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Beyond Antioxidant Supplementation: Palm Tocotrienols in Diabetic Kidney Disease—From Redox and Endothelial Injury to Preservation of Renal Function

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ABSTRACT

Diabetic kidney disease (DKD) remains a major cause of chronic kidney disease and kidney failure despite substantial advances in renin–angiotensin system blockade, sodium–glucose cotransporter-2 inhibition, non-steroidal mineralocorticoid receptor antagonism and glucagon-like peptide-1 receptor agonist therapy. Persistent residual risk reflects the multifactorial biology of DKD, including oxidative stress, advanced glycation, endothelial and glycocalyx injury, mitochondrial dysfunction, podocyte loss, tubular stress, inflammation and fibrosis. Palm-derived tocotrienol-rich vitamin E has attracted interest as a potential multitarget adjunct because tocotrienols possess antioxidant, anti-inflammatory and metabolically active properties that extend beyond conventional vitamin-E radical scavenging. This qualitative translational review synthesizes post-2020 evidence relating tocotrienols to DKD pathogenesis and renal outcomes. Particular attention is given to randomized evidence reporting improvement in serum creatinine and estimated glomerular filtration rate without comparable improvement in albuminuria, creating an important mechanistic and clinical paradox. Potential explanations include compartment-specific tubular or endothelial effects, heterogeneity of DKD phenotypes, differences in temporal responsiveness of renal endpoints and limitations of creatinine-derived filtration estimates. Existing evidence remains insufficient to establish antifibrotic mechanisms, hard renal-outcome benefits or additive efficacy with contemporary renoprotective drugs. Palm tocotrienols should therefore be considered an investigational adjunct rather than established DKD therapy. Future multicenter trials should use chronic eGFR slope, albuminuria, cystatin C, tubular injury and endothelial biomarkers, inflammatory phenotyping, standardized tocotrienol formulations and stratification by contemporary drug therapy.

Keywords: Diabetic kidney disease; Tocotrienols; Palm tocotrienol-rich fraction; Vitamin E; Oxidative stress; Endothelial dysfunction; Renal fibrosis; eGFR; Albuminuria; Adjunctive renoprotection

JEL Classification: I10 Health: General; **I11** Analysis of Health Care Markets; **I12** Health Behavior; **I15** Health and Economic Development; **I18** Government Policy, Regulation and Public Health

1. INTRODUCTION

Diabetic kidney disease (DKD) remains one of the most consequential microvascular complications of diabetes because it combines progressive loss of kidney function with substantially elevated cardiovascular morbidity and premature mortality. Contemporary understanding no longer regards DKD as a simple sequence in which chronic hyperglycemia produces albuminuria and albuminuria subsequently leads inevitably to declining glomerular filtration. Instead, DKD encompasses heterogeneous molecular and clinical phenotypes involving glomerular endothelial cells, podocytes, mesangial cells, tubular epithelial cells, interstitial cells, immune pathways and the renal microcirculation. Hyperglycemia is important, but it interacts with altered cellular metabolism, advanced glycation, oxidative stress, maladaptive renal hemodynamics, inflammation, mitochondrial injury, hypoxia and fibrosis.[1–4] Recent work also emphasizes risk-targeted phenotyping and network-based interpretation of complex kidney disease phenotypes, reinforcing the need to move beyond single-marker models of DKD.[5,6]

This biological heterogeneity is reflected in clinical presentation. The classical phenotype—progressively increasing albuminuria followed by loss of estimated glomerular filtration rate (eGFR)—remains common, but patients may also experience declining renal function in the absence of substantial albuminuria. Meta-analytic evidence concerning nonalbuminuric DKD demonstrates that albumin excretion and filtration loss are related but not interchangeable manifestations of diabetic renal injury.[7] Consequently, a therapeutic intervention that changes eGFR without producing a comparable change in urinary albumin-to-creatinine ratio (UACR) cannot automatically be dismissed as biologically implausible; instead, the pattern requires scrutiny of renal compartment, phenotype, timing and measurement methodology.

The therapeutic environment of DKD has changed profoundly. Renin–angiotensin system inhibition remains foundational in albuminuric disease, while large randomized trials have established major cardiorenal benefits from sodium–glucose cotransporter-2 (SGLT2) inhibitors. DAPA-CKD and EMPA-KIDNEY demonstrated substantial protection against progressive kidney disease across broad CKD populations, while long-term EMPA-KIDNEY follow-up strengthened evidence that treatment produces clinically meaningful kidney protection beyond the active trial period.[8–10] Finerenone has further expanded treatment by targeting mineralocorticoid-receptor-mediated inflammatory and fibrotic pathways, and the FLOW trial demonstrated kidney and cardiovascular benefit with semaglutide in people with type 2 diabetes and CKD.[11–14]

These advances do not eliminate residual renal risk. Patients receiving evidence-based therapy may continue to lose kidney function or experience cardiovascular events, in part because established treatments do not necessarily neutralize every component of metabolic stress, mitochondrial dysfunction, endothelial injury, inflammatory amplification and fibrosis.[15,16] Contemporary guidelines consequently emphasize layered management, including glycemic and blood-pressure optimization, renin–angiotensin system blockade when indicated, SGLT2 inhibition, non-steroidal mineralocorticoid receptor antagonism in appropriate patients and additional cardiometabolic risk

reduction.[17–19] The 2024 KDIGO CKD guideline further reinforces simultaneous assessment of albuminuria and GFR and the use of layered disease-modifying therapy according to CKD phenotype and risk.[20]

Residual risk creates a scientifically legitimate space in which adjunctive bioactive compounds may be investigated, provided they are not presented as alternatives to therapies with demonstrated hard clinical outcomes. Palm-derived tocotrienols are of particular interest. Tocotrienols belong to the vitamin-E family but possess an unsaturated isoprenoid side chain that distinguishes them structurally from tocopherols. Palm tocotrienol-rich fraction (TRF) contains multiple tocotrienol isoforms together with varying amounts of tocopherol, and biological effects may differ according to formulation, isoform composition, dose, fed state and delivery technology.[21–23] A growing literature attributes antioxidant, anti-inflammatory, lipid-modulating and cell-signaling effects to tocotrienols, but translation from biological plausibility to kidney protection requires a much higher evidentiary threshold.

The principal clinical reason for renewed interest is a randomized phase IIb study of tocotrienol-rich vitamin E in DKD. In that study, approximately one year of treatment was associated with improvement in serum creatinine/eGFR-based measures, with an especially notable signal among participants with stage-3 CKD. However, UACR did not improve comparably, and changes in investigated TGF-β1 and VEGF-A biomarkers did not supply an obvious mechanism.[24] This combination—an apparently favorable filtration signal without corresponding albuminuria or mechanistic biomarker improvement—is more informative than a generic claim that tocotrienols are "antioxidants." It defines the central translational problem considered in this review.

The purpose of this qualitative literature review is therefore to critically synthesize post-2020 knowledge on DKD pathogenesis, palm tocotrienol pharmacobiology and relevant human evidence. It asks whether the available data justify repositioning palm tocotrienols from a nonspecific nutritional antioxidant toward a testable adjunctive renoprotective strategy; whether reported renal effects could occur independently of HbA1c or systemic blood pressure; why eGFR and UACR responses may diverge; which patients might plausibly respond; and how future trials should determine incremental benefit against the background of contemporary SGLT2 inhibitor, finerenone and GLP-1 receptor agonist therapy.

2. LITERATURE REVIEW: MECHANISTIC AND TRANSLATIONAL FOUNDATIONS

2.1 DKD as a Redox–Metabolic–Inflammatory Network

Oxidative stress is deeply embedded in DKD pathogenesis, but describing DKD simply as an oxidative-stress disorder is inadequate. Excess glucose flux, AGE–RAGE signaling, altered fatty-acid metabolism, NADPH oxidase activity, mitochondrial dysfunction and impaired antioxidant defenses interact to create sustained redox disequilibrium. Reactive oxygen species (ROS) are not merely damaging metabolic by-products; they also act as signaling intermediates capable of amplifying inflammatory, endothelial and profibrotic pathways. Reviews of

oxidative biomarkers in diabetic nephropathy and of the NRF2/KEAP1/ARE pathway therefore describe redox stress as a network-level amplifier rather than a single linear mechanism.[25–27]

Advanced glycation provides a major bridge between persistent metabolic stress and redox inflammation. AGEs accumulate in diabetes and interact with the receptor for advanced glycation end products (RAGE), stimulating signaling pathways that include NF-κB, MAPK and TGF-β-associated processes. Activation of AGE–RAGE signaling can enhance ROS production, inflammatory gene expression, endothelial dysfunction and extracellular-matrix accumulation, thereby generating self-reinforcing injury.[28,29] This framework is relevant to tocotrienols because any clinically meaningful antioxidant intervention would have to do more than scavenge free radicals transiently; it would need to modify downstream amplification or protect cellular structures sufficiently to alter disease trajectory.

Inflammation likewise intersects rather than merely coexists with oxidative stress. NF-κB-regulated pathways, cytokines such as TNF-α and IL-6, chemokines, immune-cell recruitment and chronic sterile inflammatory signaling contribute to glomerular and tubulointerstitial injury. More broadly, CKD progression reflects interactions among tissue injury, inflammatory activation and attempted repair, which may ultimately become fibrogenic.[30] This is important when interpreting tocotrienol studies because inconsistent changes in circulating CRP or cytokines do not necessarily prove absence of tissue-level effects, but neither can tissue effects be assumed in their absence.

2.2 Endothelial Dysfunction, Glycocalyx Loss and Podocyte–Endothelial Crosstalk

The glomerular filtration barrier consists of fenestrated endothelial cells and their glycocalyx, the glomerular basement membrane and podocytes with specialized slit diaphragms. Diabetes perturbs all three layers. Endothelial glycocalyx degradation is particularly important because the glycocalyx contributes to vascular barrier properties, mechanotransduction and control of inflammatory-cell adhesion. High glucose, oxidative stress and inflammatory signaling can damage this structure and facilitate albumin leakage and endothelial activation.[31] Experimental work demonstrating restoration of glycocalyx and filtration-barrier function after inhibition of syndecan-4 shedding provides further evidence that endothelial surface integrity is not merely an epiphenomenon of DKD.[32]

Endothelial and podocyte injury are also mechanistically coupled. Podocytes require large amounts of energy to maintain cytoskeletal architecture and slit-diaphragm integrity. Mitochondrial dysfunction, oxidative injury, autophagic disturbances and altered metabolic signaling can impair podocyte function and eventually lead to podocyte depletion. A dedicated review of mitochondrial injury in diabetic podocytes emphasizes altered mitochondrial dynamics, ROS production and impaired quality control as important pathways connecting metabolic overload with structural filtration-barrier damage.[33] Thus, an intervention acting mainly on endothelial or podocyte oxidative biology might theoretically affect albumin permeability, whereas an intervention acting predominantly on

other renal compartments might affect filtration decline without substantially altering albuminuria. More recent podocyte-focused literature likewise supports the concept that podocyte depletion and dysfunction are mechanistically linked to proteinuria and progressive glomerular injury, while also highlighting opportunities for cell-specific therapy.[34]

2.3 Mitochondrial Dysfunction and Renal Hypoxia

The kidney has exceptionally high metabolic and oxygen requirements, particularly in the proximal tubule. Diabetes increases filtered glucose and sodium delivery and can increase reabsorptive workload, creating an unfavorable relationship between oxygen consumption and supply. Renal hypoxia has consequently been proposed as both a driver and an amplifier of DKD, with SGLT2 inhibitors potentially providing benefit partly by altering tubular workload and tubuloglomerular physiology.[35] Human evidence reviewed systematically by Flemming et al.[36] indicates abnormalities in mitochondrial function, mitochondrial DNA, oxidative damage and antioxidant capacity among individuals with DKD, although human mechanistic evidence remains less extensive than experimental data.

Recent work extends this model from isolated mitochondrial dysfunction toward dysfunctional organelle networks. Mitochondrial fission and fusion, mitophagy, mitochondrial DNA release, mitochondria–endoplasmic-reticulum contacts and calcium/redox signaling may influence cell survival and inflammatory activation. Cao et al.[37] synthesize these mechanisms as interconnected axes through which chronic metabolic stress can produce glomerular and tubular injury. The relevance to tocotrienols is conceptually important: lipid-soluble molecules capable of modifying membrane oxidation or intracellular redox signaling could theoretically influence mitochondrial vulnerability. Yet evidence that palm tocotrienols meaningfully correct these pathways in human DKD has not been established, and this distinction between plausible and demonstrated effects must be maintained. Recent syntheses and experimental advances further identify disturbed oxidative metabolism, fatty-acid handling and mitochondrial remodeling as central features of DKD, particularly in tubular compartments.[38,39]

2.4 Tubular Injury as a Determinant of Functional Decline

Modern DKD biology increasingly recognizes proximal-tubular and tubulointerstitial injury as central rather than secondary phenomena. Hyperglycemia, protein overload, altered lipid metabolism, oxidative stress, hypoxia, endoplasmic-reticulum stress and inflammatory signals may damage tubular epithelial cells. Tubules then contribute to chemokine production, immune recruitment, maladaptive repair and fibrosis. Reviews by Chang et al.,[40] Wang et al. [41] and Lv et al. [42] collectively emphasize that tubular dysfunction can emerge early and may be closely associated with subsequent kidney-function decline.

This shift has direct relevance to the tocotrienol clinical signal. Mohandes et al.[3] noted that podocyte and endothelial abnormalities are strongly connected with albuminuria, whereas proximal-tubular changes show an important relationship with GFR. This provides one plausible conceptual explanation for an intervention that improves a

filtration-based measure without producing parallel UACR reduction. It does not demonstrate that tocotrienols work through tubules, but it identifies a testable hypothesis. Future trials should therefore include urinary or plasma measures of tubular health rather than relying solely on UACR and serum creatinine. Candidate measures include kidney injury molecule-1 and related tubular biomarkers, although individual biomarkers require careful validation.[43,44]

2.5 Fibrosis as the Common Final Pathway

Regardless of the initiating renal compartment, sustained DKD can converge on extracellular-matrix deposition, glomerulosclerosis and tubulointerstitial fibrosis. TGF-β1 remains a central profibrotic mediator, interacting with Smad signaling, connective-tissue growth factors, cellular transdifferentiation programs and matrix turnover. Zhao et al.[45] and Tang et al.[46] describe both the centrality and therapeutic complexity of TGF-β signaling: complete suppression is unlikely to be desirable because TGF-β also performs essential physiological and immunoregulatory functions.

A claimed antifibrotic effect of tocotrienols therefore requires more than evidence that the compound possesses antioxidant activity. Human studies would ideally demonstrate changes in validated profibrotic signatures, imaging or tissue biomarkers and ultimately the chronic rate of GFR loss. Importantly, the DKD tocotrienol trial did not demonstrate a corresponding improvement in measured TGF-β1, weakening any attempt to directly attribute the observed renal function signal to suppression of that pathway.[24] This does not exclude a fibrotic mechanism, but it leaves it unproven.

2.6 Emerging Cell-Death Pathways

Ferroptosis has emerged as another potential connection between lipid oxidation and diabetic renal-cell death. Characterized by iron-dependent lipid-peroxide accumulation, ferroptosis is biologically attractive in DKD because metabolic stress, oxidative imbalance and altered iron handling can converge on vulnerable cellular membranes. Chu et al.[47] describe increasing experimental evidence implicating iron metabolism and ferroptotic processes in diabetic renal injury. A lipid-soluble antioxidant such as a tocotrienol could theoretically influence this process, but direct human evidence in DKD is lacking. Claims that tocotrienols prevent renal ferroptosis should consequently remain hypotheses for mechanistic trials rather than conclusions from current clinical evidence.

2.7 Tocotrienol Pharmacobiology

Vitamin E includes tocopherols and tocotrienols, each occurring in α-, β-, γ- and δ-forms. Tocotrienols differ structurally through their unsaturated side chain, which influences membrane behavior and metabolism. Palm oil is an important natural source of mixed tocotrienols, and commercial palm TRF formulations may contain differing

proportions of α-, γ- and δ-tocotrienol together with α-tocopherol. This heterogeneity matters because it is inappropriate to assume that findings obtained with isolated δ-tocotrienol, annatto-derived preparations or one proprietary palm formulation are pharmacologically interchangeable.[21,23]

Pharmacokinetic uncertainty is equally important. Tocotrienol absorption is influenced by food, dose, formulation and delivery technology; plasma exposure differs between preparations and isoforms. A systematic review of human pharmacokinetic studies concluded that tocotrienol bioavailability varies materially among preparations, complicating cross-trial comparison.[22] Consequently, future DKD trials should report precise tocotrienol composition, manufacturing specifications, administration relative to meals, adherence and preferably circulating tocotrienol concentrations rather than treating "vitamin E" or "TRF" as a uniform intervention.

Tocotrienols are frequently described as potent antioxidants, but their biological activity is broader than direct radical scavenging. Experimental literature suggests potential modulation of inflammatory transcriptional pathways, lipid metabolism and cell-signaling networks. A systematic review focused on NF-κB reported evidence that tocotrienols may influence this pathway, although translation across experimental systems was heterogeneous.[48] Similarly, the broader therapeutic review by Ranasinghe et al.[21] describes diverse metabolic, inflammatory and vascular effects. These findings justify mechanistic investigation but do not establish organ-specific clinical efficacy. Human evidence reinforces the need for restraint. A meta-analysis of randomized trials examining inflammation and oxidative stress found that tocotrienol supplementation did not consistently improve all evaluated markers, and pooled effects for several cytokine and oxidative outcomes were inconclusive.[49] Conversely, a randomized trial of δ-tocotrienol in type 2 diabetes reported improvements in glycemic, inflammatory and oxidative parameters, demonstrating that biological effects are possible but also highlighting formulation and population differences relative to palm TRF in DKD.[50]

The broader palm-TRF trial literature was recently synthesized by Looi et al.,[23] who reviewed 30 randomized trials across clinical populations. The review supports potential effects on inflammation and lipid peroxidation but also emphasizes heterogeneity in formulation, dose and duration and the need for stronger trials. Safety reviews of palm-derived TRF have generally been reassuring within studied doses and durations, but available studies are not large enough to exclude uncommon adverse outcomes or clinically important interactions in patients with advanced multimorbidity.[51]

Figure 1 integrates the multi-compartment biology of DKD with the principal pathways through which palm tocotrienols might plausibly act. The figure deliberately separates established DKD mechanisms from hypothesized tocotrienol intervention points so that biological plausibility is not visually mistaken for demonstrated clinical efficacy.

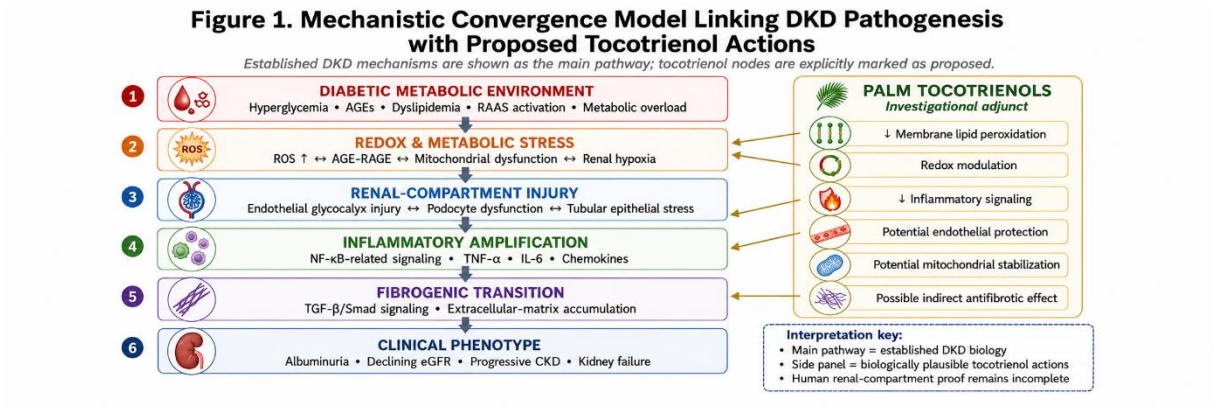

Figure 1: *Mechanistic convergence model linking DKD pathogenesis with proposed tocotrienol actions*

Figure 1 portrays oxidative stress not as a stand-alone target but as an interconnected component of metabolic, endothelial, mitochondrial, inflammatory, and fibrotic injury. This network model explains why a compound with several modest biological activities could be more relevant than an intervention that merely changes a circulating antioxidant marker. At the same time, only some proposed tocotrienol actions have been supported in humans; direct renal-compartment effects, ferroptosis modulation and antifibrotic efficacy remain largely inferential.

3. METHOD

This article uses a qualitative, narrative, and translational literature review design rather than a systematic literature review. The objective is interpretive synthesis: to connect contemporary knowledge of DKD pathogenesis with the emerging clinical literature on palm tocotrienols, identify convergent and discordant findings, and develop clinically testable hypotheses. Consequently, no PRISMA claim, claim of exhaustive study capture, or formal meta-analytic pooling is made.

The working literature corpus was constructed through iterative PubMed/MEDLINE-focused searching and targeted verification through journal and publisher sources. Literature published from January 2020 through September 2026 was prioritized to maintain alignment with contemporary DKD biology and treatment. Search concepts were combined iteratively around “diabetic kidney disease,” “diabetic nephropathy,” “tocotrienol,” “tocotrienol-rich fraction,” “palm vitamin E,” “oxidative stress,” “AGE RAGE,” “endothelial dysfunction,” “glycocalyx,” “podocyte,” “mitochondrial dysfunction,” “tubular injury,” “NF-κB,” “TGF beta,” “fibrosis,” “eGFR,” “albuminuria,” “SGLT2 inhibitor,” “finerenone,” and “GLP-1 receptor agonist.”

Priority was given to randomized controlled trials, systematic reviews, meta-analyses, high-quality translational studies and contemporary mechanistic reviews. Studies were interpreted according to population, renal phenotype, intervention composition, dose, duration, kidney function measures, albuminuria, mechanistic biomarkers and safety. Rather than applying a formal systematic risk-of-bias score, credibility was assessed narratively through design,

sample size, randomization, duration, endpoint validity, biological coherence, replication and applicability to contemporary DKD management.

The synthesis was organized into six analytical domains: (1) oxidative and metabolic stress; (2) endothelial and glomerular-barrier dysfunction; (3) mitochondrial and tubular injury; (4) inflammatory and fibrotic signaling; (5) clinical kidney endpoints; and (6) therapeutic integration. Particular weight was given to discrepancies between mechanistic predictions and human clinical outcomes because such discrepancies are especially informative in translational research.

4. RESULTS: THEMATIC SYNTHESIS

4.1 Theme 1: The Relevant Therapeutic Target Is a Network, Not "Oxidative Stress" Alone

The literature consistently portrays DKD as a network disorder in which oxidative stress communicates with metabolic overload, inflammatory signaling, AGE–RAGE activation, endothelial dysfunction, mitochondrial damage and fibrosis. Reviews focused on pathogenic mechanisms, biomarkers and emerging therapies reach a broadly similar conclusion: no single molecular pathway adequately explains progression across all patients.[52–54] This has two implications. First, it supports interest in multitarget agents. Second, it raises the evidentiary bar because broad mechanistic plausibility can easily generate overinterpretation.

A potentially favorable feature of tocotrienols is therefore their biological breadth rather than simply their antioxidant potency. Modest simultaneous effects on membrane lipid oxidation, inflammatory signaling and vascular function might theoretically influence multiple reinforcing components of DKD. However, a compound acting across many pathways can also produce modest biomarker shifts that do not translate into clinically meaningful renal preservation. Demonstration of slower eGFR decline or fewer hard renal outcomes remains essential.

4.2 Theme 2: Direct DKD Clinical Evidence Shows a Renal-Function Signal but Not a Complete Renal Response

The most important direct evidence is the phase IIb randomized controlled trial by Koay et al..[24] Participants with DKD received tocotrienol-rich vitamin E at 400 mg/day for 12 months. The study reported lower serum creatinine and improved eGFR measures after treatment, with the stage-3 CKD subgroup appearing to show a particularly persistent renal-function response during treatment. The findings were clinically intriguing because improvements occurred without corresponding major changes in HbA1c or systemic blood pressure, making a purely glycemic or systemic antihypertensive explanation less likely.

Nevertheless, the study did not demonstrate a comparable improvement in UACR. Nor were changes in TGF-β1 and VEGF-A sufficient to establish a mechanistic explanation. The apparent kidney-function effect also did not provide

evidence of sustained disease modification after treatment withdrawal. These limitations are not minor details; they define the uncertainty surrounding interpretation. A creatinine-derived eGFR change is potentially important but cannot alone establish structural renal preservation, particularly in a modestly sized study.

The results should therefore be described as a renal function signal rather than proof of renoprotection. Confirmation would require chronic eGFR-slope analysis over a longer duration, cystatin C-based filtration estimates, preferably measured GFR in a subset, reproducibility across independent populations and demonstration that the effect persists when participants receive current standard-of-care therapy.

4.3 Theme 3: Broader CKD Evidence Provides Partial Mechanistic Support

A 2025 randomized trial by Trugilho et al. investigated 300 mg/day tocotrienol-rich fraction for three months in patients with nondialysis and hemodialysis CKD. Only a small number of participants completed the study. Among nondialysis participants, CRP decreased, while hemodialysis participants showed reductions in total and LDL cholesterol. However, NRF2 and NF-κB mRNA expression did not significantly change, and the study was not designed to demonstrate long-term renal function preservation.[55]

These findings are useful precisely because they are mixed. They suggest that tocotrienol exposure may affect selected inflammatory or metabolic measures in CKD, but they do not support a simple model in which supplementation reliably activates NRF2, suppresses NF-κB and thereby improves kidney function. The broader randomized evidence synthesized by Khor et al.[49] similarly shows heterogeneous inflammatory and oxidative biomarker effects. Translational interpretation should therefore favor pathway-specific hypotheses over claims of generalized systemic antioxidant normalization.

4.4 Theme 4: eGFR and Albuminuria Should Not Be Expected to Move Identically

The absence of UACR improvement despite eGFR improvement is arguably the most important conceptual issue in this field. UACR reflects permeability and handling of albumin and is strongly influenced by the glomerular filtration barrier, podocytes, endothelial glycocalyx and proximal-tubular albumin retrieval. eGFR, in contrast, reflects global filtration and is affected by functioning nephron mass, glomerular hemodynamics and—when creatinine-based—creatinine production and handling. The two measures predict renal risk but are not biologically identical.[56]

The growing recognition of nonalbuminuric DKD provides real-world evidence of this decoupling. Shi et al.[7] demonstrated that a substantial DKD phenotype is characterized by impaired renal function without the albuminuric trajectory traditionally regarded as obligatory. Thus, absence of an albuminuria response does not logically preclude

a kidney-function effect. Conversely, an apparent eGFR improvement does not prove structural renoprotection simply because UACR is variable.

Several explanations deserve prospective testing. Tocotrienols might preferentially affect tubular metabolism or tubulointerstitial stress, preserving filtration without rapidly repairing the glomerular permeability barrier. Alternatively, endothelial or intrarenal hemodynamic effects might modify filtration independently of albumin handling. UACR variability and insufficient statistical power could obscure a modest response. The treatment duration may also have been insufficient for albuminuria and structural changes to align. Finally, creatinine-based estimates can change through non-GFR determinants of serum creatinine. The last possibility makes cystatin C and measured GFR confirmation essential.

Figure 2 highlights the central endpoint discordance and prevents the reader from interpreting DKD as a one-dimensional disease in which all renal biomarkers must improve simultaneously. It also frames the discordance as a mechanistic question that can be resolved through more specific filtration and compartment-level biomarkers.

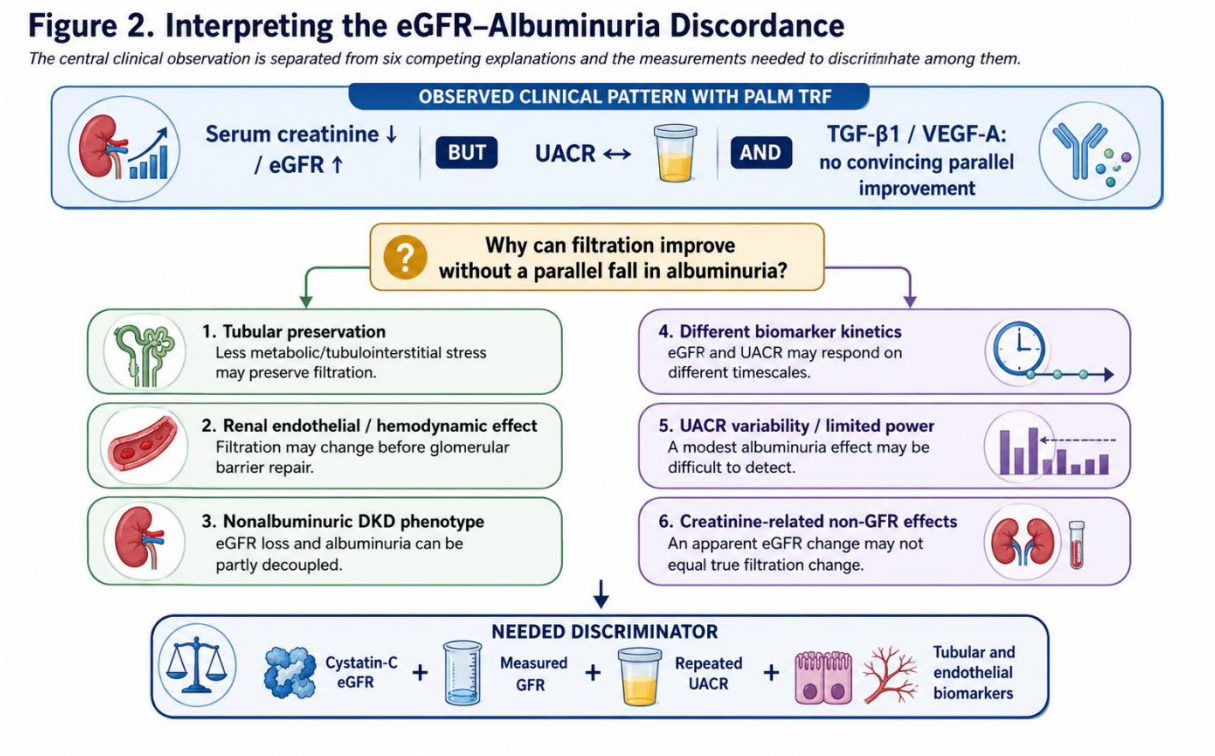

Figure 2: Interpreting the eGFR–albuminuria discordance

Figure 2 turns the apparent inconsistency into a falsifiable research question. If future studies reproduce creatinine-based eGFR improvement and also demonstrate favorable cystatin C or measured GFR changes with tubular injury

improvement, the case for genuine renal preservation would strengthen considerably. If the creatinine signal is not reproduced with noncreatinine filtration measures, the apparent benefit would require reinterpretation.

4.5 Theme 5: Tubular Biology Is a Particularly Attractive—but Untested—Explanation

The tubular hypothesis fits several strands of contemporary DKD biology. Proximal-tubular cells experience high energy demand and are exposed to excessive filtered glucose, altered sodium transport, fatty acids, albumin and inflammatory mediators. Mitochondrial dysfunction and hypoxia can amplify ROS production, while damaged tubules may produce inflammatory and fibrotic signals that accelerate interstitial scarring.[40–42] If tocotrienols stabilize membrane redox status or reduce lipid peroxidation, a tubular effect is biologically conceivable.

However, none of the existing DKD tocotrienol trials has established tubular protection using an adequate biomarker panel. Future trials should incorporate KIM-1 and other measures of tubular health, selected from biomarker literature rather than chosen opportunistically. Schrauben et al.,[57] for example, demonstrated associations between several plasma biomarkers—including KIM-1, TNFR1/2 and other inflammatory or injury markers—and DKD progression. Precision-medicine reviews similarly emphasize that biomarker panels may be more informative than a single marker when phenotyping heterogeneous DKD.[58]

4.6 Theme 6: Endothelial Effects Remain Plausible but Require Better Phenotyping

Endothelial dysfunction is another plausible interface between tocotrienol biology and DKD. Oxidative stress may reduce nitric-oxide bioavailability, promote adhesion-molecule expression and disrupt the glycocalyx. Because the glomerular endothelium is exposed directly to circulating metabolic and inflammatory signals, preservation of endothelial function could theoretically benefit both renal microvascular integrity and systemic cardiovascular risk.

Yet circulating endothelial markers are imperfect surrogates for the glomerular endothelium. The absence of convincing VEGF-A change in the tocotrienol DKD trial cautions against assigning a specific endothelial mechanism. Future trials could add soluble VCAM-1, ICAM-1, glycocalyx-associated markers and vascular-function measures while recognizing that no single circulating marker demonstrates kidney-specific endothelial repair. Integration of endothelial biomarkers with UACR, cystatin C and tubular injury markers would provide stronger compartmental inference.

4.7 Theme 7: Mitochondrial Protection Is Translationally Attractive but Clinically Unproven

Mitochondrial dysfunction could connect tocotrienol pharmacology with both glomerular and tubular protection because mitochondrial ROS, altered energetics and defective quality control occur across several renal cell types. Human DKD studies reviewed by Flemming et al.[36] show evidence of oxidative mitochondrial damage and disturbed mitochondrial biology. Contemporary mechanistic frameworks extend this to mitophagy and organelle crosstalk.[37] These pathways make lipid-soluble antioxidant intervention biologically compelling.

Nevertheless, most evidence linking tocotrienols to mitochondrial protection comes from non-DKD experimental settings. Translational proof would require demonstrating changes in relevant mitochondrial biomarkers or functional signatures in treated DKD patients and relating these changes prospectively to renal endpoints. Without such data, "mitochondrial protection" should be presented as a candidate mechanism rather than an established explanation of the observed eGFR signal.

4.8 Theme 8: Antifibrotic Claims Are Currently the Weakest Part of the Human Argument

Fibrosis is a compelling target because progression to advanced CKD depends heavily on maladaptive extracellular-matrix accumulation. TGF-β1 is a core driver, but the absence of a convincing TGF-β1 response in the clinical tocotrienol study prevents straightforward attribution of eGFR improvement to TGF-β suppression. This negative mechanistic finding should be viewed as informative rather than inconvenient.

Future studies should therefore avoid selecting one circulating TGF-β measure as a definitive fibrosis test. Multidimensional assessment could include collagen-turnover markers, imaging-based fibrosis measures where validated, urinary extracellular-matrix proteins and longer-term eGFR slope. A genuine antifibrotic effect is most credible when molecular changes are accompanied by altered disease trajectory.

4.9 Theme 9: Dose, Formulation and Exposure Are Underappreciated Sources of Heterogeneity

"Tocotrienol" is not a single standardized pharmaceutical exposure. Palm TRF, annatto preparations and isolated tocotrienol isoforms differ substantially. Even among palm preparations, α-, γ- and δ-tocotrienol content and α-tocopherol proportions may differ. Bioavailability can also vary with formulation and administration conditions.[22]
This complicates both negative and positive inference. Failure of one preparation should not automatically invalidate another, but success with one proprietary preparation cannot automatically be generalized to all palm tocotrienol products. Renal trials should therefore treat composition and pharmacokinetics as core methodological variables. Plasma tocotrienol measurements would permit exposure–response analysis, while formulation standardization would improve reproducibility.

5. DISCUSSION AND ANALYSIS

5.1 What Does the Evidence Actually Support?

The most defensible conclusion is that palm tocotrienols possess credible mechanistic plausibility and a preliminary human renal function signal, but not yet established renoprotective efficacy. This distinction matters. Renoprotection in modern nephrology implies evidence that an intervention slows progressive loss of kidney function or reduces clinically meaningful kidney outcomes. A favorable change in creatinine-derived eGFR in a small randomized trial is hypothesis-generating and clinically interesting, but it does not satisfy that standard by itself.

The phase IIb signal nevertheless deserves replication rather than dismissal. DKD is mechanistically heterogeneous, and an intervention need not reduce HbA1c, blood pressure and UACR simultaneously to influence another disease component. The absence of meaningful HbA1c and systemic blood-pressure changes may even strengthen the hypothesis that the renal-function effect, if genuine, arose through a non-glycemic mechanism. What remains unknown is whether that mechanism reflects cellular protection, altered renal hemodynamics, reduced tubular stress or a non-GFR effect on creatinine.

5.2 Renal Effects Independent of HbA1c and Systemic Blood Pressure

A key research question is whether tocotrienols could protect kidney function independently of glucose lowering. The concept is biologically credible because oxidative, inflammatory and endothelial processes persist despite acceptable glycemic control, partly as a consequence of cumulative metabolic injury and self-sustaining signaling. AGE accumulation, mitochondrial injury and fibrotic remodeling do not necessarily normalize immediately when glucose improves.[25,28]

Likewise, absence of systemic blood-pressure reduction does not exclude intrarenal effects. SGLT2 inhibitors illustrate the broader principle that renal benefits can involve tubular and glomerular physiology beyond their original glucose-lowering indication. Nevertheless, no evidence currently demonstrates that tocotrienols reproduce the well-characterized tubuloglomerular effects of SGLT2 inhibition. Mechanistic analogy must not become assumed equivalence.

5.3 The Modern Therapeutic Benchmark Is Much Higher

Interpretation of nutraceutical adjuncts must occur against the efficacy benchmark established by contemporary renal-outcome trials. DAPA-CKD demonstrated robust kidney and cardiovascular benefits with dapagliflozin,[8] and EMPA-KIDNEY broadened evidence for empagliflozin across CKD populations.[9] Long-term follow-up further supported durable benefit.[10]

The finerenone program independently demonstrated that targeting mineralocorticoid-receptor-mediated inflammatory and fibrotic signaling can improve clinical outcomes. FIDELIO-DKD established kidney benefit in patients with T2DM and CKD, FIGARO-DKD demonstrated cardiovascular benefit across a wider CKD spectrum, and pooled FIDELITY analysis reinforced cardiorenal efficacy.[11–13] The more recent CONFIDENCE trial also demonstrated that simultaneous finerenone and empagliflozin therapy produced a greater reduction in UACR than either agent alone, illustrating the increasingly high benchmark that any adjunctive intervention must meet.[59]

The therapeutic landscape has advanced further with semaglutide. FLOW demonstrated that a GLP-1 receptor agonist can reduce clinically important kidney outcomes in people with type 2 diabetes and CKD.[14] Thus, a future tocotrienol trial cannot answer the clinically meaningful question by comparing tocotrienol with placebo in undertreated patients. It should test whether tocotrienol provides incremental benefit over optimized contemporary therapy.

Earlier analyses of canagliflozin from CREDENCE similarly demonstrated renal benefit across baseline kidney-function and albuminuria strata, reinforcing the importance of clinically meaningful disease-modification benchmarks.[60,61] Guideline and consensus recommendations have consequently evolved toward layered cardiorenal protection rather than glucose control alone.[17–19]

Figure 3 is intended to establish the appropriate clinical positioning of tocotrienols. Palm TRF should not be depicted alongside proven therapies as though its evidence were equivalent.

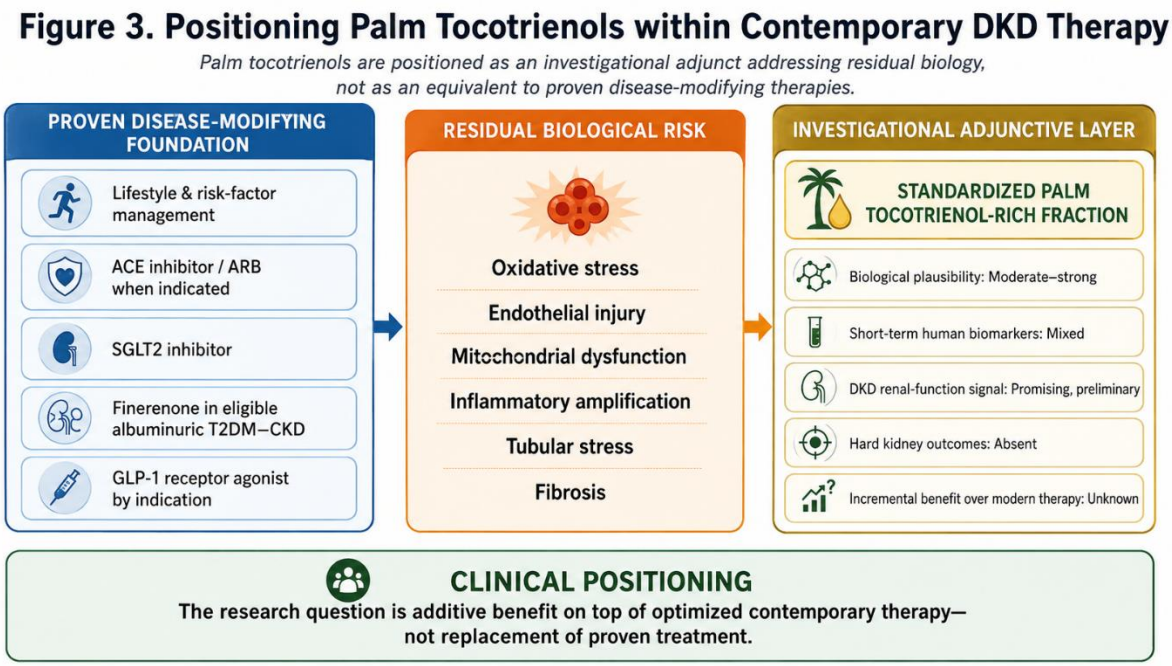

Figure 3: Positioning palm tocotrienols within contemporary DKD therapy

Figure 3 illustrates that the proposed position is explicitly adjunctive. No existing tocotrienol study provides evidence sufficient to replace SGLT2 inhibitors, renin–angiotensin system blockade, finerenone, or GLP-1 receptor agonists. The relevant clinical question is whether standardized palm TRF can address a measurable component of residual risk after evidence-based treatment has already been implemented.

5.4 Why Might Stage-3 CKD Be a Responsive Phenotype?

The reported stronger signal among participants with stage-3 CKD is intriguing because intermediate CKD may represent a window in which pathobiological stress is sufficiently pronounced to create therapeutic headroom while remaining reversible enough for functional improvement. Patients with very early disease might exhibit slow progression and ceiling effects, whereas advanced fibrotic disease may be too structurally fixed for a modest metabolic intervention to generate measurable improvement.

This hypothesis must be treated cautiously because subgroup findings from small trials are especially vulnerable to chance. A future trial should therefore prospectively stratify by eGFR category rather than retrospectively emphasizing the subgroup with the most favorable response. Stage-3 enrichment could be scientifically justified, but subgroup interaction testing should be prespecified.

5.5 Could Baseline Antioxidant Status Identify Responders?

An additional translational hypothesis is that patients with relatively low tocotrienol or broader vitamin-E status could derive greater biological benefit from supplementation. This would be consistent with nutrient pharmacology, in which deficiency or low exposure may create greater response potential than already adequate status. However, the current post-2020 evidence base does not establish a validated vitamin-E threshold for renal benefit.

Future trials should measure baseline α-tocopherol and individual tocotrienol isoforms and repeat measurements during therapy. These measurements would permit evaluation of pharmacokinetic adherence, identify low-exposure subgroups and allow exposure–response analyses. Without such data, apparent interindividual heterogeneity cannot be distinguished from formulation or adherence differences.

5.6 Biomarkers Should Be Used to Discriminate Mechanisms, Not Decorate Trials

Biomarkers in a future tocotrienol program should be selected according to explicit causal hypotheses. If tubular protection is hypothesized, tubular markers should be measured. If endothelial preservation is hypothesized, endothelial and glycocalyx-related measures should be included. If inflammation is central, the panel should extend beyond CRP to relevant cytokine/receptor systems. Schrauben et al. [57] demonstrated that biomarkers including KIM-1, TNFR1, TNFR2, MCP-1, suPAR and YKL-40 can carry prognostic information in DKD, while Sauriasari et al.[44] reviewed the expanding protein-biomarker landscape.

The goal should not be to find any statistically significant biomarker among dozens. Instead, investigators should prespecify mechanistic domains, control multiplicity and determine whether biomarker change mediates or predicts

filtration outcomes. Precision-medicine principles are particularly relevant because DKD populations may be biologically heterogeneous even when they share the same eGFR and UACR categories.[58]

5.7 Creatinine-Based eGFR Requires Independent Validation

An underappreciated issue is that creatinine-derived eGFR is not a direct measurement of filtration. Serum creatinine can be influenced by muscle mass, dietary intake, tubular secretion and other factors. A relatively modest change in creatinine may therefore produce an apparent eGFR improvement without corresponding structural renal change.

This issue can be resolved experimentally. Future tocotrienol trials should use both creatinine- and cystatin C-based eGFR, with measured GFR in a mechanistic subset. A concordant improvement across measures would materially strengthen causal inference. Chronic eGFR slope is also preferable to isolated between-group differences at selected time points because it directly quantifies trajectory. Contemporary discussions of surrogate endpoints in DKD increasingly emphasize careful interpretation of eGFR slope and albuminuria together rather than reliance on a single surrogate.[56] This measurement issue is clinically relevant because combined creatinine-cystatin C equations can improve GFR estimation, while individual-participant meta-analysis supports total eGFR slope as a valid surrogate endpoint for kidney-failure risk in appropriately designed trials.[62,63]

5.8 Cardiovascular Consequences Should Not Be Ignored

DKD is fundamentally a cardiorenal disease. Cardiovascular risk increases steeply as kidney function declines, and cardiovascular events compete with kidney failure as major outcomes.[64] If tocotrienols influence inflammation, lipid metabolism or endothelial function, cardiovascular endpoints may represent an important secondary translational domain.

The 2025 CKD study reporting lipid improvement in hemodialysis participants and CRP reduction in nondialysis CKD participants supports further investigation but is far too small to infer cardiovascular event reduction.[55] Future renal trials should therefore collect major cardiovascular events as prespecified safety and exploratory efficacy outcomes without claiming cardioprotection until sufficiently powered evidence exists.

5.9 Safety, Standardization and the Nutraceutical–Pharmaceutical Boundary

The fact that tocotrienols are naturally derived does not remove the need for pharmaceutical-quality investigation. DKD patients often receive multiple medications and may have advanced vascular disease, impaired renal clearance, anemia and altered nutrition. A formulation intended for adjunctive clinical use should therefore have verified content, stability, contaminants, batch consistency and pharmacokinetic characteristics.

Existing systematic evidence suggests that palm TRF has generally been well tolerated in studied populations.[23,51] However, the aggregate exposure remains much smaller than that available for approved DKD drugs. Large renal trials should prospectively capture bleeding events, hepatic abnormalities, gastrointestinal intolerance, medication interactions and other adverse events rather than assuming supplement-level safety.

5.10 Proposed Trial to Resolve the Current Uncertainty

A scientifically useful next trial should be a multicenter, randomized, double-blind, placebo-controlled study enrolling adults with T2DM and established DKD, with deliberate enrichment for stage-3 CKD while including both moderately and severely increased albuminuria. Background treatment should be stable and contemporary, including maximally tolerated renin–angiotensin system blockade where indicated and an SGLT2 inhibitor unless contraindicated. Finerenone and GLP-1RA use should be allowed and prespecified for stratification.

The investigational product should be a chemically standardized palm TRF with a precisely stated α-, β-, γ- and δ-tocotrienol and α-tocopherol composition. Pharmacokinetic sampling should verify exposure. Given the limitations of short trials, at least 18–24 months of follow-up would be preferable for a chronic eGFR-slope endpoint.

The primary endpoint should be chronic eGFR slope after the early treatment phase rather than a single serum creatinine comparison. Key secondary endpoints should include repeated UACR, cystatin C eGFR, a measured GFR substudy, and a composite kidney endpoint if sample size and duration permit. Biomarker domains should include tubular injury, inflammatory signaling, endothelial activation, and oxidative/lipid-peroxidation markers.

Figure 4 translates the review findings into a testable clinical-development strategy and directly addresses the limitations of previous tocotrienol trials. The design prioritizes rigorous filtration endpoints, mechanistic phenotyping and evaluation on top of contemporary standard-of-care treatment.

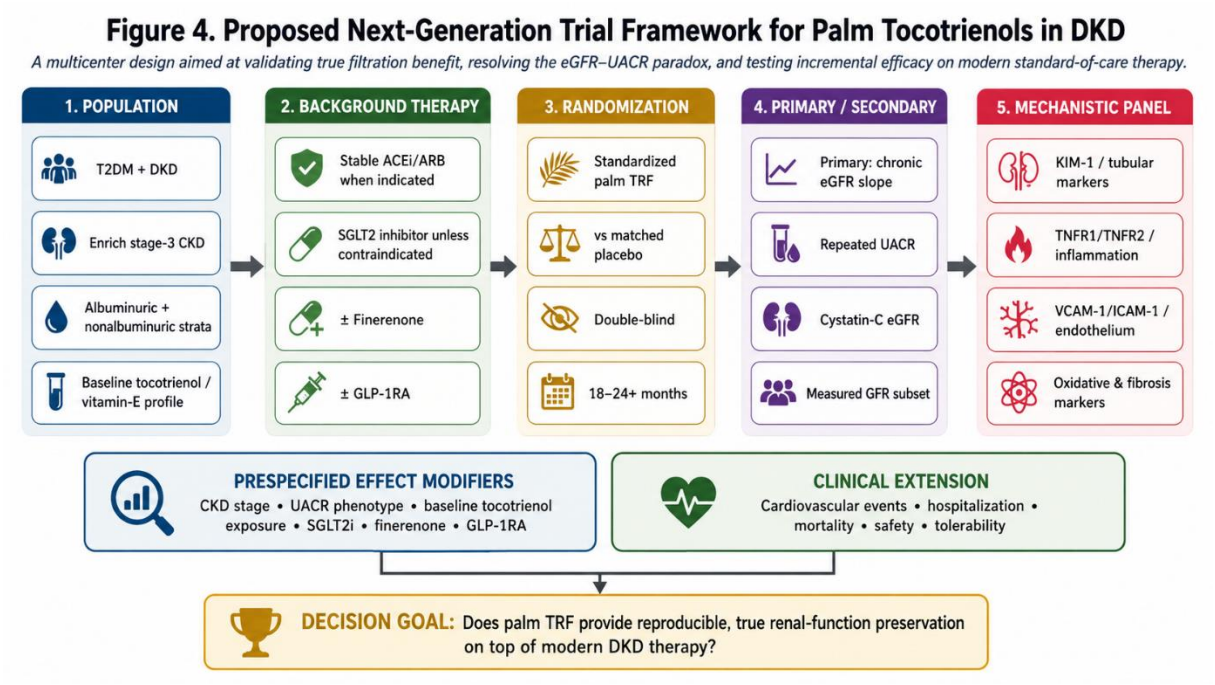

Figure 4: Proposed next-generation trial framework

Figure 4 illustrates how this design could determine whether the reported creatinine/eGFR signal represents true renal function preservation, clarify whether albuminuria is mechanistically dissociated from that effect, and establish whether tocotrienol treatment provides incremental benefit in the therapeutic era in which SGLT2 inhibitors, finerenone and GLP-1 receptor agonists are increasingly used. Such a framework would also help distinguish a pharmacologically meaningful renal effect from a formulation-specific, biomarker-specific or chance finding.

5.11 Strengths and Limitations of the Present Review

A strength of this review is its deliberate integration of modern DKD biology with the small but clinically provocative tocotrienol evidence base. Rather than inferring efficacy from antioxidant chemistry, the analysis asks which renal compartments and endpoints should change if proposed mechanisms are true. It also interprets tocotrienol findings against the much higher evidentiary standard created by recent kidney-outcome trials.

The principal limitation is the scarcity of direct renal tocotrienol trials. Much of the mechanistic discussion necessarily uses evidence from broader DKD pathophysiology or tocotrienol studies conducted outside DKD. The qualitative methodology also does not provide pooled effect estimates or a formal systematic risk-of-bias assessment. These limitations reinforce rather than weaken the central conclusion: the field currently supports a well-defined research hypothesis, not a clinical recommendation.

6. CONCLUSION

Diabetic kidney disease is driven by interacting metabolic, oxidative, endothelial, mitochondrial, inflammatory, tubular, and fibrotic processes that cannot be reduced to hyperglycemia or albuminuria alone. Palm-derived tocotrienols are scientifically interesting because their biological properties intersect with several components of this network and because randomized clinical evidence has produced a preliminary signal of improved serum-creatinine/eGFR measures in DKD.

The most important observation is not that tocotrienols are antioxidants, but that filtration-based renal measures may respond without corresponding improvement in albuminuria. This discordance creates several testable possibilities, including tubular preservation, renal endothelial or hemodynamic effects, differences in biomarker kinetics, nonalbuminuric disease biology, and non-GFR determinants of creatinine. Existing evidence cannot distinguish among these explanations.

Palm tocotrienols should consequently be regarded as an investigational adjunctive renoprotective strategy rather than an established treatment for DKD. There is presently no evidence that they should replace renin–angiotensin system inhibition, SGLT2 inhibitors, finerenone, GLP-1 receptor agonists or other guideline-directed therapy.

The next phase of research should move away from small supplement trials toward standardized pharmacological investigation. Adequately powered multicenter trials should use chronic eGFR slope, repeated albuminuria, cystatin C and measured GFR validation; characterize tubular, endothelial, inflammatory and oxidative phenotypes; quantify actual tocotrienol exposure; and test efficacy on top of contemporary standard-of-care therapy. Such studies could determine whether the renal function signal represents genuine disease modification and, if so, identify the patients and biological pathways in whom palm tocotrienols provide meaningful incremental benefit.

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