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Renoprotection Beyond Albuminuria: Palm-Derived Tocotrienols, eGFR–UACR Dissociation, and Residual Kidney Risk in Contemporary Diabetic Kidney Disease—A Critical Review

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ABSTRACT

Diabetic kidney disease (DKD) remains a major cause of chronic kidney disease and kidney failure despite substantial therapeutic advances. Renin–angiotensin system blockade, sodium–glucose cotransporter-2 inhibitors, non-steroidal mineralocorticoid-receptor antagonists, glucagon-like peptide-1 receptor agonists, and improved cardiometabolic management have transformed treatment, yet considerable residual renal risk persists. Palm-derived tocotrienols are biologically attractive adjunctive candidates because their reported activities intersect with oxidative stress, inflammation, mitochondrial dysfunction, endothelial injury, glycation, and fibrotic signalling. Importantly, human tocotrienol studies in DKD have generated an unresolved renal signal: creatinine-derived estimated glomerular filtration rate improved in a Phase IIb trial without a corresponding reduction in urinary albumin-to-creatinine ratio. This critical qualitative literature review evaluates whether such eGFR–albuminuria dissociation could reflect effects on kidney injury not adequately captured by albuminuria, including tubular, interstitial, microvascular, and mitochondrial pathways, while considering alternative explanations involving haemodynamics, creatinine biology, small-sample uncertainty, and endpoint variability. Contemporary evidence on non-albuminuric DKD, tubular biomarkers, eGFR slope, and modern cardiorenal pharmacotherapy is integrated with clinical and mechanistic tocotrienol research. Current evidence does not establish tocotrienols as disease-modifying DKD therapy. It does, however, provide sufficient mechanistic and preliminary clinical justification for rigorously designed adjunctive trials incorporating contemporary background therapy, standardized formulations, eGFR slope, serial albuminuria, cystatin C, tubular and inflammatory biomarkers, and longer-term kidney outcomes.

Keywords: Diabetic kidney disease; Tocotrienols; Palm oil; Albuminuria; Estimated glomerular filtration rate; Oxidative stress; Renal fibrosis; Tubulointerstitial injury; Residual renal risk; Precision nephrology

JEL Classification: I10; I12; I18; Q16; O32

1. INTRODUCTION

1.1 Diabetic Kidney Disease in the Contemporary Therapeutic Era

Diabetic kidney disease is one of the most consequential chronic complications of diabetes because it simultaneously increases the risks of progressive loss of kidney function, kidney failure, cardiovascular disease, heart failure, premature mortality, and substantial healthcare expenditure. The burden is particularly important in countries experiencing rapid increases in type 2 diabetes, including many Asian economies. Global burden estimates indicate that diabetes-related chronic kidney disease has continued to increase, with type 2 diabetes accounting for most of the contemporary burden and substantial regional heterogeneity in incidence, prevalence, mortality, and disability-adjusted life-years.[1,2]

The conventional description of DKD as a linear sequence beginning with hyperfiltration, followed by microalbuminuria, progressive proteinuria, declining glomerular filtration rate (GFR), and ultimately kidney failure is increasingly recognised as incomplete. Contemporary clinical and pathological evidence depicts DKD as a heterogeneous disorder involving interacting glomerular, tubular, interstitial, endothelial, metabolic, inflammatory, and microvascular abnormalities. Kidney function can decline without marked albuminuria, whereas some individuals can sustain albuminuria for prolonged periods without a similarly rapid decline in GFR. These divergent trajectories have important implications for diagnosis, prognostication, therapeutic targeting, and interpretation of clinical trial endpoints.[3–6]

Treatment of DKD has undergone a major transformation. Renin–angiotensin system (RAS) inhibition remains foundational for many patients with hypertension and albuminuria, but sodium–glucose cotransporter-2 (SGLT2) inhibitors have added substantial kidney and cardiovascular protection. The DAPA-CKD trial demonstrated that dapagliflozin reduced the risk of a composite of sustained major eGFR decline, kidney failure, or renal or cardiovascular death in patients with CKD, while EMPA-KIDNEY subsequently expanded the evidence for empagliflozin across a broad CKD population.[7,8]

Non-steroidal mineralocorticoid-receptor antagonism has further changed the therapeutic architecture. FIDELIO-DKD demonstrated that finerenone reduced kidney events among patients with type 2 diabetes and CKD receiving optimized RAS blockade, while FIGARO-DKD established cardiovascular benefit across a somewhat broader CKD spectrum. The prespecified FIDELITY pooled analysis confirmed clinically meaningful reductions in cardiovascular and kidney outcomes across more than 13,000 participants.[9–11] More recently, the FLOW trial demonstrated that semaglutide can reduce clinically important kidney outcomes in patients with type 2 diabetes and CKD, reinforcing

the emerging role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as an additional cardiorenal therapeutic pillar.[12]

Guidelines and contemporary reviews therefore increasingly conceptualize DKD treatment as layered or combination therapy rather than reliance on a single pathway. Current disease-modifying management can include RAS inhibition, SGLT2 inhibition, non-steroidal mineralocorticoid-receptor antagonism, GLP-1 receptor agonism, blood-pressure management, lipid lowering, glycaemic optimization, and lifestyle intervention according to individual clinical characteristics.[13–16]

Nevertheless, treatment success is incomplete. Patients continue to experience progression despite evidence-based multidrug therapy, establishing the contemporary problem of residual renal risk. Residual risk may arise because haemodynamic, metabolic, inflammatory, oxidative, mitochondrial, endothelial, and fibrotic pathways overlap but are not identical. Consequently, the therapeutic question has shifted from identifying a single "magic bullet" to determining whether additional interventions can target biological domains that remain active after modern standard-of-care treatment.[15–18]

1.2 Palm-Derived Tocotrienols as a Residual-Risk Candidate

Tocotrienols constitute members of the vitamin E family that differ structurally from tocopherols by possessing an unsaturated isoprenoid side chain. Palm oil represents one of the major natural sources of α-, β-, γ-, and δ-tocotrienols, usually obtained in tocotrienol-rich fractions containing differing proportions of these isoforms and tocopherols. Tocotrienols have attracted biomedical interest because their effects extend beyond classical radical scavenging and potentially include modulation of inflammatory signalling, lipid metabolism, endothelial function, cell survival, and metabolic regulation.[19–22]

Clinical translation, however, has been inconsistent. randomised studies and meta-analyses suggest that tocotrienol supplementation can influence selected metabolic and inflammatory variables, but responses vary according to formulation, isoform composition, dose, population, disease stage, baseline antioxidant status, duration of treatment, and outcome definition. A meta-analysis of randomised trials found no consistent effects on IL-6, TNF-α, or malondialdehyde across the overall evidence base, even though subgroup findings and individual interventions suggested benefit under specific conditions.[23] In patients with type 2 diabetes, another meta-analysis reported a modest improvement in HbA1c with tocotrienol-rich fraction supplementation but no consistent improvement in blood pressure or high-sensitivity C-reactive protein.[24]

The renal evidence is particularly intriguing. A Phase IIb randomised controlled trial administering 400 mg/day of tocotrienol-rich vitamin E to patients with DKD reported improvement in serum creatinine and creatinine-derived

eGFR, including a persistent signal among participants with stage 3 CKD during treatment. Yet the intervention did not produce a corresponding improvement in urinary albumin-to-creatinine ratio (UACR), and the difference in renal function was no longer apparent following post-treatment washout.[25]

This eGFR–UACR dissociation creates a scientifically more valuable research question than a conventional review asking whether tocotrienols are "good for diabetic nephropathy." It raises the possibility that tocotrienols could influence non-albuminuric dimensions of kidney injury, such as tubular metabolism, interstitial inflammation, endothelial dysfunction, mitochondrial stress, or intrarenal fibrosis. Equally, the finding could represent short-term physiology, non-GFR determinants of creatinine, regression to the mean, subgroup instability, or chance in a relatively small trial. A critical synthesis therefore requires simultaneous consideration of biological plausibility and methodological restraint.

The objective of this qualitative literature review is to evaluate whether palm-derived tocotrienols could plausibly contribute to residual-risk therapy in contemporary DKD, with particular emphasis on the dissociation between kidney filtration markers and albuminuria. The review integrates direct tocotrienol evidence with current understanding of non-albuminuric DKD, tubulointerstitial injury, mitochondrial and inflammatory biology, modern renal endpoints, and guideline-directed cardiorenal therapy. It asks not whether tocotrienols should replace proven therapy, but whether there is sufficient evidence to justify a new generation of add-on mechanistic and clinical trials.

2. LITERATURE REVIEW: CONCEPTUAL AND THEORETICAL FOUNDATIONS

2.1 DKD as a Multicompartment Disease

DKD emerges from prolonged interaction between systemic metabolic abnormalities and intrarenal haemodynamic stress. Hyperglycaemia, insulin resistance, dyslipidaemia, hypertension, activation of the RAS, altered tubuloglomerular feedback, and maladaptive sodium handling can converge on glomerular hypertension and hyperfiltration. Over time, mesangial expansion, basement-membrane changes, endothelial dysfunction, podocyte loss, glomerulosclerosis, tubular hypertrophy, inflammation, capillary rarefaction, nephron dropout, and tubulointerstitial fibrosis contribute to progressive loss of functional renal mass.[2,3,5]

The glomerular filtration barrier comprises fenestrated endothelial cells, the glomerular basement membrane, and podocytes. Diabetes can injure each component and disrupt molecular communication between podocytes and endothelial cells. Endothelial dysfunction can alter nitric-oxide availability, permeability, inflammatory signalling, and microvascular structure, while podocyte injury promotes foot-process effacement, detachment, and albumin leakage.[26] Experimental and human observations of glomerular endothelial fenestrations further demonstrate that changes in endothelial structure can influence filtration function independently of the simple presence or absence of albuminuria.[27]

The tubulointerstitial compartment is equally important. Proximal tubular cells operate under high energetic demand and are exposed to glucose, filtered proteins, lipids, oxidative molecules, inflammatory mediators, and altered sodium transport. Chronic metabolic overload can increase oxygen consumption and mitochondrial stress while promoting hypoxia, inflammatory recruitment, cellular senescence, epithelial dysfunction, and interstitial matrix deposition. Histopathologically, tubulointerstitial fibrosis is closely associated with progressive kidney function loss, making an exclusively glomerulocentric interpretation of DKD inadequate.[28–30]

2.2 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress represents a plausible mechanistic intersection between DKD and tocotrienol biology. Hyperglycaemia can increase mitochondrial reactive oxygen species (ROS), alter NADPH oxidase activity, promote lipid and protein oxidation, interact with advanced glycation pathways, and impair endogenous antioxidant defences. The NRF2–KEAP1–ARE system is particularly relevant because NRF2 regulates multiple cytoprotective and antioxidant genes. Dysregulation of this system can increase susceptibility of renal cells to metabolic and oxidative injury.[31]

Mitochondria are not passive sources of ROS; they are dynamic organelles responsible for energy generation, redox regulation, calcium handling, apoptosis, and metabolic signalling. DKD is associated with abnormalities of mitochondrial biogenesis, fission, fusion, mitophagy, electron transport, and bioenergetic efficiency in podocytes, tubular epithelial cells, endothelial cells, and immune cells.[32–34]

Podocytes provide a particularly important example. Their cytoskeletal organization and filtration-barrier function depend on metabolic homeostasis, while mitochondrial dysfunction can lead to energetic failure, excessive ROS, inflammation, and cell death. Mitochondrial abnormalities in podocytes may therefore connect hyperglycaemia to albuminuria and progressive glomerulosclerosis.[35] However, mitochondrial stress within tubular cells could also contribute to declining filtration in patients whose albuminuria remains relatively modest, reinforcing the possibility of partially independent glomerular and tubulointerstitial trajectories.

Palm-derived tocotrienols are frequently proposed to mitigate oxidative injury because of their membrane-associated antioxidant activity and additional effects on signalling pathways. Yet the human evidence should not be simplified into a claim of uniform antioxidant efficacy. Tocotrienol trials show variability in circulating oxidative and inflammatory biomarkers, suggesting that biological response depends on exposure, formulation and host phenotype.[20,21,23] Thus, oxidative stress offers strong biological plausibility but remains an insufficient standalone explanation for clinical renoprotection.

2.3 AGE–RAGE, Inflammation and Fibrosis

Advanced glycation end products accumulate under chronic hyperglycaemic and oxidative conditions. Interaction between AGEs and the receptor for advanced glycation end products (RAGE) can activate NADPH oxidases, oxidative stress, inflammatory transcription, and vascular dysfunction. The AGE–RAGE system may therefore connect metabolic exposure to inflammatory amplification and progressive renal damage.[36]

Inflammation in DKD extends beyond nonspecific elevation of circulating cytokines. Hyperglycaemia and cellular stress can activate NF-κB-related transcription, chemokine release, monocyte recruitment, and inflammasome signalling. The NLRP3 inflammasome and downstream caspase-1, IL-1β and IL-18 pathways have been implicated in renal inflammation and pyroptotic cell death. Although much of the mechanistic evidence remains experimental, inflammasome activation provides a plausible interface between metabolic stress, immune activation and structural kidney injury.[37] Anti-inflammatory effects attributed to tocotrienols could theoretically intersect with these mechanisms, although direct demonstration in adequately powered DKD trials is lacking.

Fibrosis represents a final common pathway through which repeated metabolic, vascular, inflammatory and cellular injury produces irreversible nephron loss. TGF-β/Smad signalling, fibroblast activation, epithelial and endothelial responses, and excessive extracellular-matrix deposition are central to progressive renal fibrosis. Consequently, a therapy capable of reducing oxidative and inflammatory inputs without meaningfully altering fibrogenesis might produce biomarker changes without durable preservation of kidney structure.[38] The lack of a significant TGF-β1 response in the Phase IIb tocotrienol trial is therefore noteworthy and argues against inferring a proven antifibrotic effect from the eGFR signal alone.[25]

2.4 Albuminuric and Non-Albuminuric DKD

Albuminuria remains one of the most important biomarkers in DKD. It reflects abnormalities in glomerular permeability and tubular handling of filtered albumin and strongly predicts kidney and cardiovascular risk in many populations. However, the discovery and increasing recognition of non-albuminuric DKD have challenged the assumption that substantial albuminuria must precede renal functional deterioration.

A meta-analysis comparing albuminuric and non-albuminuric DKD found systematic differences in demographic features, glycaemic control, blood pressure, retinopathy prevalence and pathological characteristics. Non-albuminuric DKD has been associated with relatively greater vascular and tubulointerstitial changes and milder classical glomerular lesions in some studies, although phenotype definitions and prognostic findings vary.[6] In the Hong Kong Diabetes Biobank, individuals with reduced eGFR without albuminuria had higher risks of heart-failure

hospitalization and CKD progression than individuals without DKD, confirming that normal albumin excretion does not equal absence of clinically important renal disease.[39]

D'Marco et al.[40] similarly emphasized that DKD may involve the glomerulus, tubules and interstitium and that reduced kidney function can occur despite normal albuminuria. This phenotype complicates interpretation of interventions evaluated only through UACR. If a therapy predominantly modifies tubular, microvascular, metabolic or interstitial processes, the magnitude and time course of its UACR effect might differ from its effect on filtration decline.

Importantly, this concept does not mean that an improvement in eGFR without improvement in UACR automatically demonstrates action on non-glomerular pathways. Rather, non-albuminuric DKD establishes the biological possibility that renal decline and albumin excretion need not move synchronously. Additional biomarkers and longer-term filtration trajectories are required to distinguish genuine compartment-specific protection from measurement noise or reversible physiology.

2.5 Biomarkers Beyond Albuminuria

Tubular biomarkers provide an increasingly important conceptual bridge. Biomarkers such as kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), α1-microglobulin, retinol-binding protein, epidermal growth factor (EGF), neutrophil gelatinase-associated lipocalin, soluble tumour-necrosis-factor receptors and uromodulin capture different dimensions of injury, inflammation, repair and tubular function.[29,41] Recent biomarker syntheses further emphasize that UACR and eGFR, although indispensable for diagnosis and monitoring, mainly reflect consequences of kidney damage and can be complemented by urine-derived molecular markers that capture injury, repair, inflammation and fibrosis.[42]

In a cohort of patients with diabetes spanning albuminuric and non-albuminuric phenotypes, Phanish et al.[30] reported that combinations involving MCP-1 and other tubular or inflammatory biomarkers were associated with CKD progression, including among individuals without conventional albuminuria. In another study of adults with diabetes and CKD, higher urinary KIM-1, α1-microglobulin and MCP-1 predicted incident kidney failure independently of baseline eGFR and albuminuria.[43]

Longitudinal biomarker evidence strengthens this argument. In DCCT/EDIC, serial KIM-1 and soluble TNFR1 were associated with subsequent macroalbuminuria and sustained low eGFR, while EGF-to-MCP-1 information also related to later renal function decline.[44] These findings demonstrate why a next-generation tocotrienol trial should not rely exclusively on UACR and serum creatinine. A mechanistic panel capable of distinguishing glomerular

leakage from tubular injury, inflammatory activity, repair and fibrosis would provide a far more informative assessment of biological response.

Precision-nephrology initiatives similarly seek to move beyond syndromic labels toward molecularly defined disease subgroups. The Kidney Precision Medicine Project integrates renal histology with transcriptomic, proteomic and metabolomic information to characterise mechanistic subtypes of kidney disease, including CKD associated with diabetes.[45] Precision-medicine reviews emphasize that variation in DKD progression and drug response provides a strong rationale for biomarker-guided treatment selection, although clinical implementation remains incomplete.[46,47] Spatial metabolomics and integrated multiomics can additionally resolve compartment-specific processes across glomeruli, tubules, blood vessels and interstitial tissue, providing a potential route from phenotype classification to mechanism-guided therapy.[48]

2.6 Tocotrienol Pharmacology and Translational Limitations

The vitamin E family consists of four tocopherol and four tocotrienol isoforms. Tocotrienols differ from tocopherols in the unsaturation of their side chain, influencing membrane behaviour, metabolism, tissue distribution and pharmacokinetics. Palm-derived tocotrienol-rich fractions commonly contain mixtures of α-, γ- and δ-tocotrienols together with variable tocopherol content, meaning that the term “tocotrienol supplementation” does not denote a single pharmacological intervention.[19,20]

Bioavailability is a major translational concern. Oral absorption of tocotrienols is affected by food intake, lipid digestion, formulation and competition with tocopherols. A systematic review of pharmacokinetics reported important differences between annatto-derived and palm-derived preparations and among individual isoforms, highlighting why dose equivalence cannot be inferred simply from labelled milligrams of total tocotrienols.[49]

This variability may help explain apparently discordant clinical findings. Mahjabeen et al.[50] reported improvements in glycaemic, oxidative and inflammatory markers with δ-tocotrienol supplementation in patients with type 2 diabetes, whereas broader meta-analytic evidence suggests considerably less uniform effects.[23,24] A randomised study in prediabetes likewise reported improved glycaemic indices with δ-tocotrienol.[51] These studies support metabolic biological activity but do not establish that the same magnitude or mechanism is present with a palm-derived mixed tocotrienol formulation in established DKD.

Cross-organ diabetic trials provide additional translational context. Tocotrienol-rich vitamin E has been studied in diabetic neuropathy, where improvements in selected nerve-conduction velocities were reported in randomised trials, although biomarker responses were not consistently concordant.[52,53] A trial in non-proliferative diabetic retinopathy reported favourable changes in retinal microhaemorrhage progression and diabetic macular oedema, again without a corresponding difference in circulating VEGF.[54]

These studies are relevant because diabetic neuropathy, retinopathy and nephropathy share oxidative, endothelial and inflammatory features. However, cross-organ consistency must not be confused with renal proof. The appropriate interpretation is that tocotrienols demonstrate sufficient human biological activity to motivate renal investigation, while organ-specific efficacy remains uncertain.

Figure 1: illustrates why DKD cannot be represented by albuminuria alone and why an intervention could theoretically produce different effects on UACR and filtration-related outcomes. It also distinguishes four clinically observable UACR-eGFR combinations, including the non-albuminuric phenotype that is central to interpreting discordant renal signals.

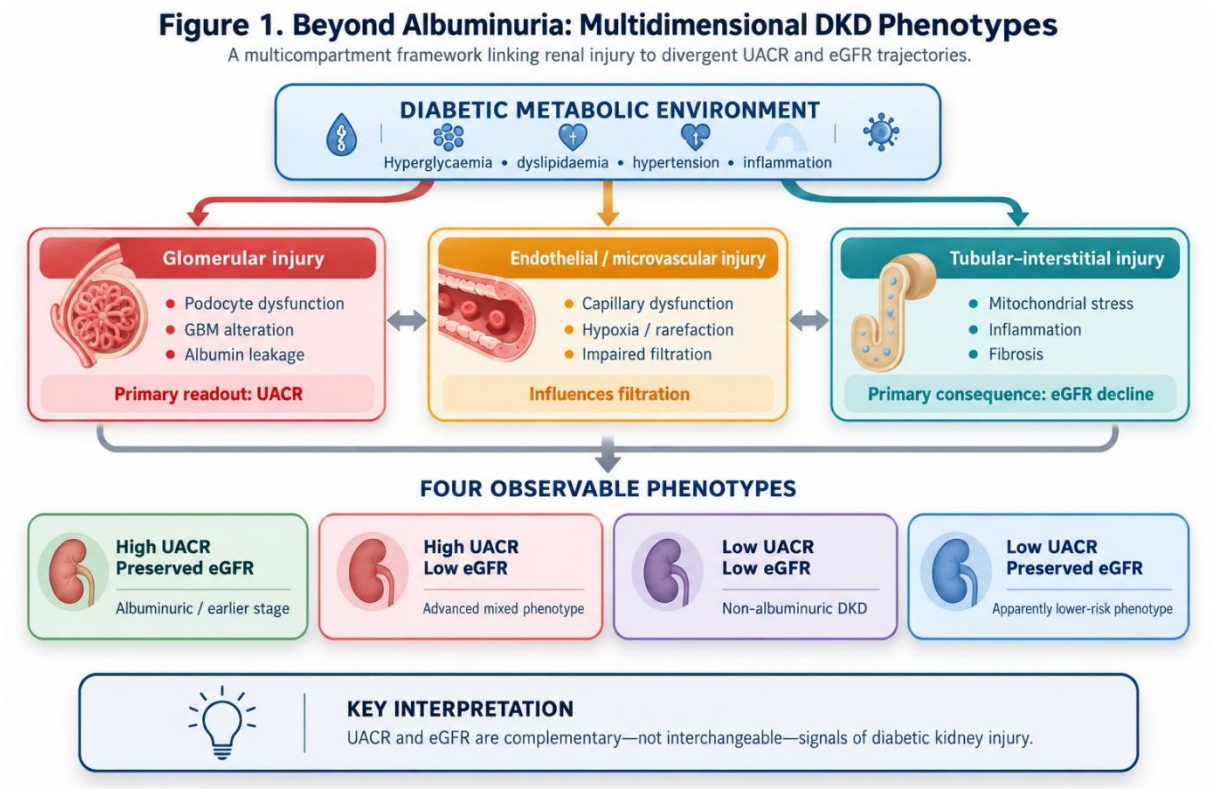

Figure 1 explains that albuminuria primarily provides information about glomerular permeability and albumin handling, whereas eGFR represents overall filtration generated by the remaining nephron population. Tubular, interstitial and vascular abnormalities can contribute to functional decline without a proportional increase in urinary albumin. The increasing recognition of non-albuminuric DKD therefore provides an appropriate conceptual framework for interpreting discordant renal endpoints, although it does not by itself prove that tocotrienols act preferentially on non-glomerular compartments.[6,30,39,40]

3. METHOD

3.1 Review Design

This study employed a critical qualitative literature review (QLR) rather than a systematic literature review or quantitative meta-analysis. The purpose was explanatory and translational: to integrate clinical evidence concerning tocotrienols with contemporary knowledge of DKD pathobiology, phenotypes, biomarkers, renal endpoints and standard-of-care therapy. The approach therefore prioritised conceptual relevance, methodological quality and explanatory power rather than exhaustive enumeration of every publication.

The review was designed around the central clinical observation that tocotrienol-rich vitamin E produced an eGFR/serum-creatinine signal without corresponding UACR improvement in a Phase IIb DKD trial. Literature was subsequently organised to examine competing interpretations of this finding: genuine kidney function preservation, compartment-specific renal activity, systemic or haemodynamic physiology, non-GFR effects on creatinine, and statistical uncertainty.

3.2 Literature Identification and Selection

Contemporary peer-reviewed journal literature published predominantly between January 2020 and September 2026 was considered, and literature identification was updated through 10 September 2026. Evidence was identified from PubMed/MEDLINE, Scopus-oriented journal searches, Web of Science-oriented searches, and citation chaining. Search concepts combined terms relating to tocotrienol, tocotrienol-rich fraction, palm vitamin E, diabetic kidney disease, diabetic nephropathy, albuminuria, UACR, eGFR, tubular injury, mitochondrial dysfunction, oxidative stress, AGE–RAGE, NLRP3, TGF-β, renal fibrosis, SGLT2 inhibitors, finerenone, GLP-1 receptor agonists, renal biomarkers, eGFR slope and residual kidney risk.

Priority was given to randomised controlled trials, large prospective cohorts, major kidney outcome trials, contemporary meta-analyses, mechanistically informative human studies, and high-quality reviews from established journals. Studies were included when they contributed directly to one or more of five evidence domains: direct clinical tocotrienol evidence; DKD pathophysiology; albuminuric versus non-albuminuric phenotypes; renal biomarkers and endpoints; or contemporary therapeutic architecture.

Because this was a qualitative rather than systematic review, no PRISMA flow diagram, formal pooled effect estimate or claim of exhaustive retrieval was used. Instead, evidence was critically compared through thematic synthesis. This approach is consistent with the manuscript's objective of explaining a translational problem rather than calculating a single treatment effect.

3.3 Critical Appraisal Framework

Tocotrienol studies were evaluated according to population, sample size, randomisation, formulation, dose, exposure duration, background diabetes and kidney therapy, outcome ascertainment, treatment adherence, biomarker selection, post-treatment follow-up and statistical interpretation. Particular caution was applied to subgroup findings, short-term creatinine changes and claims based on biomarkers without corresponding clinical outcomes.

Renal evidence was interpreted through an endpoint hierarchy. Changes in serum creatinine and eGFR were considered important but insufficient to establish structural nephroprotection on their own. Serial UACR, chronic and total eGFR slopes, cystatin-C-based filtration estimates, tubular biomarkers, cardiovascular outcomes, sustained major GFR loss and kidney failure were regarded as progressively stronger components of a confirmatory evidence package.

This approach is supported by modern surrogate-endpoint research. Combining treatment effects on UACR and GFR slope can improve prediction of later clinical benefit in Phase II CKD trials, whereas total eGFR slope has demonstrated strong association with effects on kidney failure across diverse randomised studies.[55,56]

4. RESULTS: THEMATIC EVIDENCE SYNTHESIS

4.1 Direct Human Renal Evidence

The most important direct evidence is the Phase IIb randomised, double-blind, placebo-controlled study by Koay et al..[25] Fifty-nine patients with DKD were randomised to tocotrienol-rich vitamin E at 400 mg/day or placebo for 12 months. Eligible participants had stage 3 CKD or microalbuminuria, and renal measurements included serum creatinine, eGFR and UACR at repeated intervals. Compared with placebo, tocotrienol supplementation was associated with lower serum creatinine and better eGFR after eight months. In a prespecified or reported subgroup of 37 participants with stage 3 CKD, the difference in creatinine and eGFR remained evident over 12 months. UACR, however, did not improve significantly.

The lack of concordance across renal endpoints is the trial's most important finding. If tocotrienol supplementation had simultaneously lowered UACR, slowed chronic eGFR decline, altered relevant mechanistic biomarkers, and demonstrated sustained benefit after treatment, the interpretation would be more straightforward. Instead, the trial generated a filtration-related signal without a parallel albuminuria or TGF-β1 response and without persistence of the main eGFR effect after six months of washout. This pattern is compatible with biological benefit, but it is also compatible with reversible physiology or statistical uncertainty.

The magnitude of evidence should therefore be kept in perspective. A trial of 59 participants is valuable for hypothesis generation but is underpowered to establish effects on kidney failure, sustained large GFR declines or cardiovascular outcomes. Subgroup analyses involving stage 3 CKD are particularly vulnerable to instability. Moreover, creatinine-derived eGFR can vary because of factors unrelated to structural filtration capacity, including muscle mass, dietary intake, creatinine generation, tubular secretion and analytical variation.

A 2025 randomised trial provides additional CKD-specific but not DKD-specific information. Trugilho et al. administered 300 mg/day tocotrienol-rich fraction for three months to small groups of non-dialysis and haemodialysis CKD patients. The intervention reduced CRP in the non-dialysis subgroup and improved selected lipid variables in haemodialysis participants, but NRF2 and NF-κB mRNA expression remained unchanged. The study therefore supports feasibility and possible inflammatory or lipid effects in CKD, while its small size and short duration preclude conclusions regarding preservation of kidney function.[57]

4.2 Interpreting eGFR–Albuminuria Dissociation

4.2.1 Hypothesis 1: Genuine Renal Protection Outside the Albuminuric Pathway

One interpretation is that tocotrienols influence disease pathways inadequately captured by albumin excretion. DKD can progress through vascular and tubulointerstitial mechanisms, and the non-albuminuric phenotype demonstrates that reduced filtration can occur in the absence of major albuminuria. Tubular markers can predict CKD progression independently of albuminuria, while microvascular endothelial structure can directly influence glomerular filtration.[27,30,43]

Under this hypothesis, antioxidant or anti-inflammatory actions could improve cellular metabolism, endothelial function, tubular stress or intrarenal signalling before producing measurable effects on albumin permeability. A therapy might therefore modestly improve filtration-related parameters without immediately lowering UACR.

This interpretation is biologically plausible but remains unproven. The Phase IIb trial did not include a sufficiently detailed tubular biomarker panel, measured GFR, serial cystatin C, kidney imaging or histological evaluation capable of localising the effect. The absence of significant changes in TGF-β1 and VEGF-A further reduces the ability to assign a specific mechanism.

4.2.2 Hypothesis 2: Creatinine Biology Rather Than Structural Nephroprotection

A second explanation is that changes in serum creatinine may not represent a proportional change in true GFR. Creatinine-based equations provide clinically useful approximations but are influenced by non-GFR determinants. Modern work comparing creatinine and cystatin C demonstrates that combining both markers generally improves accuracy relative to creatinine-only equations.[58,59]

Future trials should therefore test whether a tocotrienol-associated change in creatinine-derived eGFR is reproduced by cystatin-C-based eGFR or measured filtration. If creatinine improves while cystatin C and measured GFR remain unchanged, the interpretation would shift away from true filtration preservation. Conversely, concordant effects across independent filtration markers would substantially strengthen the case for nephroprotection.

4.2.3 Hypothesis 3: A Reversible Functional Effect

Renal therapies can alter GFR through haemodynamic mechanisms without immediately changing renal structure. SGLT2 inhibitors provide the best-established example: an early haemodynamic eGFR dip can be followed by a slower chronic decline and long-term protection. The direction of the early effect differs from the tocotrienol signal, but the principle demonstrates why short-term eGFR change and long-term structural protection are not synonymous.[5,7]

The disappearance of the tocotrienol eGFR difference after washout raises the possibility of a treatment-dependent functional effect. Such reversibility does not eliminate clinical value; many effective therapies provide benefit only while taken. However, it underscores the need to distinguish acute filtration effects from alteration of the chronic eGFR slope.

4.2.4 Hypothesis 4: Statistical Uncertainty

The simplest explanation cannot be excluded: the apparent effect could reflect statistical variation. Small samples magnify baseline imbalance, regression to the mean, random fluctuation and uncertainty in subgroup estimates. Multiple repeated renal measurements and subgroup comparisons increase interpretive complexity. A larger multicentre trial designed around a prespecified eGFR-slope endpoint would be needed to determine reproducibility.

4.3 Oxidative and Mitochondrial Pathways

Tocotrienols are frequently discussed as antioxidants, but a disease-modification argument must go beyond generic ROS scavenging. In DKD, oxidative stress interacts with mitochondrial dysfunction, glycation, inflammation, endothelial injury and fibrosis. NRF2 impairment and excessive oxidative signalling are therefore components of an interconnected disease network rather than isolated biochemical abnormalities.[31,60]

Tocotrienols may influence lipid peroxidation and cellular antioxidant capacity, while experimental literature suggests additional modulation of signalling pathways. However, human evidence is mixed. The meta-analysis by Khor et al.[23] found no overall significant improvement in IL-6, TNF-α or malondialdehyde, although a subgroup

receiving 400 mg/day showed a favourable malondialdehyde signal. This dose is noteworthy because it approximates the daily tocotrienol exposure used in the DKD trial.

A type 2 diabetes randomised trial using δ-tocotrienol reported reductions in malondialdehyde, high-sensitivity CRP, TNF-α and IL-6 together with improved glycaemic variables.[50] Conversely, the broader diabetes meta-analysis by Phang et al.[24] found only modest glycaemic benefit and no significant pooled effect on hs-CRP. These results imply that tocotrienol-associated biological effects are context-dependent and cannot simply be transferred from one formulation or patient group to another.

Mitochondrial biology offers a stronger future mechanistic target. Mitochondrial dynamics, quality control, and bioenergetic failure are implicated in DKD across podocytes, tubular cells, and endothelium.[32–35] A modern mechanistic tocotrienol trial could measure markers of oxidative lipid damage, mitochondrial DNA injury, metabolomic signatures, and tubular energetics alongside conventional renal endpoints. Such a design would test mechanism rather than infer it retrospectively.

Figure 2 positions tocotrienols within an interconnected DKD network and deliberately labels their effects as putative intervention nodes rather than established renal mechanisms. The visual separation of the tocotrienol panel from the core disease cascade emphasizes that mechanistic plausibility must not be conflated with demonstrated renal efficacy.

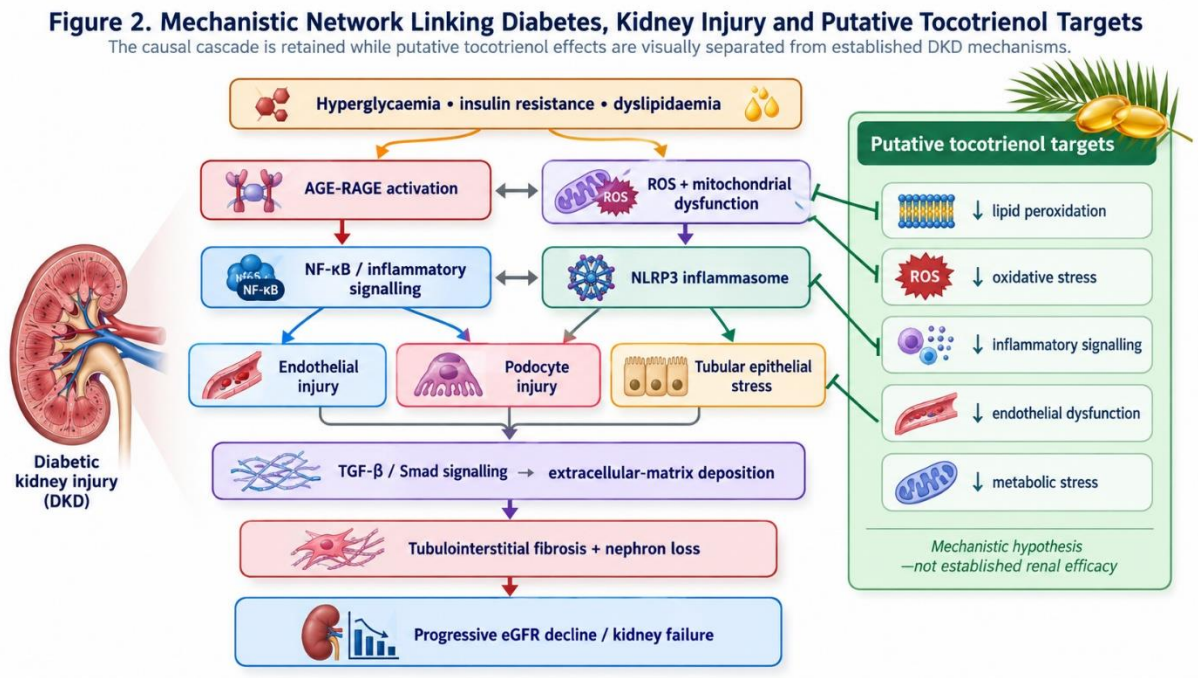

Figure 2 illustrates that the central translational issue is whether tocotrienol activity demonstrated in biochemical, preclinical or extra-renal human studies can produce sufficiently strong and durable modulation of DKD pathways to alter kidney outcomes. AGE–RAGE signalling can amplify oxidative and inflammatory injury,[36] NLRP3-associated pyroptotic pathways may contribute to renal-cell injury,[37] mitochondrial dysfunction affects multiple kidney-cell populations,[32,34] and TGF-β-related matrix accumulation contributes to fibrosis.[38] The network therefore supports biological plausibility but does not substitute for clinical validation.

4.4 Clinical Translation Across Diabetic Complications

Clinical evidence outside the kidney may help determine whether oral tocotrienol formulations achieve biologically meaningful exposure in patients with diabetes. In diabetic peripheral neuropathy, Ng et al.[52] reported improved conduction velocities after eight weeks of tocotrienol-rich vitamin E, and longer-term investigation by Chuar et al.[53] found improvement in median and sural sensory nerve-conduction velocities over 12 months. Both studies provide evidence that an orally administered palm-derived formulation can produce measurable physiological effects.

The neuropathy findings also provide a cautionary analogy. Improvements in physiological nerve-conduction endpoints were not accompanied by consistent changes in all proposed mechanistic serum biomarkers, and benefits diminished after washout in the longer trial.[53] This resembles the renal pattern in which physiological improvement was more apparent than biomarker modification. Such cross-organ similarity could represent a genuine treatment-

dependent functional effect, but it could also indicate that the proposed serum biomarkers are poor mediators or that biological interpretation remains incomplete.

Retinopathy research adds another microvascular dimension. Ho et al.[54] reported reduced progression of retinal microhaemorrhages and a decrease in diabetic macular oedema area among participants receiving tocotrienol-rich vitamin E, while serum VEGF did not differ significantly between groups. This again illustrates that a clinically or physiologically relevant phenotype can change without concordance in a selected circulating biomarker.

Metabolic evidence also remains heterogeneous. δ-Tocotrienol has produced improvements in glucose homeostasis in both type 2 diabetes and prediabetes trials.[50,51] An experimental study of annatto-derived tocotrienol further linked tocotrienol exposure with glucose homeostasis, inflammatory regulation and gut-microbiome changes, emphasizing the systemic breadth of potential biological effects.[61] However, annatto-derived preparations differ substantially from palm-derived mixed tocotrienol fractions and cannot be treated as pharmacologically interchangeable.

Taken together, these findings justify an exposure-response hypothesis rather than a definitive efficacy claim. They suggest that tocotrienols can produce measurable biological effects in humans, but they also demonstrate substantial variation across products and endpoints. For renal translation, formulation standardization is therefore not a manufacturing detail; it is central to reproducibility.

4.5 Modern Therapy as the Required Benchmark

Any claim that tocotrienols modify DKD must be evaluated against the evidence standards established by modern cardiorenal therapies. DAPA-CKD randomised 4,304 participants and demonstrated a hazard ratio of 0.61 for its primary kidney/cardiovascular composite with dapagliflozin versus placebo. EMPA-KIDNEY similarly showed meaningful protection across a broad CKD population.[7,8] These trials evaluated clinically important events rather than short-term biomarker changes alone.

Finerenone was evaluated in similarly large outcome programs. FIDELIO-DKD included 5,734 participants with type 2 diabetes and CKD and demonstrated reduction in the primary kidney composite.[9] FIGARO-DKD enrolled more than 7,000 participants and demonstrated cardiovascular benefit across a wider CKD spectrum.[10] FIDELITY pooled 13,026 participants and reported hazard ratios of 0.86 for the cardiovascular composite and 0.77 for the kidney composite.[11]

Importantly, analyses of finerenone according to concomitant SGLT2 inhibitor use suggest that layering mechanisms may be clinically plausible. In the FIDELITY analysis by Rossing et al.,[62] baseline SGLT2 inhibitor use did not appear to abolish finerenone-associated cardiorenal benefit, although the subgroup receiving both

therapies was relatively small. This concept supports further evaluation of complementary interventions while also demonstrating why additivity must be tested rather than assumed.

The FLOW trial adds GLP-1 receptor agonism to this benchmark. Semaglutide reduced the risk of clinically important kidney outcomes in patients with type 2 diabetes and CKD, meaning that future adjunctive agents will increasingly enter a therapeutic environment in which patients may already receive three or four disease-modifying drug classes.[12]

Tocotrienols consequently face a higher translational threshold than they did when early DKD trials were conceptualized. A new trial conducted without SGLT2 inhibitors or modern mineralocorticoid-receptor antagonism would have limited applicability to contemporary clinical practice. The relevant question is whether a standardised tocotrienol formulation adds measurable benefit after proven haemodynamic, metabolic, and fibrotic pathways have already been therapeutically addressed.

Figure 3 reframes tocotrienols as an experimental addition to, rather than an alternative to, modern guideline-directed DKD therapy. It therefore places the proposed intervention within a residual-risk framework in which any incremental benefit would need to be demonstrated on top of established cardiorenal treatment.

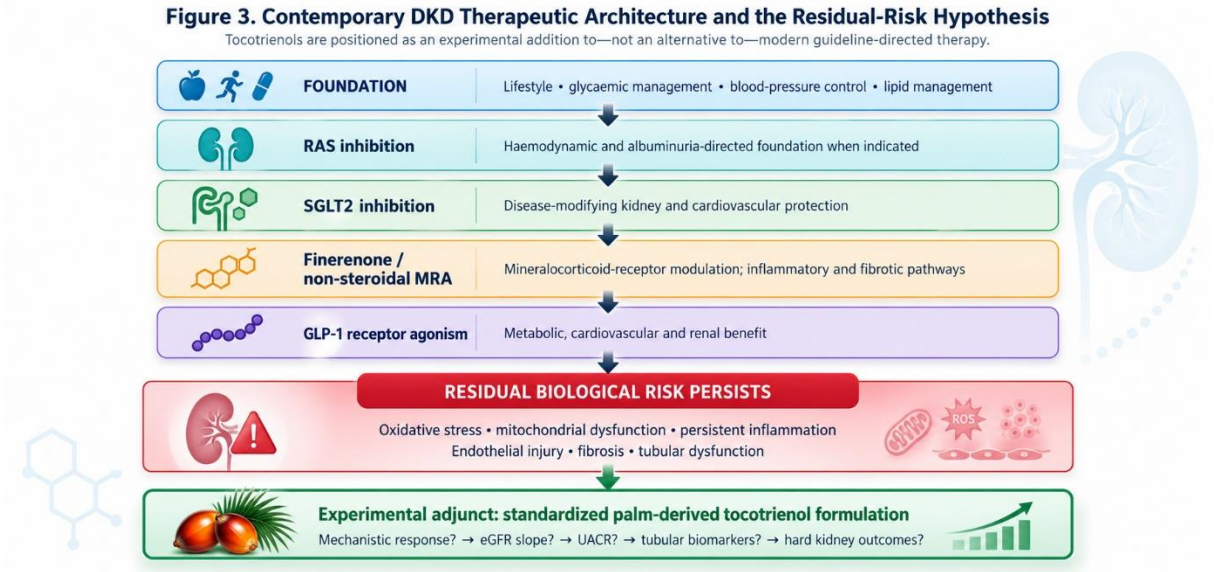

Figure 3 explains that the four-pillar model of contemporary DKD management reflects complementary mechanisms across RAS blockade, SGLT2 inhibition, mineralocorticoid-receptor antagonism and GLP-1 receptor agonism.[13–16] Despite these advances, reviews continue to identify residual inflammatory, metabolic, vascular and fibrotic

pathways and emphasize the need for additional therapies.[17,18] Tocotrienols have theoretical relevance to several residual pathways, but clinical additivity remains an unanswered research question.

5. DISCUSSION AND ANALYSIS

5.1 Does eGFR–UACR Dissociation Constitute Evidence of Renoprotection?

The major contribution of the existing tocotrienol DKD evidence is not a definitive positive efficacy result; it is the generation of an unresolved renal phenotype. Improvement in creatinine-derived eGFR without reduction in UACR challenges a simplistic interpretation in which every meaningful renal benefit must first produce albuminuria reduction. Contemporary DKD phenotyping clearly demonstrates that albuminuria and filtration decline can become dissociated.[6,39,40]

At the same time, the opposite error must be avoided. The existence of non-albuminuric DKD cannot be used retrospectively to prove that the tocotrienol effect involved tubular or interstitial protection. The necessary evidence—measured GFR, cystatin C, tubular injury biomarkers, molecular signatures, imaging or histological data—was largely absent from the Phase IIb study. Consequently, compartment-specific nephroprotection should be treated as a testable hypothesis.

Albuminuria itself remains clinically important. It predicts progression and cardiovascular risk and responds to established kidney-protective interventions. The appropriate conclusion is therefore not that UACR is obsolete but that UACR provides only one dimension of renal disease. Modern surrogate-endpoint research suggests that combining UACR with eGFR slope provides stronger inferential power than either alone.[55]

The tocotrienol trial also illustrates why renal function should be conceptualized longitudinally. A temporary difference in eGFR at a specific follow-up point is less persuasive than sustained divergence in chronic slope. Inker et al.[56] demonstrated that treatment effects on total GFR slope are strongly associated with treatment effects on kidney-failure endpoints across a large collection of randomised trials. Future tocotrienol trials should therefore prespecify acute and chronic slope analysis and avoid defining success through isolated creatinine measurements.

5.2 Is the Mechanistic Rationale Strong Enough?

The mechanistic rationale is broad but uneven. Oxidative stress is firmly implicated in DKD and represents the most obvious link to tocotrienols. Mitochondrial dysfunction, NRF2 dysregulation, lipid peroxidation, AGE–RAGE signalling and inflammatory activation form a biologically coherent network through which metabolic stress can damage glomerular, tubular and vascular cells.[31–33,36]

Inflammation provides a second plausible domain. NF-κB activity, chemokine recruitment, NLRP3 activation and inflammatory cytokines contribute to experimental and clinical features of DKD.[37,60] Tocotrienol studies report anti-inflammatory activity, and recent reviews continue to describe effects involving NF-κB, TNF-α, IL-6 and related pathways.[20,22]

However, mechanistic breadth can become a weakness if every plausible pathway is presented as clinically demonstrated. The evidence is strongest for showing that tocotrienols can influence selected oxidative, metabolic and inflammatory measures under some conditions; it is substantially weaker for proving that these changes lead to renal structural preservation. Khor et al.[23] showed how inconsistent human biomarker responses can be, while the 2025 CKD trial found no significant changes in NRF2 or NF-κB expression despite improvement in selected inflammatory or lipid measures.[57]

A publishable interpretation should therefore distinguish mechanistic compatibility from mechanistic confirmation. Tocotrienols are compatible with the pathobiology of residual DKD risk, but current human studies do not yet establish which pathways are necessary, sufficient or clinically dominant.

5.3 Potential Importance of Tubular and Interstitial Injury

The strongest theoretical explanation for an eGFR effect without a corresponding UACR effect is involvement of the tubulointerstitial or microvascular compartment. Tubular injury is increasingly recognised as an important determinant of DKD progression. Conventional eGFR and UACR incompletely represent this domain, while KIM-1, MCP-1, α1-microglobulin, EGF and other biomarkers provide complementary information.[29,43,44] Recent nephrology commentary has likewise argued that routine kidney assessment remains disproportionately glomerulocentric and that direct evaluation of tubular function deserves greater attention when characterising disease progression.[63]

Tubular cells are particularly vulnerable to metabolic and mitochondrial stress because of their high energy requirements. SGLT2 inhibition itself illustrates how altered tubular glucose and sodium handling can reshape whole-kidney physiology. Although tocotrienols do not share the same mechanism, interventions that improve mitochondrial membrane stability, redox balance or inflammatory signalling could theoretically influence tubular resilience.

This possibility also suggests a strategy for participant enrichment. A future tocotrienol trial could recruit patients with preserved or moderately elevated UACR but evidence of rapid eGFR decline or elevated tubular biomarkers. Such enrichment would directly test whether the therapy has value in a phenotype underrepresented by traditional albuminuria-centred trials.

Precision medicine provides the conceptual basis for this approach. DKD progression is highly heterogeneous, and biomarker signatures may ultimately help identify patients who respond to specific molecular interventions.[46,47] The Kidney Precision Medicine Project further demonstrates the field's movement toward molecular characterisation rather than reliance on broad clinical syndromes alone.[45]

5.4 Residual Risk and Mechanistic Complementarity

The most important clinical question is whether tocotrienols could provide incremental benefit on top of guideline-directed therapy. SGLT2 inhibitors influence tubuloglomerular feedback, intraglomerular pressure, tubular energetics and multiple downstream pathways. Finerenone reduces mineralocorticoid-receptor-mediated inflammatory and fibrotic signalling. GLP-1 receptor agonists improve metabolic risk and produce cardiovascular and renal benefits. Consequently, oxidative and inflammatory pathways are already affected indirectly by contemporary therapies.[5,15,60]

This creates two competing possibilities. Tocotrienols may provide genuine complementarity by targeting membrane oxidative injury, mitochondrial function or inflammatory signals insufficiently suppressed by established therapies. Alternatively, their mechanisms may be largely redundant once modern combination therapy is optimized, reducing the incremental effect to clinically negligible levels.

The only reliable way to resolve this question is through add-on trials. Historical efficacy against placebo in patients receiving older background therapy cannot establish residual-risk benefit in 2026. Modern trials must therefore require stable SGLT2 inhibitor therapy where tolerated and appropriate, stable RAS inhibition when indicated, and prespecified stratification according to finerenone and GLP-1 RA use.

Safety also requires contemporary evaluation. Tocotrienols are generally regarded as well tolerated in studied doses, but combination regimens can produce unexpected pharmacokinetic or clinical interactions. Formulation-specific safety, bleeding-related outcomes, hepatic parameters and drug–supplement interactions should therefore be prespecified rather than assumed from historical nutraceutical experience.[21,49]

5.5 From Nutraceutical Supplementation to Pharmacologically Defined Intervention

A major conceptual advance would be to stop treating "tocotrienols" as a homogeneous nutritional category. Palm-derived formulations differ in α-, γ- and δ-tocotrienol content, tocopherol concentration, carrier systems and bioavailability. Oral exposure varies considerably, meaning that a positive trial with one formulation cannot automatically validate another product.[19,49]

Future studies should use chemically standardised products with batch-specific documentation of tocotrienol isoform composition. Plasma concentrations should be measured to verify exposure and adherence. Pharmacokinetic substudies could test whether renal phenotype, CKD stage or concomitant therapy alters tocotrienol disposition.

This requirement is particularly important because advanced CKD can modify absorption, metabolism, protein binding and elimination of multiple compounds. The 2025 CKD tocotrienol trial demonstrates feasibility but not renal pharmacokinetic equivalence across non-dialysis and haemodialysis populations.[57]

A dose-ranging phase should therefore precede or accompany definitive efficacy evaluation. Without exposure-response information, failure could result from inadequate delivery rather than lack of biological activity, while apparent benefit could reflect an unrecognized formulation-specific characteristic.

5.6 Proposed Next-Generation Tocotrienol DKD Trial

The ideal next step would be a multicentre, randomised, double-blind, placebo-controlled Phase IIb/III programme rather than another small single-centre biomarker study. Eligible participants could include adults with type 2 diabetes, eGFR approximately 25–75 mL/min/1.73 m^2, and evidence of DKD defined by albuminuria, reduced eGFR, or a documented progressive eGFR trajectory. Albuminuric and non-albuminuric phenotypes should be prespecified rather than pooled indiscriminately.

Participants should receive stable guideline-directed background therapy. SGLT2 inhibitor treatment should be expected unless contraindicated or not tolerated. RAS inhibition should be optimized where clinically appropriate, and use of finerenone and GLP-1 receptor agonists should be documented and incorporated into randomisation stratification. This design would directly test the residual-risk hypothesis emphasized by contemporary combination-therapy frameworks.[13,15,62]

A standardised palm-derived tocotrienol intervention could initially retain the 400 mg/day exposure used in prior DKD and neuropathy trials, provided pharmacokinetic and safety assessment confirms suitability. The active formulation would require explicit quantification of individual tocotrienol isoforms and tocopherol content.

The preferred Phase II primary endpoint should be total or chronic eGFR slope over at least 18–24 months rather than an isolated change in serum creatinine. Serial UACR should be a major secondary endpoint. A combined interpretation of UACR and slope would provide stronger inference regarding future clinical benefit.[55,56]

Cystatin C should be included because creatinine-only interpretation is one of the most important uncertainties in the existing evidence. Creatinine–cystatin-C equations improve filtration estimation accuracy across many populations and would allow determination of whether any treatment effect is robust to the filtration marker used.[58,59]

A mechanistic substudy should include KIM-1, MCP-1, EGF, soluble TNFR1/TNFR2, α1-microglobulin, NGAL, oxidative-stress biomarkers and selected fibrotic markers. These measurements would test whether participants showing improvement in eGFR also display changes in tubular injury, inflammation or repair. Data from Phanish et al.,[30] Amatruda et al.,[43] Ix and Shlipak,[29] Limonte et al.[44] and Rico-Fontalvo et al.[41] provide a strong basis for this multidimensional biomarker approach.

An adequately powered later-phase trial should assess hard outcomes including sustained ≥40% or ≥50% eGFR reduction, kidney failure requiring replacement therapy, very low sustained eGFR, cardiovascular events and death. Tocotrienols should not be labelled disease-modifying until such outcomes—or well-validated surrogate combinations strongly predictive of them—show reproducible benefit.

Figure 4 establishes an evidence threshold separating plausible renoprotective biology from clinically demonstrated disease modification. It also shows how evidentiary requirements rise from biological plausibility and pharmacological validation to mechanistic testing, renal efficacy and confirmatory clinical outcomes.

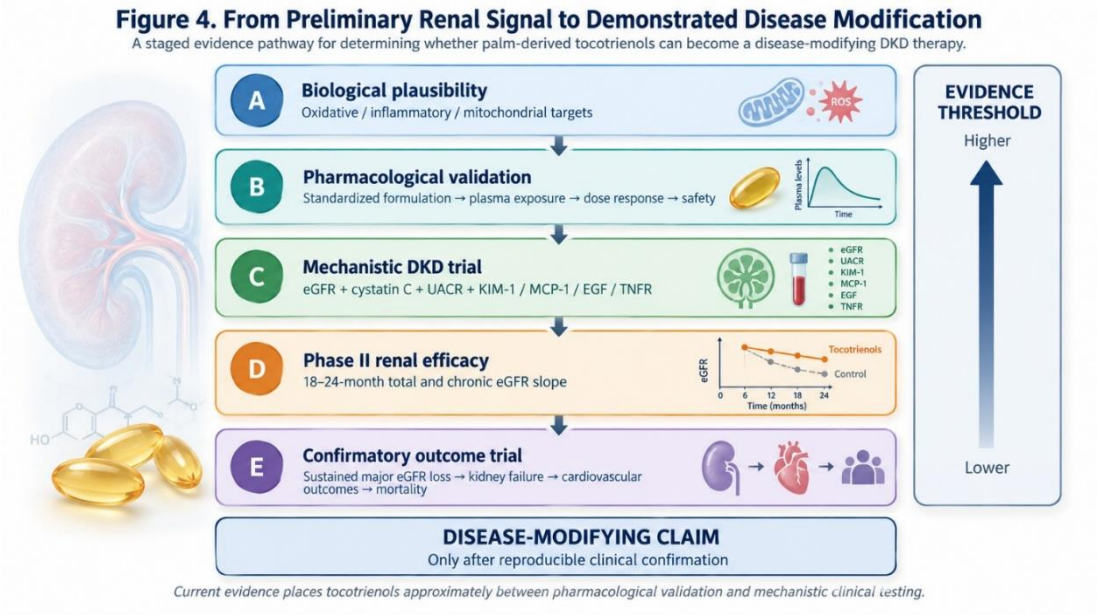

Figure 4 explains that existing evidence places palm-derived tocotrienols between Stages B and C: human exposure and preliminary physiological effects are documented, but definitive renal efficacy remains unconfirmed. Contemporary CKD trial methodology supports eGFR slope and combined UACR–slope assessment as intermediate endpoints, while hard kidney outcomes remain the strongest confirmation of clinical benefit.[55,56] The proposed pathway prevents overinterpretation of small biomarker trials and provides a practical translational roadmap.

5.7 Clinical Implications

At present, tocotrienols should not be presented as a substitute for RAS blockade, SGLT2 inhibitors, finerenone, GLP-1 receptor agonists or comprehensive cardiovascular risk reduction. The magnitude and quality of outcome evidence supporting these therapies are fundamentally different from the current tocotrienol evidence base.[7–12]

The responsible clinical interpretation is therefore one of investigational adjunctive potential. Tocotrienols possess plausible biological activity and have produced sufficiently interesting renal and microvascular signals to justify further investigation. Yet routine use specifically for slowing DKD progression cannot presently be justified as evidence-based disease-modifying therapy.

This distinction also affects communication with patients and clinicians. Describing tocotrienols as "natural antioxidants" can encourage the mistaken assumption that biological safety and efficacy are self-evident. In reality, CKD is characterised by complex pharmacology, polypharmacy and high baseline cardiovascular risk. Any adjunct intended for routine clinical use should therefore undergo the same rigorous evaluation of formulation, dose, interaction, endpoints and clinically meaningful benefit expected of other disease-modifying therapies.

5.8 Research Implications for Palm-Derived Bioactives

The topic also has implications for palm-oil downstream innovation. Moving palm-derived tocotrienols from commodity-associated nutraceuticals to evidence-based precision bioactives requires standardization, reproducible extraction and formulation, pharmacokinetic characterisation, and indication-specific clinical development. Such an approach would add substantially more scientific value than broad claims that palm vitamin E is generically "antioxidant" or "renoprotective."

The 2026 review by Ali et al.[22] emphasizes the broad metabolic and cardiovascular potential of tocotrienol-rich fractions, while Zainal et al.[20] highlight anti-inflammatory and chronic-disease applications. These emerging syntheses indicate growing translational interest, but kidney-specific development remains comparatively immature.

The opportunity is therefore not to market an established renal therapy prematurely, but to construct a scientifically credible development programme. If future studies demonstrate additive improvement in eGFR slope, tubular injury and ultimately kidney outcomes on top of guideline-directed therapy, palm-derived tocotrienols could occupy a distinctive high-value biomedical niche. If such trials are neutral, they would equally clarify the limits of antioxidant and anti-inflammatory biological plausibility in established human DKD.

6. CONCLUSION

Diabetic kidney disease has entered an era in which albuminuria, glomerular filtration, cardiovascular risk and renal molecular injury must be interpreted together. Modern therapies have substantially improved outcomes, yet patients

remain exposed to considerable residual kidney risk because DKD arises from overlapping haemodynamic, metabolic, inflammatory, oxidative, mitochondrial, vascular and fibrotic pathways.

Palm-derived tocotrienols are relevant to this therapeutic gap because their biological profile intersects with several mechanisms implicated in diabetic renal injury. Human trials demonstrate that tocotrienols are biologically active and can affect selected physiological, metabolic and microvascular outcomes. Most importantly, the available Phase IIb DKD trial generated an intriguing improvement in serum-creatinine-derived eGFR without corresponding improvement in albuminuria.

That dissociation should neither be dismissed nor overinterpreted. Contemporary recognition of non-albuminuric DKD and tubulointerstitial biomarkers provides a plausible framework in which filtration and UACR may respond differently. However, the small evidence base, absence of definitive tubular or structural measurements, reliance on creatinine-derived eGFR, lack of consistent biomarker effects and disappearance of the principal signal after washout prevent a conclusion that tocotrienols have already demonstrated disease modification.

The next research question is therefore sharply defined. Tocotrienols should be evaluated as standardised, pharmacologically characterised adjuncts to contemporary guideline-directed DKD therapy, not as replacements for proven cardiorenal treatment. Future trials require adequate sample size, modern SGLT2- and finerenone-era background therapy, prespecified albuminuric and non-albuminuric phenotypes, at least 18–24 months of follow-up, eGFR slope, serial UACR, cystatin C, tubular and inflammatory biomarkers, and ultimately clinically meaningful kidney outcomes.

The scientific opportunity lies precisely in this uncertainty. Palm-derived tocotrienols have progressed far enough to justify rigorous renal investigation, but not far enough to justify an established renoprotective claim. Demonstrating whether the observed eGFR–UACR dissociation reflects genuine residual-risk modification, reversible physiology, or statistical uncertainty is the critical step required to move the field from promising bioactivity to evidence-based renoprotection.

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