

## Review Article

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## From Nerve Conduction to Symptom Relief: Palm Tocotrienols in Diabetic Peripheral Neuropathy—Reconciling Mechanistic Promise with Clinical Discordance: A Critical Review

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**ABSTRACT**

Diabetic peripheral neuropathy (DPN) remains one of the most prevalent and disabling complications of diabetes and is characterized by progressive sensory dysfunction, neuropathic pain, loss of protective sensation, impaired mobility, foot ulceration, and increased amputation risk. Current pharmacological treatment is primarily symptom-oriented, whereas therapies capable of reliably preventing or reversing established peripheral nerve injury remain limited. Palm-derived tocotrienols have attracted clinical interest because their antioxidant, anti-inflammatory, metabolic, and neuroprotective activities intersect with several mechanisms implicated in DPN.

However, clinical evidence is discordant. Tocotrienol-rich vitamin E has produced improvements in selected nerve-conduction parameters and neurotrophic biomarkers, whereas larger clinical studies have not demonstrated consistent improvements in overall neuropathic symptoms or neurological impairment. This critical qualitative review synthesizes contemporary mechanistic, translational, and clinical evidence to explain this discrepancy. It argues that biomarker change, electrophysiological improvement, pain relief, structural nerve regeneration, and durable disease modification represent distinct levels of therapeutic evidence and should not be treated interchangeably. Differences in disease stage, painful versus painless phenotype, metabolic status, formulation, bioavailability, treatment duration, and endpoint selection may contribute to heterogeneous findings. Palm tocotrienols therefore remain investigational adjunctive neuroprotective candidates rather than established treatments for DPN. Future trials should emphasize early-stage disease, standardized formulations, pharmacokinetic verification, mechanistic phenotyping, multidimensional nerve assessment, functional outcomes, and post-treatment durability.

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**Introduction**

Diabetic peripheral neuropathy (DPN), particularly distal symmetrical sensorimotor polyneuropathy, represents one of the most frequent chronic complications of both type 1 and type 2 diabetes. Its clinical spectrum extends from subclinical small-fiber injury and asymptomatic loss of protective sensation to burning pain, electric-shock-like sensations, paresthesia, numbness, gait instability, foot ulceration, and ultimately lower-extremity amputation. Contemporary reviews estimate that a substantial proportion of individuals with diabetes develop peripheral nerve abnormalities during the course of disease, although prevalence varies according to diabetes duration, diagnostic methodology, age, cardiometabolic phenotype, and the definition of neuropathy used [1-4].

The clinical importance of DPN extends far beyond abnormal nerve conduction or sensory examination. Neuropathic pain may disrupt sleep, mobility, work productivity, mood, and social functioning, whereas painless sensory loss creates a different but

equally important hazard by removing protective warning signals from the feet. A large contemporary survey of 6,960 individuals with diabetes demonstrated marked deterioration in quality of life and mental-health indices among those with DPN, particularly in the presence of neuropathic pain [5]. Once DPN contributes to ulceration in combination with deformity, repetitive pressure, peripheral arterial disease, or infection, the risk of hospitalization and amputation becomes clinically substantial [6,7].

Current management therefore has at least three separate objectives: reducing risk-factor-driven nerve injury, treating neuropathic pain, and preventing secondary foot complications. Contemporary diabetes guidance emphasizes glycemic management together with control of weight, blood pressure, and serum lipids, while pharmacotherapy for painful DPN includes gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium-channel-active agents [8,9]. Recent US guideline syntheses likewise emphasize individualized goals, attention to function and quality of life, and escalation to topical or neuromodulatory options when conventional pharmacotherapy is inadequate [10,11]. These approaches are clinically important, but symptomatic pain reduction should not be confused with restoration of damaged peripheral nerves. Indeed, the absence of an established intervention capable of reliably reversing neuronal

loss remains one of the defining therapeutic gaps in DPN [12-14]. Recognition of this gap has encouraged investigation of mechanism-based interventions. DPN is no longer understood as a simple consequence of chronically elevated blood glucose. Hyperglycemia interacts with dyslipidemia, insulin resistance, obesity, advanced glycation, oxidative stress, mitochondrial dysfunction, endothelial injury, microvascular insufficiency, inflammation, Schwann-cell dysfunction, and impaired neurotrophic support. These mechanisms form a self-reinforcing neurovascular-metabolic network that eventually produces demyelination, axonal degeneration, and altered nociceptive processing [15-18].

Within this mechanistic context, tocotrienols are biologically interesting. Tocotrienols belong to the vitamin-E family and occur as  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -isomers. Palm oil is an important natural source of mixed tocotrienols and tocopherols, and palm-derived tocotrienol-rich fractions have been investigated in a range of inflammatory, metabolic, neurological, cardiovascular, and degenerative conditions. Tocotrienols possess an unsaturated isoprenoid side chain that distinguishes them structurally from tocopherols and influences membrane behavior, distribution, metabolism, and possibly biological activity [19-21].

The attractiveness of tocotrienols for DPN arises from the overlap between their proposed biological actions and recognized DPN mechanisms. Antioxidant activity could theoretically reduce lipid peroxidation and oxidative damage; anti-inflammatory effects could attenuate NF- $\kappa$ B-related signaling and inflammatory mediators; effects on vascular and cellular function could influence endoneurial perfusion; and neuroprotective actions might preserve vulnerable neurons or glial cells. Preclinical evidence and broader neuroprotection literature support several of these possibilities, although translation into human clinical benefit remains substantially less certain [22-24].

The central clinical problem is therefore not a simple absence of evidence. Rather, it is discordant evidence at different levels of biological organization. The VENUS randomized clinical trial of 300 adults found that oral mixed tocotrienols given for one year did not significantly improve the overall Total Symptom Score, although exploratory subgroup signals were reported [25]. A subsequent phase-II randomized trial reported improvement in several nerve-conduction velocities and an increase in serum nerve growth factor after tocotrienol-rich vitamin-E supplementation [26]. A longer trial then found improvements in median and sural sensory nerve-conduction velocity during supplementation, but these differences were no longer apparent after a six-month washout period [27]. Recent quantitative synthesis consequently suggests modest selective improvements in nerve-conduction velocity while emphasizing the absence of convincing evidence for axonal regeneration, glycemic effects, or comprehensive functional benefit [28].

This discrepancy creates the central question for the present article: how should clinicians interpret a nutraceutical intervention when mechanistic plausibility and selected neurophysiological outcomes appear more favorable than patient-reported symptom outcomes? Answering this requires a hierarchy of evidence rather than a binary classification of tocotrienols as either effective or ineffective.

Accordingly, this critical qualitative review examines the pathophysiological rationale, pharmacological characteristics, mechanistic evidence, clinical trial findings, and methodological

limitations surrounding palm-derived tocotrienols in DPN. The review specifically distinguishes pain relief, biomarker modification, electrophysiological improvement, neuroprotection, remyelination, axonal regeneration, functional recovery, and durable disease modification. Its central proposition is that these outcomes occupy different levels of therapeutic evidence and should not be used interchangeably.

### **Literature Review: Conceptual and Theoretical Foundations** **DPN as a Multihit Neurovascular-Metabolic Disorder**

The traditional glucose-centric view of diabetic neuropathy is increasingly being replaced by a multihit model. Hyperglycemia activates the polyol pathway, promotes advanced glycation, increases protein-kinase-C activity, alters hexosamine metabolism, and intensifies oxidative stress. Yet glycemic exposure alone does not adequately explain individual variability, particularly in type 2 diabetes. Obesity, insulin resistance, dyslipidemia, hypertension, smoking, and other components of cardiometabolic dysfunction contribute independently or synergistically to neuropathy risk [15,17,13].

Dyslipidemia has become especially important in contemporary models. Peripheral nerves contain extensive lipid-rich membranes and myelin, and abnormal circulating fatty acids and lipoproteins can influence oxidative injury, mitochondrial substrate handling, Schwann-cell biology, and inflammatory signaling. Clinical and experimental literature consequently supports a relationship between altered lipid metabolism and peripheral nerve dysfunction, while the broader metabolic-syndrome phenotype appears particularly relevant to early small-fiber injury [16,29].

Advanced glycation represents another mechanism linking chronic metabolic stress to nerve injury. Advanced glycation end products can modify structural proteins and interact with the receptor for advanced glycation end products, activating NF- $\kappa$ B, oxidative stress, vascular inflammation, and extracellular-matrix changes. Recent reviews continue to identify AGE-RAGE signaling as an important bridge between metabolic exposure and inflammatory neurovascular injury, although the therapeutic translation of antiglycation strategies remains incomplete [30,31].

Oxidative stress occupies a central position because several metabolic abnormalities converge on excessive formation of reactive oxygen and nitrogen species. Peripheral nerves are especially vulnerable because long axons require substantial energy to maintain ion gradients, axonal transport, membrane integrity, and interactions with supporting Schwann cells. Oxidative injury can therefore affect mitochondria, proteins, membrane lipids, DNA, microvasculature, and signaling pathways simultaneously [32-34].

Mitochondrial dysfunction further amplifies this process. Reduced ATP production impairs axonal maintenance and transport, while damaged mitochondria themselves generate additional reactive species. This bioenergetic perspective is important because it explains why DPN may progress despite moderate improvement in glucose control once a self-sustaining cycle of mitochondrial, vascular, and inflammatory injury has developed. Contemporary mechanistic reviews emphasize this interaction between metabolic overload, bioenergetic failure, glial dysfunction, and distal axonal vulnerability [12,14].

Inflammation similarly cannot be considered an isolated pathway. Hyperglycemia, AGEs, oxidized lipids, mitochondrial danger signals, and tissue injury can activate inflammatory transcriptional pathways and cytokine release. Neuroinflammation can alter

nociceptive processing while simultaneously worsening vascular and structural damage. Consequently, an intervention that lowers inflammatory activity could theoretically affect pain, neuronal survival, or vascular function, but the clinical outcome would depend on which inflammatory pathways are actually modified and whether irreversible structural loss has already occurred [35,31]. These interacting pathways explain why DPN remains difficult to treat with single-target approaches. The clinical phenotype present at a particular moment reflects not only current metabolic exposure but accumulated historical injury. Two patients with similar HbA1c may therefore have markedly different nerve reserve, small-fiber density, large-fiber involvement, inflammatory status, pain sensitization, and regenerative potential. Such heterogeneity provides an important conceptual basis for interpreting inconsistent nutraceutical trials [2,36].

### **Clinical Phenotype and Measurement**

DPN is clinically heterogeneous, and the choice of outcome measure determines what aspect of neuropathy is being observed. Conventional nerve-conduction studies predominantly assess large myelinated fibers. They are useful for documenting slowing of conduction, distal latency, and action-potential amplitude, but they are relatively insensitive to early small-fiber dysfunction. A therapy could therefore influence small fibers without substantially altering conventional conduction measures, or conversely improve myelin-related conduction velocity without producing meaningful regeneration of lost axons [1].

This distinction is increasingly important because modern diagnostic techniques can quantify components of neuropathy that routine clinical examination may miss. Corneal confocal microscopy permits non-invasive quantification of corneal small-fiber morphology and has emerged as an attractive candidate biomarker for early DPN and longitudinal nerve assessment. Contemporary reviews and meta-analyses show reductions in corneal nerve-fiber measures in patients with diabetes and neuropathy, while emphasizing the need for standardized acquisition and interpretation [37-39]. Comparative evidence also indicates that corneal confocal microscopy can have lower diagnostic sensitivity than intraepidermal nerve-fiber density in recently diagnosed type 2 diabetes, supporting its use as a complementary rather than stand-alone measure [40]. A recent review similarly highlights the promise of corneal nerve imaging for early detection while underscoring the need for harmonized evaluation methods and broader clinical validation [41].

Skin biopsy with quantification of intraepidermal nerve-fiber density remains another objective approach to small-fiber neuropathy. Although more invasive than corneal confocal microscopy, it can document actual small-fiber loss and can be repeated in longitudinal research. Its relevance to tocotrienol trials is conceptual: an intervention claimed to induce structural neuroprotection or regeneration should ideally eventually demonstrate effects on structural nerve measures rather than relying solely on circulating biomarkers or conduction velocity [42,43].

Pain represents yet another dimension. Painful DPN depends not simply on the amount of peripheral nerve loss but on patterns of abnormal excitability, surviving nociceptors, ectopic activity, spinal processing, and central sensitization. Consequently, the relationship between peripheral nerve structure and pain intensity is nonlinear. Severe sensory loss may occur without pain, while substantial pain can exist when conventional nerve-conduction

abnormalities are relatively modest [32,3]. This is one major reason why improved conduction cannot automatically be expected to produce immediate symptom relief.

### **Contemporary Treatment and the Meaning of “Disease Modification”**

The pharmacological treatment of painful DPN is dominated by agents that modulate neuronal excitability or monoaminergic pain processing. Updated clinical guidance recommends drug classes including gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium-channel blockers. Treatment selection should also consider sleep disturbance, mood, adverse effects, comorbidities, and patient preferences [9,44].

The OPTION-DM trial provided important comparative evidence by showing broadly similar analgesic efficacy among commonly used treatment pathways and demonstrating that combination treatment can benefit patients with inadequate response to monotherapy<sup>45</sup>. Reviews of pharmacotherapy similarly emphasize that available agents reduce pain rather than reverse the underlying metabolic-neurovascular disorder [46-48].

Neuromodulation has expanded options for refractory painful DPN. High-frequency spinal-cord stimulation has demonstrated substantial pain reduction in selected patients with refractory disease, illustrating that clinically meaningful analgesia can occur by modifying pain transmission without proving regeneration of damaged peripheral axons [49-51]. Longer-term SENZA-PDN follow-up reported sustained reductions in pain with improvements in health-related quality of life and sleep over 24 months [52], while a related analysis documented improved protective sensation in some treated participants [53]. These observations provide a useful analogy for tocotrienol interpretation because symptomatic, functional, and structural outcomes can move differently depending on the mechanism and endpoint being measured.

Thus, disease modification should be defined more rigorously than symptom improvement. A disease-modifying intervention should ideally alter the trajectory of underlying nerve pathology, preserve or restore nerve structure and function, reduce progression toward sensory loss and foot complications, and show persistence beyond the immediate pharmacological exposure. Recent meta-analytic work on putative disease-modifying pharmacotherapies shows that improvements in conduction and sensory measures can be demonstrated for some interventions, but these surrogate gains still require cautious interpretation in relation to durable structural and patient-centered outcomes [54]. Modern reviews consequently continue to emphasize that clinically validated disease-modifying therapies remain an unmet need [55,4].

### **Tocotrienol Biology and Translational Plausibility**

Vitamin E comprises tocopherol and tocotrienol isoforms. Although the chromanol head group is shared, tocotrienols possess an unsaturated side chain that affects membrane distribution and metabolism. Palm-derived tocotrienol-rich fractions generally contain multiple tocotrienol isomers together with varying quantities of tocopherol, meaning that “tocotrienol supplementation” is not a chemically uniform intervention [19,20]. This formulation heterogeneity has direct translational implications. Human pharmacokinetic evidence indicates that tocotrienol absorption and systemic exposure vary according to isomer, formulation, dose, food intake, and delivery system. Palm-derived mixed preparations may therefore generate different tissue exposure than purified or annatto-derived preparations, and

recent delivery-focused reviews identify poor aqueous solubility, rapid elimination, chemical instability, and saturable intestinal absorption as persistent barriers to clinical translation [56-57]. Emphasized substantial pharmacokinetic variability and the importance of bioavailability when interpreting clinical efficacy, whereas self-emulsifying delivery strategies have been proposed to improve solubility and oral exposure [58].

Mechanistically, antioxidant activity provides the most obvious link to DPN, but reducing tocotrienols to “antioxidants” is overly simplistic. Tocotrienols can influence lipid peroxidation, inflammatory signaling, cellular stress responses, and potentially endothelial and neuroprotective pathways. Reviews of palm-derived tocotrienols describe effects relevant to NF- $\kappa$ B signaling, inflammatory mediators, oxidative stress, cellular survival, and neurological injury [22,21].

At the same time, randomized evidence across conditions demonstrates why mechanism cannot substitute for clinical confirmation [23]. Found that tocotrienol supplementation did not produce uniform effects across commonly measured oxidative and inflammatory biomarkers. Likewise, broader assessments of

palm tocotrienol-rich fraction trials reveal heterogeneity in dose, duration, population, formulation, and outcome measures [59]. These findings caution against assuming that antioxidant or anti-inflammatory activity is universal across clinical settings.

Neurological evidence nonetheless supports continued interest. Contemporary reviews describe neuroprotective effects of tocotrienol-rich fractions in experimental models and suggest actions involving oxidative stress, inflammation, apoptosis, cellular metabolism, and neuronal signaling [24]. Human brain-health literature similarly indicates that tocotrienols may reach relevant tissues despite comparatively low plasma bioavailability, although clinical findings remain heterogeneous [60].

Figure 1 summarizes the central mechanistic premise of this review: tocotrienols do not target a single DPN pathway. Their proposed relevance arises because several potential actions intersect with the interconnected oxidative, inflammatory, metabolic, mitochondrial, and neurovascular processes that produce peripheral nerve dysfunction.

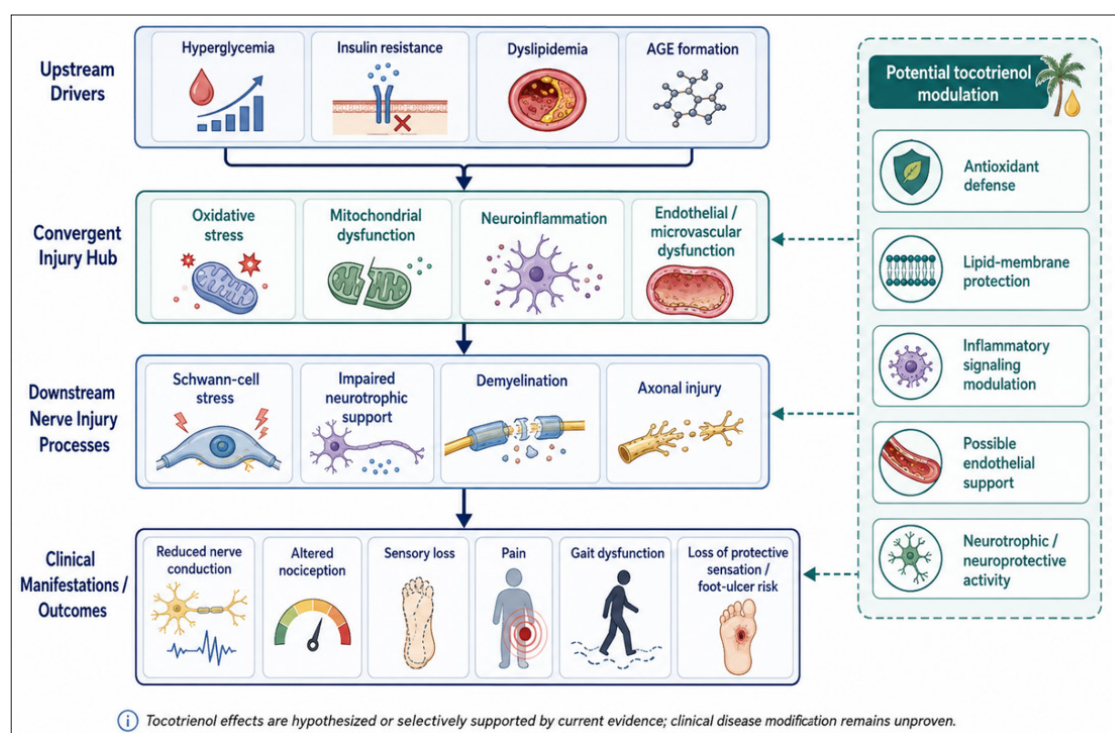


**Figure 1:** Multihit DPN Pathogenesis and Potential Tocotrienol Intervention Points

The figure should be interpreted as a hypothesis map rather than proof of clinical efficacy. Tocotrienol activity at one or more upstream pathways could theoretically slow neural dysfunction, but the extent to which such activity reaches peripheral nerves in humans, occurs at clinically sufficient exposure, and alters irreversible structural injury remains uncertain.

## Methods

This article employed a critical qualitative literature-review methodology, not a systematic literature review. The purpose was interpretive synthesis: to examine why mechanistic, biomarker, electrophysiological, symptomatic, and functional evidence concerning tocotrienols in DPN may produce different conclusions.

Literature was identified primarily through PubMed/MEDLINE, Scopus, Web of Science, and supplementary citation tracing using Google Scholar. Search concepts combined terms relating to diabetic peripheral neuropathy, painful diabetic neuropathy, distal symmetrical polyneuropathy, tocotrienol, tocotrienol-rich fraction, palm vitamin E, oxidative stress, mitochondrial dysfunction, inflammation, nerve growth factor, nerve conduction, neuropathic pain, small-fiber neuropathy, neuroprotection, and nerve regeneration.

Priority was assigned to peer-reviewed literature published from 2020 through 2026. Randomized clinical trials, contemporary clinical guidelines, high-quality narrative and systematic reviews, meta-analyses, diagnostic literature, and translational studies were

used to establish the current evidence landscape. Seminal older evidence was considered conceptually where necessary to interpret the development of tocotrienol research but was not allowed to dominate the contemporary reference base.

The literature was analyzed thematically rather than pooled quantitatively. The interpretive process focused on five questions: what pathogenic mechanism was being targeted; what form and formulation of tocotrienol was used; what biological or clinical endpoint was measured; whether the observed endpoint represented symptoms, function, electrophysiology, or structure; and whether treatment effects persisted after supplementation ceased. This approach follows the methodological objective of qualitative reviews: to explain relationships and contradictions across heterogeneous evidence rather than to generate a new pooled effect estimate.

Because this was not an SLR, no claim of exhaustive database capture, PRISMA-based study selection, formal pooled meta-analysis, or comprehensive risk-of-bias scoring is made. Published systematic reviews and meta-analyses are instead treated as individual evidence sources within the qualitative synthesis.

## **Results: Thematic Findings**

### **Theme One: Tocotrienol Plausibility Is Strongest at the Mechanistic Level**

The first major finding is that DPN biology contains several plausible targets for tocotrienol activity. Oxidative stress acts as a convergence point for hyperglycemia, AGE-RAGE signaling, dyslipidemia, mitochondrial overload, and vascular dysfunction. Tocotrienols possess chemical properties capable of interrupting lipid peroxidation and may influence redox-sensitive signaling pathways. This provides a credible foundation for investigation, particularly because peripheral nerves contain lipid-rich structures and face unusually high energetic demands [15,34].

Inflammation supplies a second rationale. NF- $\kappa$ B activation and inflammatory mediators participate in both nerve injury and nociceptive processing. Tocotrienol-rich fractions and individual tocotrienols have demonstrated anti-inflammatory activity across experimental and some human settings, although meta-analytic evidence shows that changes in CRP, IL-6, TNF- $\alpha$ , and oxidative markers are not uniformly reproducible [23,21].

A third possible pathway concerns metabolic control itself. In a randomized trial involving patients with type 2 diabetes,  $\delta$ -tocotrienol supplementation was associated with improvements in glycemic variables, oxidative-stress indices, inflammatory biomarkers, and selected microRNA expression patterns [61]. Such findings demonstrate systemic biological activity, but they should not be directly extrapolated to peripheral nerve regeneration. Metabolic improvement creates a potentially more favorable neural environment; it does not establish that lost axons have been restored.

Overall, therefore, tocotrienols satisfy an important but preliminary criterion for therapeutic development: multiple plausible biological

mechanisms intersect with DPN pathophysiology. The critical issue is how far this mechanistic plausibility travels along the clinical evidence pathway.

### **Theme Two: Neurophysiological Findings Are More Encouraging Than Symptom Outcomes**

The strongest contemporary DPN-specific tocotrienol evidence concerns nerve-conduction measurements [26]. Conducted a multicenter randomized double-blind placebo-controlled phase-II study in which tocotrienol-rich vitamin E was associated with improvement in conduction velocities of median, sural, and tibial nerves over eight weeks. Serum nerve growth factor also increased, providing a biologically coherent but indirect marker of possible neurotrophic activity.

Longer follow-up produced a similarly intriguing pattern [27]. Reported improvements in median and sural sensory nerve-conduction velocity after 12 months of tocotrienol-rich vitamin-E supplementation, with a shorter period of improvement in tibial motor conduction. Importantly, the differences were no longer evident after a subsequent six-month washout period. This suggests that continued exposure may have been necessary to maintain the observed neurophysiological effect.

The absence of persistence after withdrawal has major implications for terminology. A reversible improvement during active supplementation might reflect altered myelin function, membrane physiology, microvascular perfusion, metabolic environment, or conduction properties rather than structural regeneration. True axonal regeneration would generally be expected to produce some degree of durable structural or functional change, although the biology of nerve recovery is complex.

The most recent quantitative synthesis reinforces this interpretation [28]. Reported modest improvements in sural sensory, median sensory, and tibial motor nerve-conduction velocities across randomized trials, whereas nerve-action-potential amplitudes and HbA1c did not improve meaningfully. The authors interpreted this pattern as being more compatible with preservation or myelin-related effects than demonstrated axonal regeneration and emphasized the need for pain, gait, and quality-of-life endpoints.

This emerging evidence makes it increasingly difficult to describe tocotrienol trials simply as “positive” or “negative.” If an intervention changes nerve-conduction velocity but not amplitude, pain, disability, or treatment durability, the correct interpretation is selective neurophysiological activity, not established restoration of peripheral nerve health.

Table 1 consolidates the pivotal tocotrienol-related clinical evidence that underpins the mechanistic-clinical discordance discussed in this review. It is intended as an interpretive evidence map rather than as a quantitative ranking of efficacy, because the studies differ in design, duration, formulation, and endpoint architecture.

| Clinical interpretation of key tocotrienol-related evidence in diabetic peripheral neuropathy |                                                                           |                                                                                        |                                                                 |                                                     |
|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------|
| Evidence source                                                                               | Design / exposure                                                         | Principal endpoint signal                                                              | Key limitation                                                  | Interpretive level                                  |
| VENUS trial (ref. 25)                                                                         | Randomized, placebo-controlled; mixed tocotrienols, 400 mg/day for 1 year | No significant overall Total Symptom Score improvement; exploratory subgroup signals   | Symptom-centered outcome remained negative overall              | Symptomatic efficacy not established                |
| Ng et al. trial (ref. 26)                                                                     | Phase-II randomized trial; tocotrienol-rich vitamin E over 8 weeks        | Improved selected median, sural, and tibial conduction velocities; serum NGF increased | Short duration and surrogate neurophysiological endpoints       | Target-relevant biological / physiological activity |
| Chuar et al. trial (ref. 27)                                                                  | Randomized trial; tocotrienol-rich vitamin E for 12 months plus washout   | Selected sensory conduction velocities improved during treatment                       | Differences were not sustained after 6-month washout            | Potential exposure-dependent physiological effect   |
| Alhajaji et al. meta-analysis (ref. 28)                                                       | Meta-analysis of randomized vitamin E and tocotrienol trials              | Modest improvements in selected nerve-conduction velocities                            | No convincing amplitude, glycemic, or durable structural effect | Disease modification remains unproven               |

The table shows why the evidence cannot be reduced to a single positive-or-negative verdict. Symptom-centered evidence remains unconvincing overall, whereas selected biomarker and nerve-conduction outcomes suggest biological activity whose structural durability and patient-centered significance remain uncertain.

**Theme Three: Pain Relief and Peripheral Neuroprotection Are Different Biological Questions**

Neuropathic pain depends on abnormal sensory signaling rather than simply the quantity of surviving peripheral nerve fibers. Peripheral sensitization, spontaneous firing, sodium-channel changes, ectopic activity, spinal amplification, impaired descending inhibition, and central sensitization can all contribute to pain. Consequently, preserving or improving peripheral conduction does not guarantee an analgesic response [32].

Conversely, effective analgesic therapy can reduce pain without modifying peripheral pathology. The success of duloxetine, pregabalin, amitriptyline, and neuromodulation illustrates this distinction. OPTION-DM showed clinically useful pain reduction with combinations of standard agents, while high-frequency spinal-cord stimulation can substantially reduce refractory pain through neuromodulatory mechanisms [45,49].

Tocotrienols may therefore occupy an entirely different therapeutic category from conventional analgesics. If their principal biological activity relates to oxidative stress, myelin function, cellular survival, or microvascular biology, symptom scales may be relatively insensitive during short or intermediate treatment periods. However, the reverse argument must also be respected: failure to improve symptoms cannot simply be dismissed as an endpoint problem. Patient-centered outcomes matter, and a clinically useful DPN intervention should eventually demonstrate benefit that patients can feel or that reduces future disability.

This produces a balanced interpretation. Lack of symptom improvement does not necessarily prove absence of biological activity, but biological activity without symptomatic, functional, or prognostic benefit remains insufficient for routine therapeutic recommendation.

Figure 2 provides the evidence hierarchy required to prevent overinterpretation of tocotrienol findings. Movement up this hierarchy requires increasingly strong clinical evidence.

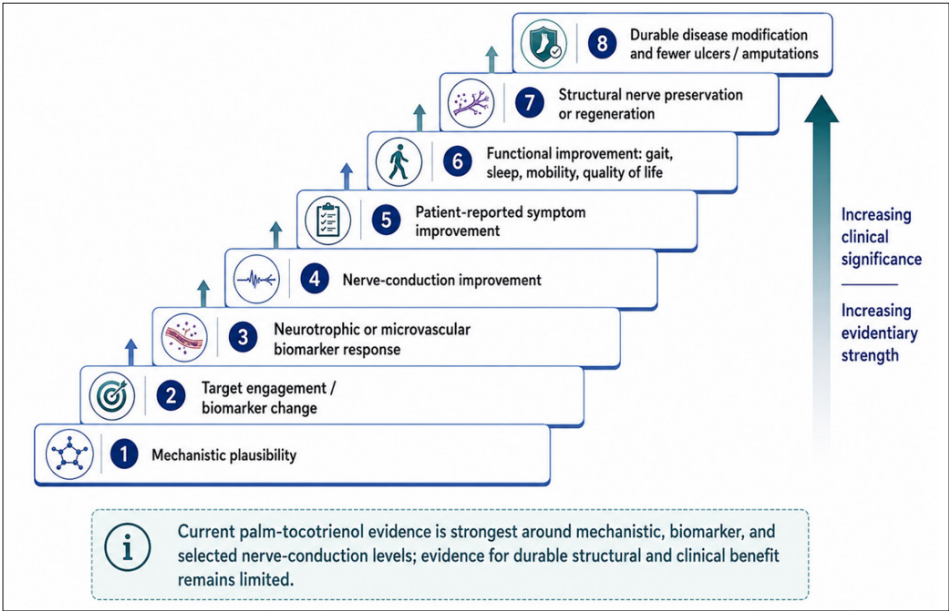


**Figure 2:** The therapeutic-evidence staircase for DPN

Current evidence for palm-derived tocotrienols is strongest around Levels 1–4. Evidence becomes markedly thinner at Levels 5–8. The central analytical error to avoid is interpreting a Level-3 or Level-4 effect as evidence for Level-7 or Level-8 efficacy.

#### **Theme Four: Conduction Velocity and Axonal Integrity Must Be Separated**

Nerve-conduction velocity is strongly influenced by myelin integrity, fiber diameter, temperature, and physiological conditions. In contrast, sensory and compound muscle action-potential amplitudes more directly reflect the number and integrity of functioning axons, although these measures are themselves imperfect. This distinction is critical to the interpretation of recent tocotrienol evidence.

If conduction velocity improves while amplitude remains unchanged, several explanations are possible. Myelin function may have improved; metabolically impaired but viable fibers may conduct more effectively; microvascular perfusion may have improved; or measurement variability may contribute. What cannot be concluded from this pattern alone is that previously lost axons have regenerated.

The issue becomes especially important in advanced DPN, where substantial axonal loss may already have occurred. At that stage, antioxidant or anti-inflammatory therapy may improve the biological environment without being capable of replacing lost neurons. This provides a plausible explanation for why an intervention might improve physiological measures in selected surviving fibers while producing little perceptible improvement in numbness or pain.

Future tocotrienol trials should therefore include complementary structural and physiological endpoints. Corneal confocal microscopy could quantify small-fiber morphology non-invasively, while intraepidermal nerve-fiber density could provide structural information in mechanistically intensive studies. Combining these measures with nerve conduction, quantitative sensory testing, symptom scores, and functional outcomes would substantially strengthen causal interpretation [37–39,43].

#### **Theme Five: Disease Stage May Determine Reversibility**

One of the most important hypotheses emerging from this synthesis is that timing matters. Early DPN may involve metabolic dysfunction, small-fiber injury, altered membrane physiology, microvascular abnormalities, and inflammatory stress before extensive irreversible axonal loss has developed. An intervention that modifies oxidative or inflammatory pathways could theoretically have greater effect at this stage than after years of established neuropathy.

This concept is consistent with contemporary calls for earlier DPN detection. Conventional bedside methods often identify neuropathy only after substantial sensory dysfunction exists, whereas corneal confocal microscopy and other small-fiber techniques can detect abnormalities earlier in the disease course [1,37]. Early detection could therefore have therapeutic as well as diagnostic significance. Late-stage DPN presents a different biological substrate. Once substantial axonal degeneration, denervation, foot deformity, and loss of protective sensation exist, reducing oxidative stress may not restore lost nerve architecture. Failure of an intervention in such a population could reflect irreversibility rather than absence of biological activity.

This hypothesis remains unproven for tocotrienols, but it generates a clear research direction. Trials should stratify participants

according to DPN duration, small-fiber versus large-fiber involvement, amplitude loss, pain phenotype, and markers of nerve reserve. Treating all DPN as a homogeneous condition may dilute signals from biologically responsive subgroups.

#### **Theme Six: Metabolic Phenotype May Modify Treatment Response**

DPN in type 2 diabetes is strongly influenced by the broader metabolic environment. Obesity, triglyceride elevation, insulin resistance, and dyslipidemia contribute to nerve injury through pathways that overlap with oxidative stress and mitochondrial dysfunction. Patients with metabolically driven small-fiber neuropathy may therefore differ from patients whose dominant pathology reflects long-standing severe hyperglycemia and established axonal loss [17,29].

This heterogeneity also affects interpretation of tocotrienol mechanisms. Tocotrienols have been studied for effects on oxidative stress, inflammation, lipid metabolism, and glucose regulation across several clinical settings. Palm tocotrienol-rich fraction trials nevertheless vary widely in formulation, baseline risk, dose, and duration, and the aggregate evidence does not justify assuming identical efficacy in all metabolic phenotypes [19,59].

The implication is that future DPN studies should not merely record HbA1c. Baseline triglycerides, obesity, renal function, inflammatory markers, micronutrient status, vitamin-B12 exposure, homocysteine, diabetes duration, and concurrent cardiometabolic therapy could provide clinically important effect modifiers.

#### **Theme Seven: Pharmacokinetic Variability Is an Underappreciated Source of Heterogeneity**

Tocotrienols have relatively complex absorption and distribution. Their bioavailability depends on formulation, accompanying food, isomer composition, and delivery technology. Palm-derived tocotrienol-rich fractions also vary in the relative proportions of  $\alpha$ -,  $\gamma$ -, and  $\delta$ -tocotrienols and  $\alpha$ -tocopherol [57].

This matters because failure to achieve adequate systemic or neural exposure can make a biologically active compound appear ineffective. Conversely, positive findings from a highly bioavailable formulation cannot automatically be generalized to all products marketed as tocotrienols.

The relationship between tocopherol and tocotrienol adds another layer of complexity. Contemporary vitamin-E literature emphasizes that individual isoforms have different biological and pharmacokinetic properties and should not be treated as interchangeable [20,60]. Future trials should consequently report exact composition, manufacturing standardization, dose, administration relative to meals, adherence, and ideally circulating tocotrienol concentrations.

#### **Theme Eight: Clinical Meaning Requires Multidimensional Outcomes**

DPN trials have historically struggled with endpoint sensitivity. Symptom scores may fluctuate and are influenced by mood, sleep, expectations, analgesic use, and central pain processing. Nerve-conduction studies capture mainly large-fiber physiology. Clinical examination is important but comparatively insensitive to subtle change. Biomarkers may demonstrate biological activity without established relationship to meaningful outcomes.

The solution is not to select a single supposedly superior endpoint but to create multidimensional endpoint architecture. A strong future tocotrienol study should combine biochemical target engagement, electrophysiology, small-fiber structure, sensory function, pain, gait, sleep, quality of life, and long-term progression.

Figure 3 reconciles the major clinical findings without forcing them into a binary efficacy judgment. It places encouraging biomarker and nerve-conduction signals alongside unresolved symptom, amplitude, regeneration, and washout findings so that each result is interpreted at the biological level it actually measures.

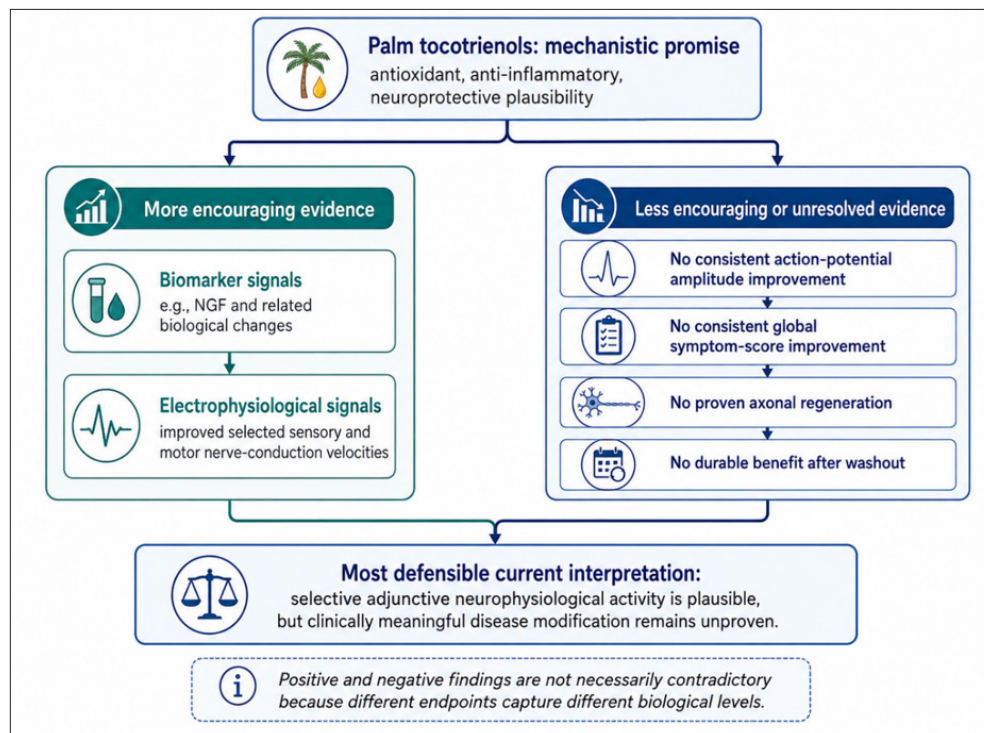


**Figure 3:** Reconciling the apparent clinical discordance

This framework allows positive neurophysiological observations to retain scientific value without elevating them beyond what the evidence supports. The figure therefore operationalizes the review’s central distinction between evidence of biological activity and evidence of clinically meaningful, durable disease modification.

## Discussion and Analysis

### Why the Evidence Is Not Truly Contradictory

The principal contribution of this review is the argument that much of the apparent contradiction surrounding tocotrienols disappears when therapeutic outcomes are separated conceptually. A compound can exert antioxidant activity without relieving pain. It can improve conduction velocity without regenerating axons. It can improve a circulating biomarker without altering long-term disability. These are not mutually exclusive outcomes; they occupy different positions in a translational sequence.

The recent DPN literature increasingly supports such multidimensional interpretation. Modern pathophysiology recognizes peripheral nerve dysfunction as the result of interacting metabolic, inflammatory, mitochondrial, vascular, and structural processes [14,34]. Similarly, modern clinical management recognizes that analgesic efficacy and nerve preservation are different therapeutic goals [9,44].

Against this background, the phase-II Tocovid findings are biologically provocative but not sufficient to demonstrate disease modification. The short-term increase in conduction velocity and NGF reported by [26]. Suggests target-relevant biological

activity. The longer trial by [27]. Strengthens the evidence that selected conduction parameters can improve during ongoing supplementation. The disappearance of differences after washout, however, argues for caution in claiming durable structural recovery.

[28]. Reinforce this interpretation at the evidence-synthesis level. Selective conduction-velocity gains without amplitude improvement are compatible with physiological preservation or remyelination-related effects, but they do not establish axonal regeneration. The absence of corresponding glycemic improvement also suggests that any neurophysiological effect need not be mediated simply by lower glucose levels.

### Why Symptom Failure Cannot Be Ignored

At the same time, it would be inappropriate to dismiss negative symptom findings on the basis that tocotrienols are “disease-modifying rather than analgesic.” Such a claim would reverse the evidentiary burden. Disease modification requires stronger, not weaker, evidence than symptom control.

Neuropathy matters because it affects patients. Pain, numbness, balance, falls, sleep, mobility, work capacity, ulceration, and quality of life represent clinically important outcomes. The substantial quality-of-life burden documented by [5]. Illustrates why clinically perceptible outcomes must eventually accompany biological claims.

Accordingly, a future intervention could be considered clinically valuable even if it did not reduce pain, provided that it convincingly slowed objective nerve loss, preserved protective sensation,

improved mobility, or reduced ulceration. Conversely, a modest electrophysiological effect with no impact on structure, function, symptoms, or long-term progression would have limited clinical significance.

### Neuroprotection Versus Regeneration

The language used in nutraceutical research frequently exceeds the evidence. “Neuroprotection,” “nerve repair,” “remyelination,” “regeneration,” and “disease modification” should not be treated as synonyms.

Neuroprotection means reducing or preventing ongoing injury to viable neural tissue. Remyelination refers to restoration of myelin around surviving axons. Regeneration requires growth or restoration of damaged axonal structures. Disease modification implies that intervention changes the natural trajectory of the disorder in a clinically meaningful and durable manner.

The available tocotrienol literature most plausibly supports investigation of neuroprotection, and perhaps myelin-related functional effects, rather than established regeneration. Neuroprotective plausibility is supported by experimental literature and contemporary reviews of tocotrienol-rich fraction [22,24]. Demonstrating regeneration, however, would require longitudinal structural evidence in humans.

This distinction has practical consequences. Trials designed to investigate regeneration should incorporate corneal nerve-fiber morphology, skin-biopsy measures, advanced peripheral-nerve imaging where feasible, and long-term action-potential amplitude. Claims of disease modification additionally require evidence that benefits persist after treatment withdrawal or meaningfully reduce progression.

### A Precision-Neuroprotection Hypothesis

The most promising future direction may be to abandon a one-size-fits-all DPN supplementation model. DPN is phenotypically and mechanistically heterogeneous. Some patients may have early small-fiber injury dominated by metabolic stress, while others have advanced axonal loss. Some have severe pain despite limited large-fiber abnormalities, whereas others have profound sensory loss without pain.

The broader DPN literature supports movement toward phenotype-sensitive assessment [2,55]. Tocotrienol research could adopt the same direction.

A future precision-neuroprotection trial could enroll participants with objectively confirmed early DPN but preserved sensory amplitudes, suggesting viable nerve reserve. Baseline phenotyping would include HbA1c, diabetes duration, body mass index, lipid profile, renal function, inflammatory markers, vitamin-B12 and homocysteine status, symptom phenotype, corneal nerve morphology, quantitative sensory testing, and nerve conduction.

Participants would then receive a chemically standardized palm-derived tocotrienol preparation with documented pharmacokinetic properties. Treatment exposure could be verified by circulating tocotrienol concentrations. Outcome assessment would distinguish target engagement from neurophysiological and patient-centered effects.

Figure 4 translates this concept into a future trial framework. It links disease staging, phenotyping, exposure standardization, multidimensional outcome measurement, durability assessment, and conservative interpretation into a single prospective research pathway.

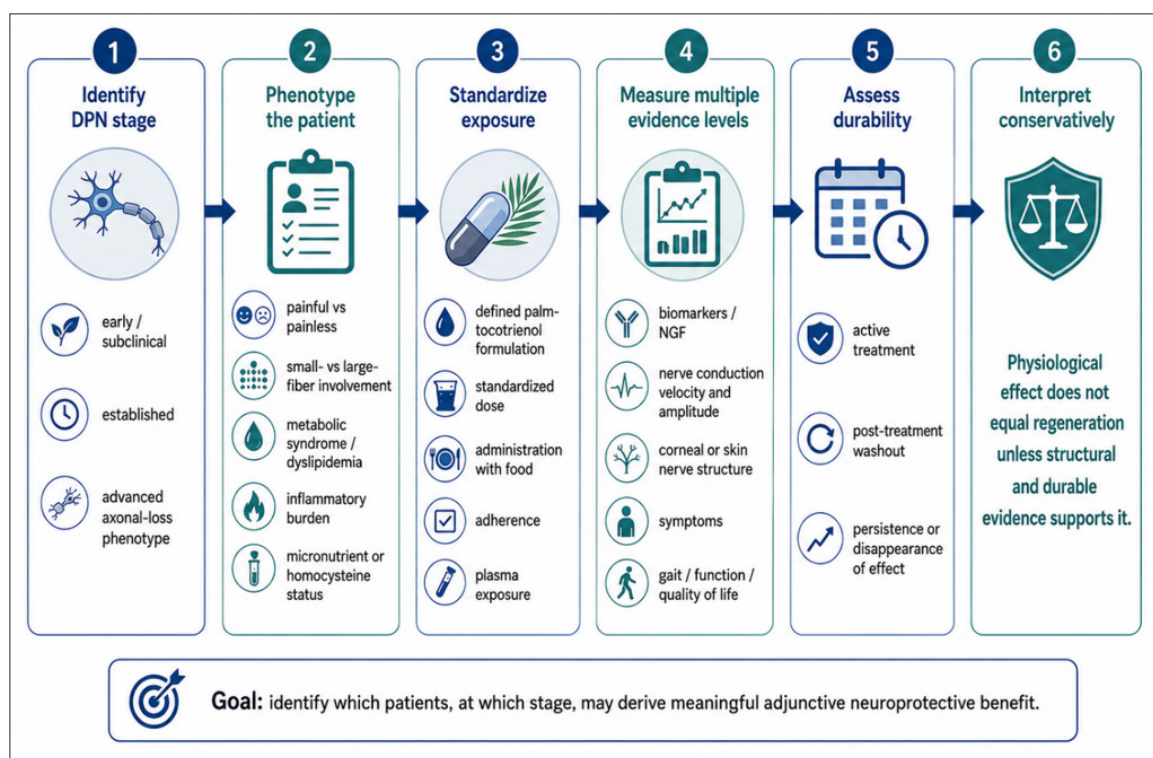


**Figure 4:** Precision-neuroprotection framework for future tocotrienol trials

This approach could identify responder phenotypes while preventing dilution of a genuine early-stage effect by inclusion of patients with irreversible neuropathy. It also makes explicit that any claim of regeneration should require concordant structural and durable evidence rather than an isolated change in a physiological surrogate.

### **Formulation Should Become a Core Clinical Variable**

The pharmacokinetic literature suggests that formulation is not a secondary methodological detail. Tocotrienol exposure varies substantially, and palm-derived TRF cannot automatically be equated with purified  $\delta$ -tocotrienol or other vitamin-E preparations [57]. Recent formulation research further indicates that low aqueous solubility, short systemic persistence, and absorption constraints can be partly addressed through optimized delivery systems, although formulation-dependent gains in exposure do not themselves establish neurological efficacy [58,56].

This issue also complicates meta-analysis. Pooling interventions labeled “vitamin E” or “tocotrienol” can obscure differences in isomer composition, tocopherol content, food-dependent absorption, and dose [59]. Documented broad heterogeneity across randomized palm-TRF studies, while contemporary brain-health reviews similarly emphasize differences in exposure and biological effects among tocopherol and tocotrienol isoforms [60].

Future DPN trials should therefore describe the intervention with pharmaceutical-level precision. Relevant information includes  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocotrienol content, tocopherol content, carrier technology, dose, capsule composition, stability, food administration, adherence, plasma concentrations, and batch consistency.

### **Tocotrienols in the Context of Modern Diabetes Therapy**

Another important issue is the rapidly evolving therapeutic environment. Contemporary diabetes management increasingly targets cardiovascular, renal, metabolic, and inflammatory risk through interventions extending beyond glucose lowering. Any future tocotrienol research will therefore occur against a background of statins, renin-angiotensin-system treatment, SGLT2 inhibitors, GLP-1-based therapies, modern antihypertensive treatment, weight management, and improved continuous glucose monitoring.

This makes adjunctive rather than substitutive positioning essential. Palm tocotrienols should not be presented as alternatives to evidence-based glycemic or cardiometabolic risk management. Nor should patients with painful DPN be expected to discontinue effective analgesic therapy on the assumption that antioxidant supplementation will produce equivalent symptom relief.

The defensible research question is instead whether tocotrienols can add a mechanistically distinct neuroprotective effect after contemporary metabolic treatment has been optimized [34]. Similarly emphasize the importance of integrating antioxidant and mitochondrial hypotheses with modern pleiotropic diabetes therapies rather than studying them in isolation.

### **Safety and Clinical Restraint**

Available trials and broader palm-TRF literature generally suggest acceptable tolerability at commonly studied doses, but long-term neurological use still requires careful safety surveillance. Nutraceutical status should not be interpreted as evidence of therapeutic harmlessness, particularly in patients with polypharmacy, chronic kidney disease, cardiovascular disease, or altered nutrient metabolism.

Clinical recommendations should therefore remain conservative. The evidence supports continued investigation but not routine designation of tocotrienols as an established DPN therapy. This position is consistent with contemporary DPN guidelines, none of which place tocotrienol supplementation among standard first-line disease-modifying treatments [8,9].

### **Research Agenda**

A more decisive tocotrienol evidence base requires several design improvements. First, study populations should be stratified by DPN stage rather than recruited solely on a broad diagnostic definition. Second, intervention products should be chemically standardized and pharmacokinetically characterized. Third, trials should be sufficiently long to distinguish temporary physiological modulation from genuine structural preservation.

Fourth, investigators should use multidimensional outcome architecture. Nerve-conduction velocity should be accompanied by action-potential amplitude, small-fiber structural measures, symptom instruments, gait or balance assessment, sleep and quality-of-life outcomes, and markers of diabetic-foot risk. Fifth, treatment withdrawal should be incorporated when ethically and methodologically appropriate to determine whether effects persist.

Sixth, responder analyses should be prespecified. Potential effect modifiers include baseline HbA1c, diabetes duration, lipid profile, obesity, inflammatory burden, homocysteine, vitamin-B12 status, renal function, painful versus painless phenotype, and baseline nerve reserve.

Finally, trials should establish explicit thresholds for interpretation. Improvement in one electrophysiological variable should not be described as “nerve regeneration.” Structural improvement without functional benefit should be reported accurately. Patient-centered benefit without structural change may still be clinically useful but should be labeled symptomatic or functional rather than regenerative.

### **Conclusion**

Palm-derived tocotrienols occupy an intriguing but unresolved position in diabetic peripheral neuropathy. Their biological properties intersect with oxidative stress, inflammation, mitochondrial dysfunction, metabolic injury, vascular impairment, and other mechanisms central to DPN, providing a credible rationale for clinical investigation. Contemporary trials additionally suggest that tocotrienol-rich vitamin E can influence selected nerve-conduction parameters, indicating that the intervention is not biologically inert.

The evidence nevertheless does not currently establish consistent relief of neuropathic symptoms, axonal regeneration, restoration of lost nerve structure, or durable disease modification. Improvement in conduction velocity should therefore be interpreted as a neurophysiological signal rather than proof that damaged nerves have regenerated. Similarly, changes in oxidative, inflammatory, or neurotrophic biomarkers demonstrate target-relevant activity but cannot substitute for patient-centered and structural outcomes. The most productive future question is therefore no longer whether tocotrienols simply “work” or “do not work.” Research should determine which patients, at which stage of DPN, receiving which tocotrienol formulation and systemic exposure, are most likely to experience which level of benefit. Early-stage disease with preserved nerve reserve may be a particularly important population for testing the neuroprotection hypothesis.

At present, palm tocotrienols should be regarded as investigational adjunctive candidates rather than replacements for glycemic optimization, cardiometabolic risk-factor management, foot protection, or established therapy for neuropathic pain. A transition toward phenotype-specific recruitment, standardized formulations, objective exposure assessment, multidimensional neural endpoints, and post-treatment follow-up could determine whether the current electrophysiological signals represent a clinically meaningful pathway toward neuroprotection or merely transient physiological modulation.

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