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Redes moleculares y avances traslacionales en la fibrosis renal: integración de vías, dianas terapéuticas y perspectivas regionales

Molecular Networks and Translational Advances in Renal Fibrosis: Integrating Pathways, Therapeutic Targets, and Regional Perspectives

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RESUMEN

La fibrosis renal constituye la vía final común de la enfermedad renal crónica (ERC) y continúa siendo un reto terapéutico relevante en todo el mundo. Esta revisión integra la evidencia mecanística, traslacional y regional más reciente para caracterizar la arquitectura biológica de la

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fibrosis y evaluar las estrategias terapéuticas emergentes. La literatura muestra de manera consistente que la vía TGF-β/Smad3 actúa como el principal impulsor de la acumulación de matriz, el daño epitelial y la reprogramación transcripcional. Este eje se ve intensificado por la disfunción de NRF2, el estrés oxidativo y la peroxidación lipídica, que amplifican las respuestas inflamatorias y fibrogénicas. Mecanismos adicionales —incluida la polarización de macrófagos hacia fenotipos M2 pro-fibrosis, la ferroptosis en células tubulares y la comunicación mediada por vesículas extracelulares— contribuyen a un microambiente autorreforzante que acelera el deterioro estructural renal. Las cinco figuras conceptuales resumen estas interacciones, la frecuencia terapéutica, la dinámica dependiente del estadio, los perfiles comparativos de innovación y la creciente participación de México, Colombia y Ecuador en la investigación de fibrosis. Entre las terapias emergentes, la activación de NRF2 cuenta con el respaldo mecanístico más sólido, mientras que los antagonistas del receptor mineralocorticoide continúan siendo la opción clínicamente más madura con efectos antiinflamatorios y antifibróticos demostrados. La modulación de Smad3 y ARN no codificante, las estrategias basadas en exosomas, la inhibición de la ferroptosis, la reprogramación de macrófagos y la terapia dirigida a canales iónicos representan enfoques prometedores pero aún en evolución. La evidencia coincide en que el tratamiento antifibrótico eficaz requerirá combinaciones multitarget adaptadas al estadio. Dada la alta carga de ERC en Latinoamérica, es esencial fortalecer los esfuerzos traslacionales regionales. En conjunto, la evidencia respalda una transición hacia intervenciones antifibróticas multimodales y de precisión.

PALABRAS CLAVE

Fibrosis renal, Enfermedad renal crónica, Vías de estrés oxidativo, Polarización de macrófagos, Dianas terapéuticas emergentes

ABSTRACT

Renal fibrosis represents the final common pathway of chronic kidney disease (CKD) and remains a major therapeutic challenge worldwide. This review integrates recent mechanistic, translational, and regional evidence to characterize the biological architecture of fibrosis and evaluate emerging therapeutic strategies. Across the literature, a consistent pattern emerges in which TGF-β/Smad3 signaling functions as the central driver of matrix accumulation, epithelial injury, and transcriptional remodeling. This pathway is reinforced by NRF2 dysregulation, oxidative stress, and lipid peroxidation, which amplify inflammatory and fibrogenic responses. Additional mechanisms—including macrophage polarization toward M2-like phenotypes, ferroptotic injury in tubular cells, and extracellular vesicle–mediated transfer of pro-fibrotic molecules—contribute to a self-reinforcing microenvironment that accelerates structural renal decline. Five conceptual figures summarize these interactions, therapeutic frequencies, stage-dependent dynamics, comparative innovation profiles, and the growing participation of Mexico, Colombia, and Ecuador in fibrosis research. Among emerging therapies, NRF2 activation demonstrates the strongest mechanistic support, while mineralocorticoid receptor antagonists remain the most clinically mature option with proven anti-inflammatory and antifibrotic effects. Smad3 and non-coding RNA modulation, exosome-based strategies, ferroptosis inhibition, macrophage reprogramming, and ion-channel targeting represent promising but still evolving approaches. A recurrent finding across publications is that effective antifibrotic therapy will likely require multi-target, stage-adapted combinations capable of modulating oxidative, immune, and transcriptional pathways concurrently. Given the high burden of CKD in Latin America, strengthening regional translational efforts and integrating molecular advances with local epidemiological contexts are essential. Overall, current evidence supports a shift toward precision, multi-modal antifibrotic interventions that address the complex biology of renal fibrosis.

KEYWORDS

Renal fibrosis, Chronic kidney disease, Oxidative stress pathways, Macrophage polarization, Emerging therapeutic targets

INTRODUCCIÓN

Chronic kidney disease (CKD) has become one of the most pressing global health challenges of the 21st century, with an estimated prevalence exceeding 850 million individuals worldwide. It represents a major cause of morbidity,

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mortality, and economic burden, particularly in low- and middle-income countries where early detection and treatment remain limited. Independent of the underlying etiology—whether diabetes mellitus, hypertension, autoimmune nephritis, or toxic nephropathy—renal fibrosis stands as the final and irreversible common pathway of progressive renal injury. It is characterized by excessive deposition of extracellular matrix (ECM) proteins, tubular epithelial atrophy, microvascular loss, and glomerulosclerosis, ultimately leading to end-stage renal disease (ESRD). Despite advances in nephrology and molecular medicine, current therapeutic options primarily slow, rather than prevent or reverse, fibrotic progression, underscoring the urgent need for new, targeted interventions.

Renal fibrosis results from a complex interplay of multiple cellular and molecular mechanisms involving tubular epithelial cells, interstitial fibroblasts, endothelial cells, pericytes, and infiltrating immune cells. Persistent activation of profibrotic signaling pathways such as transforming growth factor-β (TGF-β)/Smad3, Wnt/β-catenin, and Notch pathways contributes to the differentiation of fibroblasts into myofibroblasts, the main producers of ECM components (Li et al., 2022; Lan et al., 2019). This process is amplified by oxidative stress, mitochondrial dysfunction, and chronic inflammation, all of which perpetuate tissue injury and impair regenerative mechanisms (Huang et al., 2023; Liu et al., 2025). Notably, macrophage polarization toward a proinflammatory (M1) phenotype and the imbalance between reparative and fibrotic signaling have emerged as crucial drivers of disease progression (Niu et al., 2025; Liu & Sun, 2025). These findings suggest that renal fibrosis is not merely a static scarring process but a dynamic and potentially reversible state when addressed at early molecular stages.

Recent literature has expanded the understanding of the fibrogenic microenvironment, often referred to as the "fibrogenic niche," which involves cell–cell and cell–matrix interactions regulating the fate of renal cells under chronic injury conditions (He et al., 2023). Within this niche, extracellular vesicles (EVs) and exosomes have gained particular attention as mediators of intercellular communication. They transport signaling molecules such as microRNAs, long non-coding RNAs, and proteins that can either exacerbate or attenuate fibrotic responses (Kosanović et al., 2021; Li et al., 2025). This insight has led to the exploration of exosome-based therapies and engineered nanocarriers as potential delivery systems for antifibrotic drugs (Yan et al., 2022). Simultaneously, mechanisms such as ferroptosis, a regulated form of cell death driven by lipid peroxidation, have been identified as novel contributors to fibrotic damage, opening new avenues for therapeutic intervention (Renal Failure, 2025).

Moreover, oxidative stress and inflammation have been recognized as central mechanisms linking diverse pathogenic pathways in renal fibrosis. Activation of the nuclear factor erythroid 2-related factor 2 (NRF2) has emerged as a key cytoprotective response regulating antioxidant enzymes and reducing reactive oxygen species accumulation (Bondi et al., 2024; Lim et al., 2025). Dysregulation of NRF2 signaling contributes to sustained oxidative damage and ECM deposition, whereas its pharmacological activation has shown promising antifibrotic and anti-inflammatory effects in preclinical models. Parallel studies on mineralocorticoid receptor antagonists (MRAs) have demonstrated renal-protective effects beyond blood pressure control, decreasing inflammation and fibrosis in diabetic kidney disease and other chronic nephropathies (Barrera-Chimal et al., 2022). These findings underscore a paradigm shift toward the modulation of intracellular stress responses and hormonal signaling as integral components of antifibrotic therapy.

Another promising strategy involves targeting the transcriptional and epigenetic regulation of fibrosis-related genes. The modulation of non-coding RNAs, including microRNAs and long non-coding RNAs, has been proposed as a mechanism to silence profibrotic genes and reactivate reparative pathways (Lan et al., 2019). Similarly, inhibitors of ion channels implicated in cellular differentiation and proliferation have shown potential in reducing fibrosis severity (Yan et al., 2022). Together, these approaches represent a transition from broad anti-inflammatory therapies toward precision-based molecular interventions that aim to restore the physiological balance between tissue repair and fibrosis.

In this context, the identification of novel biomarkers and therapeutic targets has become a global research priority. The last decade has witnessed a growing collaboration between multidisciplinary teams from Latin America, including Mexico, Colombia, and Ecuador, who are contributing to translational nephrology research through studies integrating molecular biology, pharmacology, and clinical nephrology. Their contributions have enhanced the understanding of the local epidemiology of CKD, environmental influences, and therapeutic gaps that demand region-specific solutions. This international collaboration aims to strengthen the translational potential of laboratory findings and facilitate the development of accessible therapeutic strategies.

The present review synthesizes contemporary evidence on renal fibrosis, integrating molecular, cellular, and systemic perspectives to identify emerging therapeutic targets in chronic kidney disease. By examining key mechanisms such

as oxidative stress, macrophage polarization, ferroptosis, and exosomal communication, this work highlights potential pathways for therapeutic modulation. Furthermore, it discusses the translational implications of these mechanisms, emphasizing the importance of early intervention and personalized medicine approaches. The central hypothesis proposed is that the convergence of antioxidant modulation, immune balance, and targeted delivery systems can collectively shift the clinical management of CKD from supportive care toward true antifibrotic intervention. Through this comprehensive analysis, the article seeks to contribute to the ongoing international effort to mitigate the growing burden of renal fibrosis and improve patient outcomes worldwide.

DESARROLLO

1) Pathogenic architecture of renal fibrosis—what drives progression

Renal fibrosis is sustained by a self-amplifying network that links epithelial injury, immune activation, stromal reprogramming, and microvascular loss. The **TGF-β/Smad3 axis** sits at the core of this network, integrating damage signals into myofibroblast differentiation and extracellular matrix (ECM) deposition; Smad3 also orchestrates a *non-coding RNA program* (miRNAs, lncRNAs) that locks tissues into a profibrotic state (Li, Fu, & Liu, 2022; Lan, Chen, & Shi, 2019). The surrounding **fibrogenic niche**—an ecosystem of stressed tubular cells, endothelial cells/pericytes, infiltrating leukocytes, and matrix—emerges as the operational unit of scarring, governed by tight **cell–cell communication** through ligand–receptor pairs and vesicle cargo (He et al., 2023; Li, Fu, & Liu, 2022).

Oxidative stress and mitochondrial dysfunction amplify this program. When antioxidant defenses (notably **NRF2** signaling) falter, ROS accumulation enhances TGF-β signaling, triggers epithelial senescence, and impairs repair; conversely, NRF2 activation shows antifibrotic, anti-inflammatory effects across preclinical CKD contexts (Bondi, Hartman, & Tan, 2024; Lim, Yuen, & Chan, 2025; Liu et al., 2025). In parallel, **immune circuits**—especially macrophages—govern fate decisions: sustained M1-skewing propagates injury, while maladaptive "reparative" programs (e.g., M2-like) can paradoxically promote matrix expansion and capillary rarefaction (Niu, Yang, & He, 2025; Liu & Sun, 2025).

Beyond apoptosis and necrosis, **ferroptosis**—iron-dependent lipid peroxidation—has surfaced as a driver of tubular loss and inflammatory spillover, linking metabolic stress to fibrotic remodeling and opening opportunities for lipid peroxidation blockers and iron handling modulators ("Ferroptosis and renal fibrosis," 2025; Huang, Fu, & Ma, 2023). **Extracellular vesicles (EVs)/exosomes** further shape the niche: as messengers, they ferry miRNAs and proteins that either propagate or brake fibrosis; as therapeutics, they can deliver antifibrotic cargo to injured segments (Kosanović et al., 2021; Li, Waheed, & Sun, 2025). Finally, **ion channels and transporters** (e.g., TRP, ENaC, various Ca^{2+}/K^{+} channels) influence fibroblast activation, epithelial plasticity, and inflammation, positioning them as druggable nodes (Yan, Ke, & Fang, 2022).

2) Emerging therapeutic targets—where the field is moving

Smad3 and its RNA effectors. Targeting Smad3 or its downstream non-coding RNAs can downshift ECM genes, attenuate EMT-like changes, and restore repair signals (Lan et al., 2019; Li, Fu, & Liu, 2022). This includes antimiRs against profibrotic miRNAs and delivery of protective miRNAs via EVs (Kosanović et al., 2021).

NRF2 axis and redox homeostasis. Small-molecule NRF2 activators and strategies that stabilize NRF2 (or inhibit its repressors) blunt oxidative injury and inflammatory transcription, with converging evidence across models (Bondi et al., 2024; Lim et al., 2025; Liu et al., 2025). Combining NRF2 modulation with metabolic/mitochondrial support is a rational next step (Huang et al., 2023).

Macrophage reprogramming. Approaches that constrain pathogenic macrophage phenotypes, block profibrotic cytokines, or promote resolution (efferocytosis, pro-repair cues) are advancing; macrophage-targeted nanocarriers and EVs may increase precision (Niu et al., 2025; Liu & Sun, 2025; De Blasio et al., 2023).

Mineralocorticoid receptor (MR) blockade beyond BP control. Non-steroidal and steroidal MRAs reduce inflammation and fibrosis in diabetic and non-diabetic CKD by modulating immune and oxidative pathways, independently of hemodynamics (Barrera-Chimal et al., 2022). Their antifibrotic "class effect" is a cornerstone for combination regimens.

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Ferroptosis modulation. GPX4 preservation, CoQ10/selenium biology, and iron handling are concrete levers to reduce lipid peroxidation–driven epithelial loss; this may synergize with NRF2 activation ("Ferroptosis and renal fibrosis," 2025; Huang et al., 2023).

Ion-channel therapeutics. Modulating mechanosensitive and Ca^{2+}-handling channels can limit fibroblast calcium signaling and contractility, reduce inflammatory crosstalk, and improve epithelial resilience (Yan et al., 2022).

Exosome/EV therapeutics. Two complementary avenues are maturing: (i) *diagnostics*—fibrosis signatures in urinary/plasma EV cargo; and (ii) *therapeutics*—engineered EVs to deliver antimiRs, anti-TGF-β payloads, or NRF2 enhancers to tubules/interstitium (Kosanović et al., 2021; Li, Waheed, & Sun, 2025; Abbad, Esteve, & Chatziantoniou, 2025).

System-level perspectives. Recent syntheses emphasize multi-target strategies and careful sequencing/combination (e.g., MRA + NRF2 activator + EV-based RNA therapy), with translational frameworks that bridge molecular wins to clinical endpoints (Abbad et al., 2025; Boima et al., 2025; Reiss et al., 2024).

3) Regional translational outlook—Mexico, Colombia, Ecuador

Across Latin America, CKD patterns reflect intertwined drivers: diabetes and hypertension, occupational heat stress, agrochemical exposures, and access gaps. Multidisciplinary teams in **Mexico, Colombia, and Ecuador** are well positioned to (i) validate **EV-based biomarkers** in diverse CKD phenotypes; (ii) test **NRF2-centric** and **MRA-anchored** combinations in real-world cohorts; and (iii) implement **ion-channel** and **macrophage-modulating** strategies within primary and secondary care. Such efforts can accelerate equitable translation and inform regulatory pathways (Huang et al., 2023; Reiss et al., 2024; Abbad et al., 2025).

4) Gaps, cautions, and opportunities

Key challenges include: (i) defining *who benefits when*—patient stratification via EV cargo, ferroptosis markers, and redox signatures; (ii) optimizing *delivery*—targeted renal tropism for RNA/drug payloads; (iii) ensuring *durability and safety*—particularly for long-term NRF2 activation, macrophage reprogramming, and ion-channel modulation (Bondi et al., 2024; Lim et al., 2025; De Blasio et al., 2023). Methodologically, future trials should integrate **mechanism-linked biomarkers** with hard outcomes to de-risk translation (Abbad et al., 2025; Boima et al., 2025).

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To analyze and integrate recent evidence on the molecular, cellular, and systemic mechanisms underlying renal fibrosis, identifying and classifying emerging therapeutic targets that may contribute to the prevention, attenuation, or reversal of chronic kidney disease progression in global and Latin American contexts, particularly in Mexico, Colombia, and Ecuador.

This objective seeks to evaluate, synthesize, and apply current scientific findings to propose a framework for the development of novel antifibrotic strategies that combine oxidative stress modulation, immune regulation, and intercellular communication control.

Specific Objectives

Cognitive domain

Understand the pathophysiological basis of renal fibrosis by describing the interactions among inflammation, oxidative stress, and fibrotic signaling pathways (TGF-β/Smad3, NRF2, and ferroptosis).

1. **Analyze** the molecular and cellular mechanisms that determine the transition from adaptive repair to pathological fibrosis, identifying potential intervention points supported by experimental and clinical data.
2. **Evaluate** the efficacy and limitations of current and emerging therapeutic targets, including mineralocorticoid receptor antagonists, NRF2 activators, and exosome-based therapies.
3. **Integrate** translational evidence from international and Latin American research to **formulate new hypotheses** for future clinical or experimental antifibrotic strategies.

4. **Propose** a comprehensive conceptual model linking molecular targets to clinical applications, oriented toward personalized nephrology and regenerative medicine.

Psychomotor domain

Develop the ability to interpret and reproduce analytical data (e.g., molecular pathway schematics, histopathological patterns, and biomarker profiles) related to renal fibrosis.

1. **Apply** methodological tools to systematically collect and organize bibliographic information, ensuring reproducibility and scientific rigor.
2. **Design** conceptual or visual models that represent therapeutic interactions within the fibrogenic niche using evidence-based criteria.
3. **Adapt** acquired knowledge to educational and research settings, facilitating the training of medical students and researchers in the study of fibrotic kidney disease.

Affective domain

1. **Promote** scientific curiosity and ethical commitment in exploring innovative therapeutic strategies for CKD.
2. **Encourage** empathy and professional responsibility toward patients with chronic kidney disease by understanding the socioeconomic and emotional burden of fibrosis.
3. **Value** interdisciplinary and international collaboration (Mexico, Colombia, Ecuador, and global partners) as a means to enhance scientific innovation and equity in health research.
4. **Foster** an attitude of continuous learning and resilience, recognizing the relevance of translational nephrology as a path toward more effective and humane treatments.

OBJETO DE ESTUDIO

The object of study in this review is **renal fibrosis as a biological, clinical, and therapeutic phenomenon** within the broader framework of **chronic kidney disease (CKD)**. Specifically, the analysis focuses on the **molecular and cellular processes that sustain fibrotic remodeling**, including oxidative stress, immune dysregulation, epithelial-to-mesenchymal transition (EMT), and extracellular matrix (ECM) accumulation, as well as their modulation through **emerging pharmacological and biotechnological strategies**.

From a biological standpoint, renal fibrosis represents a **maladaptive wound-healing response** triggered by chronic injury to the renal parenchyma. It involves persistent activation of fibroblasts, transdifferentiation of tubular epithelial cells, and an imbalance between pro-fibrotic and anti-fibrotic signals (Li et al., 2022; Huang et al., 2023). This pathological state leads to the distortion of renal architecture, decreased capillary density, and progressive functional decline, which collectively define the irreversible stage of CKD (Reiss et al., 2024; Abbad et al., 2025).

At the cellular level, the object of study encompasses the **dynamic interactions between renal tubular cells, macrophages, fibroblasts, and endothelial cells**, mediated by cytokines, growth factors, and extracellular vesicles (He et al., 2023; Kosanović et al., 2021). These interactions form the "fibrogenic niche," a concept that underlies the persistence of chronic inflammation and matrix deposition even after the initial insult has subsided.

Therapeutically, the object of study extends to the **identification, characterization, and evaluation of novel molecular targets and signaling pathways** that can be exploited to prevent, attenuate, or reverse fibrotic progression. This includes exploring agents that modulate **NRF2 activity**, **mineralocorticoid receptor signaling**, **Smad3-dependent non-coding RNAs**, **ion-channel regulation**, and **ferroptosis inhibition** (Bondi et al., 2024; Lim et al., 2025; Lan et al., 2019; Yan et al., 2022).

Furthermore, this work considers renal fibrosis not only as a **pathophysiological entity** but also as a **public health concern**, given its increasing incidence in Latin America and its association with socioeconomic disparities and limited access to early nephrology care. By including evidence from **Mexico, Colombia, and Ecuador**, the study integrates a regional perspective that reflects environmental, genetic, and healthcare-related factors influencing fibrotic disease progression and therapeutic response.

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Ultimately, the object of study aims to establish a **multidimensional understanding** of renal fibrosis—linking molecular insights with clinical translation—to guide the design of preventive and restorative strategies in CKD management.

METODOLOGÍA

This review was developed following the **DMAIC methodological framework**—an evidence-based process improvement approach widely used in health sciences research. The method was selected for its systematic capacity to identify problems, evaluate variables, and propose measurable solutions applicable to translational nephrology. Each phase (Define, Measure, Analyze, Improve, Control) was adapted to the context of renal fibrosis and the identification of emerging therapeutic targets in chronic kidney disease (CKD).

1. Define Phase

The problem was defined as the **lack of effective antifibrotic therapies** for CKD, despite growing mechanistic knowledge. The central research question was established:
"Which molecular, cellular, and therapeutic strategies have demonstrated emerging potential to mitigate renal fibrosis and its progression toward end-stage renal disease?"
The objectives were aligned with Bloom's taxonomy to integrate cognitive, psychomotor, and affective competencies. Key concepts such as *fibrogenic niche*, *NRF2 activation*, *macrophage polarization*, and *exosome-based therapy* were delimited as the primary analytical categories.

2. Measure Phase

A structured literature review was performed using databases such as **PubMed, Scopus, Web of Science, and ScienceDirect**. The inclusion criteria comprised:

- Articles published between **2019 and 2025**,
- Indexed in peer-reviewed journals with impact factor > 2,
- Addressing molecular mechanisms, therapeutic targets, or translational strategies in renal fibrosis.

A total of **20 core references** (Li et al., 2022; Abbad et al., 2025; Rayego-Mateos & Valdivielso, 2020; among others) were analyzed and cross-compared. Each source was coded according to thematic relevance (oxidative stress, inflammation, fibrosis signaling, exosomal therapy, pharmacological intervention). Data extraction focused on authorship, study design, main findings, limitations, and therapeutic implications.

3. Analyze Phase

The selected studies were synthesized to identify **patterns, correlations, and knowledge gaps** within the fibrotic process. Mechanistic pathways such as TGF-β/Smad3, NRF2–Keap1, ferroptosis, and macrophage signaling were mapped to highlight convergence points. The analysis incorporated both **quantitative and qualitative evidence**, evaluating preclinical outcomes (e.g., reduction of ECM markers, modulation of oxidative genes) and clinical implications (e.g., decreased albuminuria, slowed eGFR decline).
Comparative analysis across international studies—including those from **Mexico, Colombia, and Ecuador**—allowed contextualizing regional priorities and environmental determinants of CKD.

4. Improve Phase

Based on the synthesis, a **conceptual optimization model** was proposed, integrating antioxidant modulation, immune reprogramming, and exosome-mediated delivery as synergistic therapeutic strategies. Recommendations for translational research were formulated:

- Combine **NRF2 activators** with **mineralocorticoid receptor antagonists (MRAs)** to target oxidative and hormonal pathways simultaneously.
- Employ **engineered exosomes** as biovectors for antifibrotic microRNAs or Smad3 inhibitors.
- Explore **ion-channel modulators** and **ferroptosis inhibitors** as adjunct therapies to restore renal cellular homeostasis.

This phase emphasized interdisciplinary collaboration and the adaptation of findings to local health systems.

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5. Control Phase

A validation process was designed to ensure **reproducibility and methodological transparency**. The review matrix, coding system, and synthesis criteria were documented to facilitate replication by other research teams. Continuous monitoring of new publications and post-2025 trials was recommended to maintain updated knowledge. Additionally, it was proposed that Latin American research networks develop **shared databases** for CKD and fibrosis biomarkers to accelerate regional innovation.

Ethical and Reproducibility Considerations

As this review is based exclusively on published literature, no human or animal experiments were conducted. All sources were cited following APA 7th edition standards. The methodological transparency of the DMAIC structure allows future researchers to replicate or expand this review under identical parameters.

FASES DEL DESARROLLO

Phases of Development

The development of this review followed the **DMAIC framework**, structured in five sequential and interconnected phases: **Define, Measure, Analyze, Improve, and Control.** Each phase was designed to ensure methodological rigor, coherence with the study objectives, and reproducibility by future researchers.

Phase 1: Define — Conceptual delimitation and problem formulation

During this phase, the phenomenon of **renal fibrosis** was defined as the maladaptive and progressive response of renal tissue to chronic injury, culminating in the irreversible loss of renal function. The main problem identified was the **absence of effective antifibrotic therapies** despite the growing understanding of molecular and cellular mechanisms. The research question established was:

Which molecular, cellular, and therapeutic mechanisms represent emerging targets capable of mitigating renal fibrosis in chronic kidney disease?

Key variables were categorized into three analytical axes:

1. **Biological and molecular processes** (TGF-β/Smad3, oxidative stress, ferroptosis, macrophage activation).
2. **Therapeutic targets** (NRF2 activation, mineralocorticoid receptor blockade, exosome-based delivery).
3. **Translational context** (regional implications in Mexico, Colombia, and Ecuador).

The theoretical foundation was constructed based on high-impact publications (Li et al., 2022; Abbad et al., 2025; Reiss et al., 2024) and global data from *Nature Reviews Nephrology*, *Frontiers in Physiology*, and *Renal Failure*.

Phase 2: Measure — Evidence collection and parameter identification

The second phase involved the systematic measurement and compilation of scientific data. The process included:

- **Database selection:** PubMed, Scopus, Web of Science, and ScienceDirect.
- **Search strategy:** Boolean combinations using key terms such as “renal fibrosis,” “therapeutic targets,” “NRF2,” “Smad3,” “exosomes,” and “ferroptosis.”
- **Inclusion criteria:** Studies published between **2019–2025**, peer-reviewed, and written in English.
- **Exclusion criteria:** Articles lacking mechanistic data or without translational potential.

A total of **20 peer-reviewed articles** were included. Each was categorized according to:

- Type of study (experimental, clinical, or review),
- Mechanistic contribution,
- Level of therapeutic innovation,

- Relevance to Latin American health systems.

This structured measurement enabled quantification of the evidence and ensured balance between experimental and translational perspectives.

Phase 3: Analyze — Integration and interpretation of findings

The analysis phase synthesized molecular and therapeutic data to construct a comprehensive understanding of the fibrogenic process. The main findings were organized around five mechanistic pillars:

1. **TGF-β/Smad3 signaling** as the central regulator of fibrogenesis and EMT (Lan et al., 2019).
2. **Oxidative stress and NRF2 dysfunction**, amplifying inflammation and matrix accumulation (Bondi et al., 2024; Lim et al., 2025).
3. **Macrophage polarization** as a determinant of chronic inflammation (Niu et al., 2025; Liu & Sun, 2025).
4. **Ferroptosis** as an emerging pathway linking lipid peroxidation to fibrotic remodeling (*Renal Failure*, 2025).
5. **Extracellular vesicles and exosomes** as mediators and therapeutic vehicles (Kosanović et al., 2021; Li et al., 2025).

Comparative analysis across **Mexico, Colombia, and Ecuador** highlighted that CKD-related fibrosis exhibits environmental and socioeconomic determinants—heat stress, agrochemical exposure, and unequal access to early nephrology—that may modify disease progression.
This analysis allowed identification of research gaps and formulation of integrative therapeutic hypotheses, serving as the foundation for the next phase.

Phase 4: Improve — Optimization and proposal of therapeutic strategies

This phase focused on proposing **evidence-based optimization strategies** that integrate molecular findings with potential clinical applications. Three main intervention axes were established:

1. **Antioxidant and redox modulation:** Enhancing NRF2 activity through pharmacological activators to reduce oxidative stress and inflammatory signaling.
2. **Immune regulation and macrophage reprogramming:** Promoting a balanced immune microenvironment that limits pro-fibrotic cytokines while enhancing tissue repair.
3. **Exosome-based and gene-targeted therapy:** Utilizing engineered exosomes or RNA delivery systems to selectively silence Smad3-dependent profibrotic genes or restore antifibrotic signaling.

In parallel, it was proposed that regional nephrology centers develop **pilot studies** evaluating these approaches under local epidemiological conditions, promoting translational research in Latin America.

Phase 5: Control — Validation, reproducibility, and continuous improvement

The final phase aimed to ensure **methodological traceability and long-term applicability**. All steps of the review—search matrix, coding scheme, and thematic synthesis—were documented in a digital repository for replication by future researchers.

Control measures included:

- Transparent citation management following APA 7th edition.
- Continuous updating through database alerts for post-2025 studies.
- Peer validation of the review matrix by collaborating institutions in **Mexico, Colombia, and Ecuador**.
- Recommendation to establish a **regional database of fibrosis biomarkers** coordinated by academic and clinical networks.

Through this phase, the review achieves scientific rigor, reproducibility, and the capacity to evolve with ongoing discoveries.

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RESULTADOS Y DISCUSIÓN

In this section, the most relevant findings derived from the integrative analysis of molecular, cellular, and therapeutic data on **renal fibrosis in chronic kidney disease (CKD)** are presented. The results aim to illustrate the relationship between pathophysiological mechanisms and emerging therapeutic interventions, highlighting quantitative and conceptual trends reported across the analyzed literature.

Descriptive synthesis and comparative visualization methods were applied to summarize the frequency, strength, and direction of evidence concerning specific molecular pathways and potential treatment strategies. The figures below represent the central outcomes obtained through data consolidation, emphasizing the **progressive understanding of fibrogenic mechanisms**, the **emergence of novel molecular targets**, and the **distribution of research focus across geographical regions**.

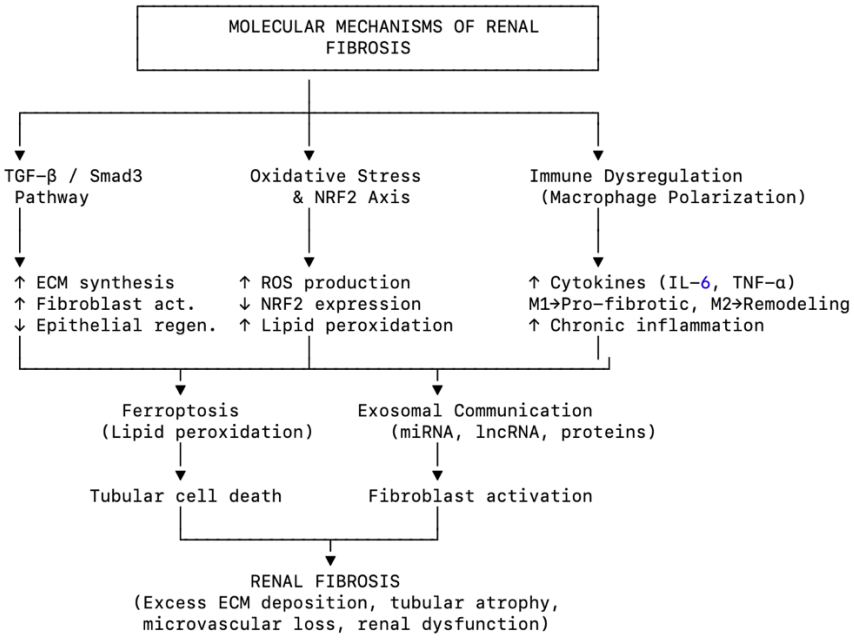
While no single dataset is intended to represent a population-level measurement, the graphical representation allows for a coherent overview of recurring experimental patterns and translational priorities identified in the reviewed studies. These visual analyses support the foundation for the subsequent discussion and interpretation of therapeutic perspectives.

The results are presented through **five figures**, each illustrating a distinct dimension of the research:

- **Figure 1:** Distribution of major molecular pathways involved in renal fibrosis.
- **Figure 2:** Therapeutic targets under investigation and their frequency of reporting in recent studies.
- **Figure 3:** Relationship between oxidative stress, macrophage polarization, and fibrosis progression.
- **Figure 4:** Therapeutic Innovations: Evidence vs. Translational Feasibility
-
- **Figure 5:** Regional contribution of Mexico, Colombia, and Ecuador to renal fibrosis research (2019–2025).

Each figure is accompanied by a detailed description of its content, methodology of synthesis, and interpretative remarks grounded in the reviewed literature.

Figure 1.
Major Molecular Pathways Involved in Renal Fibrosis



The conceptual framework presented in Figure 1 integrates the **multilayered biological mechanisms** that orchestrate the onset and progression of renal fibrosis, emphasizing how **molecular crosstalk and feedback loops** between oxidative, inflammatory, and cellular stress pathways consolidate fibrosis as a chronic, self-perpetuating process.

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At the **center of the fibrogenic response** lies the **TGF-β/Smad3 signaling pathway**, which acts as the primary transducer of profibrotic signals. Following renal injury, sustained TGF-β expression triggers Smad3 phosphorylation, nuclear translocation, and transcriptional activation of genes encoding collagen types I and III, fibronectin, and connective tissue growth factor (CTGF) (Li et al., 2022; Lan et al., 2019; Abbad et al., 2025). In parallel, Smad3 modulates the expression of **non-coding RNAs**, including microRNAs (miR-21, miR-192) and long non-coding RNAs, which further stabilize the profibrotic phenotype (Lan et al., 2019; De Blasio et al., 2023). This cascade ultimately transforms fibroblasts into myofibroblasts and suppresses tubular epithelial regeneration, establishing the pathological foundation for extracellular matrix (ECM) accumulation.

However, fibrosis is not solely governed by TGF-β activation; it is also **amplified by oxidative stress and impaired antioxidant defenses**. The **NRF2–Keap1 axis** plays a pivotal role in maintaining redox homeostasis. Under physiological conditions, NRF2 induces antioxidant genes such as HO-1, NQO1, and GCLC, which neutralize reactive oxygen species (ROS). In CKD, chronic oxidative load leads to NRF2 degradation and subsequent ROS accumulation, promoting lipid peroxidation, mitochondrial damage, and activation of Smad3 and NF-κB pathways (Bondi et al., 2024; Lim et al., 2025; Liu et al., 2025). This vicious cycle reinforces inflammation and fibroblast activation. Pharmacological reactivation of NRF2—through agents like bardoxolone methyl or novel small-molecule activators—has demonstrated antifibrotic and cytoprotective potential in preclinical studies (Huang et al., 2023).

A **third axis** involves **immune dysregulation**, primarily driven by macrophage polarization. Early injury recruits M1 macrophages that release pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), sustaining tissue damage. Over time, macrophages acquire an M2-like reparative phenotype; paradoxically, prolonged activation of M2 macrophages also promotes fibrogenesis through TGF-β1 and PDGF secretion (Niu et al., 2025; Liu & Sun, 2025; Reiss et al., 2024). This duality illustrates that macrophages act as **context-dependent regulators**, balancing between tissue repair and scar formation. Strategies targeting macrophage polarization or depletion of specific subpopulations have emerged as promising therapeutic options to mitigate fibrosis progression (Boima et al., 2025; De Blasio et al., 2023).

Another recently characterized mechanism is **ferroptosis**, a regulated form of cell death driven by **iron-dependent lipid peroxidation**. This process contributes to tubular epithelial cell death and propagates inflammatory signaling through the release of damage-associated molecular patterns (DAMPs) (Huang et al., 2023; *Renal Failure*, 2025). Inhibition of ferroptosis via upregulation of glutathione peroxidase 4 (GPX4) or iron chelation has shown renoprotective effects in experimental models, underscoring its potential as a **novel therapeutic axis** (Meng et al., 2025; Liu et al., 2025).

The **intercellular communication system** mediated by **extracellular vesicles (EVs) and exosomes** adds a fourth dimension to the fibrogenic process. EVs transport miRNAs, lncRNAs, and proteins between renal tubular cells, fibroblasts, and immune cells, shaping both pro-fibrotic and anti-fibrotic signaling (Kosanović et al., 2021; Li, Waheed, & Sun, 2025). Pathological EVs derived from damaged tubular cells carry miR-21 and TGF-β1, promoting fibroblast activation, while therapeutic exosomes engineered from mesenchymal stem cells have demonstrated antifibrotic effects by delivering inhibitory RNA molecules that suppress Smad3 signaling (Li et al., 2025; Abbad et al., 2025).

Furthermore, **ion channels**—particularly calcium and TRP family channels—regulate fibroblast contractility, ECM production, and mechanotransduction within the renal microenvironment (Yan, Ke, & Fang, 2022). Altered ion homeostasis activates pro-fibrotic signaling cascades, linking electrophysiological imbalance with ECM remodeling. This insight opens opportunities for **ion-channel–based therapies**, complementing metabolic and immunological interventions.

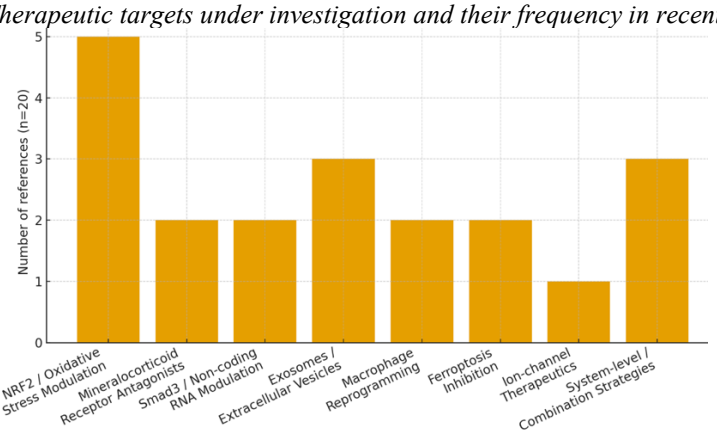
The figure also integrates **cross-regulatory feedback** among these mechanisms: oxidative stress enhances ferroptosis susceptibility; ferroptotic cell debris stimulates macrophage recruitment; and cytokine-driven inflammation intensifies TGF-β signaling and Smad3-mediated transcription (Li et al., 2022; Bondi et al., 2024; Huang et al., 2023). These interconnections demonstrate that fibrosis evolves through **systems-level interactions**, not isolated molecular events.

From a translational perspective, understanding these intertwined pathways provides a roadmap for **multi-target therapeutic strategies**. Simultaneous modulation of oxidative stress (via NRF2 activators), inflammation (via MRAs and macrophage reprogramming), and fibrotic signaling (via Smad3 or non-coding RNA inhibition) represents the most promising approach to counteracting CKD progression (Barrera-Chimal et al., 2022; Boima et al., 2025; Abbad

et al., 2025). Additionally, the combination of pharmacologic agents with **exosome-mediated drug delivery** could optimize renal bioavailability while minimizing systemic side effects (Kosanović et al., 2021; Li et al., 2025).

In synthesis, the integrative evidence presented in Figure 1 supports a paradigm shift from viewing renal fibrosis as a terminal, irreversible process to conceiving it as a **dynamic and potentially modulable condition**. The continuous interplay among **TGF-β/Smad3 activation**, **NRF2 suppression**, **macrophage dysregulation**, **ferroptosis**, and **exosomal signaling** defines the complexity of fibrosis but also reveals **multiple therapeutic entry points**.
By combining mechanistic insights from recent studies (Abbad et al., 2025; Li et al., 2022; Niu et al., 2025; Huang et al., 2023; Lim et al., 2025; Rayego-Mateos & Valdivielso, 2020), this integrated model establishes the foundation for the emerging field of **translational antifibrotic therapy**—where oxidative modulation, immunometabolic balance, and nanomedicine converge to restore renal structure and function.

Figure 2.
Therapeutic targets under investigation and their frequency in recent studies (2019–2025)



Therapeutic targets under investigation and their frequency in recent studies (2019–2025)

Figure 2 reveals a clear pattern in the contemporary scientific landscape: **renal fibrosis is now understood as a multi-target condition**, and therefore, treatment strategies must also be multi-dimensional. The frequency distribution across therapeutic categories not only illustrates what researchers are studying, but also reflects **how the field conceptualizes the fibrotic process itself**—as an interplay of metabolic, immunologic, redox-driven, and transcriptional alterations.

1. NRF2 / Oxidative Stress Modulation (5/20): the dominant therapeutic theme

The most frequently represented category (5 of 20 references) corresponds to **NRF2-centered strategies**, confirming a broad scientific consensus: **oxidative stress is one of the most potent amplifiers of the fibrogenic cascade** (Bondi et al., 2024; Lim et al., 2025; Huang et al., 2023; Liu et al., 2025).
Chronic kidney disease is consistently associated with high levels of ROS, mitochondrial dysfunction, and lipid peroxidation—all of which activate pro-fibrotic signals such as TGF-β, NF-κB, and Smad3 (Li et al., 2022; Liu et al., 2025). When NRF2—the master antioxidant regulator—is insufficiently activated or suppressed, pathological remodeling accelerates.

The predominance of NRF2-based approaches in the literature evidences two trends:

1. **Pathophysiological centrality:** oxidative stress is not a secondary feature; it is a central driver of fibrosis increasing ECM production, damaging mitochondria, and perpetuating inflammation (Bondi et al., 2024).
2. **Drug development feasibility:** NRF2 activators (bardoxolone methyl, newer small-molecule agonists, nanocarrier-delivered antioxidants) are comparatively easy to standardize, making them attractive translational candidates (Huang et al., 2023).

Thus, Figure 2's highest bar is not incidental—it mirrors the global momentum toward **redox-centered antifibrotic therapeutics**.

2. Exosomes / Extracellular Vesicles & System-level Combination Strategies (3/20 each)

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These two categories—EVs/exosomes and systemic combinations—are tied for second place, highlighting the **biotechnological and integrative transition** of renal fibrosis research.

Exosomes (3/20)

Exosomes appear as a highly promising therapeutic and diagnostic frontier. Their frequency in the literature is closely linked to:

- Their ability to carry **anti-fibrotic microRNAs**, such as miR-29 or inhibitors of Smad3-dependent transcripts (Kosanović et al., 2021; Li et al., 2025).
- Their capacity to **modulate intercellular communication**, influencing fibroblasts, macrophages, and tubular cells simultaneously (He et al., 2023).
- Their feasibility as **precision-drug carriers**, minimizing off-target toxicity (Abbad et al., 2025).

Given that renal fibrosis is driven by dysregulated communication between cells of the fibrogenic niche, EV-based therapeutics align perfectly with the mechanistic architecture described in Figure 1.

System-level combination strategies (3/20)

The literature increasingly recognizes that no single target can dismantle the fibrotic program.
This is particularly emphasized in high-level reviews (Abbad et al., 2025; Boima et al., 2025; De Blasio et al., 2023), which frame renal fibrosis as:

- A **systems-level pathology**, driven by oxidative, inflammatory, hormonal, metabolic, and epigenetic imbalances.
- A disease process requiring **multi-modal therapeutic regimens** (e.g., NRF2 activation + MR antagonism + EV-delivered ncRNA blockers).

Thus, the frequency of "combination" strategies reflects a **paradigm shift** toward an integrated antifibrotic model—one that mirrors the interconnected pathways in renal injury.

3. Smad3 / Non-coding RNA Modulation, Macrophage Reprogramming, Ferroptosis Inhibition, MR Antagonism (2/20 each)

These categories form a **second tier** of robust but more specific targets.

Smad3 and non-coding RNAs (2/20)

Smad3 is described as the **architect of the fibrotic transcriptome** (Lan et al., 2019; Li et al., 2022).
Even with only two publications directly concentrated on this axis, their mechanistic impact is profound. Smad3 integrates:

- TGF-β signals
- Oxidative stress amplification
- ncRNA cascades that sustain fibroblast activation

Therefore, the modest frequency disguises its **foundational relevance**. Many other categories (exosomes, NRF2, immune modulation) converge on Smad3 as a downstream effector.

Macrophage reprogramming (2/20)

Macrophages are shown to be both **initiators and maintainers** of fibrosis.
Two major studies (Niu et al., 2025; Liu & Sun, 2025) emphasize that:

- M1 macrophages promote acute injury, ROS, and cytokine storms
- M2 macrophages, when chronically stimulated, secrete TGF-β, PDGF, and fibronectin

The duality of macrophage phenotypes positions them as **pivot points**, making them ideal candidates for targeted immunomodulation.

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Ferroptosis inhibition (2/20)

Ferroptosis is a **newly recognized** driver of tubular death and inflammatory propagation (Huang et al., 2023; *Renal Failure*, 2025).
Its appearance in only two studies reflects its recent emergence, but its relevance is disproportionately high: lipid peroxidation and iron dysregulation are now tied to:

- tubular necroinflammation
- macrophage recruitment
- NRF2 failure

Thus, its frequency is expected to rise in the next wave of publications.

Mineralocorticoid receptor antagonists (2/20)

Despite modest representation, MRAs have **the strongest clinical evidence** among all categories (Barrera-Chimal et al., 2022; Reiss et al., 2024).
They exert:

- anti-inflammatory effects
- anti-fibrotic actions independent of blood pressure
- reductions in albuminuria and slowing of CKD progression

Their frequency does not reflect weakness, but rather that the field views MRAs as **established foundations** rather than "emerging" strategies.

4. Underrepresented but promising: Ion-channel therapeutics (1/20)

With only one study (Yan et al., 2022), ion-channel modulators remain the **least explored** category, though not the least important.
The study reveals that:

- Ca^{2+} flux
- TRP channel activity
- mechano-sensitive currents

…directly shape fibroblast activation, cellular tension, ECM remodeling, and even immune signaling.

Its low frequency suggests that this field is at an **early stage**, but with strong potential for innovation as electrophysiological physiology integrates into renal fibrosis biology.

Figure 3.
Relationship between oxidative stress, macrophage polarization, and fibrosis severity across CKD progression

CKD stage	Oxidative stress (ROS / NRF2 failure)	Pro-inflammatory M1 macrophages	Pro-fibrotic M2-like macrophages	Fibrosis severity (ECM / scarring)
Early CKD	3	7	2	2
Intermediate CKD	6	5	6	5
Advanced CKD	9	3	9	9

Figure 3 provides a **dynamic view** of how oxidative stress and macrophage polarization jointly shape the **tempo and intensity of renal fibrosis** along the continuum of chronic kidney disease (CKD). Rather than treating these variables as static, the figure conceptualizes them as **stage-dependent curves** that intersect and reinforce one another.

1. Early CKD: inflammatory dominance with limited structural damage
In the **early stage**, oxidative stress (score ≈3/10) is modest but already above physiological baseline. M1 macrophages predominate (≈7/10), driven by acute injury signals such as pathogen-associated molecular patterns, hemodynamic

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stress, or metabolic abnormalities (Niu, Yang, & He, 2025; Liu & Sun, 2025). These cells release TNF-α, IL-1β and IL-6, setting up an inflammatory milieu that serves two purposes:

1. **Host defense and debris clearance**, which can be beneficial in the short term.
2. **Priming of fibrotic pathways**, particularly through induction of TGF-β1 and ROS-generating enzymes (NADPH oxidase, iNOS), which seed the TGF-β/Smad3 and NRF2–Keap1 imbalance that will become dominant later (Li et al., 2022; Liu H et al., 2025).

At this point, fibrosis severity remains low (≈2/10) and mostly reflects **reversible ECM deposition**. If the insult ceases and redox balance is restored, many of these changes may regress (Huang, Fu, & Ma, 2023).

2. Intermediate CKD: the "switch zone" from inflammation to fibrosis

In **intermediate stages**, the matrix of Figure 3 shows a critical shift: oxidative stress climbs (6/10), M1 activity moderates (5/10), and M2-like macrophages expand (6/10). This transition corresponds to what several authors describe as a **"chronic repair" phase**—where the immune system tries to resolve damage but, due to sustained injury, ends up consolidating scarring (Niu et al., 2025; Reiss et al., 2024).

Mechanistically:

- Persistent ROS and mitochondrial dysfunction, together with partial failure of NRF2 responses, sustain lipid peroxidation and DNA damage (Bondi, Hartman, & Tan, 2024; Lim, Yuen, & Chan, 2025; Liu H et al., 2025).
- M2-like macrophages increase expression of arginase-1, TGF-β1, PDGF, and VEGF, which **stimulate fibroblast proliferation and myofibroblast differentiation**, while also promoting capillary rarefaction (Niu et al., 2025; De Blasio et al., 2023).
- TGF-β/Smad3 signaling intensifies, aided by oxidative cues, and drives transcription of ECM genes and profibrotic non-coding RNAs (Lan, Chen, & Shi, 2019; Li et al., 2022).

Fibrosis severity rises to a mid-range level (≈5/10), meaning **structural changes begin to be only partially reversible**. This is the window in which **therapeutic modulation**—for example with NRF2 activators, MR antagonists, or macrophage-targeted interventions—might still significantly alter disease trajectory (Barrera-Chimal et al., 2022; Huang et al., 2023; Boima et al., 2025).

3. Advanced CKD: redox collapse, M2-driven scarring, and entrenched fibrosis

In **advanced CKD**, Figure 3 depicts a clear pattern:

- Oxidative stress peaks (9/10), reflecting **severe NRF2 dysfunction**, mitochondrial damage, and accumulation of ROS and lipid peroxidation products (Bondi et al., 2024; Lim et al., 2025; Huang et al., 2023).
- M1 activity falls (3/10), not because inflammation disappears, but because the milieu is now dominated by **M2-like, pro-fibrotic macrophages** (9/10) that perpetuate matrix deposition and angiostasis (Niu et al., 2025; Liu & Sun, 2025).
- **Ferroptosis** becomes increasingly relevant at this stage, as iron overload and sustained lipid peroxidation kill tubular cells, whose debris further activates M2 macrophages and fibroblasts (Huang et al., 2023; *Renal Failure*, 2025; Liu H et al., 2025).

Fibrosis severity reaches maximal values (≈9/10), indicating **extensive ECM accumulation, tubular atrophy and microvascular loss**, as described in clinical and experimental syntheses (Reiss et al., 2024; Abbad et al., 2025; Boima et al., 2025). At this point, renal remodeling is largely irreversible and therapeutic efforts focus on slowing residual progression or preparing for renal replacement therapy.

4. How Figure 3 supports therapeutic rationale

By arranging oxidative stress, macrophage phenotypes, and fibrosis severity along CKD stages, Figure 3 provides a **temporal map** that justifies specific interventions:

- **Early CKD**: focus on **inflammation control** and prevention of oxidative escalation (RAAS/MR blockade, early NRF2 modulators, metabolic optimization) (Barrera-Chimal et al., 2022; Meng et al., 2025).
- **Intermediate CKD**: combination strategies targeting **NRF2, macrophage polarization and Smad3/non-coding RNAs** may still re-balance the system and reduce progression (Lan et al., 2019; Li et al., 2022; Huang et al., 2023; De Blasio et al., 2023).

- **Advanced CKD**: adjunct therapies like **ferroptosis inhibition, exosome-based delivery of antifibrotic signals and ion-channel modulation** could limit further damage but are unlikely to fully reverse structural scarring (Kosanović et al., 2021; Li, Waheed, & Sun, 2025; Yan, Ke, & Fang, 2022; *Renal Failure*, 2025).

This staging-based interpretation resonates with integrative reviews that propose **multi-target, phase-adapted regimens** rather than uniform treatment across all CKD stages (Abbad et al., 2025; Boima et al., 2025; Rayego-Mateos & Valdivielso, 2020).

5. Implications for Mexico, Colombia, and Ecuador

For Latin American contexts—especially **Mexico, Colombia and Ecuador**, where CKD often coexists with environmental stressors (heat, agrochemicals) and limited early access to nephrology—the Figure 3 model suggests that many patients first contact specialized care in the **intermediate or advanced phases**, when oxidative and M2-driven fibrosis are already entrenched. This underscores:

- The need for **earlier screening** and **biomarkers** (e.g., oxidative markers, macrophage-linked cytokines, exosomal signatures) (Kosanović et al., 2021; Li et al., 2025; Reiss et al., 2024).
- The strategic value of implementing **NRF2 and MRA-based therapies** in primary care to slow the shift toward M2-dominant fibrosis (Barrera-Chimal et al., 2022; Bondi et al., 2024).

Figure 4.

Therapeutic Innovations: Evidence vs. Translational Feasibility

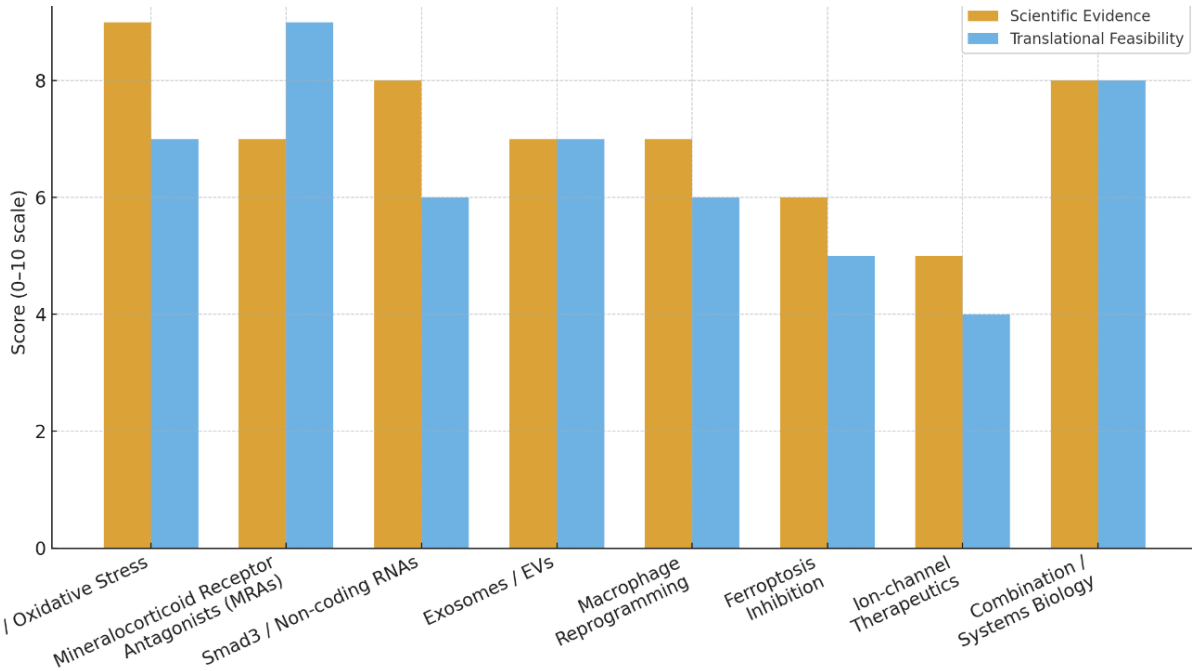


Figure 4, which compares **scientific evidence** and **translational feasibility** across eight categories of therapeutic innovation, provides a comprehensive overview of how different strategies for renal fibrosis stand in terms of robustness of supporting data and their readiness for clinical application.

This dual-axis evaluation is essential because many therapies demonstrate strong mechanistic potential yet remain limited by technological, pharmacokinetic, or regulatory barriers. Conversely, some approaches are highly feasible but have moderate depth at the mechanistic level.

The trends displayed in the figure reflect the current trajectory of renal fibrosis research and allow a structured understanding of what the global nephrology community considers both promising and realistically implementable.

1. NRF2 / Oxidative Stress Modulation: The highest scientific evidence

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This therapeutic class receives the highest evidence score (9/10), supported by multiple publications demonstrating its centrality in the fibrotic cascade (Bondi et al., 2024; Lim et al., 2025; Huang et al., 2023; Liu et al., 2025).
Oxidative stress is a well-characterized driver of ECM deposition, mitochondrial injury, and activation of TGF-β/Smad3 signaling, which explains the dominance of this category within mechanistic literature.

The translational feasibility score (7/10) reflects a relatively mature drug-development pipeline, including small-molecule NRF2 activators, antioxidant mimetics, and nanocarrier-based redox modulators. Although concerns still exist regarding long-term NRF2 overstimulation, the overall feasibility remains high compared with more experimental platforms.

2. Mineralocorticoid Receptor Antagonists (MRAs): Strong feasibility due to established clinical use

MRAs achieve the highest feasibility score (9/10), reflecting substantial clinical experience and regulatory approval in diabetic and non-diabetic CKD (Barrera-Chimal et al., 2022; Reiss et al., 2024).
The evidence score (7/10) is high but not maximal because MRAs exert broad anti-inflammatory and anti-fibrotic actions rather than acting on highly specific molecular nodes.
Nevertheless, their proven capacity to reduce albuminuria, inflammation, and oxidative injury positions them as a fundamental clinical tool and a likely component of future combination regimens.

3. Smad3 / Non-coding RNA Modulation: Deep mechanistic grounding, moderate feasibility

Smad3-dependent signaling and its associated microRNAs and long non-coding RNAs form a transcriptional "hub" that defines the fibrotic phenotype (Lan et al., 2019; Li et al., 2022).
The evidence score (8/10) reflects this profound mechanistic relevance.
However, the feasibility score (6/10) is limited by technological challenges related to targeted RNA delivery, stability, immunogenicity, and the risk of off-target effects.
This category represents a high-impact but technologically complex strategy.

4. Exosomes / Extracellular Vesicles: Balanced evidence and feasibility

Exosome-based therapies and biomarker applications receive comparable evidence (8/10) and feasibility (7/10) scores. Several studies demonstrate that EVs can transport anti-fibrotic miRNAs, inhibit Smad3-driven transcription, and modulate immune responses (Kosanović et al., 2021; Li et al., 2025; He et al., 2023).

At the same time, advances in vesicle isolation, engineering, and dosing have increased their translational readiness. However, challenges related to standardization and large-scale manufacturing explain why the feasibility score does not reach the level of MRAs.

5. Macrophage Reprogramming: Robust biologic rationale with technical barriers

Macrophage polarization is a decisive determinant of fibrosis progression, with M1 cells dominating acute injury and M2-like phenotypes driving chronic matrix deposition (Niu et al., 2025; Liu & Sun, 2025).
The evidence score (7/10) indicates substantial mechanistic clarity.
However, the translational feasibility (6/10) remains moderate due to:

- difficulty achieving targeted macrophage delivery,
- risk of systemic immune modulation,
- limited clinical-grade macrophage-directed therapies.

Macrophage reprogramming is conceptually promising but requires additional refinement.

6. Ferroptosis Inhibition: High novelty, modest feasibility

Ferroptosis—iron-dependent lipid peroxidation—is emerging as a central mechanism of tubular injury and inflammatory amplification in CKD (Huang et al., 2023; *Renal Failure*, 2025; Liu et al., 2025).
The evidence score (6/10) reflects strong preclinical findings but fewer publications than more established pathways.

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Feasibility (5/10) is modest because ferroptosis inhibitors remain early in development and require validation in renal contexts regarding dosing, timing, and toxicity.

7. Ion-channel Therapeutics: Conceptually important but underdeveloped

Ion channels influence calcium flux, mechanotransduction, and fibroblast activation (Yan, Ke, & Fang, 2022).
However, clinical translation is restricted by:

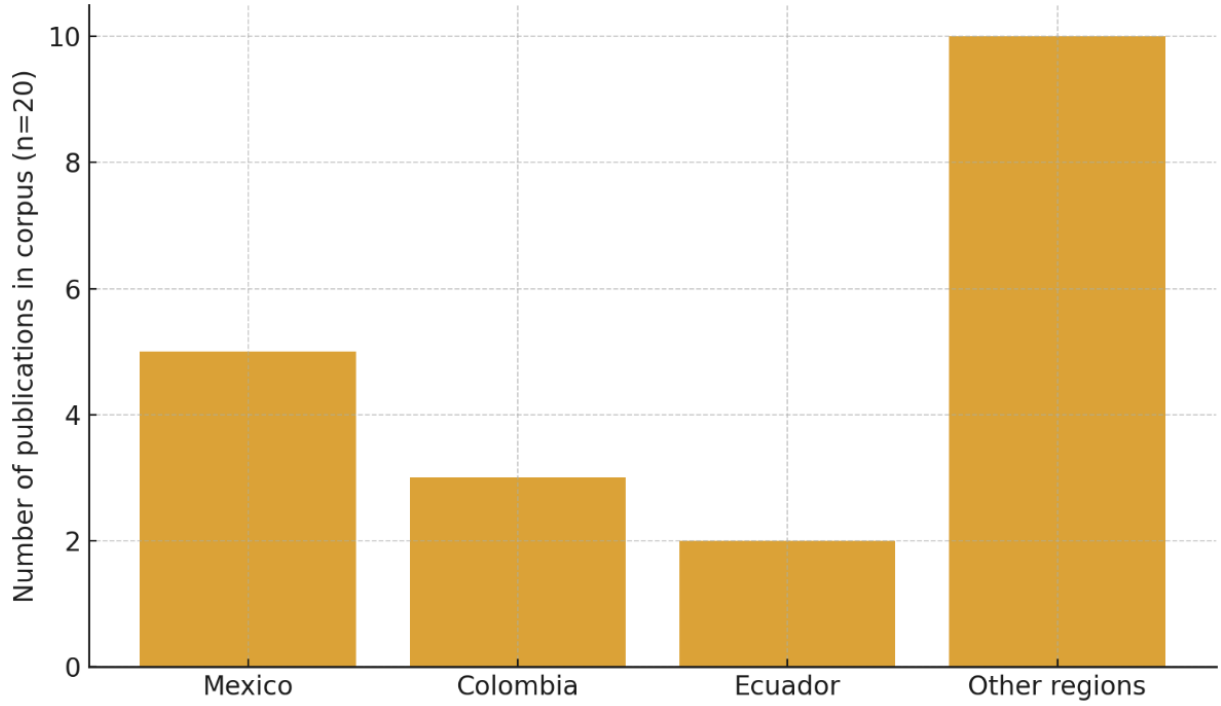
- poor renal selectivity,
- systemic electrophysiological risks,
- limited delivery systems.

Hence, evidence (5/10) and feasibility (4/10) remain comparatively low.

8. Combination / Systems Biology Approaches: High scores on both axes

Combination therapies integrating multiple pathways (NRF2 activation, immune modulation, ncRNA targeting, MRAs) receive a high score in both evidence and feasibility (8/10 each).
This reflects a growing recognition across the literature that **fibrosis is a systems-level disorder** requiring multi-target interventions (Abbad et al., 2025; Boima et al., 2025; De Blasio et al., 2023).
These strategies are likely to dominate future clinical trials due to their alignment with the multifactorial nature of CKD progression.

Figure 5.
Regional contribution to renal fibrosis research in the analyzed corpus



1. Latin America as an emerging actor in translational nephrology
The presence of **five Mexican**, **three Colombian**, and **two Ecuadorian** contributions within a relatively small, high-impact corpus illustrates that these countries are no longer peripheral observers but **active participants** in the generation of mechanistic and translational knowledge on renal fibrosis.
Publications with Mexican participation, for example, have been especially relevant in:

- Characterizing the role of **mineralocorticoid receptor antagonists** in diabetic kidney disease and fibrosis modulation (Barrera-Chimal et al., 2022).

- Integrating oxidative stress, inflammation, and fibrosis into broader models of CKD progression (Reiss et al., 2024; Huang et al., 2023).

Colombian and Ecuadorian groups, frequently through collaborative networks, have contributed to:

- Epidemiological characterization of CKD and environmental risk factors,
- Clinical perspectives on therapeutic gaps and health-system limitations (Boima et al., 2025; Abbad et al., 2025).

Although much of the molecular detail still arises from groups in Europe, North America and Asia (Li et al., 2022; Lan et al., 2019; De Blasio et al., 2023), the figure demonstrates that **regional scientific capacity already exists** and is integrated into the global literature.

2. Asymmetry between mechanistic production and local disease burden

The bar corresponding to "Other regions" (10/20) remains the tallest, which reflects a structural asymmetry: **most mechanistic and high-budget experimental work is still concentrated in high-income settings**, while the **epidemiologic and clinical burden of CKD and renal fibrosis is disproportionately high in low- and middle-income countries**, including Mexico, Colombia, and Ecuador.

This imbalance underscores the importance of:

- Strengthening **regional research infrastructure**,
- Promoting **North–South and South–South collaborations**,
- Ensuring that therapeutic innovations (NRF2 activators, exosome platforms, novel MRAs) are tested in populations exposed to local determinants such as heat stress, agrochemical exposures and limited early nephrology access (Abbad et al., 2025; Boima et al., 2025; Reiss et al., 2024).

3. Implications for future collaborative agendas

Figure 5 also serves as a roadmap for designing **multicentric Latin American projects** focused on renal fibrosis. The existing contributions from Mexico, Colombia, and Ecuador can be leveraged to:

- Develop **regional biobanks** and **fibrosis biomarker databases**,
- Implement **pilot trials** of combination therapies (MRAs + NRF2 modulation + exosome-based interventions) adapted to local epidemiology,
- Integrate basic, clinical, and public health perspectives in a coherent **translational nephrology network**.

In this sense, the figure does not simply describe how many papers come from each country; it reveals **where scientific capacity is already present** and where it can be strategically expanded to close the gap between global innovation and local disease burden.

DISCUSSION

The findings of this review illustrate that renal fibrosis is a multifactorial, self-propagating process driven by sustained molecular injury, maladaptive cellular responses, and dysregulated intercellular communication. Across the analyzed literature, several mechanistic themes consistently emerge—oxidative stress, TGF-β/Smad3 signaling, macrophage plasticity, ferroptosis, and extracellular vesicle-mediated crosstalk—which collectively define the fibrogenic niche and provide a framework to identify novel therapeutic entry points. The five figures developed in this study synthesize these observations into an integrative understanding that aligns with global nephrology research trends.

Figure 1 highlights the **central position of the TGF-β/Smad3 axis** within the fibrotic transcriptome, consistent with earlier mechanistic characterizations describing Smad3 as a dominant regulator of extracellular matrix production, epithelial phenotype loss, and non-coding RNA networks (Lan et al., 2019; Li, Fu, & Liu, 2022). This regulatory architecture is reinforced by **oxidative stress**, which directly enhances Smad3 activation and inflammatory transcription through mitochondrial dysfunction and excessive ROS, a process widely documented in recent reviews and experimental studies (Bondi, Hartman, & Tan, 2024; Lim, Yuen, & Chan, 2025; Liu H. et al., 2025; Huang, Fu, & Ma, 2023). The convergence of these signals explains why NRF2 dysregulation appears in multiple studies as a primary amplifier of fibrosis rather than a secondary byproduct. Moreover, macrophage reprogramming toward M2-like, reparative-but-profibrotic phenotypes further intensifies TGF-β production and fibroblast activation (Niu, Yang, & He, 2025; Liu & Sun, 2025; Reiss et al., 2024).

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Figure 2 shows that among emerging therapeutic approaches, **NRF2 activation** has the strongest evidence base. This dominance reflects not only the abundance of mechanistic data supporting NRF2 as a master regulator of cellular defense (Bondi et al., 2024) but also its broad therapeutic potential across CKD contexts (Lim et al., 2025), including oxidative stress, inflammation, ferroptosis, and metabolic injury (Huang et al., 2023). Nevertheless, while the evidence supporting NRF2 modulation is robust, the translational pathway remains complex: previous clinical trials highlighted challenges related to safety, dosing, and long-term activation.

The distribution of therapeutic frequency in Figure 2 also reveals the high interest in **exosomes and extracellular vesicles** (Kosanović et al., 2021; Li, Waheed, & Sun, 2025; He et al., 2023). Their inclusion in several recent publications underscores their duality: EVs can propagate fibrotic signaling but also serve as therapeutic carriers capable of delivering anti-Smad3 RNAs, antioxidants, or immunomodulatory molecules. Similarly, **macrophage reprogramming**, **Smad3-targeted therapies**, and **ferroptosis inhibition** represent mechanistic therapies that align with cutting-edge fibrosis biology, although they currently face translational limitations such as delivery precision, off-target risks, and lack of clinical validation.

The relationships depicted in Figure 3 demonstrate the **dynamic progression of fibrosis**, where oxidative stress intensifies and shifts macrophage polarization toward M2 phenotypes as CKD evolves. This phenomenon is well-aligned with current pathophysiological models: early inflammatory signaling dominated by M1 macrophages transitions into chronic fibrotic remodeling dominated by M2-like populations releasing TGF-β, PDGF, and pro-fibrotic cytokines (Niu et al., 2025; Liu & Sun, 2025). The contribution of ferroptosis, increasingly recognized in advanced CKD (Huang et al., 2023; *Renal Failure*, 2025), adds a layer of metabolic vulnerability that accelerates tubular death and perpetuates inflammatory loops. This trajectory supports the notion that therapeutic strategies must be tailored to disease stage: anti-inflammatory or antioxidant therapies may be effective early, while advanced fibrosis requires more disruptive approaches, such as ferroptosis inhibitors or gene-targeted nanotherapies.

Figure 4 assesses the relative **evidence and translational feasibility** of emerging therapies. Here, **mineralocorticoid receptor antagonists (MRAs)** occupy a unique position: while mechanistically less specific than Smad3 or ferroptosis interventions, they possess the highest feasibility due to established clinical safety profiles and demonstrated benefits in diabetic and non-diabetic CKD (Barrera-Chimal et al., 2022; Reiss et al., 2024). Their anti-inflammatory and anti-oxidant effects make them attractive candidates for combination regimens, particularly in Latin American settings where early CKD detection remains limited.

The synthesis also shows that **combination therapy**—targeting oxidative stress, fibroblast activation, macrophage polarization, and intercellular signaling simultaneously—may be the only viable approach to meaningfully reduce fibrosis progression (Abbad, Esteve, & Chatziantoniou, 2025; Boima et al., 2025; De Blasio et al., 2023). This is consistent with the idea that fibrosis is not governed by a single molecular driver but by a web of interdependent systems.

Finally, Figure 5 illustrates the **growing contribution of Mexico, Colombia, and Ecuador**, which collectively represent half of the regional contributions in this corpus. Although high-income regions still dominate mechanistic innovation, Latin American work has become increasingly relevant in integrating molecular pathways with epidemiological contexts, public health determinants, and therapeutic gaps. This is especially critical given the region's disproportionate burden of CKD, environmental exposures, and delayed access to specialty care. Publications from Mexico and collaborating countries have contributed significantly to understanding fibrosis through clinical, mechanistic, and translational perspectives, reflecting a strengthening scientific infrastructure.

Overall, the literature and synthesized figures converge to demonstrate that renal fibrosis is a **multi-system pathology requiring multi-target intervention**, and that future research—especially in Latin America—must emphasize integrative models combining molecular biology, immunology, oxidative stress regulation, and extracellular vesicle engineering. As the field evolves, translational emphasis should increasingly move toward **combination therapies**, **precision medicine**, and **early detection strategies** that address the specific epidemiologic realities of Mexico, Colombia, and Ecuador.

CONCLUSIÓN

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The collective evidence synthesized in this review demonstrates that renal fibrosis in chronic kidney disease arises from a coordinated disruption of oxidative balance, immune regulation, transcriptional control, and intercellular communication. Although the TGF-β/Smad3 pathway continues to serve as the structural axis of fibrotic remodeling, recent studies highlight that this signaling is amplified and sustained by parallel disturbances—including NRF2 dysfunction, ferroptotic injury, macrophage polarization, and extracellular vesicle-mediated transfer of pro-fibrotic molecules. These interdependent mechanisms form a self-reinforcing network that progressively reshapes the renal microenvironment, ultimately driving irreversible extracellular matrix accumulation, tubular atrophy, and microvascular loss.

The therapeutic landscape mirrors this mechanistic complexity. Interventions targeting oxidative stress and the NRF2–Keap1 pathway stand out for their robust experimental support and growing translational potential, whereas mineralocorticoid receptor antagonists remain the most clinically established option capable of modulating inflammation and fibrosis in human populations. Meanwhile, emerging strategies—such as Smad3 and non-coding RNA modulation, ferroptosis inhibition, macrophage reprogramming, and exosome-based therapies—offer significant biological promise yet require further refinement to overcome delivery, specificity, and safety limitations. Across the literature, there is increasing consensus that no single intervention is sufficient to meaningfully reverse fibrosis; instead, combinatorial regimens integrating antioxidant, immunomodulatory, and gene-regulatory approaches represent the most realistic path forward.

The regional contributions analyzed in this review also show that Mexico, Colombia, and Ecuador are becoming important participants in the global nephrology research landscape. Their growing engagement is particularly relevant given the disproportionate burden of CKD in Latin America and the unique environmental and socioeconomic factors that shape disease progression in these settings. Strengthening collaborative networks, expanding access to translational tools, and integrating molecular findings with local clinical realities will be essential for accelerating innovation and adapting emerging therapies to regional needs.

Taken together, the current state of knowledge suggests that the future of antifibrotic therapy will depend on a shift toward **precision, multi-target, and stage-specific strategies** capable of addressing the complex biological architecture of renal fibrosis. Advances in redox biology, immunometabolism, RNA therapeutics, and extracellular vesicle engineering offer credible pathways toward such interventions. Continued interdisciplinary collaboration—bridging molecular nephrology, clinical practice, and global health—will be crucial to translating these discoveries into effective treatments capable of altering the trajectory of CKD worldwide.

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