acid, and glycerophospholipid metabolism pathways, and its molecular mechanism may involve modulation of NF-κB and MAPK signaling pathways [102]. Xiao et al. developed a new integrated analysis method combining network pharmacology and metabolomics, and identified the PPAR-α-CPT1A-l-palmitoyl-carnitine axis as a potential target of rhein in anti-renal fibrosis. This result was validated in UIRI rats and TGF-β/oleic acid-induced NRK-52E and HK-2 cells [103]. Based on combined transcriptomics and metabolomics analyses, rhein may exert its anti-renal fibrosis effect by regulating EMT. Cellular studies have confirmed that rhein promotes fatty acid oxidation (FAO) by regulating the SirT1/STAT3/Twist1 pathway, thereby inhibiting trans-differentiation of renal tubular epithelial cells (TECs) [104]. In the UUO rat model, rhein treatment significantly alleviates renal fibrosis, possibly through inhibition of the SHH-Gli1-Snail signaling pathway, a finding confirmed in SHH-induced NRK-49F cells [105]. Similar studies suggest that rhein mitigates renal fibrosis by restraining p-STAT3-mediated apoptosis [106]. Additionally, in the UUO-induced renal fibrosis model, abnormal expression of methyltransferases 1 and 3a leads to hypermethylation of the promoter of the endogenous protective factor Klotho, and rhein can correct these epigenetic abnormalities, exerting a renal protective effect [107].

Chrysophanol ($C_{15}H_{10}O_4$, 1,8-dihydroxy-3-methyl-anthraquinone) is an anthraquinone isolated from Rheum, exhibiting various pharmacological activities. Treatment with chrysophanol in UUO mice reverses abnormal serum and urine biochemical parameters and reduces expression of fibrosis markers such as FN, collagen I/III, and α-SMA. Rhein also inhibits the secretion of TGF-β and p-Smad3 while promoting Smad7. Mechanistic studies suggest that chrysophanol alleviates fibrosis by blocking the crosstalk between Smad3 and TGF-β receptor I [108]. In the same renal fibrosis models, chrysophanol significantly inhibits NF-κB activation and NKD2 expression, and reduces inflammatory factors such as IL-1β, IL-6, and TNF-α. Molecular docking and microscale thermal analysis indicate that NKD2 is a direct target of chrysophanol. Therefore, chrysophanol improves the fibrotic state by directly inhibiting NKD2 [109]. However, the poor water solubility and unstable physical properties of chrysophanol limit its efficacy. To address this, Wei et al. synthesized *N*-octyl-*O*-sulfate chitosan and developed nanoparticles loaded with chrysophanol. Their research shows that compared to free chrysophanol, the bioavailability of chrysophanol nanoparticles is 2.57 times higher, and its anti-renal fibrosis effect is enhanced [110].

7.2. Stilbenes

Stilbenes, though less abundant than anthraquinones, are notable for their bioactive potential. The primary stilbene in Rhubarb is *trans*-resveratrol and its glycoside, polydatin (resveratrol-3-*O*-*β*-*D*-glucoside). These compounds feature a C6-C2-C6 structure with a central ethylene bond [111]. Stilbenes are renowned for their cardioprotective, neuroprotective, and anti-aging properties [112], largely attributed to sirtuin pathway activation and suppression of pro-inflammatory cytokines [113]. Additionally, recent studies highlight their role in improving insulin sensitivity [114]. Their presence underscores Rhubarb's potential in managing chronic metabolic [115] and degenerative diseases [116].

Resveratrol ($C_{14}H_{12}O_3$, 3,5,4'-trihydroxy-trans-stilbene), a non-flavonoid polyphenolic compound, is an antitoxin produced by various plants under stress. Resveratrol suppresses myofibroblast phenotype and fibrosis formation in UUO kidneys by targeting EMT and fibroblast-to-myofibroblast transition (FMT), which is associated with inactivation of Smad2/3 signaling [117]. In 5/6 nephrectomy (5/6Nx) rats, resveratrol alleviates fibrosis by inhibiting TGF-β and CTGF, while also improving CKD-associated muscle atrophy [118]. Research has shown that resveratrol significantly inhibits high glucose-induced fibroblast proliferation and activation by reducing NOX4-derived ROS production. Further *in vivo* studies confirmed that resveratrol alleviates renal fibrosis in db/db mice by increasing p-AMPK and inhibiting NOX4 [119]. Xiao et al. [120] found that resveratrol inhibits the EMT process to alleviate kidney injury and fibrosis, attributed to upregulation of SIRT1, leading to deacetylation of Smad4 and inhibition of MMP7 expression [120]. Moreover, resveratrol's effect on renal fibrosis is dose-dependent. At low doses (≤ 25 mg·kg^{-1}), resveratrol reduces TGF-β-induced EMT *via* Sirt1-dependent Smad3/Smad4 deacetylation, exerting anti-fibrotic effects. However, at high doses (≥ 50 mg·kg^{-1}), resveratrol induces mitochondrial oxidative stress and ROCK1-mediated cytoskeletal disruption, promoting EMT in HK-2 cells and exacerbating fibrosis. Therefore, the risk of resveratrol use in CKD patients should be carefully considered [121]

Picetannol ($C_{14}H_{12}O_4$, 3,3',4,5'-tetrahydroxy-trans-stilbene) is a metabolite of resveratrol, found in rhubarb, red wine, and grapes. In UUO mice, picetannol significantly inhibits ECM deposition. Mechanistic research indicates that picetannol may exert its effect by inhibiting HDAC4/5 expression and p38 MAPK signaling activation, rather than through the TGF-β/Smad2/3 pathway [122].

7.3. Flavonoids

Rhubarb contains diverse flavonoids, including flavonols (e.g., quercetin, kaempferol) and flavan-3-ols (e.g., catechin, epicatechin). These compounds are characterized by a C6-C3-C6 skeleton with hydroxyl, glycosyl, or methoxy substitutions [123]. Flavonoids contribute to Rhubarb's antioxidant capacity by scavenging free radicals and chelating metal ions. They also modulate inflammatory pathways by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) enzymes [124]. Additionally, certain flavonoids enhance vascular integrity and exhibit cardiovascular protective effects, making them valuable in treating oxidative stress-related disorders [125]. Their synergistic interactions with anthraquinones may mitigate oxidative damage caused by the latter.

7.3.1. Flavonoids (flavan-3-ols)

Epigallocatechin-3-gallate (EGCG, $C_{22}H_{18}O_{11}$, (2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl 3,4,5-trihydroxybenzoate), a green tea polyphenol, is known for its strong antioxidant activity. Iheanacho et al. investigated whether EGCG alleviates arsenic-induced renal fibrosis in TECs. The results indicate that EGCG significantly alleviates arsenic-induced cytotoxicity and abnormal expression of fibrogenic growth factors through its antioxidant and epigenetic regulatory abilities [126]. In the high glucose-treated human podocyte cell line HPC, the actin α4 gene promoter is highly methylated. EGCG treatment reverses this hypermethylation, upregulates ACTN4 levels, downregulates DNA methyltransferase 1 (DNMT1), and inhibits the NF-κB pathway and its mediated fibrotic pathology [127]. The dynamic trans-differentiation of epithelial cells from EMT to mesenchymal-epithelial transition (MET) has attracted widespread attention in fibrosis treatment. Research has shown that EGCG inhibits SNAI1 overexpression and promotes the MET process, providing a novel strategy for preventing renal fibrosis [128]. In TGF-β-induced HK-2 cells, EGCG pretreatment significantly eliminates the EMT process and reduces fibroblast and ECM deposition. This mechanism is related to EGCG deactivating the GSK-3β/β-catenin/Snail1 pathway and activating the Nrf2 pathway [129, 130]. Additionally, studies suggest that EGCG's anti-renal fibrosis effect is highly correlated with inhibition of inflammatory response [131] and cell apoptosis [132].

Chrysin ($C_{15}H_{10}O_4$, 5,7-dihydroxyflavone) is a raw material for synthesizing drugs with anti-cancer, lipid-lowering, cardiocerebrovascular disease prevention, anti-bacterial, and anti-inflammatory properties. Chrysin treatment alleviates cyclosporin A-induced renal dysfunction in rats and reduces renal tubular injury and collagen deposition by inhibiting the TGF-β/Smad3/Snail and Akt/GSK-3β pathways [133]. In diabetic renal tubulointerstitial fibrosis, chrysin inhibits high glucose-induced renal EMT by suppressing vimentin, α-SMA, and FSP-1 expression in human proximal TECs and db/db mice [134]. To address chrysin's poor water solubility, Kang et al. synthesized 5.7-di-*O*-acetylchrysin, which has higher solubility than salicylic acid. In db/db mice, this derivative improved renal injury caused by glomerulosclerosis and tubulointerstitial fibrosis [135].

Luteolin ($C_{15}H_{10}O_6$, 3′,4′,5,7-tetrahydroxyflavon) is mostly present in glycosidic form in various plants, including whole leaf orchids, chili peppers, wild chrysanthemums, honeysuckle, and perilla. After treatment with luteolin in mice with renal fibrosis, renal function and fibrosis were significantly improved. Transcriptomic analysis revealed significant increases in SIRT1 and FOXO3, validated both *in vivo* and *in vitro*. Molecular docking confirmed strong direct binding between luteolin and SIRT1. Therefore, luteolin may alleviate renal fibrosis *via* the SIRT1/FOXO3 pathway [136].

7.3.2. Flavonoids (flavonols)

Quercetin ($C_{15}H_{10}O_7$, 3,5,7,3′,4′-pentahydroxyflavonoid dihydrate) is a widely distributed and biologically active flavonoid that shows potential to inhibit fibrosis in various diseases. Recent research confirms that quercetin improves the fibrotic area in UUO rats and alleviates TGF-β-induced EMT in HK-2 cells. Mechanistic studies show that quercetin exerts anti-renal fibrosis effects by inhibiting the AREG/EGFR signaling pathway [137]. Similar studies indicate that quercetin inhibits NLRP3 inflammasome activation in renal TECs both *in vivo* and *in vitro*, thereby reducing EMT and ECM accumulation [138]. Tubulointerstitial fibrosis is also a key pathological feature in lupus nephritis progression. Quercetin administration significantly improves renal function in MRL/lpr mice and inhibits fibrosis and inflammatory responses. In the IL-33-induced HK-2 cell model, quercetin improves fibrosis and cell pyroptosis *via* the IL-33/ST2 pathway, suggesting its potential in treating lupus nephritis-associated renal fibrosis and inflammation [139]. The combination of quercetin and dasatinib significantly improves fibrosis in db/db mice and reduces lipid deposition. Further investigation found that quercetin inhibits the FAO pathway by upregulating PPARα. Knocking out PPARα reverses this inhibition and weakens quercetin's renal protective effect. Molecular docking and dynamic simulation analysis indicate direct binding between quercetin and PPARα [140]. To improve quercetin's water solubility, absorption, and bioavailability, Sánchez Jaramillo et al. developed a quercetin-nanoparticle formulation. Results showed that low-dose nanoparticles produced the same beneficial effect as high-dose quercetin in preventing kidney injury [141]. Additionally, quercetin reduces renal fibrosis in chronic renal failure rats by targeting the PI3K/Akt pathway and reduces water retention and toxin accumulation by regulating AQP1 and AQP2 expression [142]. Quercetin may also reduce renal TEC (RTEC) aging by activating SIRT1/PINK1/parkin-mediated mitophagy, thereby alleviating renal fibrosis [143].

Rutin ($C_{27}H_{30}O_{16}$, 3,3′,4′,5,7-pentahydroxyflavon-3-(*O*-rhamnosylglucoside)) is a natural antioxidant that scavenges ROS by donating hydrogen atoms to peroxides, superoxide anions, singlet oxygen, and hydroxyl radicals. After inducing chronic renal failure in adult Wistar rats *via* 5/6 nephrectomy, oral rutin treatment significantly improved renal function indicators, alleviated tubulointerstitial injury, and reduced glomerulosclerosis scores. This mechanism may involve rutin's antioxidant activity and inhibition of the Smad pathway [144]. After four weeks of treatment in alloxan-induced diabetic nephropathy rats, rutin significantly reduced serum triglyceride and cholesterol levels, and histopathological results showed marked improvement in renal fibrosis [145].

7.3.3. Flavonoids (Isoflavones)

Daidzein ($C_{15}H_{10}O_4$, 7,4'-dihydroxyisoflavone) is a major isoflavone found in leguminous plants and grains such as soybeans, kudzu, clover, and alfalfa. Daidzein has two hydroxyl groups at the 7 and 4' positions, which are key to its antioxidant properties. Oophorectomized (OVX) rats subjected to UUO were used to simulate pathological damage in postmenopausal CKD. Daidzein treatment alleviates renal dysfunction, fibrosis, and cell apoptosis, especially when combined with losartan. The mechanism involves regulation of miR-33a and miR-27a expression and their interaction with angiotensin AT1 and Mas receptors [146, 147].

Puerarin ($C_{21}H_{20}O_9$, 8-(*β-D*-glucopyranosyl)-4',7-dihydroxyisoflavone) is a flavonoid derivative originally isolated from Pueraria lobata, known for its coronary vasodilatory effect. It has been reported that puerarin inhibits ECM production by regulating iron homeostasis and alleviating ferroptosis, thereby reducing high glucose-induced cell damage, ROS production, and excessive collagen fiber accumulation, ultimately reducing renal fibrosis in diabetic nephropathy rats [148]. Jian et al. also suggested that puerarin alleviates ferroptosis during renal fibrosis in a renal ischemia-reperfusion model by inhibiting the TLR4/NOX4 pathway [149]. In the db/db mouse model of type 2 diabetic nephropathy, puerarin plays a renal protective role by inhibiting the cAMP/PKA/CREB pathway in podocytes activated *via* Gnai1 [150]. In a rat model of chronic renal failure induced by adenine, puerarin treatment significantly alleviated renal injury and fibrosis while increasing miR-342-3p levels. Elevated miR-342-3p negatively regulates the TGF-β/Smad axis, inhibiting IL-1β and IL-18 secretion and pyroptosis. This was confirmed in LPS-induced HK-2 cells [151]. Additionally, puerarin inhibits inflammatory factor recruitment and ECM deposition by regulating the NF-κB/STAT3 and TGF-β/Smads pathways, thereby alleviating UUO-induced inflammation and fibrosis [152]. Zhou et al. found that puerarin improves renal fibrosis by inhibiting oxidative stress-induced epithelial cell apoptosis *via* the MAPK pathway [153].

7.3.4. Flavonoids (chalcones)

Isoliquiritigenin ($C_{15}H_{12}O_4$, 2',4,4'-trihydroxy-trans-chalcone) is a flavonoid initially isolated from licorice, reported to inhibit inflammation and fibrosis. In LPS/TGF-β-induced bone marrow-derived macrophages and UUO mice, isoliquiritigenin exerts renal protective effects by inhibiting the Mincle/Syk/NF-κB signaling pathway, reducing α-SMA and Col III expression [154]. Long-term treatment improves adenine-induced renal fibrosis by activating sGC and increasing cGMP and its downstream PKG [155]. In diabetic patients, hyperglycemia-related advanced glycation end products (AGEs) can lead to renal fibrosis by increasing renal tubular EMT and ECM synthesis. Isoliquiritigenin treatment significantly inhibits the TGF-β/STAT3 pathway and its mediated collagen secretion in AGEs-induced HK-2 cells, alleviating TEMT and fibrosis progression [156]. In the STZ-induced diabetic nephropathy model, isoliquiritigenin improves renal fibrosis in rats by inhibiting the JAK2/STAT3 signaling pathway [157]. Isoliquiritigenin also exerts anti-diabetic nephropathy and anti-fibrotic effects by directly binding to SIRT1, inhibiting MAPK activation, and inducing Nrf2 activation [158].

7.4. Other phytochemicals

Rhubarb contains hydrolyzable tannins, primarily gallotannins and galloyl glucoses, which are polymers of gallic acid bound to a glucose core. These compounds contribute to the astringent

taste of Rhubarb and possess astringent and anti-diarrheal properties, counterbalancing the laxative effects of anthraquinones [159]. Tannins also exhibit anti-microbial activity by disrupting bacterial cell membranes and inhibiting enzyme function [160]. Moreover, their antioxidant and anti-inflammatory effects make them useful in gastrointestinal protection and wound healing [161]. Interestingly, tannins may reduce the bioavailability of anthraquinones *via* complexation, highlighting the plant's inherent chemical equilibrium. Rhubarb also produces minor constituents such as chromones (e.g., rheumone), dianthrones, and polysaccharides. Chromones exhibit anti-allergic and vasodilatory effects, while dianthrones (dimers of anthrone units) display laxative activity similar to anthraquinones. Polysaccharides, including pectins and glucomannans, contribute to Rhubarb's immunomodulatory and prebiotic properties by promoting gut microbiota diversity. Additionally, organic acids (e.g., citric acid, malic acid) enhance the solubility and absorption of other bioactive compounds. These components collectively broaden Rhubarb's therapeutic spectrum beyond its classical applications.

Gallic acid ($C_7H_6O_5$, 3,4,5-trihydroxybenzoic acid) is a polyphenolic compound widely found in plants such as *Rheum palmatum*, *Eucalyptus grandiflorus*, and *Cornus officinalis*. It is widely used in the food, biological, pharmaceutical, and chemical industries. Yousuf et al. investigated the protective effect of gallic acid on experimental rat renal fibrosis induced by glyoxal. The results indicated that glyoxal induces renal fibrosis by enhancing ROS production *via* AGE receptors, while gallic acid significantly counteracts this effect through its ROS quenching and anti-glycation activity [162].

Chlorogenic acid (CGA, $C_{16}H_{18}O_9$, 1,4,5-trihydroxycyclohexanecarboxylic acid 3-(3,4-dihydroxycinnamic acid)) is an organic compound commonly used in anti-bacterial and anti-viral treatments. In renal ischemia-reperfusion injury (IRI) mice, renal tubular injury was observed, with increased inflammatory mediators, macrophage count, and myofibroblast expansion. After treatment with CGA, the number of macrophages and myofibroblasts significantly decreased. These findings are related to the inhibition of inflammatory factors such as TLR-4, TNF-α, NF-κB, and MCP-1 by CGA [163]. In hyperuricemic nephropathy, CGA treatment promotes renal function recovery and reduces renal fibrosis damage. Gut microbiota studies showed that CGA acts by regulating trimethylamine N-oxide (TMAO)-associated microbiota and inhibiting the PI3K/Akt/mTOR pathway cascade [164].

7.5. The multi-dimensional interaction of Rhubarb against renal fibrosis

TCM is characterized by multiple components acting on multiple targets, and Rhubarb exemplifies this complexity. Based on a synthesis of existing literature, we analyzed the anti-fibrotic effects of Rhubarb's chemical constituents and illustrated their complex interactions with molecular targets using Sankey plots (Fig. 6). This multi-dimensional pharmacological profile operates at three levels. First, individual components exert single-target effects, for example, Aloe-emodin modulates the PI3K/Akt pathway. Second, certain compounds engage multiple pathways; Emodin, for instance, regulates NF-κB, MAPK, and PPARα signaling. Third, multiple constituents converge on shared targets: Emodin, Resveratrol, and Rutin all influence the TGF-β/Smad pathway. This multi-level regulatory network reflects Rhubarb's therapeutic advantages in anti-renal fibrosis through a holistic mechanism, consistent with TCM's systemic approach, while also highlighting the intricate pharmacology of herbal medicine. As previously noted, the TGF-β/Smad pathway drives fibrotic factor expression and ECM deposition, serving as a central and downstream mediator of fibrosis. Consequently, it remains the most extensively studied target, aligning with our analytical findings. Notably, current research on Rhubarb's anti-renal fibrosis effects highlights Rhein as the most frequently investigated constituent, suggesting its potential significance in CKD and renal fibrosis. Network pharmacology analyses further support this: one study identifies Catechin, Aloe-emodin, Rhein, and Emodin as core components in preventing diabetic nephropathy [165], while another implicates Rhein, β-sitosterol, and Aloe-emodin as key agents against diabetic nephropathy [166]. Collectively, these findings indicate that Rhein may represent the most promising Rhubarb-derived compound for combating renal fibrosis. However, this conclusion is based on current literature, which may contain publication bias, and the efficacy of Rhubarb's constituents can vary across different pathological contexts. Comparative studies among major components are therefore still required.

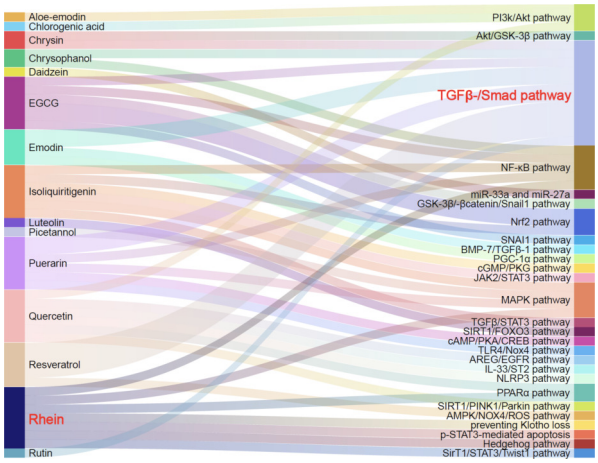


Fig. 6 The multi-dimensional interaction between the chemical components of Rhubarb and the targets in renal fibrosis.

8. Perspectives

8.1. Integrating multi-disciplinary approaches to decipher mechanism synergies

Despite advances in identifying Rhubarb's anti-fibrotic constituents, most studies focus on isolated pathways, such as TGF-β/Smad or NF-κB inhibition, without elucidating how its complex phytochemical composition produces synergistic effects. For example, while emodin suppresses fibroblast activation and resveratrol mitigates oxidative stress, their combined actions within the renal microenvironment remain uncharacterized. Future research should employ multi-omics technologies, including single-cell sequencing and spatial transcriptomics [167], to map the dynamic interactions between rhubarb's constituents and renal cellular networks. Advanced computational models, such as network pharmacology [168] and artificial intelligence [169], could predict system-level targets and optimize compound ratios for enhanced efficacy. Moreover, *in vivo* validation using genetically engineered models, such as cell-specific knockout mice, is essential to confirm these interactions. By integrating reductionist and holistic methodologies, such approaches will clarify how rhubarb's multi-component system achieves therapeutic specificity while minimizing off-target effects, ultimately guiding the development of standardized polyherbal formulations for CKD.

8.2. Optimizing processing methods and pharmacokinetic profiling

The pharmacological effects of rhubarb's various processing methods, such as raw, wine-fried, or carbonized forms, on renal fibrosis remain poorly characterized. Traditional processing tech-

niques alter the composition of bioactive compounds; for instance, heating reduces anthraquinone glycosides while increasing free aglycones, potentially influencing bioavailability and renal tissue targeting [170]. However, systematic studies correlating these processing methods with *in vivo* pharmacokinetics or tissue distribution are limited [171, 172], particularly across different stages and etiologies of kidney disease. Future research should employ advanced analytical tools, such as HPLC-QTOF-MS and MALDI imaging, to quantify how processing influences the spatiotemporal release of key constituents in renal tissues [173]. Concurrently, *in vitro–in vivo correlation (IVIVC)* models could help predict dose-response relationships and guide the development of standardized processing protocols that maximize anti-fibrotic efficacy while minimizing gastrointestinal toxicity. Furthermore, novel delivery systems, such as nanoparticles [174] or phytosomes [175], may enhance the stability and renal accumulation of labile compounds like resveratrol. Addressing these knowledge gaps will facilitate evidence-based standardization of Rhubarb preparations, thereby ensuring reproducibility in clinical applications.

8.3. Translating preclinical findings into clinical validation

Although preclinical studies highlight Rhubarb's anti-fibrotic potential, clinical evidence remains sparse and fragmented. While clinical trials on Rhubarb-containing formulations, such as Niaoduqing Granules, have been conducted [176-180], randomized controlled trials (RCTs) evaluating Rhubarb as a single agent are scarce [35] (Table 4). Moreover, a substantial number of clinical studies on rhubarb and its formulations have been carried out in China, but many suffer from methodological limitations, including small sample sizes, lack of rigorous design, incomplete data reporting, absence of subgroup analyses, and potential ethnic or regional biases [43, 181]. Rigorous, large-scale, multicenter phase II/III RCTs are therefore urgently needed to evaluate rhubarb's efficacy as an adjunct therapy in CKD populations stratified by fibrosis severity and underlying etiology (e.g., diabetic nephropathy versus hypertensive nephrosclerosis). Additionally, biomarker-driven approaches, such as monitoring urinary TGF-β or collagen IV levels, could provide mechanistic insights alongside clinical endpoints like eGFR decline. Long-term safety assessments are equally critical, particularly regarding anthraquinone-associated risks such as electrolyte imbalances or tubular toxicity [182]. Complementary models, including patient-derived organoids [183, 184] and microphysiological systems [185, 186], may enable personalized rhubarb regimens based on individual genetic and microbiome profiles. Finally, interdisciplinary collaboration among phytochemists, nephrologists, and regulatory agencies is essential to address challenges in quality control, intellectual property, and global regulatory acceptance. By prioritizing translational rigor, rhubarb may transition from empirical use to a clinically validated, cost-effective intervention in the growing CKD pandemic.

Table 4 Clinical research on Rhubarb and its formulations for the treatment of chronic kidney disease.

No.	Research type	Research subject	Research drugs	Dosage	Grouping and sample size	Primary outcome indicators	Pharmacodynamic results	Ref
1	Randomized, prospective, double-blinded, and parallel group study	CKD patients (stages 3 & 4)	Rhubarb Capsule	350 mg, thrice daily for 12 weeks	Control: (conservative management treatment, *n* =71) Rhubarb: (conservative management treatment + Rhubarb Capsule, *n* =74)	B. urea, Scr, TUP, TUV, GFR	Compared to control group, blood glucose, B. urea, Scr, TUP decreased; Hb, TUV increased	35
2	Randomized, single-blind, and parallel-control study	CKD patients staged G1-G3b with hyperuricemia	Dahuang Mudan Tang	8 weeks	Control group: (Allopurinol Tablets, *n* = 40) Treated group (allopurinol + Dahuang Mudan Tang, *n* = 40)	Kidney function and proteinuria indicators	Treated group showed a better recovery in kidney function, proteinuria, oxidative stress, a higher efficiency rate	176
3	Randomized, double-blind, placebo-controlled, multicenter clinical study	CKD patients staged 3b-4	Niaoduqing Particles	5 g thrice daily and 10 g before bedtime for 24 weeks	Control group: (placebo, *n* = 146) Test group: (Niaoduqing Particles, *n* = 146)	Scr, eGFR	Compared to control group, significantly reduced Scr and increased eGFR	177
4	Post-trial, open-label, follow-up study	CKD patients staged 3b-4	Niaoduqing Particles	daily and 10 g before bedtime for 48 weeks	Control group: (placebo, *n* = 146) Test group: (Niaoduqing Particles, *n* = 146)	Scr, eGFR	The early use of Niaoduqing Particles seems to ameliorate the worsening of renal function	178
5	Retrospective cohort study	CKD patients staged 3–5	Niaoduqing Particles	NA	Control group: (never taken Niaoduqing Particles, *n* = 232) Niaoduqing group: (Niaoduqing prescription duration/follow-up duration > 80%, *n* = 1039)	All-cause mortality, ESRD, eGFR, SCr.	The long-term use of Niaoduqing granules improved SCr variation and lowered the risk of CKD progression	179
6	Retrospective study	non-diabetic patients with stage IV CKD	Niaoduqing Particles	5 g thrice daily and 10 g before bedtime for 24 weeks	Control group: (only Western medicine, *n* = 220) Test group: (Niaoduqing Particles, *n* = 252)	Deaths, doubling of Scr, ESRD	Niaoduqing Particles reduced Scr and BUN, delayed dialysis time, improved the incidence of compound outcome	180

Note: BUN: blood urea nitrogen, B. urea: blood urea, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, GFR: glomerular filtration rate, Hb: haemoglobin, Scr: serum creatinine, TUP: 24-hour total urine protein, TUV: 24-hour total urine volume. NA: not available.

9. Conclusion

Rhubarb exhibits significant potential as a phytotherapeutic agent for mitigating renal fibrosis, supported by its diverse bioactive constituents, including anthraquinones, stilbenes, and tannins, and multi-target mechanisms involving anti-inflammatory and antioxidant activities, as well as modulation of the TGF-β/Smad signaling pathway. Preclinical evidence indicates differential efficacy among processed forms and isolated compounds; however, clinical validation remains limited. Future research should prioritize standardized quality control of Rhubarb-derived preparations, comprehensive pharmacokinetic profiling of bioactive metabolites, and rigorously designed human trials to establish dose-response relationships and long-term safety profiles. Integrating modern pharmacological approaches with traditional knowledge of processing methods may enhance the therapeutic utility of Rhubarb in CKD management.

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Declaration of competing interests

The authors have no conflict of interest to declare.

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