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Saif MYS , ACE Reno in CKD
Volume 8, Issue 4
Review Article

Pico Cell Matrix of ACE Reno and its effect on Adenine induced chronic Kidney disease . Review Article

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Abstract

Chronic Kidney Disease (CKD) is a progressive and multifactorial condition characterized by nephron loss, glomerulosclerosis, tubulointerstitial fibrosis, and vascular compromise. Current therapeutic strategies are largely palliative and fail to address the regenerative deficits underlying CKD. This study explores the safety, efficacy, and regenerative potential of **ACE Reno**, a bioactive Pico Cell Matrix derived from sheep fetal kidney, placenta, atrial tissue, and mesenchymal stem cells (MSCs), in an adenine-induced CKD model in Alpine rats. ACE Reno is processed via the ACE Pico Protocol to retain regenerative peptides and signaling molecules while eliminating immunogenic material. Histopathological analysis of treated kidneys demonstrated notable improvements in glomerular architecture, podocyte integrity, tubular brush border reconstitution, and peritubular capillary density. Mechanistically, ACE Reno delivers essential factors that modulate key CKD pathways—suppressing TGF-β and EMT, promoting PGC1-α-mediated mitochondrial repair, enhancing VEGF-A and Ang1-driven angiogenesis, and restoring antifibrotic and anti-inflammatory balance through miRNA modulation (e.g., miR-29 upregulation). Moreover, the formulation supports podocyte survival via WT1/nephrin signaling and reduces senescence-associated secretory phenotypes. These effects collectively arrest the fibrotic cascade, promote nephron regeneration, and improve renal function. The findings position ACE Reno as a promising organ-specific, cell-free therapeutic capable of targeting multiple CKD hallmarks, representing a paradigm shift from conventional monotherapy to systemic regenerative intervention. Further studies are warranted to validate these outcomes in larger animal models and clinical trials.

Keywords : Chronic Kidney Disease, Nephron Regeneration, ACE Reno, Pico Cell Matrix, Anti-fibrotic Therapy

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Anatomy of the kidney

Gross anatomy

The kidney is a vital excretory organ that plays a central role in maintaining the body's fluid and electrolyte balance, filtering blood, regulating blood pressure, and producing hormones such as erythropoietin and renin. Structurally, it is bean-shaped, measuring approximately 10–12 cm in length, 5–7 cm in width, and 3–4 cm in thickness, with a weight ranging between 120–170 grams in the average adult. It is typically darker red in color due to its rich vascularization.

Each kidney is located in the retroperitoneal space of the posterior abdominal cavity, lying on either side of the vertebral column between the levels of the T12 and L3 vertebrae. Because of the anatomical position of the liver, the right kidney is typically situated slightly lower than the left. Despite being retroperitoneal, they are not fixed organs—they exhibit respiratory movement and positional shifts during changes in posture.[i]

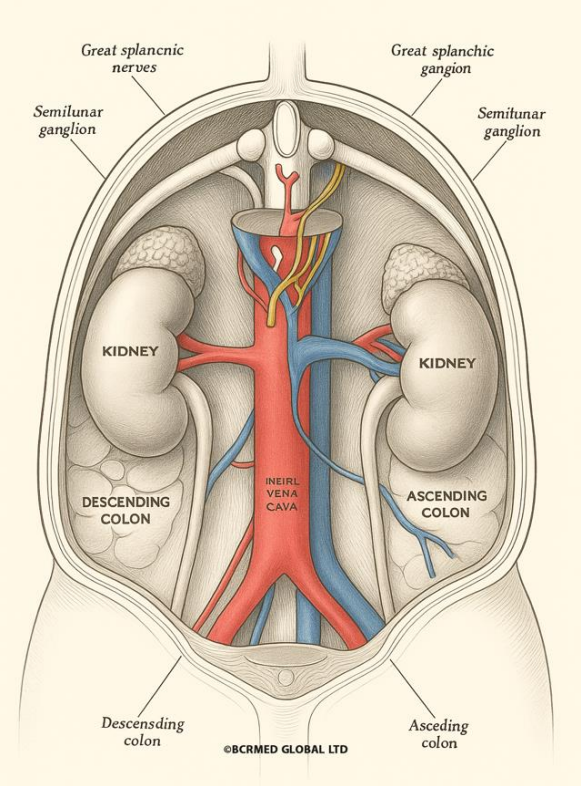

FIGURE 1 ANATOMY OF THE KIDNEYS (©BCRMED GLOBAL)

The external morphology of the kidney (Figure 2)reveals a smooth convex lateral border, and a deeply concave medial borderknown as the hilum. This hilum serves as a passage for essential

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structures entering and exiting the kidney. From anterior to posterior, the hilum typically contains the renal vein, renal artery, and renal pelvis, which continues inferiorly as the ureter. Associated lymphatics and autonomic nerve fibers also pass through this point.

Surrounding each kidney are multiple protective and supporting layers, which provide mechanical protection, thermal insulation, and structural anchorage. These layers, from innermost to outermost, include:[ii]

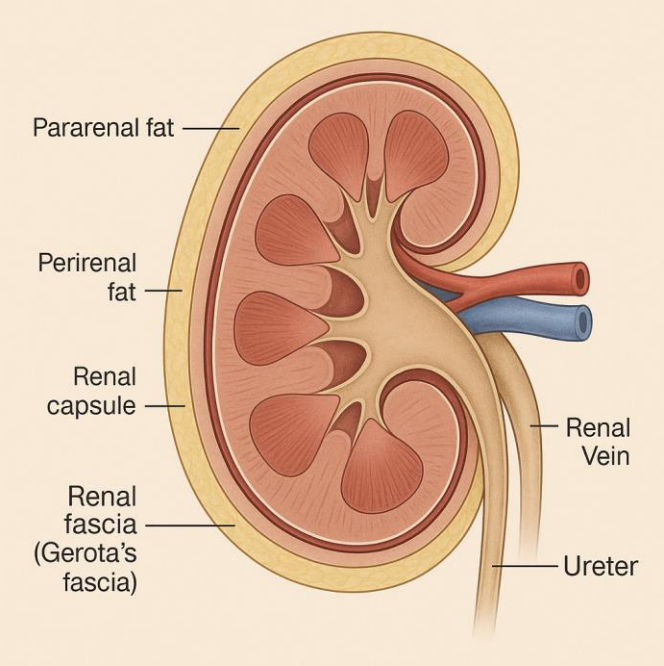

FIGURE 2 EXTERNAL LAYERS OF THE KIDNEYS (©BCRMED GLOBAL)

1. Renal (fibrous) capsule: A thin, tough layer of dense irregular connective tissue that tightly adheres to the kidney surface. It serves as the kidney's first line of defense against trauma and infection. This capsule can be separated easily from a healthy kidney but may be adherent in cases of inflammation or chronic disease.
2. Perirenal fat (adipose capsule): A thick layer of adipose tissue that encases the renal capsule. This fat layer acts as a major cushion to absorb physical shocks and provides a degree of thermal insulation. It also contributes to the positional stability of the kidney within the retroperitoneal space.
3. Renal fascia (Gerota's fascia): A double layer of connective tissue that envelopes both the kidney and the perirenal fat. This fascia also encloses the adrenal gland superiorly. The anterior layer (Toldt's fascia) and posterior layer (Zuckerkandl's fascia) fuse laterally

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and superiorly, anchoring the kidney to surrounding structures such as the psoas major muscle posteriorly and the diaphragm superiorly.

4. Pararenal fat: This is the outermost layer of fat situated posterior to the renal fascia. It is more variable in thickness and lies between the posterior renal fascia and the posterior abdominal wall. Although less involved in direct support, it still plays a role in cushioning and insulation.

Together, these layered structures help anchor the kidney within the retroperitoneal space, protect it from trauma and mechanical stress, and allow for slight movements during respiration and positional changes without compromising vascular or ureteric integrity.

Anatomically, the orientation of the kidney places the upper pole closer to the vertebral column and posterior abdominal wall, with the lower pole lying more anterior and lateral. The anterior surface of the kidney is related to various intra-abdominal organs: on the right side, it contacts the liver, duodenum, and ascending colon; on the left side, it contacts the spleen, stomach, pancreas, jejunum, and descending colon.

Internally, the kidney is organized into two major regions: an outer renal cortex and an inner renal medulla, each with distinct structural and functional characteristics. The renal cortex lies directly beneath the renal capsule and extends inward between the medullary pyramids as structures known as renal columns (columns of Bertin). The cortex appears granular under the microscope due to the presence of numerous renal corpuscles, which are composed of glomeruli surrounded by Bowman's capsules. It also houses the proximal convoluted tubules (PCT) and distal convoluted tubules (DCT)—critical sites for the reabsorption and secretion of solutes and water during urine formation.

The renal medulla lies deeper within the kidney and consists of multiple renal pyramids—cone-shaped masses with their bases facing the cortex and apices pointing toward the renal sinus. Each pyramid contains parallel arrangements of straight tubular segments, including the descending and ascending limbs of the loop of Henle, collecting tubules, and the vasa recta (straight capillaries) that descend from the juxtamedullary glomeruli. These structures contribute to the striated appearance of the medulla under gross and microscopic observation. At the apex of each pyramid is the renal papilla, which projects into a small funnel-shaped chamber called a minor calyx. Several minor calyces merge to form major calyces, and the convergence of major calyces forms the renal pelvis—a large, dilated cavity that narrows to become the ureter, through which urine is conveyed to the bladder.

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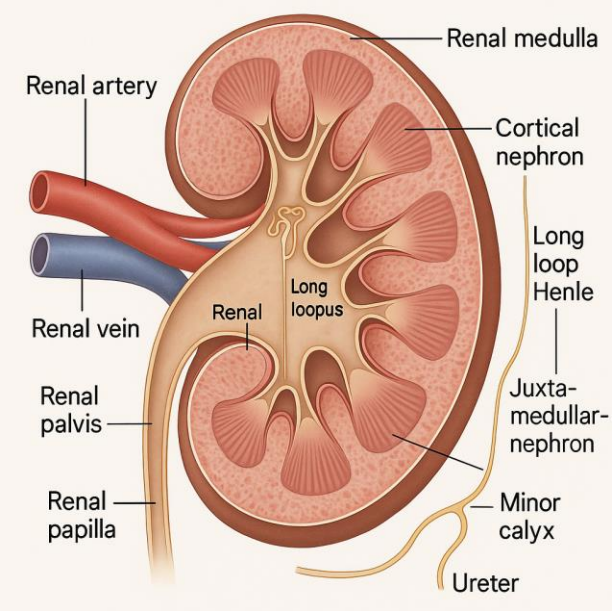

FIGURE 3 INTERNAL GENERAL STRUCTURE OF THE KIDNEY (©BCRMED GLOBAL)

At the microscopic level, the nephron is recognized as the essential structural and functional unit of the kidney, responsible for filtering blood plasma and forming urine. Each human kidney contains approximately 0.8 to 1.5 million nephrons, though the number can vary with age and individual health status. A nephron is composed of a renal corpuscle and a renal tubule. The renal corpuscle comprises a glomerulus, a tuft of capillaries derived from an afferent arteriole, surrounded by the Bowman's capsule, which has a visceral layer (composed of podocytes) and a parietal layer (simple squamous epithelium). This structure initiates the filtration of blood.

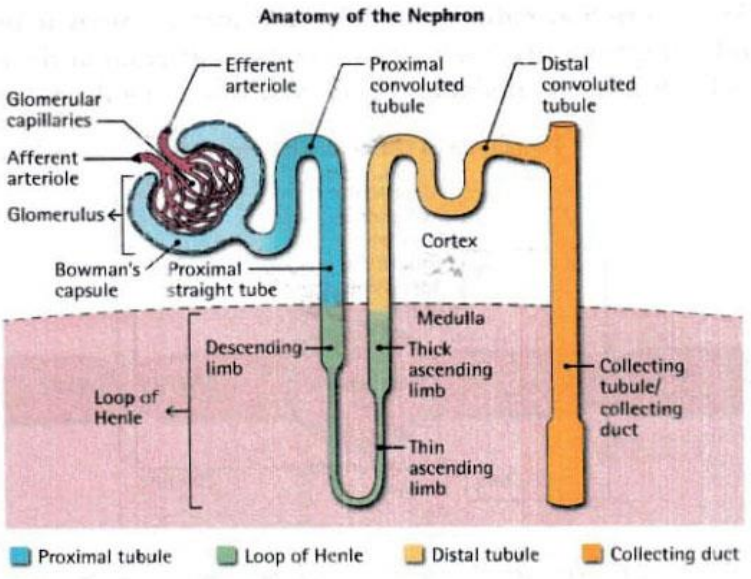

FIGURE 4 ANATOMY OF THE NEPHRON[iii]

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The renal tubule is divided into several morphologically and functionally distinct segments: the proximal convoluted tubule, loop of Henle (which includes descending thin limb, ascending thin limb, and thick ascending limb), distal convoluted tubule, and the collecting duct system. These segments are responsible for the selective reabsorption of water, electrolytes, glucose, and other solutes, as well as secretion of waste products and maintenance of acid–base balance.

Nephrons are classified into two major types based on their location and loop length:

1. Cortical nephrons constitute approximately 85% of all nephrons. Their glomeruli are located superficially in the outer portion of the renal cortex. The loops of Henle in cortical nephrons are relatively short and extend only slightly into the outer medulla. Because of this shallow penetration, cortical nephrons are primarily involved in bulk reabsorption of filtered solutes and water and are less effective in urine concentration. Their peritubular capillaries form a dense network around the convoluted tubules but do not significantly contribute to the formation of the medullary osmotic gradient.

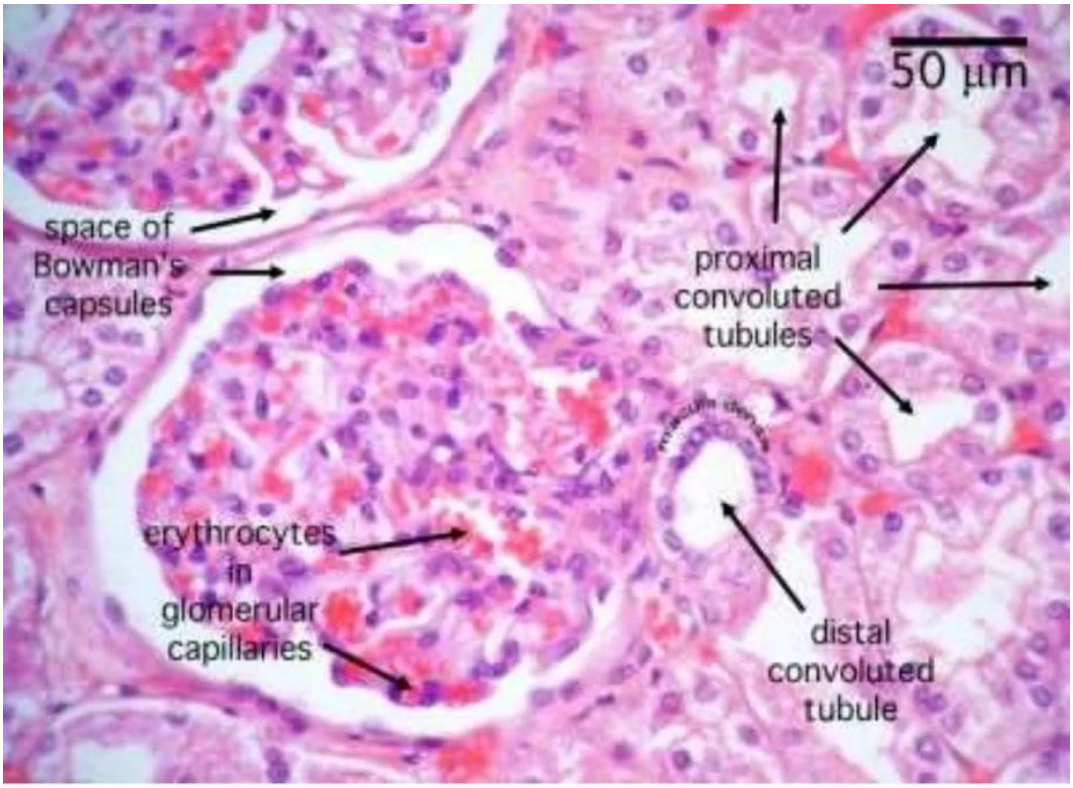

FIGURE 5 NORMAL HISTOLOGICAL STRUCTURE OF THE NEPHRON[iv]

2. Juxtamedullary nephrons, which account for approximately 15% of the total nephron population, have their glomeruli situated near the corticomedullary junction—the border between the renal cortex and medulla. These nephrons are characterized by long loops of Henle that descend deep into the inner medulla, sometimes reaching the renal

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papillae. This long loop is accompanied by a specialized vascular network known as the vasa recta, which plays a pivotal role in the countercurrent exchange mechanism and the generation of the medullary osmotic gradient. This gradient is essential for the concentration of urine, allowing the kidney to conserve water and produce hyperosmotic urine when necessary. Juxtamedullary nephrons are therefore critical for maintaining fluid homeostasis, especially under conditions of dehydration or low fluid intake.

The highly coordinated arrangement of nephrons, interstitial tissues, and vascular structures within the cortex and medulla enables the kidney to effectively perform filtration, selective reabsorption, and excretion functions. This architecture ensures that blood entering the kidney via the renal artery is thoroughly processed, with waste products excreted into the forming urine and valuable solutes and water retained according to physiological need.

Types of cells in the kidney:

The human kidney comprises a diverse range of specialized cells that collaborate intricately to perform vital roles in filtration, reabsorption, secretion, fluid balance, and endocrine regulation. At the level of the renal corpuscle, which marks the beginning of the nephron, several distinct cell types are present. The glomerular endothelial cells are fenestrated and allow plasma to be filtered while excluding blood cells. These endothelial cells are intimately associated with podocytes, which are specialized visceral epithelial cells. Podocytes extend foot processes (pedicels) that interdigitate to form slit diaphragms, crucial for size-selective filtration. Sandwiched between the capillary loops are mesangial cells, which come in intraglomerular and extraglomerular forms. Intraglomerular mesangial cells provide structural support, contractile regulation of capillary flow, and phagocytic functions. Extraglomerular mesangial cells—also called Lacis cells—reside at the vascular pole and participate in signaling within the juxtaglomerular apparatus (JGA). Surrounding the urinary space is a layer of parietal epithelial cells, which are flattened squamous cells forming the outer wall of Bowman's capsule.

Immediately after the glomerulus, the proximal convoluted tubule (PCT) begins with a lining of cuboidal epithelial cells characterized by an abundance of mitochondria and a dense brush border of microvilli, which maximize surface area for reabsorbing nearly 65–70% of the filtered load—including glucose, amino acids, sodium, and water. The proximal straight tubule, a continuation of the PCT into the outer medulla, has similar but slightly attenuated features. As filtrate progresses into the loop of Henle, the epithelium transitions. The thin descending and ascending limbs are lined with simple squamous epithelium, with the descending limb highly permeable to water and the ascending limb more permeable to solutes. In the thick ascending limb (TAL), the epithelium becomes cuboidal and is specialized for active transport of sodium, potassium, and chloride—essential for generating the medullary osmotic gradient required for urine concentration.[v]

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The distal convoluted tubule (DCT) is lined with simple cuboidal epithelial cells that lack a brush border, distinguishing them from PCT cells. These cells are responsible for fine-tuning electrolyte concentrations, particularly under the influence of parathyroid hormone (PTH), which increases calcium reabsorption. One segment of the DCT that contacts the glomerulus forms the macula densa, a cluster of columnar epithelial cells that sense sodium chloride concentration in the filtrate and communicate with nearby juxtaglomerular (JG) cells in the wall of the afferent arteriole. These JG cells are modified smooth muscle cells that synthesize and secrete renin, a key regulator of blood pressure and sodium balance. Along with the extraglomerular mesangial cells, these three cell types form the juxtaglomerular apparatus, an essential feedback system for glomerular filtration rate (GFR) regulation.

The collecting duct system, which receives filtrate from multiple nephrons, contains two main types of epithelial cells. Principal cells are pale-staining cuboidal to columnar cells that reabsorb sodium and water through channels such as ENaC and aquaporin-2, the latter being regulated by antidiuretic hormone (ADH). These cells also secrete potassium under the influence of aldosterone. Interspersed among them are intercalated cells, which are darker and more densely packed with mitochondria. These exist in two main forms: Type A intercalated cells secrete hydrogen ions to acidify urine, while Type B cells secrete bicarbonate, contributing to systemic pH regulation. These cell types play a vital role in maintaining acid–base balance.

Beyond the epithelial components, the renal vasculature includes various endothelial cells—from fenestrated glomerular endothelium to continuous and fenestrated capillaries in the peritubular network and vasa recta. Pericytes, located along capillary walls, regulate blood flow and vessel integrity. The renal interstitium, especially prominent in the medulla, houses fibroblasts, which produce extracellular matrix and, in the cortical peritubular region, serve as the primary source of erythropoietin, the hormone that stimulates red blood cell production. The interstitium also contains resident immune cells, including macrophages, dendritic cells, and lymphocytes, which contribute to immunologic surveillance and the kidney's response to injury or infection.

Finally, the kidney receives innervation from sympathetic nerve fibers, which modulate vascular tone, tubular sodium reabsorption, and renin release. There are also rare neuroendocrine-like cells, under investigation, which may secrete peptides involved in renal signaling.

Histopathological changes in kidney in CKD

Chronic Kidney Disease (CKD) is a progressive, irreversible deterioration in renal function that occurs over months to years, marked by persistent structural damage and functional decline. One of the most prominent gross anatomical features in advanced CKD is a reduction in kidney size, particularly in non-diabetic and non-cystic etiologies. The kidneys typically appear symmetrically shrunken with finely granular cortical surfaces caused by widespread scarring and loss of parenchymal tissue. The renal capsule becomes fibrotic and often adheres tightly to the

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underlying cortex, making surgical removal difficult. On sectioning, the cortex is markedly thinned and may be less than half its normal thickness. The corticomedullary demarcation becomes indistinct, and the medullary pyramids appear flattened or atrophic. The renal pelvis and calyces may appear mildly dilated due to chronic compensatory changes or previous obstructive episodes.

Microscopically, CKD induces profound changes across all compartments of the kidney: the glomeruli, tubules, interstitial space, and vasculature. Glomerular pathology often begins with segmental injury, progressing toward global glomerulosclerosis. This is characterized by the obliteration of glomerular capillary lumens and replacement with collagen and mesangial matrix. Podocytes—essential components of the glomerular filtration barrier—undergo effacement, detachment, or apoptosis, leading to leakage of proteins and subsequent tubulointerstitial injury. The glomerular basement membrane (GBM) progressively thickens, often irregularly, and may show lamellation or splitting, especially in diabetes mellitus or immune-mediated glomerulopathies. Mesangial expansion is another hallmark of CKD, typically caused by accumulation of extracellular matrix proteins and mesangial hypercellularity. In advanced disease, hyaline material derived from plasma proteins accumulates in the capillary walls, a process known as hyalinosis, which further impairs filtration.

As CKD progresses, the tubular system suffers extensive injury. Tubular epithelial cells, especially in the proximal convoluted tubules, lose their brush border and undergo flattening, cytoplasmic vacuolization, and eventually cell death. These degenerative changes contribute to tubular atrophy, a key pathological feature that correlates closely with renal function decline. Atrophic tubules often appear as dilated lumens lined by flattened epithelial cells or filled with eosinophilic proteinaceous casts—particularly in proteinuric states. A striking feature in chronic pyelonephritis, and sometimes in advanced CKD of other causes, is "thyroidization" of the tubules: atrophic tubules with luminal colloid-like material mimicking thyroid follicles. Furthermore, the tubular basement membranes become thickened and wrinkled, compromising cellular polarity and nutrient exchange.

In parallel with tubular injury, the interstitial compartment undergoes fibrotic remodeling. Interstitial fibrosis involves excessive deposition of collagen types I and III, fibronectin, and other matrix components by activated fibroblasts and pericytes that have often transitioned into myofibroblasts. This process is stimulated by a complex interplay of growth factors, notably Transforming Growth Factor-beta (TGF-β) and Connective Tissue Growth Factor (CTGF), which are upregulated in response to tubular injury, proteinuria, and oxidative stress. Concomitant with fibrosis is a chronic inflammatory infiltrate, predominantly composed of lymphocytes and macrophages, occasionally accompanied by plasma cells and eosinophils in immunologically mediated diseases. These immune cells secrete cytokines (such as TNF-α, IL-1, and MCP-1) that amplify tissue damage and fibrosis. Moreover, capillary rarefaction—loss of peritubular capillaries—occurs as a consequence of endothelial injury and hypoxia, exacerbating ischemic injury and promoting further interstitial fibrosis in a self-perpetuating cycle.

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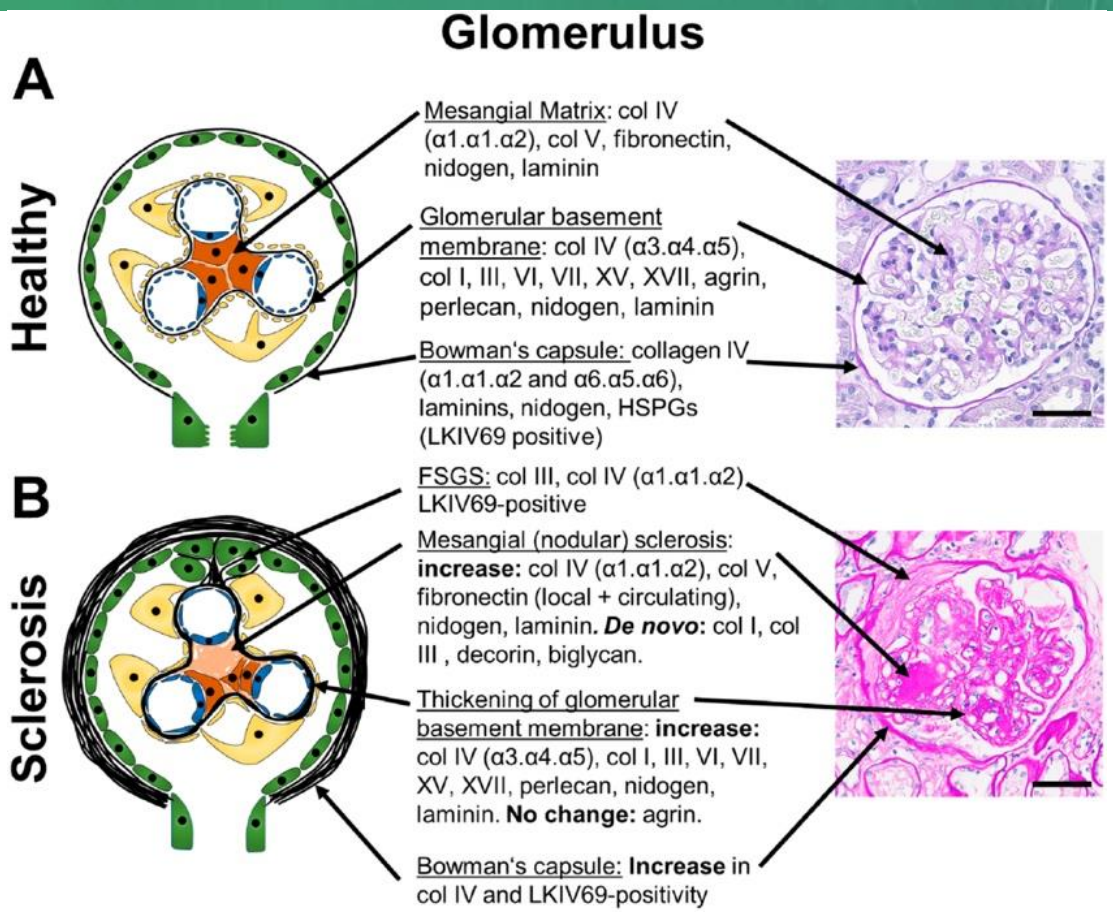

FIGURE 6 COMPARISON BETWEEN HEALTHY AND SCLEROSED GLOMERULUS[vi]

The vascular component of the kidney is also profoundly affected in CKD. Arteriolar sclerosis, a common finding, includes both hyaline and hyperplastic forms. Hyaline arteriolosclerosis involves the deposition of homogeneous, glassy material in the walls of small arterioles, typically in the setting of long-standing hypertension or diabetes. In contrast, hyperplastic arteriolosclerosis—often seen in malignant hypertension—features concentric, laminated thickening of arteriolar walls resembling an "onion-skin" appearance, caused by smooth muscle hyperplasia and basement membrane duplication. Larger arteries may develop intimal fibrosis and medial hypertrophy, which contribute to luminal narrowing and chronic ischemia of the downstream nephrons. In some cases, particularly in thrombotic microangiopathies or systemic sclerosis, thrombotic occlusion and fibrinoid necrosis of arterioles and glomerular capillaries can be observed.

At the cellular and molecular level, a variety of maladaptive responses underpin these structural changes. Podocyte depletion and dysfunction play a central role in initiating glomerulosclerosis. Tubular epithelial cells, when injured, may undergo epithelial-mesenchymal transition (EMT), acquiring mesenchymal markers and contributing directly to the myofibroblast pool. Oxidative stress, mitochondrial dysfunction, and impaired autophagy further exacerbate

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tubular damage. Profibrotic mediators such as TGF-β and platelet-derived growth factor (PDGF) are persistently expressed. Epigenetic alterations, such as DNA methylation of anti-fibrotic genes or histone modifications, lock cells into a pro-fibrotic phenotype. MicroRNAs (e.g., miR-21, miR-29) and long non-coding RNAs also play regulatory roles in sustaining inflammation and fibrosis. Importantly, tubular cells, fibroblasts, and even immune cells become a source of erythropoietin deficiency, contributing to the anemia of CKD.

There are also disease-specific variants of chronic injury. In diabetic nephropathy, typical findings include glomerular basement membrane thickening, mesangial matrix expansion, and formation of Kimmelstiel–Wilson nodules (nodular glomerulosclerosis). In hypertensive nephrosclerosis, pathology is dominated by global glomerulosclerosis, interstitial fibrosis, and arteriolosclerosis. Lupus nephritis displays a spectrum of histologic classes, often with immune complex deposition in glomerular capillaries, subendothelial and mesangial locations, and characteristic "wire-loop" lesions. Polycystic kidney disease, although not fibrosing in early stages, ultimately leads to loss of functional nephrons due to compression and replacement by enlarging cysts. Chronic pyelonephritis features interstitial scarring, patchy tubular atrophy, and tubular thyroidization, with frequent deformities of the calyces and pelvicalyceal system.

Ultimately, CKD progresses along a final common pathway of interstitial fibrosis, tubular atrophy, glomerulosclerosis, and vascular compromise—regardless of the initial insult. This progression is tightly correlated with declining glomerular filtration rate (GFR) and the onset of systemic complications such as hypertension, metabolic acidosis, anemia, and disturbances in calcium-phosphate metabolism. Importantly, while glomerular changes often receive clinical attention, the degree of tubulointerstitial fibrosis is the strongest histologic predictor of renal functional decline. This has redirected therapeutic focus toward preserving tubular integrity, preventing interstitial inflammation, and halting fibrosis as core strategies in CKD management.

Biomolecular changes in CKD

In Chronic Kidney Disease, nephron degeneration is driven by a complex interplay of biomolecular mechanisms. Within the glomerulus, particularly in podocytes, extensive injury occurs through multiple programmed cell-death pathways—apoptosis, autophagy dysfunction, pyroptosis, necroptosis, ferroptosis, and mitotic catastrophe—leading to irreversible podocyte depletion and proteinuria[vii] . Structural injury is further exacerbated by foot process effacement, a disruption in cytoskeletal architecture mediated by changes in actin-binding proteins like nephrin, podocin, and CD2AP. This loss of terminally differentiated podocytes— which cannot re-enter the cell cycle without risking mitotic failure—constitutes a critical path to glomerulosclerosis[viii].

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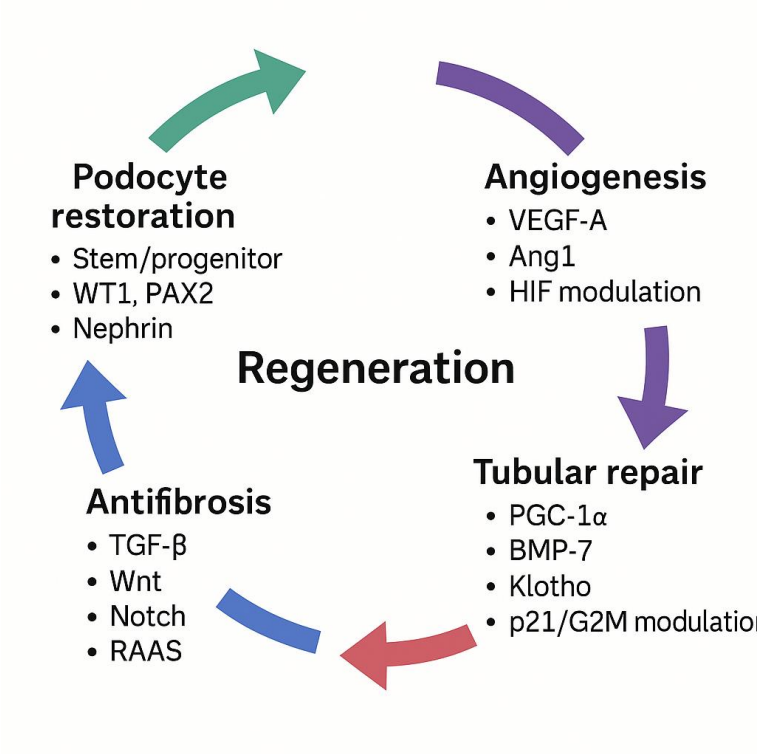

FIGURE 7 REGENERATION CYCLE (©BCRMED GLOBAL)

Beyond the glomerulus, tubular epithelial cells exhibit profound metabolic and phenotypic shifts. Proximal tubule cells lose mitochondrial function—fueled by decreased PGC-1α expression and blunted fatty acid oxidation—and undergo partial epithelial-to-mesenchymal transition (EMT), marked by loss of E-cadherin and gain of mesenchymal markers like α-SMA, contributing to interstitial fibrosis[ix]. Concurrently, these cells enter a senescent state, releasing pro-inflammatory cytokines (IL-1β, IL-6, TGF-β) that perpetuate fibrotic signaling and attract immune cells.

Error! Reference source not found. shows Glomerular ECM components and changes during glomerulosclerosis. A schematic of a healthy glomerulus (A) and a glomerulus with nodular or focal segmental glomerulosclerosis (B) with description of the major ECM-components and their alterations in fibrosis in the mesangial ECM, the glomerular basement membrane and the Bowman's capsule are shown. Apart from increased Collagen IV- and LKIV69-positivity, little is known on the exact composition of the Bowman's capsule and the ECM forming FSGS lesions, albeit the ECM of FSGS is likely similar to the ECM of Bowman's capsule, as it is mainly produced by the parietal epithelial cells. The right panel shows representative PAS stained human sections. (B): PAS-Stain was provided by Dr. Cannata-Ortiz. Scale bars indicate 50 µm. Abbreviations: BC, Bowman's capsule; PAS, periodic acid-Schiff; FSGS, focal segmental glomerulosclerosis; ECM, extracellular matrix; HSPGs, heparan sulfate proteoglycans.

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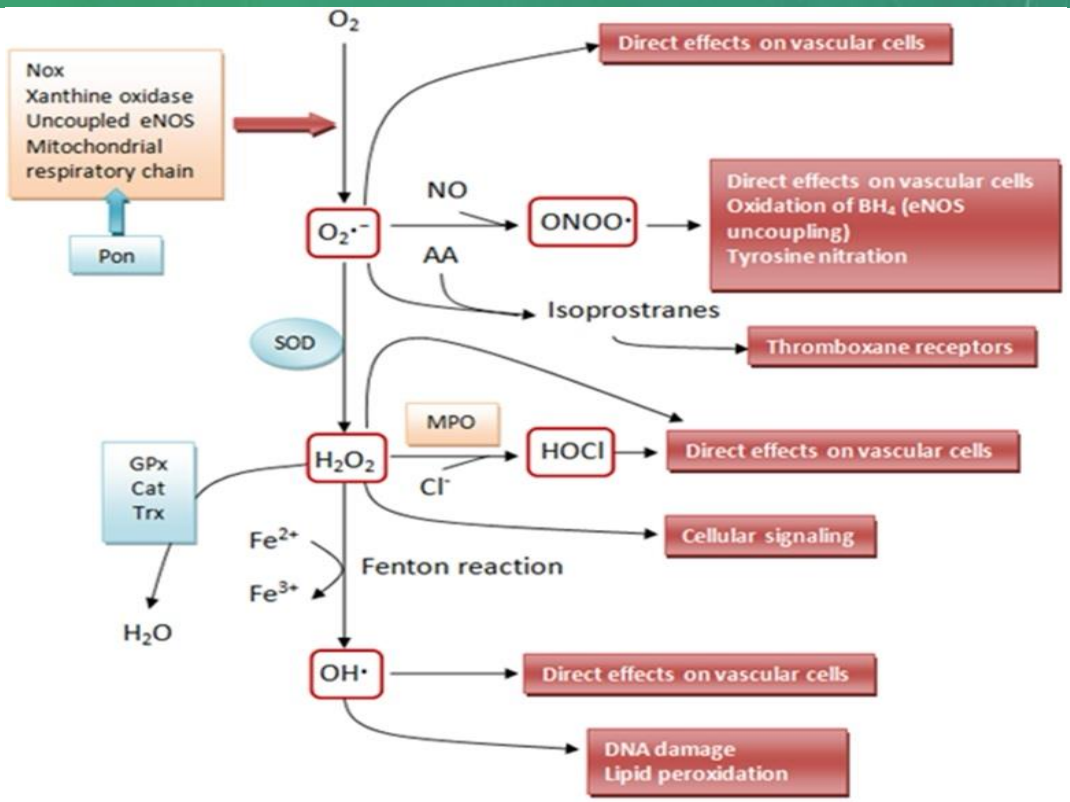

FIGURE 8 SCHEMATIC OUTLINE IF THE INTERRELATIONSHIP BETWEEN SOME RELATIVE REACTION OXYGEN SPECIES (ROS) THAT AFFECT VASCULAR WALL[x]

The interstitium and microvasculature suffer from endothelial dysfunction and capillary loss, a consequence of decreased VEGF and eNOS activity, oxidative stress, and chronic inflammation . The resultant hypoxia-inducible factor (HIF) activation further amplifies fibrotic pathways. Persistent activation of pathways like TGF-β/Smad, Notch, Wnt/β-catenin, RAAS, NF-κB, and JAK-STAT drives myofibroblast proliferation, extracellular matrix synthesis (collagen I/III, fibronectin), and sustained fibrosis[xi]. Ultimately, this creates a self-reinforcing "final common pathway" of nephron loss and reduced functionality.

From an epigenetic perspective, CKD involves DNA hypermethylation of reno-protective genes (e.g., Klotho, BMP-7), histone modifications that silence antifibrotic proteins, and dysregulation of non-coding RNA—particularly the upregulation of pro-fibrotic miR-21 and downregulation of miR-29—further fortifying a fibrogenic phenotype .

Given the comprehensive damage, regeneration demands restoring several critical elements. Podocyte restorationrequires either stem/progenitor derivation or reactivation of developmental genes like WT1, PAX2, and nephrin, and stabilization of structure via Rac1 inhibition. Tubular repair demands mitochondrial repair via PGC-1α upregulation, reversal of EMT through BMP-7/Klotho, and controlled regrowth by modulating p21/G2-M checkpoints. Antifibrotic strategies must target TGF-β/Smad, Wnt/Notch, and RAAS pathways,

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possibly harnessing BMP-7, HGF, or recombinant Klotho to reverse extracellular matrix deposition and myofibroblast activation.

In parallel, angiogenesis must be restored, requiring VEGF-A and Ang1 for endothelial repair, alongside controlled HIF modulation to prevent pathological scarring. Chronic inflammation and cellular senescence may be addressed through senolytics (e.g., Navitoclax), shifting macrophage polarization toward reparative phenotypes, and therapies enhancing regulatory cytokines (IL-10) and T-regulatory cell activity.

Finally, epigenetic reprogramming—via HDAC inhibitors, DNMT blockers, miRNA modulation (inhibiting miR-21, promoting miR-29), and even CRISPR-based editing—could reset transcriptional landscapes, supporting a shift from fibrotic to regenerative gene expression states.

The role ACE Reno can play in the regeneration process

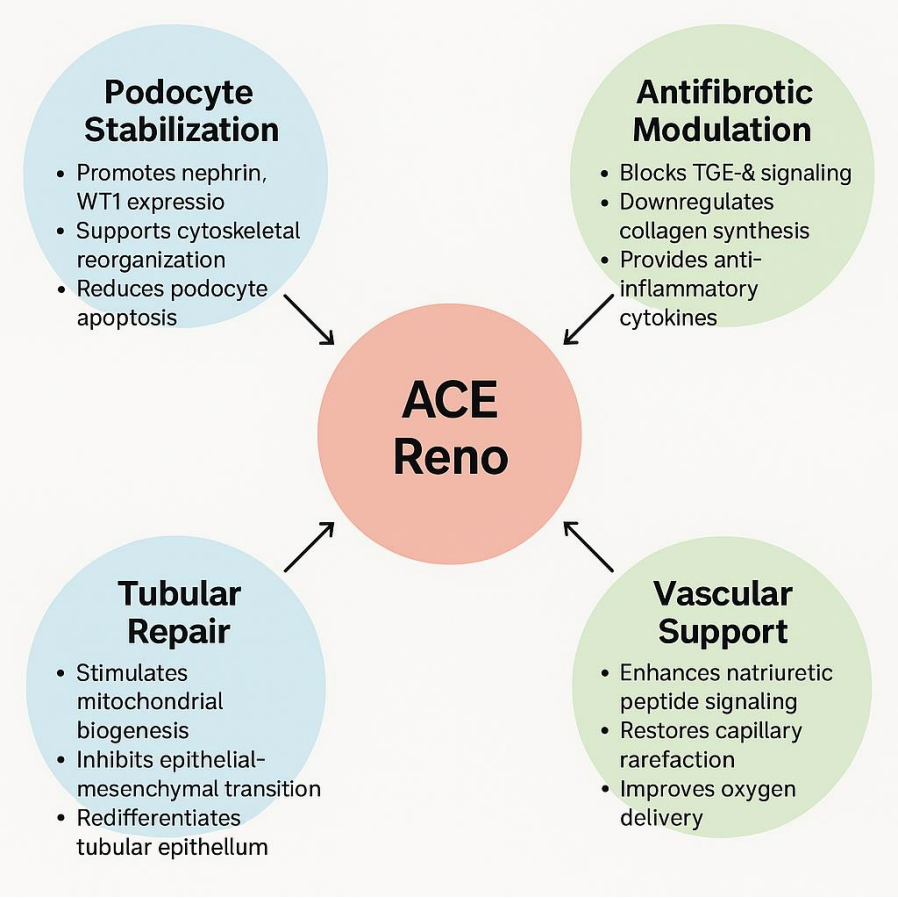

FIGURE 9 ROLE OF ACE RENO IN THE REGENERATION PROCESS OF NEPHRON (©BCRMED GLOBAL)

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ACE Reno, formulated from a combination of sheep fetal kidney tissue, atrial tissue, placenta, and mesenchymal stem cells (MSCs), processed using the ACE Pico Protocol, is designed to provide organ-specific regenerative cues through a cocktail of bioactive peptides, enzymes, membrane lipids, and signaling molecules. The ACE Pico Protocol ensures that these biomolecules are preserved in their functional state while eliminating nuclear material, making the extract non-immunogenic yet biologically potent. This composition allows ACE Reno to act as a multi-targeted therapeutic matrix for nephron regeneration in Chronic Kidney Disease (CKD).

One of the primary targets of ACE Reno appears to be the restoration of podocyte integrity and function. The inclusion of fetal kidney-derived peptides likely contributes nephron-specific transcriptional cues such as WT1 and nephrin fragments, essential for maintaining the slit diaphragm structure and cytoskeletal organization in podocytes. Given that podocytes are terminally differentiated and unable to proliferate under normal physiological conditions, the delivery of these regenerative signals may stabilize podocyte phenotype, prevent further detachment, and protect against glomerulosclerosis. Additionally, exosome-like vesicles from MSCs and placenta may deliver regulatory RNAs, such as miR-132 and miR-30, known to suppress podocyte apoptosis and support actin remodeling.

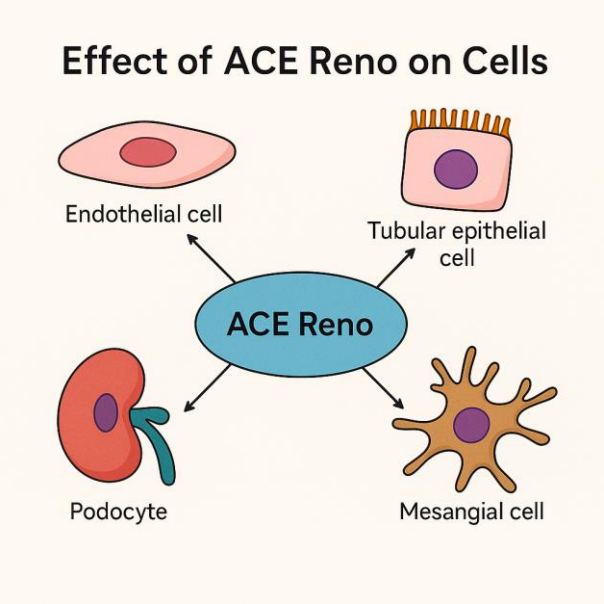

FIGURE 10 (©BCRMED GLOBAL)

In the tubular compartment, ACE Reno offers bioactive factors that are critical for re-establishing epithelial integrity and metabolic competence. The peptides derived from MSCs and fetal kidney tissue are expected to stimulate mitochondrial biogenesis through PGC-1α activation and restore oxidative phosphorylation, particularly in the proximal tubules, which are highly vulnerable to energy depletion in CKD. Furthermore, the presence of BMP-7 and Klotho-like peptides may directly inhibit epithelial-to-mesenchymal transition (EMT)[xii], promote redifferentiation of

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surviving epithelial cells, and aid in the regeneration of the brush border. These actions collectively enhance solute reabsorption and delay tubulointerstitial fibrosis.

ACE Reno also plays a significant anti-fibrotic[xiii] and anti-inflammatory role in the renal interstitium. It is likely to contain antagonists to TGF-β signaling, as well as microRNA mimetics like miR-29, which suppress collagen synthesis and fibroblast activation. Placental and MSC-derived molecules are known to downregulate the secretion of pro-fibrotic mediators such as fibronectin, α-SMA, and CTGF, while upregulating antifibrotic pathways including BMP-7 and HGF. Simultaneously, ACE Reno may modulate immune cell behavior by promoting anti-inflammatory cytokines such as IL-10, limiting the infiltration of M1-type macrophages and reducing the senescence-associated secretory phenotype (SASP) that exacerbates chronic injury in CKD.

Another crucial domain influenced by ACE Reno is the renal vasculature. The inclusion of atrial peptides—most notably fragments of atrial natriuretic peptide (ANP)[xiv]—can improve intrarenal hemodynamics, enhance glomerular filtration dynamics, and support natriuresis. Moreover, angiogenic peptides derived from MSCs and placenta, such as VEGF-A and Angiopoietin-1, contribute to the repair and regrowth of the peritubular capillary network, addressing one of the hallmark features of CKD: capillary rarefaction. Improved vascularization not only restores oxygen delivery but also reduces hypoxia-inducible fibrosis, thereby enhancing the microenvironment necessary for nephron survival.

Taken together, ACE Reno presents a comprehensive regenerative strategy that aligns with the four critical domains of nephron recovery: podocyte stabilization, tubular repair, antifibrotic modulation, and vascular support. By delivering a multi-factorial, cell-free peptide matrix derived from embryonic and progenitor-rich tissues, ACE Reno intervenes at multiple pathophysiological checkpoints of CKD progression. Its mechanism stands in contrast to single-target drugs by offering a systemic regenerative platform, shifting the nephron environment from a state of chronic degeneration to one of controlled cellular renewal and repair.

Conclusion

The findings of this study demonstrate that ACE Reno, a novel Pico Cell Matrix derived from fetal and progenitor-rich tissues, offers a promising regenerative approach for the treatment of Chronic Kidney Disease (CKD). Through its multifactorial composition, ACE Reno effectively targets key pathological mechanisms of CKD, including podocyte injury, tubular epithelial degeneration, interstitial fibrosis, inflammation, and capillary rarefaction. The observed histological and functional improvements in the adenine-induced CKD rat model suggest that ACE Reno facilitates nephron repair by restoring cellular homeostasis, modulating profibrotic signaling pathways, and enhancing vascular support. Unlike conventional therapies that primarily delay disease progression, ACE Reno provides a cell-free, organ-specific regenerative platform with the potential to reverse chronic kidney damage. These findings support further preclinical

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investigation and pave the way for clinical trials to assess its translational potential in human CKD patients.

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