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Beyond Pain Scores: Can Palm Tocotrienols Modify Diabetic Peripheral Neuropathy? Reconciling Nerve-Conduction Gains With Inconsistent Symptom Relief

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A R T I C L E I N F O

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A B S T R A C T

Diabetic peripheral neuropathy (DPN) is a prevalent and disabling complication of diabetes characterized by sensory loss, neuropathic pain, impaired balance, foot ulceration risk, and progressive deterioration of peripheral nerve function. Its pathogenesis extends beyond hyperglycemia and involves oxidative stress, mitochondrial dysfunction, advanced glycation, neuroinflammation, microvascular impairment, disrupted neurotrophic signaling, Schwann-cell dysfunction, and progressive axonal degeneration. Because currently available pharmacological therapies predominantly target neuropathic pain rather than the underlying neural injury, interest has grown in compounds capable of modifying several pathogenic pathways simultaneously. Palm-derived tocotrienols are of particular interest because clinical studies have demonstrated measurable improvements in selected sensory and motor nerve-conduction parameters and increases in circulating nerve growth factor. However, electrophysiological improvement has not consistently translated into comparable symptomatic relief, while some gains diminish following treatment withdrawal. This critical qualitative review synthesizes peer-reviewed evidence published from January 2020 through December 2024 to explain this apparent discordance. The review argues that nerve-conduction velocity, small-fiber integrity, neuropathic pain, and functional recovery represent overlapping but non-equivalent domains of DPN. Current evidence supports biological and electrophysiological activity of tocotrienol-rich vitamin E but remains insufficient to demonstrate durable structural neuroregeneration or definitive disease modification. Future trials should prioritize early-stage DPN, patient stratification, pharmacokinetic characterization, multidomain neurological endpoints, and post-treatment follow-up

INTRODUCTION

Diabetic peripheral neuropathy (DPN), particularly distal symmetrical sensorimotor polyneuropathy, represents one of the most common chronic complications of diabetes mellitus and remains an important source of disability, impaired quality of life, foot morbidity, and health-care utilization. Although prevalence estimates vary according to diagnostic criteria, population characteristics, diabetes duration, and the sensitivity of the assessment technique, contemporary epidemiological evidence demonstrates that a substantial proportion of people with type 1 or type 2 diabetes develop clinically detectable peripheral neuropathy during the course of their disease (Sun et al., 2020; Shiferaw et al., 2020; Yovera-Aldana et al., 2021). DPN is therefore not simply an uncomfortable sensory complication but a major determinant of long-term neurological and lower-limb outcomes. The clinical spectrum of DPN is heterogeneous. Some patients develop burning pain, tingling, allodynia, hyperalgesia, or lancinating sensations, whereas others experience progressive numbness and sensory loss with little pain. Large myelinated fibers, small myelinated Aδ fibers, and unmyelinated C fibers may be affected to different degrees and at different points in disease evolution. Consequently, a patient may have disabling neuropathic pain while routine nerve-conduction testing remains relatively preserved, whereas another patient may demonstrate severe electrophysiological abnormalities accompanied predominantly by numbness rather than pain (Malik, 2020; Sloan et al., 2021; Dillon et al., 2024). This phenotypic diversity becomes particularly important when evaluating therapies because pain relief, electrophysiological recovery, small-fiber regeneration, and prevention of neurological progression are not interchangeable outcomes.

DPN also has substantial consequences beyond sensory symptoms. Progressive impairment in proprioception and motor control contributes to gait instability, falls, and reduced mobility. Protective sensation may deteriorate to the point that repetitive mechanical trauma is not perceived, increasing the risk of callus formation, ulceration, infection, and ultimately amputation. These clinical consequences are compounded by the fact that conventional bedside screening techniques often identify DPN only after substantial neurological damage has already occurred. Contemporary diagnostic literature therefore increasingly emphasizes detection of early small-fiber abnormalities before advanced large-fiber loss becomes irreversible (Malik, 2020; Aso, 2022; Naruse, 2024). The therapeutic challenge mirrors the complexity of the disorder. Optimal glycemic management remains foundational, particularly in type 1 diabetes, while aggressive management of cardiovascular and metabolic risk factors is increasingly recognized as important in type 2 diabetes. Nevertheless, no pharmacological therapy has achieved universal acceptance as a reliable means of reversing established diabetic polyneuropathy. Current treatments for painful DPN—including duloxetine, pregabalin, gabapentin, amitriptyline, and related agents—primarily attenuate the perception or transmission of pain rather than repairing injured peripheral nerves (Alam et al., 2020; Ziegler et al., 2021; Staudt et al., 2022; Ziegler, 2023; Sayed et al., 2024). Even when clinically meaningful analgesia is obtained, underlying axonal degeneration may continue.

This persistent therapeutic gap has stimulated interest in interventions capable of modulating multiple components of DPN pathogenesis. The pathobiology of diabetic neuropathy includes oxidative stress, mitochondrial dysfunction, activation of advanced glycation pathways, altered lipid metabolism, inflammation, microvascular injury, impaired neurotrophic support, Schwann-cell dysfunction, and progressive axonal degeneration (Pang et al., 2020; Kobayashi and Zochodne, 2020; Ratan et al., 2024). A compound capable of acting simultaneously on several of these processes could theoretically provide more than symptomatic pain control. Palm-derived tocotrienols are a particularly intriguing candidate. Tocotrienols are unsaturated members of the vitamin E family and occur naturally in palm oil in α-, β-, γ-, and δ-isomeric forms. Their unsaturated isoprenoid side chain distinguishes them structurally and functionally from tocopherols. Contemporary pharmacological literature attributes antioxidant, anti-inflammatory, membrane-stabilizing, lipid-regulatory, vascular, metabolic, and neuroprotective properties to tocotrienols, although the magnitude of these effects varies according to isomer, formulation, dose, tissue, and disease context (Ismail et al., 2020; Ranasinghe et al., 2022).

Human studies of tocotrienol-rich vitamin E in DPN have generated an especially interesting pattern. In a phase II randomized controlled trial, Ng et al. (2020) reported significant improvements in median, sural, and tibial nerve-conduction velocities following eight weeks of tocotrienol-rich vitamin E administration. Serum nerve growth factor (NGF) also increased, suggesting potential engagement of neurotrophic pathways. A subsequent longer randomized trial demonstrated improvement in selected median and sural sensory conduction parameters during 12 months of supplementation, but the differences were no longer apparent after a six-month washout period (Chuar et al., 2021). These findings create an important scientific tension. An objective electrophysiological parameter appears responsive to tocotrienol treatment, yet improvement in clinical symptoms and pain has not been uniformly convincing. Moreover, disappearance of electrophysiological gains following discontinuation raises questions about whether tocotrienols induce durable structural repair or instead temporarily optimize the physiological environment of surviving nerve fibers. The apparent contradiction may arise partly from the assumption that nerve-conduction velocity and neuropathic pain measure the same biological phenomenon. They do not. Routine nerve-conduction studies primarily interrogate large myelinated fibers, whereas painful neuropathy can be strongly influenced by small-fiber pathology, ectopic nociceptor activity, altered ion-channel expression, neuroimmune signaling, spinal sensitization, and supraspinal pain processing (Calcutt, 2020; Chen and Song, 2024). It is therefore biologically plausible for conduction velocity to improve without a proportional reduction in pain. A second unresolved question concerns the meaning of "disease modification." Improvement in conduction velocity during active therapy is evidence of biological activity, but disease modification should imply alteration of the underlying pathological trajectory rather than temporary improvement in a surrogate measure. Demonstrating disease modification would ideally require convergence between physiological, structural, functional,

and patient-centered endpoints together with evidence that disease progression is slowed and that at least part of the benefit persists beyond immediate drug exposure. This critical qualitative review therefore examines the evidence published between January 2020 and December 2024 concerning palm-derived tocotrienols and DPN. Its objectives are to assess the biological rationale for tocotrienols, critically evaluate direct clinical evidence, reconcile electrophysiological improvement with inconsistent symptom relief, examine the importance of small- versus large-fiber pathology, assess the implications of pharmacokinetics and treatment withdrawal, and propose a research framework capable of determining whether tocotrienols can genuinely modify the natural history of diabetic neuropathy.

LITERATURE REVIEW

1. DPN as a Multifactorial Neurological Disorder

DPN develops through interacting metabolic, vascular, inflammatory, and neurodegenerative mechanisms rather than through a single pathogenic pathway. Chronic hyperglycemia initiates several biochemical processes, including increased formation of advanced glycation end products, activation of polyol and protein kinase pathways, oxidative stress, and mitochondrial dysfunction. These processes interact with dyslipidemia, insulin resistance, systemic inflammation, endothelial dysfunction, and impaired neural repair to damage neurons and supporting cells (Pang et al., 2020; Kobayashi and Zochodne, 2020; Sloan et al., 2021; Zhu et al., 2024). Oxidative stress has received particular attention because peripheral neurons possess long axons with high metabolic requirements. Excessive reactive oxygen species can damage mitochondrial components, membrane lipids, proteins, and DNA while disturbing cellular signaling and ATP generation. Importantly, oxidative stress is not a self-contained pathway. It amplifies inflammatory responses, endothelial dysfunction, and mitochondrial injury, thereby creating a self-reinforcing network of neural damage (Pang et al., 2020; Ratan et al., 2024). Mitochondrial dysfunction is especially relevant to distal axons because energy production and axonal transport must be maintained across considerable anatomical distances. Metabolic overload can disrupt mitochondrial membrane potential, increase reactive oxygen species, and interfere with axonal transport. Progressive failure of these processes may transform initially reversible metabolic dysfunction into structural axonal degeneration (Kobayashi and Zochodne, 2020). Inflammation constitutes another important component of the diabetic neural environment. Hyperglycemia, oxidative stress, and metabolic dysregulation can activate inflammatory transcription pathways and increase circulating and tissue inflammatory mediators. Neuroimmune activation contributes not only to axonal and Schwann-cell injury but also to neuropathic pain through altered excitability of sensory neurons and spinal pain pathways (Stoian et al., 2024; Chen and Song, 2024). Microvascular injury further links metabolic disease with neural dysfunction. Peripheral nerves depend on small endoneurial vessels to maintain oxygen and nutrient supply. Endothelial dysfunction, impaired nitric-oxide signaling, basement-membrane abnormalities, and altered microvascular blood flow can reduce endoneurial perfusion. Even without immediate axonal

death, reduced neural perfusion may disturb membrane function and conduction physiology (Sloan et al., 2021; Atmaca et al., 2024). DPN progression is therefore best viewed as a continuum. Early disease may consist largely of metabolic stress and small-fiber dysfunction. More advanced disease includes large-fiber slowing, demyelinating-functional abnormalities, loss of sensory axons, and declining regenerative capacity. Eventually, extensive axonal loss and chronic denervation may substantially constrain the ability of pharmacological interventions to restore function (Malik, 2020; Aso, 2022; Naruse, 2024).

2. Small-Fiber Versus Large-Fiber Neuropathy

The distinction between small- and large-fiber dysfunction is fundamental to the interpretation of tocotrienol trials. Routine nerve-conduction studies are particularly useful for assessing large myelinated sensory and motor fibers. They provide quantitative measurements of conduction velocity, latency, and amplitude. However, conventional nerve-conduction testing does not directly measure unmyelinated C fibers or thinly myelinated Aδ fibers, which are frequently affected early in DPN and play major roles in pain and temperature sensation (Malik, 2020; Naruse, 2024). A patient with early small-fiber neuropathy may therefore report burning pain, thermal dysesthesia, or allodynia despite a normal routine nerve-conduction study. Conversely, a patient with advanced large-fiber degeneration may exhibit markedly abnormal nerve conduction yet experience relatively little pain because sensory axons capable of generating painful signals have been lost. This dissociation is clinically relevant because early tocotrienol trials have focused principally on nerve-conduction studies. Demonstrating improvement in median or sural conduction provides objective evidence of large-fiber physiological improvement, but it does not establish repair of small nociceptive fibers. Corneal confocal microscopy (CCM) has emerged as a promising tool for assessing small-fiber pathology. The cornea contains a dense network of small sensory nerves that can be imaged non-invasively, and meta-analytic evidence indicates that CCM detects reductions in corneal nerve-fiber measures in both subclinical and established DPN (Ferdousi et al., 2021; Petropoulos et al., 2021; Perkins et al., 2021; Gad et al., 2022). Longitudinal work has further shown that CCM can detect progressive small-fiber loss in diabetic neuropathy alongside deterioration in other neurological measures (Dhage et al., 2021). However, diagnostic performance is context dependent: a 2023 Neurology study found relatively low sensitivity for CCM compared with intraepidermal nerve-fiber density and thermal thresholds in recently diagnosed type 2 diabetes, underscoring the value of multimodal rather than single-test phenotyping (Gylfadottir et al., 2023). Other techniques include quantitative sensory testing, intraepidermal nerve-fiber density measured by skin biopsy, sudomotor assessment, laser-based techniques, and newer biomarkers of axonal injury. Serum neurofilament light chain and nerve ultrasonography, for example, are being investigated as complementary measures of neural damage and structural abnormalities (Nasr-Eldin et al., 2024). Taken together, these approaches make multidomain assessment increasingly

feasible and reduce the risk of equating one surrogate measure with the totality of neuropathic recovery.

3. Tocotrienols: Chemistry and Neuroprotective Rationale

Vitamin E comprises tocopherols and tocotrienols. Both groups contain α-, β-, γ-, and δ-isomers, but tocotrienols possess an unsaturated side chain that influences their distribution and interaction with cell membranes. Palm oil is among the major dietary sources of mixed tocotrienols and forms the basis of several commercially developed tocotrienol-rich fractions. Preclinical evidence suggests that tocotrienols may modulate oxidative stress, inflammatory pathways, cellular survival, lipid metabolism, and neuroprotective signaling. A systematic review of palm oil and palm-derived tocotrienol-rich fraction reported substantial preclinical evidence of neuroprotective activity, although translation to clinical disease remains incomplete (Ismail et al., 2020). A broader review by Ranasinghe et al. (2022) likewise identified antioxidant, anti-inflammatory, cardiometabolic, and neuroprotective actions while emphasizing limitations in bioavailability and clinical translation. The antioxidant hypothesis is particularly attractive in DPN. Tocotrienols may scavenge lipid radicals, influence membrane-associated oxidation, and modulate pathways associated with oxidative injury. However, clinical evidence should not be reduced to the simplistic proposition that "tocotrienols are antioxidants, therefore they prevent neuropathy." A meta-analysis of randomized trials found heterogeneous effects of tocotrienol supplementation on inflammatory and oxidative-stress biomarkers, with no universal reduction across major markers such as inflammatory cytokines or oxidative products (Khor et al., 2021). The potential mechanisms relevant to DPN are likely broader. Tocotrienols may influence membrane integrity, mitochondrial signaling, lipid metabolism, vascular endothelial function, inflammatory transcription, and neurotrophic signaling. The observed rise in circulating NGF in the phase II DPN study makes the neurotrophic pathway particularly worthy of further investigation (Ng et al., 2020).

4. Neurotrophic Signaling and NGF

NGF plays important roles in survival, maintenance, differentiation, and regenerative responses of peripheral sensory neurons. Diabetes can interfere with normal neurotrophic signaling, reducing the ability of peripheral nerves to maintain and regenerate axons. Contemporary reviews of biomarkers and regenerative medicine in diabetic neuropathy therefore identify neurotrophic factors as potential indicators and therapeutic targets (Fujita et al., 2021). The increase in circulating NGF observed after tocotrienol-rich vitamin E supplementation provides one possible link between tocotrienol exposure and improved nerve physiology. If the intervention creates a more favorable redox, vascular, or inflammatory environment while simultaneously enhancing neurotrophic signaling, surviving axons might conduct impulses more effectively. Nevertheless, serum NGF should not be interpreted as direct proof of neural regeneration. Circulating concentrations do not identify the tissue of origin, demonstrate receptor activation in the affected peripheral nerve, or

establish the growth of new axonal structures. Structural measures such as CCM or intraepidermal nerve-fiber density would provide more direct evidence.
NGF is also involved in nociceptive physiology, meaning that higher NGF does not necessarily produce immediate analgesia. This further illustrates why improved neurotrophic signaling and unchanged pain intensity can coexist without being biologically contradictory.

5. Tocotrienol Pharmacokinetics and Formulation

The pharmacokinetics of tocotrienols represent an important but frequently underestimated source of heterogeneity. Tocotrienols are lipophilic compounds whose absorption is influenced by gastrointestinal lipid processing, food intake, isomer composition, formulation, and delivery technology. Pharmacokinetic studies have demonstrated substantial differences in exposure between preparations (Sharif et al., 2023). Self-emulsifying delivery systems are particularly relevant. Lee et al. (2022) demonstrated that solid self-emulsifying formulations can substantially improve tocotrienol bioavailability compared with conventional oily non-self-emulsifying formulations. This finding has major implications for clinical interpretation because identical nominal doses do not necessarily produce equivalent circulating or tissue exposure. Consequently, the term "tocotrienol supplementation" should not be treated as though it describes a single pharmacological intervention. Studies differ in the proportion of individual tocotrienol isomers, presence of tocopherols, delivery technology, dose, timing relative to meals, and treatment duration. The broader clinical literature confirms that tocotrienol-rich preparations can produce measurable systemic biological effects. Meta-analysis in type 2 diabetes found a modest improvement in HbA1c at doses broadly within the range used clinically, although effects on blood pressure and high-sensitivity CRP were not consistently significant (Phang et al., 2023). Trials in diabetic kidney disease and metabolic liver disorders have likewise reported selected physiological effects, supporting systemic bioactivity but not establishing neuropathy-specific efficacy (Koay et al., 2021; Pervez et al., 2020). Postprandial studies also show that antioxidant responses vary according to dose and biological context rather than following a simple linear dose-response relationship (Fairus et al., 2020). These observations reinforce the importance of measuring exposure rather than assuming it from administered dose.

METHODOLOGY

1. Review Design

This article employed a **critical qualitative literature review** methodology rather than a systematic literature review or meta-analysis. The objective was not to calculate a pooled treatment effect but to interpret heterogeneous findings across electrophysiological, biochemical, clinical, pharmacokinetic, diagnostic, and mechanistic domains. A qualitative approach was selected because the principal research problem concerns an apparent conceptual inconsistency: why can a treatment improve nerve-conduction velocity while producing inconsistent symptom relief? Resolving this question requires examination of what different

endpoints actually measure rather than statistical combination of outcomes that may represent different biological processes. The methodology is therefore consistent with the contemporary recognition that DPN should be assessed using multidimensional diagnostic and outcome frameworks rather than a single neurological test. This multidomain perspective is especially important because electrophysiology, CCM, intraepidermal nerve-fiber density, and sensory testing capture partially overlapping rather than interchangeable aspects of DPN (Aso, 2022; Atmaca et al., 2024; Dillon et al., 2024; Gylfadottir et al., 2023).

2. Evidence Window and Literature Identification

The review considered peer-reviewed journal literature published between **January 2020 and December 2024**. This temporal restriction was selected to capture contemporary developments in DPN pathophysiology, small-fiber assessment, neuroregenerative biomarkers, painful neuropathy management, tocotrienol clinical research, and formulation science. Literature was identified through concept-based searches using combinations of terms including diabetic peripheral neuropathy, diabetic polyneuropathy, painful diabetic neuropathy, tocotrienol, palm tocotrienol, tocotrienol-rich fraction, vitamin E, nerve conduction, nerve growth factor, small-fiber neuropathy, corneal confocal microscopy, neuroregeneration, oxidative stress, inflammation, pain, bioavailability, and pharmacokinetics. Priority was given to randomized controlled clinical studies directly involving tocotrienols, contemporary reviews of DPN pathogenesis and management, trials of painful DPN therapies useful for interpreting endpoint discordance, diagnostic studies involving small-fiber measures, and pharmacokinetic studies relevant to tocotrienol exposure.

3. Thematic Synthesis

Evidence was organized around seven major themes: electrophysiological responsiveness; neurotrophic signaling; oxidative and inflammatory mechanisms; discrepancy between objective and subjective outcomes; durability of treatment effects; pharmacokinetic and formulation heterogeneity; and patient-stage heterogeneity. This thematic structure was selected to preserve discordant findings rather than collapse biologically different endpoints into a single efficacy judgment. Results were interpreted according to the biological level measured. Nerve-conduction velocity was considered evidence of large-fiber physiological function. Pain instruments were treated as patient-centered measures influenced by both peripheral and central nervous-system mechanisms. CCM and intraepidermal nerve-fiber density were interpreted as structural small-fiber measures. Circulating NGF and inflammatory biomarkers were considered mechanistic indicators rather than validated surrogate endpoints for clinical recovery.

4. Limitations of the Review Method

Because the study is qualitative, it does not claim exhaustive study capture, pooled effect-size estimation, formal publication-bias testing, or meta-analytic certainty. The direct tocotrienol evidence base is also comparatively small, which restricts the strength of causal claims. The value of the approach lies instead in

conceptual integration. Specifically, it allows seemingly contradictory outcomes to be examined rather than averaged together and provides a framework for designing trials capable of distinguishing neuroprotection, physiological improvement, analgesia, and true disease modification.

RESULTS

1.Theme 1: Tocotrienols Demonstrate Objective Electrophysiological Activity

The strongest direct evidence supporting tocotrienols in DPN comes from randomized clinical studies incorporating nerve-conduction testing. Ng et al. (2020) evaluated tocotrienol-rich vitamin E in patients with diabetic neuropathy and demonstrated statistically significant improvements in conduction velocity of the median sensory, sural sensory, and tibial motor nerves after eight weeks of treatment compared with placebo. The reported improvements were approximately 1.25 m/s for median nerve conduction, 1.60 m/s for sural conduction, and 0.75 m/s for tibial nerve conduction. Although the numerical changes were modest, they were internally consistent across the tested nerves and provided objective evidence that tocotrienol-rich vitamin E altered peripheral nerve electrophysiology (Ng et al., 2020). This observation is important because nerve-conduction studies are less dependent on subjective reporting than symptom questionnaires. The results therefore provide stronger evidence of biological activity than would an isolated improvement in a self-reported pain outcome. The longer phase II trial reinforced this signal. Chuar et al. (2021) randomized individuals with type 2 diabetes to tocotrienol-rich vitamin E or placebo for 12 months and reported significant improvements in median and sural sensory nerve-conduction velocities. Tibial motor conduction improvement was observed during part of the active treatment period, although the longer-term pattern was less consistent. The convergence between the two clinical studies suggests that sensory conduction is a reproducible candidate response domain. However, these studies should still be interpreted as phase II evidence. They were not designed or powered as definitive multicenter trials capable of establishing broad clinical effectiveness.

2. Velocity is Not Equivalent to Axonal Regeneration

Improvement in nerve-conduction velocity is physiologically meaningful, but its interpretation requires precision. Conduction velocity is influenced by myelin integrity, membrane properties, ion-channel activity, temperature, metabolic state, and other features of surviving axons. Improvement can therefore occur without formation of new axons. By contrast, nerve action-potential amplitude is more closely related to the number of functioning axons, although it too has technical and biological limitations. A therapy that increases conduction velocity without clearly improving amplitude may therefore be enhancing the performance of surviving fibers rather than regenerating fibers that have been lost. This distinction is particularly important when the treatment is described as potentially "disease-modifying." Neuroregeneration is a structural claim and requires structural evidence. Neither faster conduction nor increased NGF alone directly demonstrates that lost epidermal or peripheral

axons have regrown. Evidence from contemporary regenerative research shows that the diabetic tissue environment may actively constrain axonal repair. Kan et al. (2022), for example, demonstrated that diabetes can create a non-permissive tissue environment that interferes with peripheral nerve regeneration. Reviews of regenerative medicine in DPN similarly emphasize that restoring nerves requires more than correction of oxidative stress alone (Fujita et al., 2021; Raghav et al., 2022).

3. Theme 2: NGF Provides a Neurotrophic Signal

Ng et al. (2020) additionally observed increased serum NGF following tocotrienol supplementation. This finding creates a potentially important mechanistic bridge between tocotrienol exposure and improved nerve conduction. Diabetes can disturb neurotrophic signaling, and reduced growth-factor support may impair axonal maintenance and regeneration. Tocotrienol-mediated improvement in oxidative balance, cellular signaling, or vascular conditions might facilitate neurotrophic processes and thereby improve function in stressed but viable axons. Nevertheless, serum NGF is an indirect biomarker. Future studies would need to determine whether changes in circulating NGF correspond to structural improvements in nerve fibers or to altered signaling within affected tissues. Without such corroboration, NGF should be treated as evidence of possible target engagement rather than a validated surrogate for regeneration.

4. Theme 3: The Antioxidant Mechanism is Plausible But Incomplete

DPN is strongly associated with oxidative stress, making the antioxidant activity of tocotrienols an intuitively plausible mechanism. Contemporary DPN reviews consistently implicate oxidative and mitochondrial pathways in disease progression (Pang et al., 2020; Kobayashi and Zochodne, 2020; Ratan et al., 2024). However, clinical tocotrienol evidence does not show uniform suppression of systemic oxidative or inflammatory markers. Khor et al. (2021) found heterogeneous effects across randomized controlled trials and did not demonstrate consistent improvement in all major biomarkers of inflammation and oxidative stress.

Similarly, the meta-analysis by Phang et al. (2023) found that tocotrienol-rich fraction modestly reduced HbA1c in type 2 diabetes but did not produce significant pooled reductions in blood pressure or high-sensitivity CRP. Thus, systemic biological activity exists, but it is selective rather than universal.

These observations imply that improved nerve conduction cannot simply be attributed to a generalized systemic antioxidant effect. Potential explanations include tissue-specific redox effects, membrane stabilization, improved endothelial function, altered lipid signaling, mitochondrial effects, and neurotrophic support.

5. Theme 4: Pain and Conduction Velocity Assess Different Biological Systems

The central paradox of this literature concerns the contrast between improved electrophysiological parameters and inconsistent symptom relief. This becomes substantially less paradoxical once measurement domains are

separated. Large myelinated fibers dominate conventional nerve-conduction recordings. Neuropathic pain, however, frequently originates in small sensory fibers and is subsequently amplified by changes in dorsal-root ganglia, spinal dorsal horn circuitry, descending modulation, and supraspinal pain networks (Calcutt, 2020; Chen and Song, 2024). Consequently, an intervention could improve large-fiber membrane physiology or conduction speed without suppressing spontaneous discharges in injured C fibers or reversing central sensitization. Pain may persist even though one component of peripheral nerve physiology has improved. The inverse is also true. Effective analgesia does not prove neural regeneration. Duloxetine, pregabalin, gabapentinoids, and tricyclic antidepressants reduce painful DPN largely through modulation of neurotransmission rather than reconstruction of damaged peripheral nerves (Alam et al., 2020; Ardeleanu et al., 2020; James et al., 2022). The OPTION-DM trial provides an important clinical illustration. Different combinations and sequences of amitriptyline, duloxetine, and pregabalin produced clinically relevant improvements in painful diabetic neuropathy, yet the objective of treatment was symptom reduction, not reversal of peripheral axonal pathology (Tesfaye et al., 2022). Network meta-analysis similarly demonstrates that several pharmacological treatments can reduce pain through differing mechanisms without corresponding evidence of nerve regeneration (Lian et al., 2021). Contemporary clinical guidance therefore clearly distinguishes treatment of neuropathic pain from pathogenetically oriented management (Tesfaye and Kempler, 2023; Mallick-Searle and Adler, 2024).

6. Central Sensitization Further Separates Pain From Peripheral Nerve Physiology

Persistent diabetic neuropathic pain can promote long-term changes in central pain-processing systems. Ongoing abnormal afferent input may increase spinal neuronal excitability, reduce inhibitory control, and alter supraspinal networks. Once established, these changes may sustain pain even if peripheral metabolic conditions subsequently improve (Calcutt, 2020; Chen and Song, 2024). Psychological factors further influence pain experience. Anxiety, depression, sleep disturbance, catastrophizing, activity avoidance, and coping influence pain intensity and disability. Twiddy et al. (2021) emphasize the substantial psychological burden associated with painful DPN, while Vileikyte (2023) highlights the complex relationship between neuropathic symptoms and quality of life. Meta-analytic evidence indicates that psychological interventions can improve pain-related and quality-of-life outcomes in diabetic neuropathy without necessarily altering large-fiber nerve conduction (Bai et al., 2022). This reinforces the conclusion that subjective symptom improvement and electrophysiological restoration represent distinct therapeutic targets.

7. Neuromodulation Demonstrates the Reverse Dissociation

High-frequency spinal cord stimulation provides a useful comparator because it illustrates the opposite endpoint pattern. Petersen et al. (2021) demonstrated substantial pain relief with 10-kHz spinal cord stimulation in patients with refractory painful diabetic neuropathy. The analgesic benefit of neuromodulation demonstrates that pain can improve dramatically without requiring immediate regeneration of damaged peripheral axons. Thus, lack of parallel movement between pain and nerve-conduction velocity should not automatically be interpreted as a contradiction. Research involving capsaicin 8% patch provides another useful comparison because investigators have examined both symptom changes and peripheral nerve-fiber measures. Anand et al. (2022) reported findings compatible with the possibility that pain reduction and peripheral nerve regeneration may coexist under some circumstances. This illustrates why structural biomarkers are essential when a disease-modifying claim is made. The pathogenesis of DPN can be conceptualized as a progression from metabolic stress to oxidative and mitochondrial dysfunction, followed by neuroinflammation, microvascular compromise, impaired neurotrophic support, small-fiber damage, large-fiber dysfunction, and ultimately irreversible axonal loss. Tocotrienols may theoretically act at several upstream and intermediate points within this cascade rather than through a single antioxidant mechanism **(Figure 1)**.

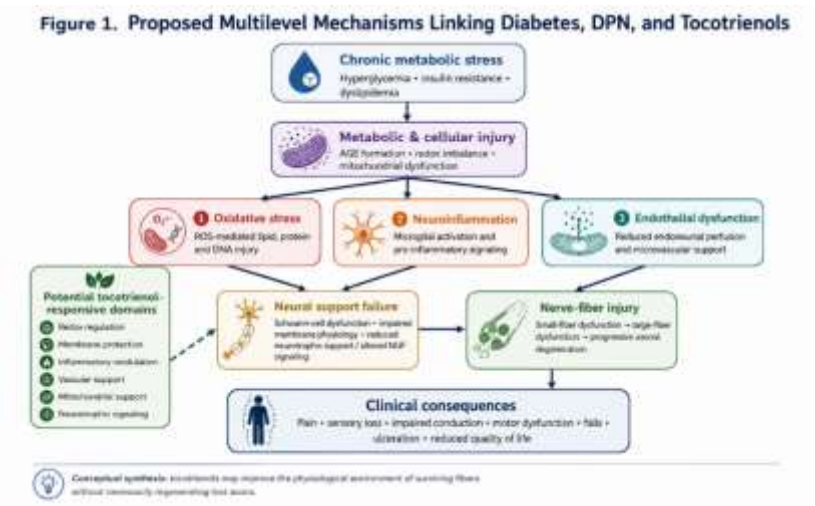


Figure 1. Proposed Multilevel Mechanisms Linking Diabetes, DPN, and Tocotrienol Action

Figure 1 emphasizes that DPN is produced by interacting mechanisms rather than a single oxidative pathway. Tocotrienols could improve the metabolic and physiological environment of surviving neurons without necessarily regenerating axons that have already been destroyed. This distinction provides a plausible explanation for relatively rapid electrophysiological improvement despite incomplete symptomatic recovery.

8. Theme 5: Small-Fiber Pathology is the Major Missing Endpoint

The most important measurement gap in current tocotrienol trials is the lack of comprehensive small-fiber assessment. Small fibers may be affected before conventional nerve-conduction abnormalities become apparent, and painful DPN can therefore develop at a stage when large-fiber electrophysiology is still relatively preserved (Malik, 2020; Naruse, 2024). CCM offers an attractive solution. Ferdousi et al. (2021) demonstrated significant reductions in corneal nerve-fiber parameters in both type 1 and type 2 diabetes and established the diagnostic utility of CCM for DPN. Perkins et al. (2021) subsequently demonstrated that baseline corneal nerve-fiber length could predict development of future DPN in a multinational longitudinal cohort. Participants with lower baseline corneal nerve-fiber length had greater subsequent neuropathy risk. Dhage et al. (2021) also demonstrated longitudinal deterioration of CCM parameters together with conventional measures of neuropathy. These findings indicate that CCM is sensitive to progressive small-fiber injury and is therefore suitable for disease-modification studies. A future tocotrienol trial incorporating CCM could determine whether electrophysiological improvement is accompanied by preservation or regeneration of small sensory fibers. If both nerve-conduction velocity and corneal nerve morphology improved, the argument for genuine neural modification would become considerably stronger.

9. Theme 6: The Washout Phenomenon Challenges Durable Disease Modification

One of the most informative findings in the tocotrienol literature comes from the six-month washout phase reported by Chuar et al. (2021). During active treatment, median and sural sensory conduction improved relative to placebo. After treatment cessation, however, the between-group differences were no longer significant. This finding should not be interpreted as evidence that tocotrienols are ineffective. Many effective chronic therapies require continuous administration. Antihypertensive drugs, for example, lower blood pressure while they are being taken without permanently eliminating the biological tendency toward hypertension. The washout result nevertheless has major implications for the term "disease-modifying." If tocotrienols permanently regenerated a meaningful population of lost axons, at least some structural or physiological improvement might reasonably be expected to persist after discontinuation. Disappearance of benefit is more consistent with an exposure-dependent process such as improved membrane physiology, endothelial function, redox status, metabolic support, or reversible neurotrophic signaling. These processes may still be clinically useful, but they represent a different biological phenomenon from durable anatomical repair. A comparable interpretive issue arises in the diabetic kidney disease tocotrienol literature, where treatment-related renal effects were not uniformly sustained after treatment withdrawal (Koay et al., 2021). Although kidney and nerve biology differ, the broader lesson is that active-treatment effects must be distinguished from permanent modification of tissue trajectory.

The apparent disagreement between nerve conduction and pain can therefore be resolved by separating DPN into three overlapping biological compartments: large-fiber function, small-fiber pathology, and central pain processing. Different clinical instruments interrogate different levels of this system **(Figure 2)**.

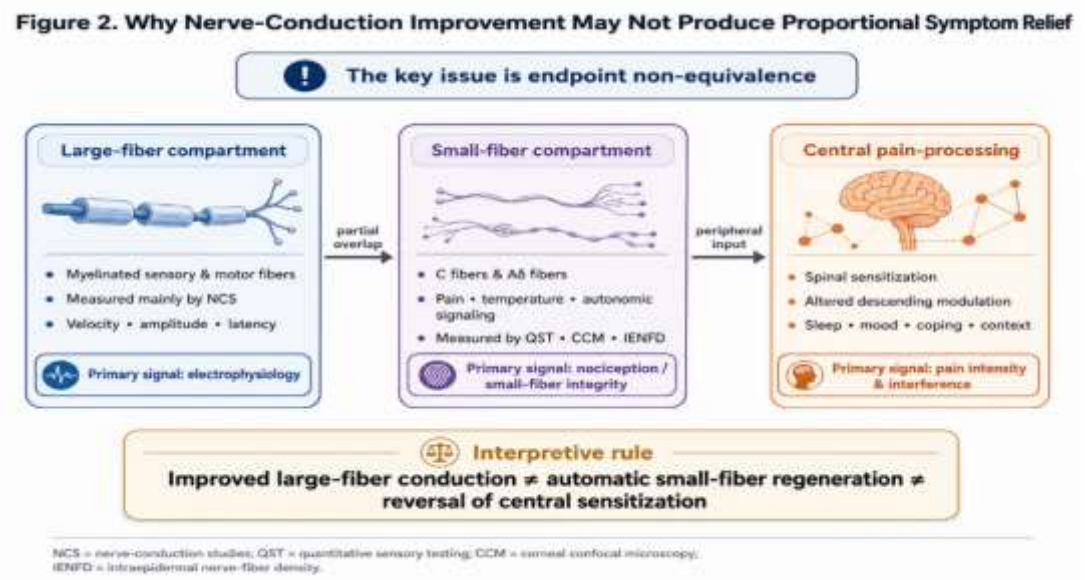


Figure 2. Why Nerve Conduction May Improve Without Proportional Symptom Relief

Figure 2 illustrates that routine nerve-conduction studies preferentially measure large myelinated fibers. Painful DPN can persist because the principal pathological drivers of pain may lie in small nociceptive fibers or central pain networks. Accordingly, improved nerve conduction and unchanged pain are not mutually exclusive findings.

10. Theme 7: Disease Stage is Likely to Determine Treatment Responsiveness

The biological reversibility of DPN probably decreases as neuropathy progresses. Early disease may involve metabolic, mitochondrial, vascular, and membrane abnormalities in structurally viable nerve fibers. These abnormalities may be at least partially reversible. Later disease is characterized by progressive loss of axonal structures, impaired regenerative signaling, reduced skin innervation, and secondary alterations in central neural circuits. Experimental and translational evidence suggests that diabetes creates a tissue environment increasingly hostile to regeneration (Kan et al., 2022; Raghav et al., 2022). This creates a logical stage-response hypothesis for tocotrienols. Patients with early metabolic or electrophysiological dysfunction and preserved axonal reserve may have greater potential for improvement than those with longstanding severe neuropathy. The hypothesis is consistent with broader tocotrienol metabolic evidence. Phang et al. (2023) observed greater glycemic effects of tocotrienol-rich fraction in some subgroups with shorter diabetes duration, suggesting that disease duration may modify physiological responsiveness, although this finding should not be directly extrapolated to neuropathy.

Glycemic variability may also be important. Yang et al. (2021) found that continuous-glucose-monitoring-derived time in range was associated with painful diabetic polyneuropathy. This suggests that mean HbA1c alone may inadequately characterize the metabolic environment affecting nerve function. Consequently, future trials should record HbA1c, glucose variability, diabetes duration, renal function, lipid profile, body composition, smoking, blood pressure, nutritional status, and concurrent medications rather than relying on diagnosis alone. These covariates should be prespecified because they may influence both baseline nerve injury and the probability of detecting a treatment response. Based on the available evidence, a stage-dependent model predicts that tocotrienol responsiveness will be greatest before extensive irreversible axonal loss has occurred. The hypothesis should be tested prospectively rather than inferred retrospectively **(Figure 3)**.



Figure 3. Hypothesized Therapeutic Window for Palm Tocotrienols In DPN

Figure 3 illustrates that tocotrienols are biologically more likely to preserve or normalize stressed but viable neural tissue than to reconstruct long-standing axonal loss. The highest-value future trials may therefore involve early or intermediate DPN rather than populations selected exclusively for severe chronic pain.

DISCUSSION

1. What Does the Current Evidence Actually Prove?

The most defensible conclusion from the 2020–2024 evidence is that palm tocotrienol-rich vitamin E demonstrates **biological and electrophysiological activity in DPN**. The randomized trials by Ng et al. (2020) and Chuar et al. (2021) provide objective evidence of improvement in selected nerve-conduction velocities during treatment. This evidence is stronger than purely theoretical antioxidant reasoning because the target organ itself—peripheral nerve function—was objectively measured. The consistent sensory conduction signal across two related phase II trials is therefore clinically interesting.

What the evidence does **not** yet prove is equally important. It does not establish widespread structural axonal regeneration, resolution of small-fiber pathology, durable analgesia, prevention of foot ulceration, improvement in mobility, or sustained alteration of neuropathy progression after treatment discontinuation. Accordingly, describing tocotrienols simply as either "effective" or "ineffective" loses important biological information. A more accurate formulation is that they appear capable of modifying selected aspects of peripheral nerve physiology during active treatment, while their effect on the broader clinical syndrome remains uncertain.

2. Reconciling Nerve Conduction and Symptoms

The central finding of this qualitative synthesis is that electrophysiological improvement and inconsistent symptom relief are not inherently contradictory. Rather, the two outcomes interrogate different levels of DPN biology and should be interpreted as complementary rather than interchangeable measures.

Nerve-conduction velocity is an objective measurement of impulse propagation through selected large fibers. Pain scores represent a multidimensional perceptual outcome affected by small-fiber activity, central sensitization, emotion, attention, sleep, medication exposure, and expectations. The relationship between these outcomes is therefore neither linear nor immediate. A 1–2 m/s improvement in sensory nerve conduction may reflect meaningful physiological restoration in surviving large fibers while being too small or biologically unrelated to reverse chronic burning pain generated predominantly through small-fiber and central mechanisms. This concept is supported by the broader DPN therapeutic literature. Effective analgesic therapies improve pain without requiring improvements in nerve conduction (Alam et al., 2020; Lian et al., 2021; Tesfaye et al., 2022). Neuromodulation can generate substantial analgesia without being interpreted as proof of metabolic reversal (Petersen et al., 2021). Therefore, the correct interpretation is domain specific: tocotrienols may currently have stronger evidence for electrophysiological efficacy than for analgesic efficacy. This distinction should be stated explicitly to avoid overinterpreting a change in nerve-conduction velocity as equivalent to patient-perceived recovery.

3. Should Nerve-Conduction Velocity Be Considered a Surrogate Endpoint?

Nerve-conduction testing is valuable because it is objective, standardized, quantitative, and widely accepted in neurological research. Nevertheless, an outcome can be objectively measurable without being a validated surrogate for clinical recovery. For nerve-conduction velocity to function as a surrogate endpoint for disease modification, changes would need to correlate reliably with long-term meaningful outcomes such as sensory preservation, reduced ulceration, improved balance, improved function, or reduced neuropathy progression. Until such relationships are demonstrated, nerve-conduction velocity should be treated as an important physiological endpoint rather than a validated substitute for clinical recovery. Such validation has not yet been demonstrated for tocotrienols. Therefore, statistically significant improvements

in conduction should be reported as electrophysiological outcomes rather than automatically translated into claims of clinically important regeneration.
Amplitude should also receive greater emphasis. Improvement in conduction velocity may indicate better function in existing fibers, while stabilization or increase in amplitude could offer additional evidence of preserved functional axons. Future trials should therefore prespecify both velocity and amplitude endpoints.

4. What Would Constitute Convincing Disease Modification?

The term disease-modifying should have a higher evidentiary threshold than symptomatic improvement or transient physiological enhancement. Contemporary pathogenetic-treatment frameworks likewise distinguish interventions aimed at underlying neuropathy from therapies whose primary purpose is pain relief (Ziegler, 2023). For DPN, a convincing disease-modifying intervention should ideally demonstrate sustained improvement or reduced deterioration in objective nerve function together with structural preservation or regeneration of small and/or large fibers. The case would be strengthened further by clinically meaningful gains in neurological symptoms or functional capacity, slower progression toward advanced sensory loss or foot complications, mechanistically coherent target engagement, and persistence of at least part of the benefit after treatment withdrawal. Current tocotrienol evidence primarily satisfies the first criterion during active treatment and provides partial mechanistic support through NGF. Evidence for the remaining domains is insufficient. This does not imply failure of the intervention. Rather, it identifies precisely what needs to be tested next.

5. Importance of Treatment Duration

DPN is a chronic disorder evolving over years. Short-term biological effects may therefore precede clinically visible structural recovery. The eight-week study by Ng et al. (2020) is particularly valuable for detecting relatively rapid physiological effects. However, eight weeks is unlikely to be sufficient for substantial structural regeneration of chronically damaged nerves. The 12-month Chuar et al. (2021) study improves upon this limitation, but even one year may remain relatively short when compared with decades of metabolic nerve injury. Future trials should consider treatment durations of 18–24 months, especially when structural endpoints such as CCM are included. A longer study would also permit evaluation of whether early changes in conduction predict later changes in small-fiber morphology or clinical function.

6. Pharmacokinetic Standardization is Essential

Formulation is another underappreciated source of uncertainty. Tocotrienol preparations should not be treated as interchangeable. Sharif et al. (2023) demonstrated variation in tocotrienol pharmacokinetic profiles across formulations and isomers. Lee et al. (2022) demonstrated that self-emulsifying formulations can substantially enhance bioavailability compared with non-self-emulsifying oily preparations. This means that negative or positive results

obtained with one formulation cannot automatically be generalized to all palm tocotrienol supplements. Future trials should report isomer composition, tocopherol content, delivery technology, dosing schedule, food conditions, adherence, and preferably circulating tocotrienol concentrations. Pharmacokinetic confirmation is particularly important in nonresponders. Without measurement of exposure, investigators cannot determine whether failure reflects biological resistance or inadequate absorption.

7. Patient Stratification Should Become a Central Design Feature

Large clinical trials commonly enroll patients under the broad diagnosis of DPN, but this approach can obscure biologically distinct subgroups. Such heterogeneity may dilute treatment effects when a therapy is active only in patients with a particular fiber phenotype, disease stage, metabolic profile, or degree of preserved axonal reserve. Future tocotrienol trials should therefore stratify participants by painful versus painless neuropathy, small-fiber versus large-fiber predominance, electrophysiological severity, nerve amplitude and preserved axonal reserve, and diabetes duration. Glycemic variability and time in range, renal function, cardiovascular risk profile, baseline vitamin E status, and concomitant neuropathic-pain therapy should also be documented, while potentially relevant metabolic modifiers such as homocysteine and nutritional deficiencies can be incorporated as prespecified exploratory variables. This approach would enable treatment-effect heterogeneity to be examined prospectively rather than through post hoc subgroup interpretation. Risk-factor literature demonstrates that DPN develops through multiple interacting exposures rather than glycemia alone (Fakkel et al., 2020; Sloan et al., 2021). Stratification could therefore reveal a subgroup in which tocotrienols exert greater biological benefit.

8. Preventive Therapy Versus Rescue Therapy

Another major conceptual problem is the tendency to combine prevention, disease modification, and analgesia into a single therapeutic question. These objectives require different populations, endpoints, and time horizons, so they should be separated explicitly in future trial designs. A preventive therapy would be administered before substantial neural loss with the objective of reducing future neuropathy development. A disease-modifying therapy would slow or reverse measurable neurological deterioration after early neuropathy is established, whereas a symptomatic therapy would reduce pain or other symptoms irrespective of whether underlying axonal pathology changes. These distinctions are clinically important because success in one domain does not establish efficacy in the others. Tocotrienols may ultimately be more useful in prevention or early disease modification than in rescue treatment of advanced painful neuropathy, and this possibility deserves explicit testing. Contemporary diagnostic developments make such trials increasingly feasible because CCM and other small-fiber techniques can identify early neural injury before conventional bedside tests become abnormal, although multimodal confirmation remains preferable because individual tests differ in sensitivity and specificity

(Petropoulos et al., 2021; Perkins et al., 2021; Gad et al., 2022; Gylfadottir et al., 2023; Naruse, 2024).

9. Pain Should Remain a Secondary But Essential Endpoint

Arguing that pain and nerve conduction are different does not mean that pain can be ignored. Pain relief is important to patients and remains a fundamental measure of clinical relevance. Future tocotrienol trials should therefore include validated pain instruments while avoiding the expectation that pain must track electrophysiology perfectly. Contemporary painful-DPN guidance also supports multidimensional assessment that considers pain intensity, function, tolerability, and the broader clinical context rather than relying on a single symptom score (Sayed et al., 2024). Measures should ideally include pain intensity, pain interference, sleep disturbance, patient global impression of change, quality of life, and functional capacity. Psychological status should also be assessed because chronic neuropathic pain is strongly influenced by mood and coping (Twiddy et al., 2021; Vileikyte, 2023). Clinical-management literature similarly emphasizes that meaningful DPN outcomes extend beyond pain intensity to walking, sleep, daily activity, and quality of life (Preston et al., 2023; Basem et al., 2023; Mallick-Searle and Adler, 2024; Sayed et al., 2024).

10. Tocotrienols Should be Investigated as Adjunctive Rather Than Replacement Therapy

At present, there is no basis for recommending tocotrienols as a substitute for established DPN management. Glycemic optimization, management of cardiovascular risk factors, foot surveillance, education, appropriate footwear, and evidence-based pain therapy remain essential components of comprehensive care (Ziegler et al., 2021; Ziegler, 2023; Atmaca et al., 2024; Sayed et al., 2024). The most rational potential role is adjunctive. Standard pharmacological therapy could address pain while tocotrienol therapy, if proven effective, could target underlying neural physiology; this complementary model is consistent with chronic-disease management in which symptom control and disease-modifying strategies act through different mechanisms. The value of tocotrienols would therefore depend on whether they provide reproducible neural preservation or functional benefit beyond that achieved by established symptomatic therapy. Combination-treatment research in painful DPN also shows that clinically meaningful management frequently requires more than one therapeutic mechanism (Dantas et al., 2023). Tocotrienols would therefore not need to outperform duloxetine or pregabalin as analgesics to be clinically valuable if they could reliably preserve peripheral nerve function. A definitive next-generation trial should measure treatment effects across several independent neurological domains rather than relying exclusively on nerve-conduction velocity or pain intensity. This architecture is designed to separate symptomatic, electrophysiological, structural, mechanistic, and durability signals before any disease-modification claim is made (Figure 4).

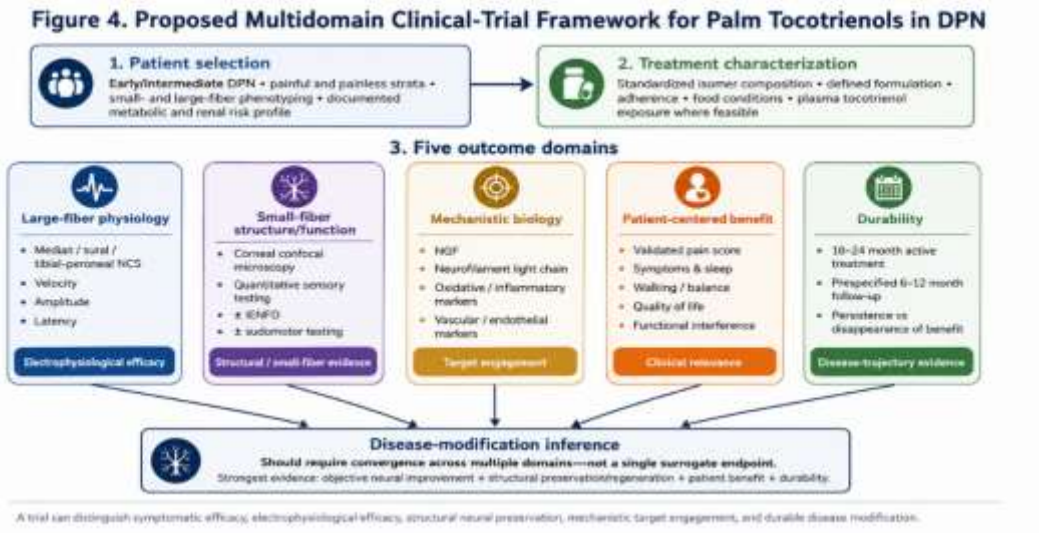


Figure 4. Proposed Multidomain Clinical-Trial Framework for Palm Tocotrienols in DPN

Figure 4 illustrates that the proposed trial architecture uses triangulation to distinguish different types of therapeutic response. Improvement in pain alone would demonstrate symptomatic efficacy. Improvement in conduction alone would demonstrate electrophysiological efficacy. Convergent improvement in large-fiber function, small-fiber structure, clinical function, mechanistic biomarkers, and post-treatment durability would provide substantially stronger evidence for disease modification.

11. Broader Implications for Nutraceutical Research

The tocotrienol-DPN literature also illustrates a broader issue in nutraceutical research. Bioactive dietary compounds are often discussed in terms of generalized mechanisms such as "antioxidant," "anti-inflammatory," or "neuroprotective" activity. Such labels can obscure clinically important distinctions. A nutraceutical should be evaluated according to the same endpoint logic applied to conventional pharmacotherapy. Biological plausibility is necessary but insufficient. Objective target engagement, appropriate dosing, reproducible exposure, clinically meaningful outcomes, and durability are required for strong therapeutic claims. The inconsistent systemic biomarker findings reported by Khor et al. (2021), alongside selective metabolic improvements summarized by Phang et al. (2023), demonstrate why broad antioxidant claims are inadequate. Palm tocotrienols should therefore be viewed as pharmacologically active bioactive compounds requiring rigorous clinical characterization rather than as generic vitamin supplementation.

12. Strengths of the Current Tocotrienol Evidence

Several strengths of the current tocotrienol evidence deserve recognition. First, the direct DPN literature includes randomized placebo-controlled clinical trials rather than relying exclusively on animal models. Second, those trials incorporated objective electrophysiological outcomes, which provide a more direct indication of peripheral nerve physiology than symptom reports alone.

Third, the NGF finding provides a mechanistically interesting neurotrophic signal, while the 12-month study incorporated a washout phase that offers unusually valuable information concerning persistence of effect. Fourth, the observed findings are biologically compatible with the broader neuroprotective literature on tocotrienols (Ismail et al., 2020; Ranasinghe et al., 2022). Together, these characteristics justify further investigation and distinguish the tocotrienol hypothesis from nutraceutical claims supported primarily by in vitro evidence.

13. Limitations of the Evidence

The principal limitation is the small number of direct contemporary DPN trials. Independent multicenter replication remains necessary. The second limitation is incomplete neuropathy phenotyping. The existing studies provide substantial large-fiber electrophysiological information but comparatively little structural small-fiber information. Third, the available studies have not established clinically meaningful reductions in long-term complications such as ulceration, falls, or functional deterioration. Consequently, the relationship between statistically significant physiological changes and outcomes that matter directly to patients remains uncertain. Fourth, formulation-specific pharmacokinetics limit generalizability. Tocovid or another bioenhanced formulation should not automatically be equated with all commercially available palm-derived tocotrienol supplements. Fifth, the washout data raise uncertainty concerning whether the observed physiological improvements represent structural regeneration or reversible biological support. This uncertainty is central to any disease-modification claim because durable neural repair should ideally be supported by structural or persistent functional evidence. Finally, surrogate outcomes may be statistically significant without producing changes large enough to matter to patients. Future research therefore needs both objective neurological outcomes and patient-centered clinical thresholds.

14. Implications for Clinical Practice

Current evidence does not justify positioning palm tocotrienols as established disease-modifying therapy for diabetic peripheral neuropathy. The available data are better interpreted as an encouraging phase II signal that requires independent replication and more comprehensive phenotyping before routine clinical adoption. However, it would also be overly dismissive to characterize the clinical evidence as negative. Repeated improvement in objective conduction parameters indicates biological activity worthy of further study. Clinicians and researchers should therefore adopt a balanced interpretation: tocotrienol-rich vitamin E is a promising investigational adjunct rather than a proven replacement for established DPN care. Any clinical use should remain accompanied by glucose management, cardiovascular risk reduction, foot protection, assessment of alternative causes of neuropathy, and evidence-based management of pain.

CONCLUSIONS AND RECOMMENDATIONS

The 2020–December 2024 evidence supports a biologically plausible but still unproven role for palm-derived tocotrienols in diabetic peripheral neuropathy. Randomized clinical evidence demonstrates that tocotrienol-rich vitamin E can improve selected median, sural, and tibial nerve-conduction parameters during active treatment, while short-term supplementation has also been associated with increased circulating nerve growth factor. These findings provide objective evidence that tocotrienols interact with peripheral nerve physiology. They are therefore more substantial than a purely theoretical antioxidant rationale. Nevertheless, improvement in nerve-conduction velocity cannot be equated automatically with neural regeneration, symptomatic recovery, or durable disease modification. Routine nerve-conduction studies primarily assess large myelinated fibers, whereas painful DPN frequently involves small-fiber pathology, ectopic nociceptive activity, neuroimmune signaling, and central sensitization. Consequently, electrophysiological improvement may coexist with persistent pain without representing a scientific contradiction. The disappearance of significant between-group nerve-conduction differences after treatment withdrawal is especially important. It suggests that at least part of the benefit may depend on continued tocotrienol exposure and may reflect reversible improvement in metabolic, vascular, membrane, or neurotrophic conditions rather than permanent reconstruction of damaged nerves. The most appropriate current conclusion is therefore that palm tocotrienols represent a candidate disease-modifying adjunct with demonstrated electrophysiological activity but insufficient evidence of durable structural neuroregeneration. This formulation acknowledges a reproducible physiological signal while avoiding a stronger claim than the current evidence can support.

Future trials should move beyond binary treatment-versus-placebo comparisons. Participants should be stratified according to disease stage, painful versus painless phenotype, small- versus large-fiber involvement, axonal reserve, diabetes duration, renal status, and glycemic variability. Tocotrienol formulation and systemic exposure should be documented rigorously. Most importantly, future efficacy studies should combine nerve-conduction velocity and amplitude with CCM, quantitative sensory testing, small-fiber assessment, NGF and other prespecified mechanistic biomarkers, neurofilament measures, pain scales, functional outcomes, and quality of life. Treatment should continue sufficiently long to detect structural change, followed by a prespecified withdrawal phase capable of testing durability. Such multidomain studies would make it possible to distinguish three clinically different effects: symptomatic analgesia, reversible enhancement of peripheral nerve physiology, and genuine alteration of the underlying neuropathic process. Clear separation of these outcomes would also make future positive and negative findings more clinically interpretable. If future multicenter trials demonstrate concordant improvement in large- and small-fiber structure and function, meaningful patient-centered benefits, slowed neurological progression, and persistence after treatment withdrawal, palm tocotrienols could credibly emerge as a disease-modifying adjunct for DPN. Until then, the evidence should be interpreted with cautious

optimism: biologically compelling, electrophysiologically encouraging, but not yet sufficient to claim modification of the natural history of diabetic neuropathy.

FURTHER STUDY

This study still has some limitations, so more research is needed on the topic Beyond Pain Scores: Can Palm Tocotrienols Modify Diabetic Peripheral Neuropathy? Reconciling Nerve-Conduction Gains With Inconsistent Symptom Relief to improve this study and give both the authors and readers a better understanding

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