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Review

Toll-like Receptor Signaling in Chronic Kidney Disease: Implications of Vitamin Supplementation and Therapeutic Targeting

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Abstract

Toll-like receptors (TLRs) are key innate immune sensors that recognize damage-associated molecular patterns (DAMPs) released during metabolic stress, oxidative injury, and renal inflammation. Renal TLR cascades, particularly TLR2 and TLR4, are increasingly activated in chronic kidney disease (CKD). CKD affects more than 700 million people worldwide. TLR activation modulates downstream NF-κB, MAPK, and IRF signaling pathways, promoting pro-inflammatory cytokine production, interstitial fibrosis, and loss of renal function. Current CKD treatments focus on symptom and hemodynamic management, but targeting TLR-mediated inflammatory pathways could be a novel disease-modifying strategy. Recent findings suggest that fat- and water-soluble vitamins can act as multi-target immunomodulators, altering TLR signaling at the transcriptional and epigenetic levels. Fat-soluble vitamins have been shown in preclinical and clinical models to suppress TLR2/4 expression, impair TLR4–MD-2 assembly, and enhance antioxidant defense through Nrf2. Meanwhile, water-soluble vitamins indirectly reduce TLR-mediated inflammation by reducing mitochondrial oxidative stress, regulating homocysteine, and blocking toxic glycolytic flux. This narrative review evaluates the potential role of fat-soluble (A, D, E and K) and water-soluble (B-complex and C) vitamins in modulating TLR-associated inflammatory responses in kidney diseases and summarizes the literature on small-molecule inhibitors and vitamin-based therapeutics, including current preclinical, clinical, and marketed therapies. This evidence also highlights key translational research gaps and provides a scientific basis for future investigations into the therapeutic potential of vitamins for CKD management.

Keywords: kidney diseases; Toll-like receptor; NF-κB; MAPK signaling; diabetic nephropathy; fat-soluble vitamins; water-soluble vitamins

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1. Introduction

Chronic kidney disease (CKD) is a complex, progressive disorder characterized by persistent inflammation, immune dysregulation, oxidative stress, and progressive loss of renal function. The global burden of CKD has increased substantially, with the number of affected adults rising from 378 million in 1990 to 788 million in 2023, corresponding to an age-standardized prevalence of 14.2%. CKD accounted for approximately 1.48 million deaths in 2023 and ranked as the ninth leading cause of death worldwide [1]. Its prevalence varies geographically, with a particularly high burden in North Africa, the Middle East, and South Asia. In India, diabetes mellitus and hypertension remain major contributors to CKD, with diabetic nephropathy accounting for a substantial proportion of cases.

Furthermore, impaired renal function independently increases cardiovascular risk, highlighting the systemic consequences of CKD [2]. At the molecular level, Toll-like receptors (TLRs) are key innate immune sensors that recognize exogenous and endogenous danger signals and initiate downstream NF-κB, mitogen-activated protein kinase (MAPK), and interferon regulatory factor (IRF) signaling pathways, promoting the release of pro-inflammatory cytokines, chemokines, and profibrotic mediators [3,4]. TLR2, TLR3, TLR4, TLR7, and TLR9 are expressed in renal tissues, including glomerular endothelial cells, podocytes, mesangial cells, tubular epithelial cells, and dendritic cells, where they contribute to immune surveillance and tissue homeostasis [5]. However, their sustained activation can amplify inflammatory responses, promote oxidative damage and maladaptive tissue repair, and accelerate renal fibrosis and CKD progression [6,7]. The growing global burden of CKD and the limitations of existing disease-modifying therapies therefore underscore the importance of investigating TLR-mediated inflammatory pathways as potential therapeutic targets for preventing or slowing renal disease progression.

Clinical and experimental data increasingly implicate TLR2 and TLR4 as central mediators of renal inflammation, oxidative stress, and fibrosis, positioning them as both biomarkers and therapeutic targets for mitigating CKD. Current treatments primarily rely on indirect immunomodulators that attenuate TLR-mediated inflammation, underscoring the need to develop direct TLR-targeted therapies for CKD. Recent evidence suggests that vitamins play a critical role in TLR modulation by targeting TLR-mediated renal inflammation and immune responses [8]. Water-soluble vitamins, such as the B vitamins and vitamin C, and fat-soluble vitamins A, D, E, and K exert biological effects beyond their classical metabolic roles. Emerging research demonstrates that vitamins regulate TLR expression by modulating mitochondrial function, transcriptional activity, and epigenetic mechanisms [9]. A preclinical finding showed that vitamin D downregulated TLR4 expression in renal macrophages and tubular cells, attenuating chronic inflammation and oxidative stress in adenine-induced CKD at 500–1000 IU/kg/day [10]. Vitamin C supplementation protected renal function by scavenging ROS, inhibiting lipid peroxidation, and reducing urinary protein, thereby indirectly mitigating TLR4 priming by DAMPs in ischemia–reperfusion injury (IRI) and streptozotocin-induced diabetic rats at a dose of 200–500 mg/kg/day [11]. Furthermore, marketed formulations for various diseases, such as Nephro-Vite, Rocaltrol, and Alphacalcidol containing vitamin D or vitamin C, serve as therapeutic candidates for CKD or CKD-related complications [12]. Figure 1 illustrates the role of vitamins in CKD.

Beyond triggering intracellular signaling cascades, TLRs are significant in CKD because these cascades release soluble mediators. The binding of TLR2 and TLR4 receptors on tubular epithelial cells, podocytes, endothelial cells, and infiltrating macrophages activates NF-κB and MAPK pathways, which in turn stimulate TNF-α, IL-1β, IL-6 and chemokine synthesis. These mediators perpetuate leukocyte infiltration and tubular damage and contribute to TGF-β1 synthesis, the kidney's major profibrotic cytokine. TGF-β1 stimulates fibroblast activation, myofibroblast differentiation, and excessive accumulation of extracel-

lular matrix components (e.g., collagen and fibronectin), which causes renal fibrosis and dysfunction. This connection is supported experimentally: TLR4 signaling increases TGF-β1 sensitivity and fibroblast activation in fibrosis, while TLR4 blockade or deletion reduces fibrosis and preserves renal function in obstructive and chronic kidney injury models. Thus, situating TLR-mediated inflammation within this pathophysiological chain, from receptor activation and cytokine release to fibroblast activation, matrix deposition, and functional impairment, helps explain the results described in this review.

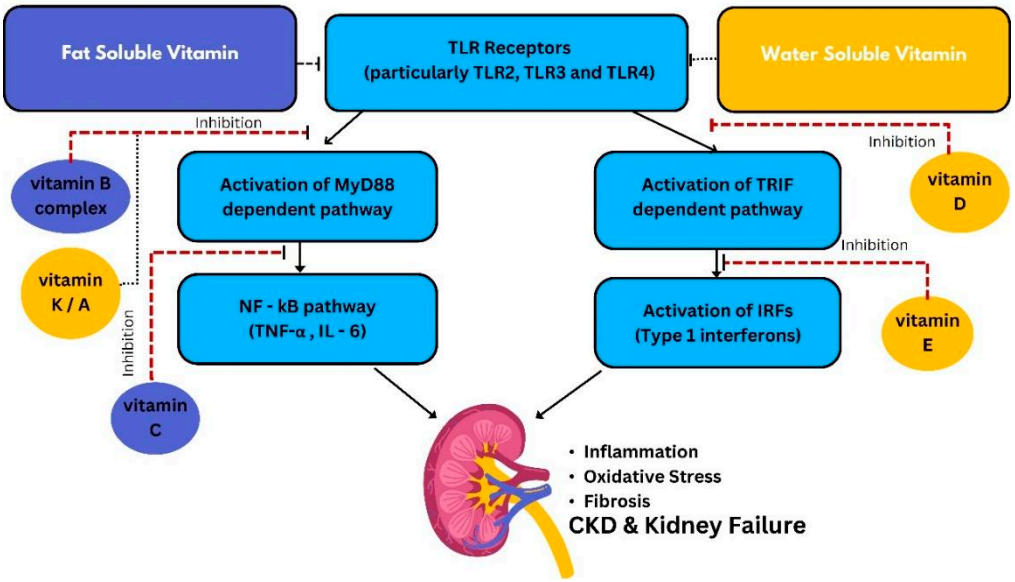


Figure 1. Diagrammatic representation of the role of vitamins in managing CKD. The figure shows how vitamin supplementation reverses oxidative stress, inflammation, metabolic imbalance, and mineral dysregulation in CKD. Antioxidant vitamins reduce reactive oxygen species, B-complex vitamins regulate homocysteine levels, and vitamin D helps maintain calcium-phosphate balance and modulates inflammatory and hormonal pathways. TLR: Toll-like receptors; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α: tumor necrosis factor alpha; IL-6: interleukin-6; TRIF: TIR-domain-containing adapter-inducing interferon-β; CKD: chronic kidney disease.

This review highlights the role of TLR signaling in CKD progression and elucidates the modulatory effects of vitamins on TLR-mediated pathways, supported by preclinical and clinical research. Furthermore, it explores the mechanistic insights, therapeutic potential, and translational challenges associated with vitamins as emerging candidates for TLR regulation in CKD [13].

2. Methods of Data Collection

This narrative review summarizes preclinical and clinical evidence on vitamin-mediated modulation of Toll-like receptor (TLR) signaling in kidney diseases. We retrieved literature published between 2015 and 2026 from PubMed, Scopus, and Web of Science and included selected earlier studies for mechanistic context. Keywords included "vitamins," "TLR signaling," "TLR2," "TLR4," "NF-κB," "chronic kidney disease," "acute kidney injury," "renal inflammation," "oxidative stress," "fibrosis," and "clinical trials." We selected relevant studies investigating the effects of vitamins on TLR-associated pathways and renal outcomes after screening titles, abstracts, and full texts, and removed duplicates. We collected evidence on therapeutic formulations and patents from the World Intellectual Property Organization (WIPO) and Google Patents databases. We excluded irrelevant publications, editorials, and non-scientific reports. Publications were excluded

if they were unrelated to vitamin-mediated effects or renal pathophysiology, lacked relevant experimental or clinical outcomes, or did not provide sufficient scientific information for meaningful interpretation. Studies were considered eligible when they were written in English and investigated one or more of the following: (i) the effects of vitamins or vitamin-derived therapeutic formulations on TLR expression or signaling; (ii) modulation of downstream inflammatory pathways, particularly NF-κB and associated cytokines; (iii) effects on oxidative stress, inflammatory responses, and fibrotic processes in renal tissues; and (iv) renal functional or clinical outcomes associated with vitamin supplementation or intervention. Where studies reported conflicting findings, the differences were critically examined in relation to the vitamin formulation, dose, treatment duration, route of administration, disease model, study population, experimental endpoints, and methodological limitations. Greater interpretative weight was assigned to studies with more direct mechanistic evidence, appropriate controls, and clinically relevant outcomes. As this was a narrative review, we selected studies based on scientific relevance and did not apply a formal systematic-review protocol.

3. Toll-like Receptor Signaling in Kidney Diseases: Pathophysiological Roles and Current Therapeutic Strategies

TLRs are a family of pattern recognition receptors conserved throughout evolution that play a central role in the innate immune system by triggering pro-inflammatory signaling pathways in response to exogenous pathogen-associated molecular patterns (PAMPs) and tissue injury via endogenous danger-associated molecular patterns (DAMPs). These receptors are expressed on various kidney cell types, mainly myeloid cells [14]. Emerging evidence shows that TLRs activate these cells during CKD progression. Ten human TLRs (TLR1-10) and three additional TLRs (TLR11, 12, and 13) have been identified in mice across different regions of the kidney, where they participate in various progressive CKD conditions [15], as summarized in Table 1.

Table 1. TLR subtypes involved in CKD and various kidney diseases.

TLR Type	Location	Ligand Type	Key Signaling Pathway	Role in Kidney Disease Pathogenesis	References
TLR1, TLR2, TLR6	Tubular epithelial cells (proximal and distal), mesangial cells, podocytes, glomerular endothelial cells	Bacterial lipopeptides (tri- and di-acyl), peptidoglycan, fungal components	MyD88 activates NF-κB, leading to inflammation-related gene expression	Promotes tubular and mesangial cell cytokine production to drive sterile and infectious inflammation; participates in tubular injury and podocyte cytoskeletal changes; and contributes to fibrosis and glomerulosclerosis in ischemia–reperfusion injury, nephrotoxic AKI, immune-mediated GN, and diabetic nephropathy. Expression increases with poor kidney function.	[16]
TLR3	Tubular epithelial cells, mesangial cells, and glomerular cells; overexpressed in lupus nephritis and sepsis-associated AKI	Viral dsRNA, endogenous nucleic acids from necrotic cells	Activation of the TRIF-dependent signaling pathway leads to downstream activation of IRF3 and NF-κB, resulting in the induction of type I interferons and pro-inflammatory cytokines	Participates in antiviral and nucleic acid-driven sterile inflammation; overactivation promotes type I interferon signaling, tubular injury, and histologic response in lupus nephritis and septic AKI.	[17]
TLR4	Highly expressed in tubular epithelial cells, podocytes, glomerular endothelial cells, and mesangial cells	LPS, DAMPs (HMGB1, HSPs, biglycan, fibrinogen), oxidized lipoproteins, AGEs in diabetic conditions.	MyD88- and TRIF-dependent signaling activates NF-κB, MAPKs, and IRFs, resulting in induction of pro-inflammatory cytokines and chemokines	Main contributor to renal inflammation and fibrosis; mediator of tubular and podocyte damage, macrophage infiltration, and interstitial fibrosis secondary to diabetic nephropathy, IRI, sepsis-related AKI, immune-related GN, and vasculitis; associated with proteinuria and reduced GFR expression.	[18]

Table 1. *Cont.*

TLR Type	Location	Ligand Type	Key Signaling Pathway	Role in Kidney Disease Pathogenesis	References
TLR5	Tubular epithelial cells (distal nephron, collecting duct)	Bacterial flagellin	MyD88 activation leads to NF-κB overexpression and inflammation	Plays a potential role in defense against A-UTIs, and overactivation increases tubular cytokine production and contributes to sepsis-induced AKI and tubulointerstitial nephritis.	[19]
TLR7, TLR8, TLR9	Podocytes, tubular epithelial cells, glomerular endothelial cells, infiltrating immune cells, overexpressed in lupus nephritis and some GN	ssRNA, unmethylated CpG DNA, mitochondrial/self-DNA complexes	MyD88 activates NF-κB, leading to inflammation-related gene expression	Induces interferon-driven autoimmunity and inflammation and is involved in podocyte injury, albuminuria, and chronicity of lupus nephritis and immune-mediated GN; TLR9 expression is associated with the activity index, but protective roles have been suggested in certain contexts.	[20,21]
TLR10	Low basal renal expression, infiltrating immune cells and some glomerular cells	Ligands poorly defined, inhibitory sensing of lipopeptides	Dual role in the MyD88–NF-κB signaling pathway	Acts as a negative regulator of exaggerated TLR2-mediated inflammatory responses; it may also modulate immunity with protective effects, but its role in kidney disorders is still being explored.	[22,23]

These TLRs initiate pro-inflammatory signaling pathways via the adaptor protein MyD88, the TIR-domain-containing adaptor protein (TIRAP), and TRAM (TIR-related adaptor molecule). Through these adaptor proteins, TLRs transmit downstream signals that activate NF-κB, mitogen-activated protein kinase (MAPK), p38, and IRF [24]. The two major adaptor pathways are the MyD88-dependent and TRIF-dependent downstream signaling pathways [25]. Almost all TLR pathways activate the MyD88-dependent pathway, except TLR3 [26]. MyD88 subsequently recruits IRAK4, which phosphorylates and activates IRAK1 and IRAK2, allowing the recruitment and oligomerization of TRAF6 [27]. The latter complex gains E3 ubiquitin ligase activity, producing K63-linked polyubiquitin chains through TRAF6 and Pellino proteins, thereby activating the TAK1 kinase complex [28]. TAK1 activates the IKK complex and MAPK pathways, leading to IκB degradation, NF-κB nuclear translocation, transcription of pro-inflammatory cytokines, and activation of immune genes, thereby promoting fibrosis and CKD progression. In contrast, TLR3 and the MyD88-independent arm of TLR4 engage TRIF, which associates with TRAF3 and the kinases TBK1 and IKKε. These kinases phosphorylate IRF3 and IRF7, promoting type I interferon production, which contributes to tissue injury and inflammatory amplification in renal pathology [29].

TLR4 and TLR2 are the most studied TLRs in kidney pathophysiology. Their endogenous DAMP counterparts, HMGB1 and fibronectin, activate them, leading to NF-κB-induced inflammation that contributes to ischemia–reperfusion injury and diabetic nephropathy [30,31]. Under different pathophysiological conditions, TLR1 and TLR6 act mainly as TLR2 chimeras and show increased expression in aged kidneys, particularly in fibrotic kidneys (Leemans et al., 2009) [32]. Intracellular TLR3, TLR7, TLR8 and TLR9 recognize nucleic acids [33]. In particular, TLR7 and TLR8 have been shown to mediate the recognition of endogenous miR21 in the context of kidney fibrosis [34]. TLR9 is essential in mediating lupus nephritis and immune-complex glomerulonephritis [35]. TLR5 recognizes bacterial flagellin, which is essential in bacterial urinary infections and leads to pyelonephritis [31]. TLR10 is the most recently identified TLR in humans and may have a distinct anti-inflammatory effect because it competes with TLR ligands or forms homomeric associations with TLR1, TLR2, or TLR6 [36]. In particular, continuous activation of all TLR members triggers kidney inflammation by creating a profibrotic environment through macrophage recruitment and increased production of inflammatory cytokines IL-6 and TNF-α [37]. Thus, targeting TLR signaling pathways could offer a novel approach

with significant potential to slow CKD progression. The entire TLR activation pathway is presented in Figure 2.

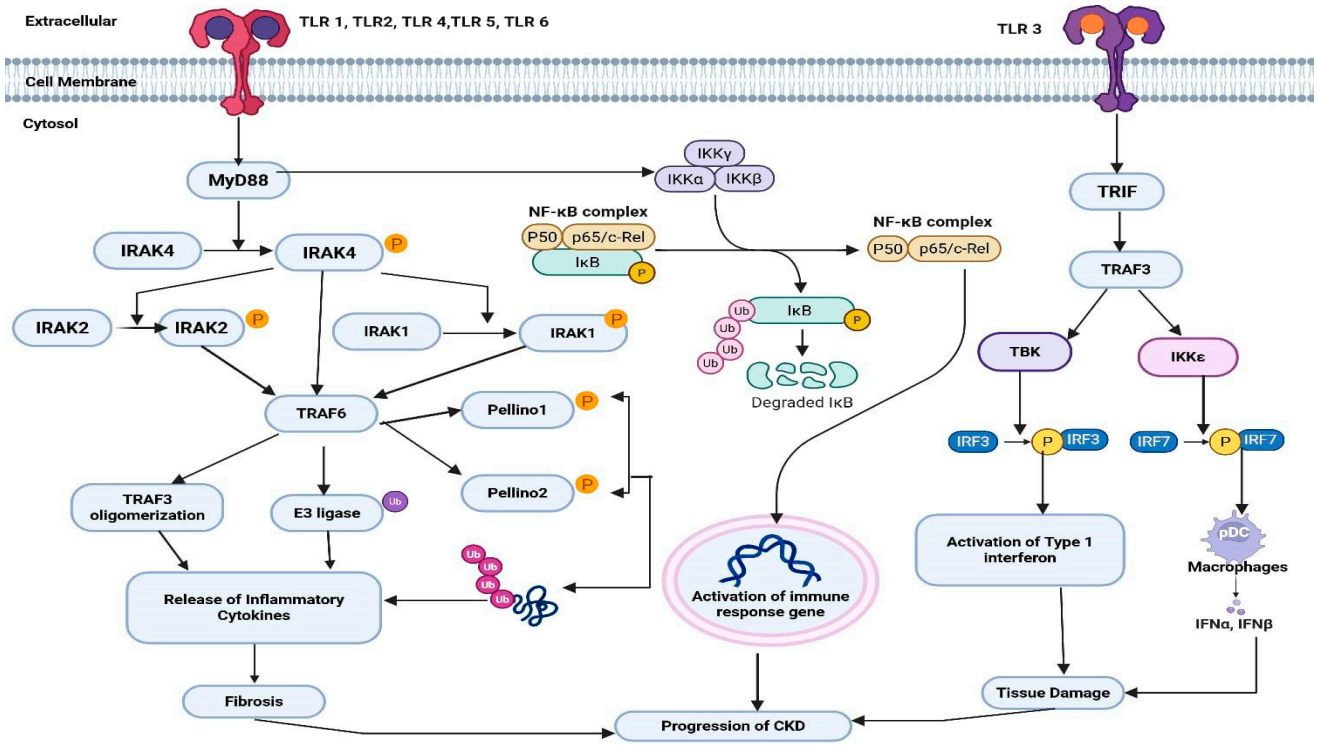


Figure 2. Diagrammatic representation of intracellular TLR signaling pathways involved in the progression of CKD. Vitamin-mediated modulation of Toll-like receptor (TLR) signaling in chronic kidney disease (CKD). TLR2, TLR3, and TLR4 activate MyD88-dependent and TRIF-dependent pathways, inducing NF-κB-mediated cytokine production (TNF-α and IL-6) and interferon regulatory factor (IRF)-mediated type I interferon responses. Persistent activation promotes renal inflammation, oxidative stress, fibrosis, and kidney failure. Vitamins A, D, E, K, B-complex, and C may modulate these pathways and exert renoprotective effects. The proposed inhibitory interactions require further mechanistic and clinical validation. TLR: toll-like receptor; MyD88: myeloid differentiation primary response 88; IRAK: interleukin-1 receptor-associated kinase; TRAF: tumor necrosis factor receptor-associated factor; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; IKK: IκB kinase; IκB: inhibitor of κB; Rel: Rel homology domain protein (part of NF-κB family); Pellino 1/2: Pellino E3 ubiquitin-protein ligase 1/2; E3 ligase: ubiquitin-protein ligase E3; TRIF: TIR-domain-containing adapter-inducing interferon-β; TBK: TANK-binding kinase; TRAF3: TNF receptor-associated factor 3; TRAFs: TNF receptor-associated factors; IRF3/7: interferon regulatory factor 3/7; IFN: interferon; NF-κB complex: nuclear factor kappa B complex; P: phosphate; Ub: ubiquitin; TRADD: tumor necrosis factor receptor type 1-associated DEATH domain protein; TAK1: transforming growth factor-β-activated kinase 1; CKD: chronic kidney disease.

Because TLR signaling centrally mediates CKD progression, targeting TLRs offers a compelling strategy for renal disease management, with interventions ranging from direct receptor antagonism to downstream and multi-target modulation showing renoprotective efficacy in preclinical and clinical studies. The therapies that target TLRs are summarized in Table 2. Direct TLR antagonists such as resatorvid (TAK-242), a selective TLR4 inhibitor, have shown substantial renoprotection in septic and ischemia–reperfusion kidney injury models by suppressing TLR4–MyD88–NF-κB signaling, improving renal function and mitigating tubular and endothelial damage; these effects are supported by in vitro studies in NRK-52E rat tubular epithelial cells and human proximal tubular epithelial (HK-2) cells, where TAK-242 at 0.5–5 μM under LPS, hypoxic or high-glucose conditions inhibited MyD88-

and TRIF-dependent NF-κB and IRF3 activation, cytokine release, ROS generation, apoptosis and fibrotic gene transcription [38,39]. Similarly, tomaralimab (OPN-305), a humanized IgG4 monoclonal antibody targeting TLR2, has advanced to clinical trials for the prevention of delayed graft function after transplantation and has demonstrated anti-inflammatory efficacy in HK-2 cells and tubular–macrophage co-culture systems at 1–10 μg/mL by suppressing TLR2–MyD88–NF-κB signaling and inflammatory crosstalk [40].

Table 2. Current treatments targeting TLR subtypes directly.

Category	Agent	Molecular Target	Dosage/ Concentration	Key Effects and Findings	References
Direct TLR4 antagonism	Resatorvid (TAK-242)	TLR4 (selective)	0.5–5 μM (in vitro)	Inhibits MyD88/TRIF pathways, NF-κB, and IRF3; reduces ROS, apoptosis, and fibrotic transcription in HK-2 and NRK-52E cells.	[38,41]
Direct TLR4 antagonism	Eritoran	TLR4–MD2 complex	5 mg/kg	Renal ischemia–reperfusion injury in rats.	[42]
Direct TLR2 antagonism	Tomaralimab (OPN-301)	TLR2 (IgG4 mAb)	0.5–10 mg/kg	Suppresses TLR2–MyD88–NF-κB signaling; demonstrates anti-inflammatory efficacy in tubular–macrophage co-culture systems.	[40]
Natural compounds	Berberine, curcumin, montelukast	TLR4/NF-κB/ upstream triggers	20, 100, 200 mg/kg	Concurrent suppression of TLR4 signaling and oxidative stress.	[43]

Natural compounds such as berberine, curcumin, and montelukast further exert renoprotective effects by concurrently suppressing TLR4 and NF-κB signaling and modulating upstream triggers, including endotoxemia and oxidative stress, while mitochondria-targeted antioxidants like mitoquinol mesylate (MitoQ) restore mitophagy and antioxidant defense. Given the dualistic roles of TLRs, particularly TLR4 and TLR9, in injury versus repair, timing-dependent modulation remains critical to avoid impairing beneficial immune or regenerative responses. The future of TLR-targeted therapy lies in multi-target combination strategies that integrate TLR antagonists with standard-of-care agents such as ACE inhibitors, SGLT2 inhibitors, and endothelin receptor blockers to achieve synergistic renoprotection [44]. Advancing toward precision nephrology, future research must emphasize pharmacogenomic profiling, biomarker-guided patient stratification, and cell-type-specific modulation of adaptor proteins (MyD88, TRIF) or kinases (TAK1, IKKβ, TBK1) to overcome pathway redundancy and minimize the risk of immunosuppression, ultimately translating mechanistic insights into clinically effective renal therapeutics.

4. Emerging Roles of Fat-Soluble Vitamins as Therapies Targeting TLR Signaling in CKD Pathogenesis

Fat-soluble vitamins such as vitamins A, D, E, and K are needed in small amounts for healthy metabolism, immune response, and proper growth [45]. Kidney disease, such as CKD, significantly alters fat-soluble vitamin metabolism and balance because of impaired kidney function, dietary restrictions, and systemic inflammation [46].

Vitamin A and its active metabolite, all-trans retinoic acid (ATRA), regulate epithelial differentiation and immune homeostasis and exert renoprotective effects in diabetic nephropathy (DN) and CKD. Through RAR/RXR activation, ATRA suppresses innate immune signaling by downregulating TLR4/2 expression, disrupting TLR4–MD-2 complex formation, and inhibiting the MyD88–IRAK–TRAF6–TAK1–NF-κB/MAPK cascades, thereby limiting NLRP3 inflammasome activation [47]. These actions reduce oxidative

stress, cytokine production, DAMP release, and TGF-β/Smad-driven fibrosis, thereby improving renal structure and reducing proteinuria in experimental models of DN and AKI. Although higher retinol status is associated with better renal outcomes, safety concerns and the scarcity of large-scale trials limit its clinical relevance [48].

Vitamin D deficiency in CKD results from impaired renal 1α-hydroxylation, uremic toxin-induced CYP24A1 upregulation, reduced cutaneous synthesis, proteinuria, and progressive inflammation–eGFR decline. Active vitamin D (calcitriol), via VDR–RXR signaling, transcriptionally represses TLR2/4 and inhibits MyD88/TRIF–IRAK–TRAF6–TAK1–NF-κB/MAPK pathways, thereby reducing pro-inflammatory cytokine expression in renal and immune cells [17]. In DN and AKI models, VDR agonists suppress TLR4–NLRP3 inflammasome activation, enhance mitochondrial and antioxidant defenses, and attenuate TGF-β-driven fibrosis, and clinical studies show reduced inflammation and proteinuria, although large biomarker-guided RCTs are still required [49].

Vitamin E, comprising α-tocopherol and tocotrienols, is a lipid-soluble antioxidant that preserves membrane integrity and endothelial–mitochondrial function. In CKD and diabetic nephropathy (DN), altered vitamin E status reflects persistent oxidative stress and inflammation, and higher dietary or circulating levels are associated with reduced CKD prevalence and slower disease progression [50]. Vitamin E attenuates renal inflammation by scavenging ROS, disrupting lipid-raft-dependent TLR4–MD-2 complex formation, and inhibiting downstream kinases that drive NF-κB activation. Tocotrienols further activate Nrf2 signaling, enhancing antioxidant enzyme expression and suppressing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), p38 MAPK activation, and mitochondrial dysfunction, thereby limiting renal inflammation and fibrosis [51].

Vitamin K is essential for γ-carboxylation of vitamin K-dependent proteins, including matrix Gla protein (MGP), thereby maintaining renal and vascular integrity by limiting inflammation and calcification. Vitamin K deficiency is common in CKD because of dietary restriction, impaired absorption, uremia, and metabolic alterations, leading to undercarboxylated VKDPs, vascular stiffness, glomerulosclerosis, and accelerated disease progression [52]. Both phylloquinone (K1) and menaquinones (K2; MK-4/MK-7) exert anti-inflammatory and antioxidant effects by suppressing TLR4–MyD88–NF-κB and NLRP3 inflammasome signaling, reducing pro-inflammatory cytokines and fibrotic responses in preclinical CKD models [53]. Clinically, low vitamin K status correlates with elevated inflammatory biomarkers, while K_2 supplementation improves MGP carboxylation, endothelial function, and vascular stiffness in hemodialysis patients. However, direct clinical evidence targeting TLRs remains limited.

Growing evidence links TLR signaling in kidney disease to changes in the gut microbiota and to gut-derived metabolites. As kidney function declines, uremia increases, dietary patterns change, and fiber fermentation in the colon decreases. This shifts the gut community from bacteria that make short-chain fatty acids to bacteria that produce potentially toxic compounds. These toxins, including indoxyl sulfate, p-cresyl sulfate, and trimethylamine N-oxide, build up in the blood and are strongly linked to inflammation and kidney damage. When the good bacteria that make short-chain fatty acids disappear, this also affects the gut lining and how the body handles inflammation [54]. A weaker lining makes it easier for gut contents, like lipopolysaccharide, to enter the bloodstream. Lipopolysaccharide is a known trigger for TLR4. When TLR4 and TLR2 are activated in kidney and blood vessel cells, they trigger a chain reaction that increases inflammation, stress, and scarring in kidney tissue. This impairs normal kidney function and gut health, creating a cycle between the gut, the kidneys and TLRs. In this situation, vitamins might help before the receptors are activated. They can also directly affect the TLR pathways. They may support the gut lining and immune system, reducing TLR triggers. They may also change the bacteria and what

they produce, which affects toxin and short-chain fatty acid levels. They may also reduce TLR2/TLR4 activity and NF-κB activation, which increases stress signals. However, most evidence on how vitamins affect the gut, metabolites, and TLRs in kidney disease comes from animal studies. It remains unclear to what extent vitamins modulate TLR signaling directly or indirectly through alterations in gut microbiota, intestinal barrier integrity, and microbiota-derived metabolites. This critical research gap warrants further mechanistic investigation and experimental validation.

Low-grade chronic inflammation and the gut–kidney axis are key contributors to persistent TLR4 stimulation in CKD. Uremia alters intestinal microbiota composition and impairs epithelial barrier integrity, leading to translocation of microbial components such as LPS into the bloodstream and the induction of systemic inflammation. Because LPS is the canonical ligand for TLR4 and TLR4 is expressed in tubular epithelial cells, podocytes, glomerular endothelial cells, and mesangial cells, LPS acts as a persistent extrinsic stimulus. Meanwhile, DAMPs released from damaged renal cells activate the same receptors and enhance the innate immune response [55]. Thus, exogenous (PAMP) and endogenous (DAMP) stimuli can form a vicious cycle in which TLR-mediated inflammation and tissue damage increase DAMP release and, due to impaired barrier function, sustain LPS translocation, driving disease progression.

5. Emerging Roles of Water-Soluble Vitamin Therapies Targeting TLR Signaling in CKD Pathogenesis

Vitamin B1 (thiamine) plays a critical role in renoprotection, primarily by serving as a cofactor for thiamine pyrophosphate-dependent enzymes, especially transketolase, a major regulator of the pentose phosphate pathway. Diabetes is characterized by increased urinary thiamine excretion, which reduces transketolase activity, thereby shunting excessive glucose flux into toxic pathways, including protein kinase C, advanced glycation end products, and the hexosamine pathway, all of which contribute to increased ROS generation, oxidative stress, inflammation, and subsequent renal fibrosis [56]. Supplementing thiamine or its lipophilic analog, benfotiamine, restores transketolase activity, shunts glycolytic flux into the pentose phosphate pathway, reduces AGEs, and inhibits PKC pathway activity [57].

Vitamin B_2 maintains kidney integrity through its critical roles in mitochondrial energy metabolism, redox reactions, and transcriptional regulation. As the biosynthetic precursor of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), riboflavin is required by flavoprotein enzymes in the electron transport chain, fatty acid beta-oxidation, and glutathione reductase [58]. These pathways are greatly diminished in diabetic nephropathy. Riboflavin deficiency damages kidney mitochondria by further increasing reactive oxygen species generation and worsening oxidative damage in diabetic kidneys. In contrast, adequate riboflavin maintains antioxidant enzyme activity. Moreover, this vitamin deficiency reduces the activity of PPAR-alpha-controlled target genes in diabetic kidneys. This condition reduces lipid levels in diabetic kidneys by diminishing fatty acid beta-oxidation. This condition also increases damage severity due to lipotoxins in diabetic kidneys [59].

Vitamin B_3 provides renoprotection through NAD+ and NADP+ redox cycling and metabolism, which are crucial for redox homeostasis and cellular metabolism and are highly impaired in diabetic nephropathy. Niacin benefits patients with diabetes and hyperlipidemia by preventing adipocyte lipolysis, decreasing triglyceride, LDL-C, and VLDL levels, and increasing HDL-C levels [60]. Niacin exerts anti-inflammatory and antioxidant effects by preventing NADPH oxidase-mediated ROS production and NF-κB-mediated cytokine production, including TNF-α and MCP-1. An important CKD-specific action of niacin is

counteracting hyperphosphatemia by preventing NADPH oxidase-mediated expression of sodium-phosphate cotransporters (NaPi-2a and b), thereby preventing arterial calcification.

Vitamin B_5 is essential to renal cell metabolism due to its role in coenzyme A. Experimental studies have demonstrated that pantothenic acid deficiency in animal models exacerbates oxidative stress in the kidneys, whereas supplementation with dexpanthenol at doses of 50 to 200 mg/kg/day in STZ-induced or toxin models of CKD improves mitochondrial efficiency, increases lipid metabolism, and enhances kidney tissue. These outcomes are associated with increased glutathione redox indices and inhibition of NF-κB-mediated inflammation. Vanin-1 (VNN1) signaling pathways are also associated with enhanced renal protection and coenzyme A recycling. Although human clinical trials for CKD are limited, commercial vitamin supplements can prevent pantothenic acid deficiency [61].

Vitamin B_6, especially its active form, pyridoxal-5′-phosphate (PLP), has known renoprotective properties through antiglycative, antioxidant and anti-inflammatory mechanisms. PLP readily reacts with reactive carbonyl species to suppress AGE formation, thereby reducing downstream RAGE-mediated inflammation and fibrosis [56]. In STZ-induced diabetic nephropathy, PLP treatment at 10–50 mg/kg/day reduces albuminuria, prevents glomerular disorganization, and suppresses profibrotic mediators such as TGF-β1 and RAGE. Vitamin B6 also acts by activating the Nrf2-HO-1 signaling cascade, reducing ROS production, and suppressing NF-κB-mediated inflammation to prevent oxidative damage to DNA and lipids.

Vitamin B_7 contributes to kidney protection in CKD by regulating metabolism, inflammation, and epigenetics. Biotin acts as a cofactor for biotin-requiring enzymes, including biotinidase, which is involved in glucose, lipid, and amino acid metabolism. These processes are often deranged in diabetes [62]. Biotin also modulates glucose metabolism by upregulating glucokinase expression via the sGC-cGMP-PKG pathway, thereby protecting the kidneys from hyperglycemia-induced stress [60]. It also inhibits hepatic gluconeogenesis and modulates lipid metabolism via acetyl-CoA carboxylase, helping protect the kidneys from lipid-induced injury.

Vitamin B_9, also known as folate, plays an essential role in kidney protection. Its role in one-carbon metabolism, homocysteine regulation, DNA synthesis, and methylation supports this. It activates 5-methyltetrahydrofolate and enhances eNOS, increasing nitric oxide levels while inhibiting glomerular hyperfiltration in diabetic kidney disease. It also activates glutathione synthesis, thereby inhibiting NF-κB inflammatory pathways and M1 macrophage activation [63]. It also reduces homocysteine levels, thereby reducing oxidative stress, vascular injury, and hypertension. In STZ-diabetic rats and in 5/6 nephrectomized models, folic acid reduces kidney fibrosis. Folate deficiency increases the risk of kidney disease, whereas folic acid reduces inflammatory markers and improves survival in dialysis patients [64].

Vitamin B_{12} has nephroprotective effects by modulating homocysteine metabolism and maintaining mitochondrial energy pathways. As a cofactor for methionine synthase, B12 modulates homocysteine remodeling, reducing oxidative damage, endothelial damage, and inflammation. As an active component in methylmalonyl-CoA mutase, it also modulates mitochondrial sensitivity and glucose-mediated apoptosis. In STZ models of CKD, experimental studies show that methylcobalamin at 0.5–1 mg/kg/day suppresses NF-κB pathways, reduces glomerulosclerosis, and maintains structural integrity [65]. In human studies, B_{12} deficiency occurs in chronic nephropathy because impaired B12 reuptake reduces its availability. Supplementation with B_{12}, folate, and B_6 reduces circulating homocysteine levels and may help manage diabetic neuropathy with few adverse effects, although its role in CKD progression remains uncertain [59].

Vitamin C is a highly potent water-soluble antioxidant with increasing importance in CKD and diabetic nephropathy. It exerts cytoprotective effects on kidney cells by ac-

tivating Nrf2 pathways, which downstream stimulate antioxidant proteins such as HO-1, NQO1, catalase, superoxide dismutase, and glutathione-dependent pathways. Vitamin C also inhibits NF-κB-mediated inflammation, decreases pro-inflammatory cytokine expression, and mitigates interstitial fibrosis. As an epigenetic modifier, it acts as a co-factor for TET proteins and histone demethylases, thereby upregulating transcription of repair-related genes.

6. Preclinical Studies with Vitamins

Preclinical studies show that both water- and fat-soluble vitamins significantly protect kidneys in kidney injury models, primarily by modulating TLR signaling, reducing oxidative stress, and inhibiting inflammation and fibrosis [66]. As summarized in Table 3, vitamin D and its receptor (VDR) agonists consistently attenuate lipopolysaccharide (LPS)-induced AKI, ischemia–reperfusion injury (IRI), and diabetic nephropathy (DN) in rodent models by suppressing TLR4/NF-κB activation, reducing cytokine production (TNF-α, IL-6), and inhibiting tubular apoptosis and interstitial fibrosis while preserving podocyte integrity and VDR expression [67]. Vitamin C, often combined with vitamin E, alleviates hyperoxaluria-induced nephropathy and CaOx crystal deposition in rats by lowering urinary oxalate, restoring antioxidant status, and improving glomerular/tubular function, with synergistic effects enhancing proximal tubular protection against oxidative damage [68]. Vitamin B12 emerges as a potent modulator in IRI, D-galactose-induced aging nephropathy, and high-fat models, reducing superoxide production, TLR4/NF-κB signaling, fibrosis (↓TGF-β, α-SMA), and glomerular damage while preserving renal structures, as evidenced by Masson's trichrome staining and improved creatinine clearance [69]. Collectively, these findings position vitamins as multi-target agents that intersect TLR pathways to mitigate sterile and septic renal inflammation, though optimal dosing, combinations, and translation to human CKD phenotypes require further validation.

Beyond vitamins C, D, E and B12, other vitamins and their derivatives exhibit renoprotective effects in experimental models of kidney injury, although their involvement in Toll-like receptor (TLR) signaling varies. All-trans retinoic acid (ATRA), a vitamin A derivative, attenuated TLR4/NF-κB signaling and inhibited NF-κB nuclear translocation in the glomeruli and proximal tubules of streptozotocin-induced diabetic rats [70]. In cisplatin-induced nephrotoxicity, retinoic acid improved renal function and reduced tubular injury, lipid peroxidation, inflammation and apoptosis, with evidence implicating autophagy-dependent mechanisms [71]. Similarly, α-tocopherol (vitamin E), administered alone or with baicalein, reduced TLR2, TLR4, NF-κB, TNF-α, and IL-6 levels while enhancing Nrf2-associated antioxidant responses in cisplatin-treated rats. Its protective effects in diclofenac-induced renal injury were also associated with reduced NF-κB activation, TNF-α and malondialdehyde, potentially through reactive oxygen species scavenging and modulation of the Nrf2/NQO1 pathway [72].

Vitamin D has demonstrated antifibrotic effects in experimental kidney disease. In unilateral ureteral obstruction (UUO) models, vitamin D supplementation attenuated renal fibrosis, tubular injury and myofibroblast accumulation, with TLR4 among the assessed molecular markers. Paricalcitol, an active vitamin D analog, also modulated non-canonical signaling pathways in UUO and folic acid-induced kidney injury, suggesting that some renoprotective effects may extend beyond conventional vitamin D receptor-dependent mechanisms. In contrast, vitamin K research has focused primarily on CKD-associated vascular calcification, and preclinical benefits from menaquinone-7 have not been consistently replicated in clinical trials. Among B-vitamin derivatives, pyridoxamine (a vitamin B6 analog) reduced serum creatinine, urinary albumin, advanced glycation end products (AGEs), RAGE expression, and NF-κB/Rho–ROCK signaling in diet-induced metabolic

injury. Nicotinamide riboside, an NAD^+ precursor, improved mitochondrial function and reduced albuminuria and renal pathology in db/db mice, with its anti-inflammatory effects linked to cGAS–STING rather than TLR signaling [73].

Collectively, these findings indicate that vitamins and their derivatives converge on shared inflammatory, oxidative and profibrotic pathways, including NF-κB, Nrf2, TGF-β and AGE–RAGE signaling. However, direct evidence of TLR modulation remains limited and largely comes from vitamin A-, D-, and E-related interventions in experimental diabetic or acute toxic kidney injury models, rather than in established chronic kidney disease (CKD). Differences in dose, route of administration, treatment timing, and species further limit cross-study comparisons and clinical extrapolation. Moreover, excessive or prolonged supplementation may cause toxicity, particularly with fat-soluble vitamins A and D, highlighting the importance of dose optimization and safety evaluation. Future studies should investigate whether vitamin-mediated modulation of renal TLR signaling arises from direct kidney effects or indirectly through alterations in gut barrier integrity, microbiota composition and circulating endotoxin or uremic toxin levels.

Table 3. Therapeutic effects of vitamins observed in preclinical studies of kidney disease.

Vitamin	Active Forms and Common Names	Dietary Sources	Mechanism of Action (Evidence and Proposed Action)	Therapeutic Effects	References
FAT-SOLUBLE VITAMINS					
Vitamin A	Retinol, all-trans retinoic acid (ATRA)	Liver, carrots, egg yolk, dairy products	Modulates the TLR4–NF-κB–NLRP3 axis and affects MyD88 signaling	Reduces fibrosis, inflammation, and ROS capture; improves tubular integrity	[70,74]
Vitamin K	Phylloquinone (K_1), menaquinones (K_2: MK-4, MK-7)	Leafy greens, fermented foods, liver	Decreases TLR-NF-κB downstream signaling, reducing inflammation	Affects TLR signaling and holds potential in kidney disease	[75]
Vitamin D	Ergocalciferol (D_2), cholecalciferol (D_3), 25$(OH)_2D_3$ (calcitriol)	Sunlight, oily fish, eggs, dairy	Suppresses MyD88/TRIF-dependent NF-κB and NLRP3 inflammasome activation	Calcium homeostasis, bone health, RAAS modulation, antifibrosis	[76]
Vitamin E	α-Tocopherol, tocotrienols	Nuts, seeds, vegetable oils	Inhibits ROS-mediated TLR4 activation; enhances Nrf2 antioxidant signaling	Reduced oxidative stress, cytokine expression, and lipid peroxidation; improved renal histology	[70]
WATER-SOLUBLE VITAMINS					
Vitamin B1	Thiamine	STZ-diabetic rats	Suppresses TLR4/NF-κB activation and reduces inflammatory cytokine and fibrotic signaling in kidney cells	Acts as a cofactor for transketolase; reduces AGE, PKC signaling, oxidative stress, inflammation; prevents fibrosis	[77]

Table 3. *Cont.*

Vitamin	Active Forms and Common Names	Dietary Sources	Mechanism of Action (Evidence and Proposed Action)	Therapeutic Effects	References
Vitamin B2	Riboflavin	Mouse glomerulonephritis	Reduces TLR-mediated inflammation by improving mitochondrial electron transport and antioxidant enzyme function	Enhances mitochondrial and antioxidant enzymes, regulates PPAR, inhibits AGEs and NF-κB signaling	[59]
Vitamin B3	Niacin (nicotinic acid)	Diabetic nephropathy rodent models	Modulates the TLR-MyD88 signaling cascade, further inhibiting the NF-κB inflammatory output	Acts as an NAD/NADP precursor, improves lipid metabolism, suppresses NADPH oxidase/NF-κB, reduces phosphate absorption	[78]
Vitamin B5	Pantothenic acid	STZ-induced diabetic mice	Indirectly reduces TLR-driven inflammation through metabolic stabilization	Acts as a precursor of CoA, improves mitochondrial function, modulates NF-κB, and antioxidant defenses	[61]
Vitamin C	Ascorbic acid (citrus fruits)	Rats (nephrotoxicity/ AKI models)	Reduces NF-κB activation and cytokine production and can blunt downstream inflammasome activation, thereby potentially modulating TLR-mediated effects	Activates Nrf2 antioxidant pathway, inhibits NF-κB, modulates epigenetic enzymes, reduces oxidative stress and fibrosis	[79]

7. Clinical Studies

Clinical studies on water- and fat-soluble vitamins in chronic kidney disease (CKD) report variable effects on renal function, albuminuria, inflammation, oxidative stress, and cardiovascular risk. These findings suggest that vitamin supplementation may provide supportive therapeutic benefits in selected patient populations, particularly those with documented deficiencies; however, its efficacy as a disease-modifying intervention remains incompletely established. Vitamin D has received considerable attention because of its immunomodulatory properties mediated through the vitamin D receptor (VDR). Clinical studies evaluating cholecalciferol, ergocalciferol, calcitriol, and paricalcitol have shown improved vitamin D status and, in some studies, reduced proteinuria in patients with CKD and diabetic nephropathy (DN). These effects may reflect modulation of inflammatory signaling, including suppression of NF-κB-associated responses and altered expression of pro-inflammatory mediators such as interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) [80]. Vitamin C trials show inverse correlations between serum levels and CKD risk, albuminuria, and eGFR decline, and supplementation reduces urinary albumin, oxidative stress, and proteinuria in type 2 diabetes and hemodialysis cohorts, though high doses are associated with oxalate nephropathy. Experimental evidence further suggests that VDR activation may attenuate TLR4-associated inflammatory signaling, providing a plausible mechanistic link between vitamin D activity and renal protection. Nevertheless, it remains unclear how much these mechanisms contribute to clinical improvement, as changes in inflammatory biomarkers do not necessarily translate into sustained preservation

of estimated glomerular filtration rate (eGFR) or prevention of kidney failure. Table 4 summarizes clinical trials and highlights benefits in deficient populations for proteinuria, inflammation, endothelial function, and kidney disease.

Researchers have also investigated vitamin C, a water-soluble antioxidant, in patients with diabetes, CKD, and end-stage kidney disease receiving hemodialysis. Clinical observations have linked lower circulating vitamin C concentrations to adverse renal outcomes and increased oxidative stress. Supplementation studies have reported improvements in selected oxidative stress markers and, in some cohorts, reductions in albuminuria or proteinuria [81]. These findings are biologically relevant because oxidative stress can amplify innate immune responses and interact with TLR-mediated pathways, thereby promoting inflammatory injury in renal tubular and glomerular cells. However, the clinical evidence remains heterogeneous, and the available findings do not establish that vitamin C supplementation consistently slows CKD progression. Furthermore, patients with advanced CKD require particular caution because impaired renal clearance and excessive vitamin C intake may increase oxalate accumulation, potentially contributing to calcium oxalate deposition and oxalate nephropathy [82]. Therefore, supplementation strategies should consider baseline vitamin C status, renal function, dietary intake, and the risks of high doses. Vitamin E, a lipid-soluble antioxidant, has been evaluated for its capacity to reduce lipid peroxidation and oxidative injury in patients with diabetes and kidney disease [83]. Some clinical studies, including those investigating vitamin E alone or in combination with vitamin C, have reported improvements in oxidative stress biomarkers and selected measures of renal function [84]. These findings may relate to TLR signaling because oxidative stress and inflammatory pathways can reinforce one another, contributing to endothelial dysfunction, glomerular injury, and tubulointerstitial inflammation in the kidney. Nevertheless, evidence for a consistent reduction in albuminuria or preservation of eGFR remains limited, and improvements in surrogate biomarkers should not be interpreted as definitive evidence of renoprotection. The effects of vitamin E may also depend on the formulation, dose, treatment duration, and clinical characteristics of the study population.

Researchers have primarily investigated water-soluble B vitamins, particularly folate, vitamin B6, and vitamin B12, in CKD because they are involved in homocysteine metabolism [85]. Hyperhomocysteinemia is frequently observed in CKD and has been associated with endothelial dysfunction, oxidative stress, and increased cardiovascular risk [86]. Although B-vitamin supplementation can reduce circulating homocysteine concentrations in some patients, clinical trials have not consistently demonstrated corresponding improvements in renal outcomes or cardiovascular events. These findings highlight the distinction between biochemical efficacy and clinically meaningful disease modification. In the context of TLR signaling, reductions in oxidative stress and endothelial injury could theoretically influence inflammatory activation; however, direct clinical evidence that B-vitamin supplementation improves CKD outcomes by modulating specific TLR pathways remains insufficient [87].

Clinical evidence on vitamin supplementation in CKD remains inconsistent because patient characteristics, vitamin dosage, treatment duration, and outcome measures vary. Although improvements in albuminuria and inflammatory biomarkers have been reported, their translation into sustained renal protection remains uncertain. From a TLR-centered perspective, vitamin D may modulate inflammatory signaling through VDR-associated pathways, while vitamins C and E may influence oxidative stress, and B vitamins may improve homocysteine metabolism [88]. However, direct clinical evidence linking vitamin supplementation to TLR pathway modulation remains limited. Future well-designed clinical trials integrating TLR-related biomarkers and long-term renal outcomes are needed to establish therapeutic efficacy and safety.

Table 4. Therapeutic effects of vitamins observed in clinical studies of kidney diseases.

Trial Number	Title of the Study	Dose and Method of Administration	Disease Population	Safety and Efficacy	Key Findings	References
FAT-SOLUBLE VITAMINS NCT01680198	Paricalcitol and endothelial function in chronic kidney disease patients	Oral paricalcitol 2 µg/day for 12 weeks, double-blind vs. placebo, $n = 88$	Adults with stage 3–4 CKD (eGFR 15–59 mL/min/1.73 m^2), secondary hyperparathyroidism, not on dialysis	Oral paricalcitol improved endothelial function and biomarkers of vascular health in adults with stage 3–4 CKD, and it was generally well tolerated, although calcium, phosphate and PTH levels need monitoring.	Oral paricalcitol improved endothelial function and biomarkers of vascular function.	[89]
NCT01476501	Randomized controlled trial of vitamin D3 in diabetic kidney disease	Oral cholecalciferol, 2000 IU daily, for one year	22 adults with type 2 diabetes, albuminuria (micro–macroalbuminuria), preserved eGFR (≥60 mL/min/1.73 m^2), and early diabetic kidney disease	Cholecalciferol at 2000 IU daily effectively raised 25(OH)D levels, with a non-significant trend toward lower albuminuria and improved cardiac and renal structural endpoints.	Cholecalciferol at a dosage of 2000 IU daily or 40,000 IU monthly for about 6 months was found to be safe, reducing the risk of 25(OH)D deficiency as well as showing a trend toward lowering albuminuria and improving cardiac/renal structural endpoints.	[90]
WATER-SOLUBLE VITAMINS NCT01476501	Vitamin D supplementation in diabetic nephropathy	Oral cholecalciferol, 2000 IU daily or 40,000 IU monthly, for 6 months	Adults with type 1 or 2 diabetes plus CKD living in northern Alberta, with suboptimal vitamin D status and elevated albuminuria	Both daily 2000 IU and monthly 40,000 IU cholecalciferol were safe and equally effective at raising 25(OH)D over 6 months, with small improvements in bone markers and quality of life but only a modest, non-significant trend for albuminuria and hard endpoints.	Daily 2000 IU versus monthly 40,000 IU cholecalciferol for 6 months was found to be safe and equally effective in increasing 25(OH)D, with a small improvement in bone markers and health-related quality of life, whereas its impact on albuminuria and hard endpoints was modest and non-significant.	[91]
Prospective cohort	Water-soluble vitamin status in CKD		Adults with CKD (non-dialysis and dialysis) followed for vitamin B12, folate, B6, and vitamin C status and clinical outcomes	This observational study reported no intervention effect, so safety is not applicable, but it showed that deficiencies of vitamins B12, B6, folate and C are common in CKD, with low B6 and high homocysteine linked to new CKD and faster progression.	Cohort data demonstrate a common problem of vitamin B12, B6, folate, and vitamin C deficiencies, a relationship between reduced B6 and elevated homocysteine and new CKD and rapid CKD progression, and a relationship between more prevalent B12 deficiency and CKD duration.	[92]

8. Marketed Formulations for Vitamins Used in CKD Therapy

Vitamin supplementation represents an essential candidate for supportive therapy in CKD. Some marketed vitamin formulations are designed to correct nutrient deficiencies, modulate oxidative and inflammatory stress, and prevent complications associated with dialysis and impaired renal metabolism [60]. In patients with advanced CKD, specific multivitamin formulations such as Rena-Vite and Nephrocaps provide water-soluble B-complex vitamins and vitamin C in various doses to compensate for dialytic loss while avoiding accumulation of fat-soluble counterparts like vitamin A and vitamin E [93]. Clinicians administer active vitamin D analogs, including calcitriol (Rocaltrol) and doxercalciferol (Hectorol), to manage secondary hyperparathyroidism and mineral-bone disorders associated with CKD. Together, as summarized in Table 5, these marketed preparations support exploration of vitamin-mediated mechanistic pathways, such as TLR signaling, to mitigate CKD progression.

Table 5. Summary of marketed formulations of vitamins used for CKD therapy.

Marketed Brand	Marketing Companies	Type of Vitamin	Indications	Key Features
Nephrocaps	Torrent Pharmaceuticals, (Ahmedabad, Gujarat, India)	B-complex + vitamin C renal multivitamin	CKD stages 3–5 and dialysis; nutritional support for deficiency prevention associated with dialysis and anorexia	Over-the-counter renal vitamin alternative
Rena-Vite	CYPRESS Pharmaceuticals. (Madison, MS, USA)	B-complex + vitamin C renal multivitamin	Nutritional deficiency replacement in CKD stages 3–5 and dialysis patients	Generic equivalent to Nephro-Vite; a lower-cost alternative available in tablet or capsule formulations
Zemplar	Abbott laboratories (Abbott Park, IL, USA)	Selective vitamin D receptor activator (SVDRA)	Treatment of secondary hyperparathyroidism (SHPT) in CKD stages 3–5 and dialysis patients	Selective VDRA that targets bone and parathyroid glands preferentially
Rocaltrol	Abbott Laboratories. (Abbott Park, IL, USA)	Active form of vitamin D (1,25-dihydroxyvitamin D3)	Treatment of secondary hyperparathyroidism and hypocalcemia in CKD stages 3–5, dialysis patients and renal osteodystrophy	First-generation active vitamin D analog offering potent PTH suppression but with a higher risk of hypercalcemia and hyperphosphatemia vs. selective VDRAs
Calcijex	Abbott Laboratories (Abbott Park, IL, USA)	Active vitamin D (1,25-dihydroxyvitamin D3)	SHPT and hypocalcemia in CKD patients on dialysis	IV-only formulation optimized for dialysis patients with precise dosing control
Hectorol	Sanofi (Paris, France)	Synthetic vitamin D2 analog	Treatment of SHPT in CKD stages 3–4 (non-dialysis) and CKD patients on dialysis	Available in both oral and intravenous injection forms

Note: We do not endorse any marketing company or vitamin product shown in Table 5.

Patents on vitamin-based formulations highlight studies aimed at optimizing the delivery, stability, and renoprotective potential of both water- and fat-soluble vitamins across renal diseases. Various patents claim modified-release and selective vitamin D analog formulations such as calcitriol, paricalcitol, and cholecalciferol, designed to achieve sustained plasma exposure, improved safety profiles, and enhanced efficacy in CKD-mineral and bone disorder and hyperparathyroidism by modulating downstream TLR and NF-κB signaling.

Moreover, a few patents describe advanced technological systems, such as water-soluble folate compositions, stable multivitamin solutions, and co-formulations aimed at enhancing bioavailability, chemical stability, and synergistic anti-inflammatory actions relevant to kidney injury. Collectively, the patented formulations summarized in Table 6 highlight a growing trend toward using vitamins in CKD and for related immune modulation via TLR signaling.

Table 6. Summary of patents with vitamin and mineral combinations.

Patent ID	Title	Inventor	Vitamin Composition	Indications	References
WATER-SOLUBLE VITAMINS					
US7696219B2	Method and composition for supplementation of nutritional deficiencies in renal patients	Everett Laboratories Inc	B-complex + vitamin C + selenium + zinc	Nutritional support in CKD and dialysis patients and replacement of lost water-soluble vitamins during dialysis treatment	[94]
US20090074883A1	Multivitamin and mineral compositions for individuals having renal disease	Ajay Gupta	B-complex multivitamin + trace elements + antioxidants	CKD stages 1–5 and dialysis treatment; prevention of physiological antioxidant deficiency induced by dialysis and a restricted diet	[95]
CA2691691A1	Compositions and methods of treating chronic kidney disease	Seth J. Baum	Includes vitamin C, D, E and B-complex vitamins, minerals such as zinc and selenium, and amino acids or protein components	Various stages of renal disease and ESRD; supplementation of nutrient deficiencies in renal patients with restricted diets and in dialysis patients	[96]
FAT-SOLUBLE VITAMINS					
US20060030549A1	Paricalcitol (Zemplar) capsule controls secondary hyperparathy-roidism (SHPT) in CKD stage 5 patients	Ping Qiu, Joel Melnick and Laura Williams	Paricalcitol (selective vitamin D receptor activator/VDRA)	Primary prevention and treatment of SHPT in patients with CKD Stages 3 to 5 and those undergoing dialysis	[97]

However, patent claims and formulation advances do not establish clinical efficacy or direct modulation of TLR signaling. Although some vitamins have demonstrated anti-inflammatory and renoprotective effects in experimental studies, their specific effects on TLR-associated pathways require independent experimental validation. Therefore, the patents summarized in Table 6 should be interpreted as evidence of formulation development and potential therapeutic applications rather than proof of TLR-mediated renoprotection and established clinical benefit in CKD.

9. Conclusions and Future Perspectives

Toll-like receptor (TLR) signaling plays a pivotal role in the pathogenesis of kidney diseases, including acute kidney injury, diabetic kidney disease, and chronic kidney disease, by activating inflammatory, oxidative stress, and profibrotic pathways involving NF-κB,

TNF-α, and TGF-β. Emerging preclinical evidence suggests that water- and fat-soluble vitamins may exert renoprotective effects by attenuating inflammatory cytokine production, modulating immune responses, enhancing antioxidant defenses, and preserving renal tubular and endothelial integrity, with some of these effects linked to modulation of TLR signaling. However, the scarcity of well-designed human studies, variability in experimental models, differences in vitamin formulations, doses, and treatment duration, and insufficient evidence establishing direct causal relationships between vitamin supplementation and TLR modulation limit their clinical application. Furthermore, the bioavailability, optimal therapeutic doses, long-term safety, and potential toxicity of high-dose supplementation require careful evaluation, particularly in patients with impaired renal function. Standardized preclinical protocols, dose-finding and pharmacokinetic studies, and adequately powered, randomized, placebo-controlled clinical trials incorporating TLR-related biomarkers, inflammatory mediators, and validated renal outcomes could address these limitations. Future investigations should also distinguish direct effects on renal TLR signaling from indirect mechanisms involving oxidative stress, metabolic regulation, and gut microbiota-derived inflammatory stimuli. Integrating these approaches may help identify specific vitamin interventions, responsive patient subgroups, and clinically relevant dosing strategies, thereby facilitating the translation of promising experimental findings into safe and effective adjunctive therapies for kidney diseases. Vitamin supplementation should complement, rather than replace, established renoprotective treatments until sufficient clinical evidence supports its therapeutic efficacy.

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Abbreviations

ACE	Angiotensin-converting enzyme
AGEs	Advanced glycation end products
AKI	Acute kidney injury
AMPK	AMP-activated protein kinase
ATRA	All-trans retinoic acid
A-UTIs	Ascending urinary tract infections
BMD	Bone mineral density
CaOx	Calcium oxalate
cGAS	Cyclic GMP-AMP synthase
CKD	Chronic kidney disease
CoA	Coenzyme A
CpG	Cytosine-phosphate-guanine
CYP24A1	Cytochrome P450 family 24 subfamily A member 1

DAMPs	Damage-associated molecular patterns
DN	Diabetic nephropathy
dsRNA	Double-stranded ribonucleic acid
eGFR	Estimated glomerular filtration rate
ER	Endoplasmic reticulum
ESRD	End-stage renal disease
FAD	Flavin adenine dinucleotide
FMN	Flavin mononucleotide
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HDL-C	High-density lipoprotein cholesterol
HK-2	Human proximal tubular epithelial cell line
HMGB1	High mobility group box 1
HO-1	Heme oxygenase-1
HSPs	Heat shock proteins
IKK	IκB kinase
IL	Interleukin
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IRAK	Interleukin-1 receptor-associated kinase
IRF	Interferon regulatory factor
IRI	Ischemia–reperfusion injury
JNK	c-Jun N-terminal kinase
LDL-C	Low-density lipoprotein cholesterol
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MD-2	Myeloid differentiation factor 2
MGP	Matrix Gla protein
miR	MicroRNA
mTOR	Mammalian target of rapamycin
MyD88	Myeloid differentiation primary response 88
NaPi	Sodium-phosphate cotransporter
NAD^+	Nicotinamide adenine dinucleotide
$NADP^+$	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NICU	Neonatal intensive care unit
NLRP3	NOD-like receptor pyrin domain-containing protein 3
NQO1	NAD(P)H quinone dehydrogenase 1
Nrf2	Nuclear factor erythroid 2-related factor 2
OPN-305	Tomaralimab (anti-TLR2 monoclonal antibody)
PAMPs	Pathogen-associated molecular patterns
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator-1 alpha
PKC	Protein kinase C
PLP	Pyridoxal-5′-phosphate
PPAR	Peroxisome proliferator-activated receptor
RAAS	Renin–angiotensin–aldosterone system
RAR	Retinoic acid receptor
RAGE	Receptor for advanced glycation end products
RCT	Randomized controlled trial
RLRs	RIG-I-like receptors
ROS	Reactive oxygen species
RXR	Retinoid X receptor
sGC	Soluble guanylate cyclase
SHPT	Secondary hyperparathyroidism
siRNA	Small interfering ribonucleic acid
SGLT2	Sodium-glucose cotransporter 2
Smad	Mothers against decapentaplegic homolog
SREBP-1c	Sterol regulatory element-binding protein-1c
STING	Stimulator of interferon genes
STZ	Streptozotocin

SVDRA	Selective vitamin D receptor activator
TAK1	Transforming growth factor-β-activated kinase 1
TBK1	TANK-binding kinase 1
TET	Ten-eleven translocation enzyme
TGF-β	Transforming growth factor-beta
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha
TPN	Total parenteral nutrition
TRAF	TNF receptor-associated factor
TRAM	TIR-related adaptor molecule
TRIF	TIR-domain-containing adaptor-inducing interferon-β
VDRA	Vitamin D receptor activator
VDR	Vitamin D receptor
VLDL	Very-low-density lipoprotein

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