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Mini Review

Neuroprotective Potential of Palm Oil-Derived Tocotrienols: Evidence from Neurodegenerative Disease Models and Emerging Clinical Data

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Abstract

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, vascular dementia, diabetic neuropathy, and diabetic retinopathy impose a growing global health burden. At the same time, currently available therapies remain largely symptomatic and do not adequately halt neuronal injury or disease progression. Palm oil-derived tocotrienols, especially within the Tocotrienol-Rich Fraction (TRF), have attracted increasing attention as neuroprotective agents because they combine antioxidant, anti-inflammatory, anti-apoptotic, vasculoprotective, and membrane-stabilising properties. Preclinical studies published since 2020 indicate that palm oil-derived tocotrienols improve cognition, reduce amyloid-beta burden, attenuate retinal neurodegeneration, preserve dopaminergic neurons, and protect against vascular and metabolic injury in the nervous system. Experimental evidence suggests that these effects are mediated through suppression of oxidative stress, modulation of NF-kB-linked inflammatory cascades, preservation of mitochondrial function, regulation of apoptotic signalling, improvement of endothelial and cholinergic function, and enhancement of neurovascular repair. Emerging human studies, particularly in diabetic microvascular complications and cerebrovascular conditions, suggest that tocotrienol-rich supplementation may improve selected neurological and vascular biomarkers, although robust phase III efficacy data remain limited. This mini review synthesises recent mechanistic evidence, disease-specific findings, translational barriers, safety, and future clinical prospects of palm oil-derived tocotrienols in neurodegenerative and neurovascular disorders. Current evidence supports strong biological plausibility and promising preclinical efficacy, but larger randomised trials with standardised formulations, longer duration, and clinically meaningful neurological endpoints are still needed before palm oil-derived tocotrienols can be integrated into routine neuroprotective practice.

Keywords: Tocotrienol, Palm oil, Neuroprotection, Alzheimer's disease, Parkinson's disease, Vascular dementia, Diabetic retinopathy, Diabetic peripheral neuropathy, Oxidative stress, Neuroinflammation

JEL Classification Codes: I12; I18; I19; O33; Q16

Introduction

Neurodegenerative disorders are among the most consequential medical challenges of ageing societies because they produce progressive disability, cognitive decline, loss of independence, and high long-term care costs. Alzheimer's Disease (AD) and Parkinson's Disease (PD) remain the best-known examples, but

the clinical burden extends to Vascular Dementia (VaD), Diabetic Peripheral Neuropathy (DPN), Diabetic Retinopathy (DR), and mixed neurovascular-metabolic syndromes that share overlapping mechanisms of neuronal injury. Across these conditions, oxidative stress, mitochondrial dysfunction, neuroinflammation, endothelial injury, impaired neurovascular coupling, excitotoxicity, and apoptotic cell death are recurrent pathogenic themes [1-3]. This mechanistic convergence has strengthened interest in multifunctional neuroprotective compounds that can act on several injury pathways simultaneously. Tocotrienols, members of the vitamin E family, are especially relevant in this regard. Palm oil is one of the richest natural sources of tocotrienols, and the palm oil-derived tocotrienol-rich fraction contains a mixture of tocotrienol isomers, along with smaller amounts of tocopherols. Unlike tocopherols, tocotrienols possess an unsaturated isoprenoid side chain that improves membrane mobility and may contribute to broader biological actions in neural tissues [4-8]. A 2020 systematic review of palm oil and palm oil-derived TRF concluded that all included preclinical studies demonstrated enhanced cognitive performance or neuroprotective effects, particularly through attenuation of oxidative stress, neuroinflammation, and apoptosis. Since then, additional studies have expanded the evidence base across AD, PD, VaD, DR, and DPN, while reviews published in 2021–2025 have emphasised anti-inflammatory mechanisms, improved neurovascular function, and the need for bioavailability-enhancing formulations. This mini review synthesises recent evidence on the neuroprotective potential of palm oil-derived tocotrienols, focusing on molecular mechanisms, disease-specific evidence, translational barriers, emerging clinical findings, and future directions [6-12].

Palm Oil-Derived Tocotrienols and Mechanistic Basis of Neuroprotection

Palm oil-derived tocotrienols are increasingly regarded as pleiotropic neuroprotective agents rather than simple antioxidants. Experimental studies indicate that TRF and individual tocotrienol isomers can reduce lipid peroxidation, preserve endogenous antioxidant defences, modulate inflammatory mediators, stabilise neuronal membranes, and reduce apoptosis in neuronal and glial systems. Their actions appear particularly relevant in tissues vulnerable to chronic oxidative injury, such as hippocampal neurons, retinal cells, and dopaminergic pathways [4,6,11,13,14]. The major mechanistic pathways through which palm oil-derived tocotrienol-rich fraction may exert neuroprotective effects are summarised in Figure 1.

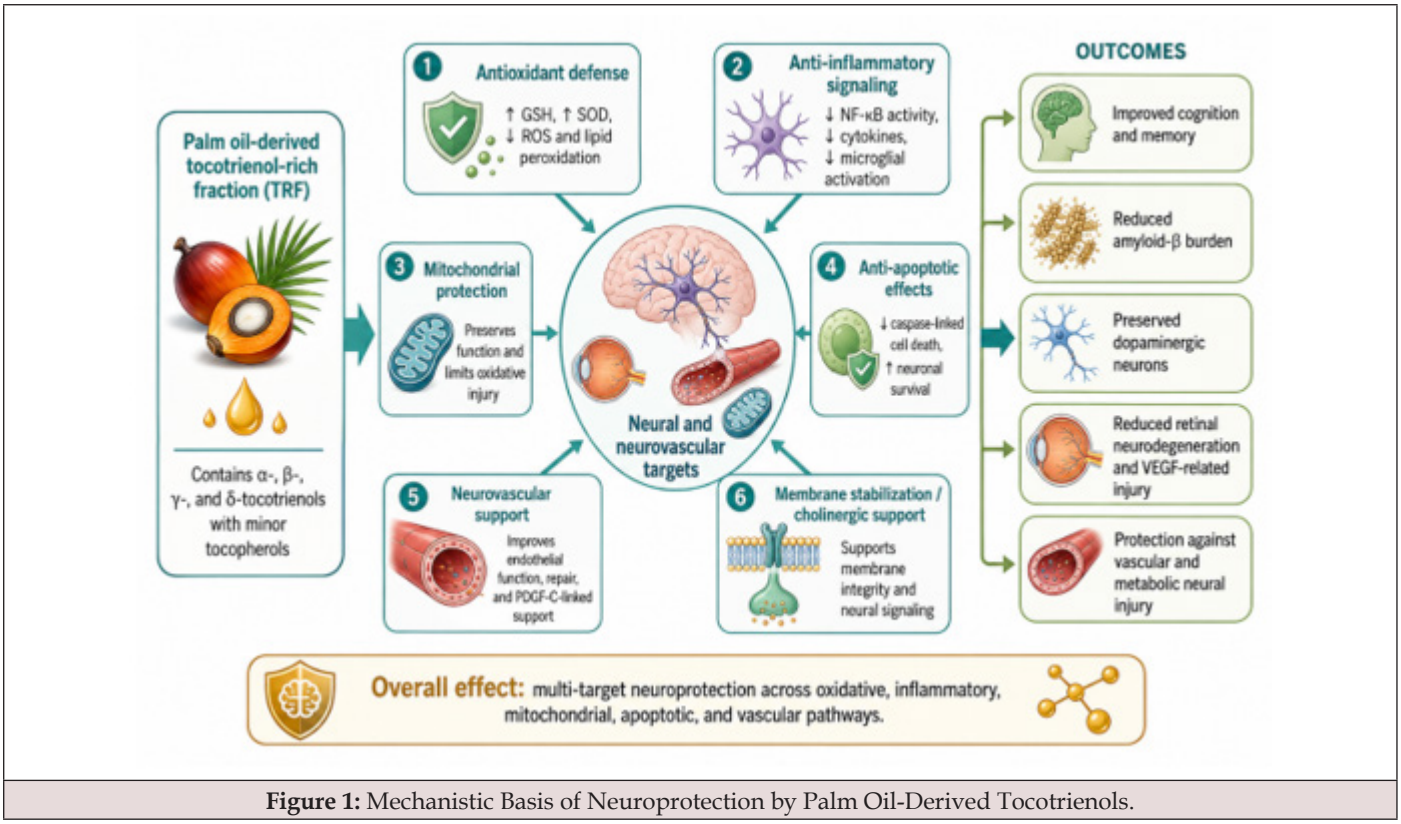

Figure 1: Mechanistic Basis of Neuroprotection by Palm Oil-Derived Tocotrienols.

Figure 1 illustrates the proposed mechanistic basis of neuroprotection by palm oil-derived tocotrienol-rich fraction. The figure emphasises that TRF contains multiple tocotrienol isomers and may act through complementary antioxidant, anti-inflammatory, mitochondrial, anti-apoptotic, neurovascular, membrane-stabilising, and cholinergic-support pathways. These convergent mechanisms target both neural and neurovascular compartments and are linked to improved cognition, reduced

amyloid-β burden, preservation of dopaminergic neurons, attenuation of retinal neurodegeneration, and protection against vascular and metabolic neural injury. One consistent mechanism is the suppression of oxidative stress. Several studies report that tocotrienol treatment increases Glutathione (GSH) and Superoxide Dismutase (SOD), while lowering markers of oxidative injury and tissue degeneration. In diabetic vascular dementia models, TRF restored antioxidant balance while improving memory performance and histopathology. In retinal studies, TRF reduced retinal apoptosis and VEGF-associated injury, again supporting an antioxidant-linked neuroprotective pathway [13,15-18].

Anti-inflammatory activity is another major mechanism. Reviews published since 2021 emphasise that tocotrienols downregulate neuroinflammatory cascades implicated in AD, PD, amyotrophic and vascular neurodegeneration, with likely involvement of NF-kB-linked pathways, microglial activation, and inflammatory cytokines. In PD models, α- and γ-tocotrienol reduced inflammation and preserved dopaminergic structures. In AD-related models, TRF reduced amyloid-linked neuroinflammatory changes and improved behavioural outcomes [17,19-25]. Tocotrienols also influence mitochondrial integrity and neuronal survival signalling. Preclinical work suggests that tocotrienols protect against neuronal death by maintaining mitochondrial function, reducing ROS-mediated membrane damage, and modulating apoptosis-related pathways. In Parkinsonian cellular and murine models, tocotrienols, especially the γ- and δ-isomers, exhibited cytoprotective activity via PI3K/Akt signalling, with estrogen receptor beta implicated as an upstream mediator. This suggests that tocotrienols may exert non-antioxidant neuroprotective effects by modulating signalling pathways [19,26-30]. Another emerging mechanism is neurovascular protection. In diabetes-associated and aluminium chloride-associated vascular dementia models, TRF improved endothelial function, increased PDGF-C expression in the hippocampus, reduced myeloperoxidase and lipid peroxidation markers, and enhanced parameters related to neovascular support and tissue repair. These findings are important because many neurodegenerative syndromes include a vascular component, and neurovascular dysfunction is now recognised as a major contributor to cognitive decline [31-38].

Alzheimer's Disease and Cognitive Decline

Alzheimer's disease is characterised by progressive cognitive impairment, extracellular amyloid-beta deposition, tau-related pathology, synaptic dysfunction, oxidative stress, and chronic neuroinflammation. Tocotrienols have attracted interest in AD because they target several of these processes simultaneously. The 2020 systematic review found that TRF enhanced cognition in transgenic AD animal models and reduced amyloid-beta deposition by altering the expression of genes associated with neuroprotection and AD-related pathways [17,24,39-46].

Subsequent reviews reinforced this conclusion. A 2021 interactive review summarised in vitro and in vivo evidence showing that tocotrienols can combat oxidative stress, mitochondrial dysfunction, and neuronal degeneration in AD-related systems, although it also noted that no definitive clinical trial had yet established efficacy in AD patients. A more recent scoping review similarly concluded that TRF demonstrates promising neuroprotective effects in AD models, including reduced DNA damage, increased antioxidant activity, and lower neuronal cell death in amyloid-beta-exposed neuroblastoma systems [7,19,24,45,47]. Mechanistically, TRF supplementation has been linked to attenuation of amyloid-related pathology and modulation of hippocampal gene expression. Experimental work showed that TRF improved motor learning and spatial memory, reduced ROS production, lowered neuronal apoptosis, and decreased amyloid plaque aggregation in transgenic AD mice. These effects suggest that tocotrienols may work not only by neutralising oxidative injury but also by reprogramming molecular pathways involved in amyloid processing, inflammation, and synaptic resilience [7,19,44,48,49]. Despite the encouraging preclinical data, the translational gap remains substantial. The 2021 review stressed that the therapeutic role of tocotrienols in AD remains under debate, precisely because clinical trial evidence is absent or insufficient. Therefore, while tocotrienols show strong biological plausibility for slowing AD-related injury, their place in clinical management remains investigational [19,24,29,45,50].

Parkinson's Disease

Parkinson's disease is driven by progressive degeneration of dopaminergic neurons in the substantia nigra, accompanied by oxidative stress, mitochondrial dysfunction, neuroinflammation, and accumulation of toxic protein species. Tocotrienols have been investigated in PD because these mechanisms overlap closely with their known biological actions [19,23,24,28,51]. A 2021 experimental study demonstrated that oral supplementation with α- and γ-tocotrienol for 28 days ameliorated motor deficits induced by 6-hydroxydopamine in rats, improved neuronal function, reduced inflammation, reversed neuronal degeneration, and limited further reduction of dopaminergic neuron density in the substantia nigra and striatal fibres. α-Tocotrienol appeared to produce earlier and somewhat stronger functional benefits, although both isomers were active [52]. Related mechanistic work showed that tocotrienols, particularly γ- and δ-tocotrienols, exert cytoprotective effects in PD models by activating PI3K/Akt signalling, with estrogen receptor beta acting upstream. This observation is noteworthy because it suggests that tocotrienols may directly influence neuronal survival signalling, rather than acting solely as chain-breaking antioxidants. Such signalling-based effects strengthen the rationale for exploring tocotrienols in chronic neurodegenerative conditions where cell survival pathways are progressively exhausted [26,28]. At the clinical level, evidence remains preliminary. A registered trial on tocotrienols in Parkinson's disease indicates growing translational interest, but robust published efficacy outcomes remain limited. Consequently, the current state of evidence supports tocotrienols as promising neuroprotective candidates in PD, but not yet as validated therapeutic agents [53].

Vascular Dementia and Neurovascular Dysfunction

Vascular dementia is the second most common form of dementia and is strongly associated with cerebrovascular injury, endothelial dysfunction, metabolic disease, inflammation, and oxidative stress. Because palm oil-derived TRF appears to influence both neuronal and vascular pathways, VaD has become an especially important target for recent tocotrienol research [13,31,54-56]. In a 2022 study using a rat model of type 2 diabetes-induced vascular dementia, oral TRF at doses of 30, 60, and 120 mg/kg for 21 days significantly attenuated memory deficits in the Morris water maze. TRF also improved cholinergic function, reduced homocysteine, increased GSH and SOD, protected hippocampal structure, and enhanced PDGF-C expression, suggesting improved neurovascular repair capacity. These findings are important because they connect behavioural improvement with biochemical and histopathological evidence of neuroprotection [13]. A 2023 study further showed that TRF ameliorated aluminium chloride-induced neurovascular dysfunction-associated vascular dementia in rats by improving memory, increasing serum nitrite, decreasing MPO and TBARS, and inducing hippocampal PDGF-C expression. The investigators interpreted these findings as evidence that TRF reduces brain oxidative stress, improves endothelial function, supports neovascularisation, and protects neurons [31]. These data suggest that palm oil-derived tocotrienols may be particularly relevant in mixed neurodegenerative states where vascular pathology, metabolic disease, and oxidative injury coexist. Given that many older adults with cognitive decline have overlapping Alzheimer-type and vascular mechanisms, this area may be especially promising for future translational studies [11-13,31].

Diabetic Retinopathy and Retinal Neurodegeneration

Diabetic retinopathy is commonly discussed as a microvascular ocular disease, but it also involves early retinal neurodegeneration, neuronal apoptosis, inflammation, and angiogenic signalling. Palm oil-derived TRF has shown notable activity in this domain [16,5,57-60]. A 2020 study in streptozotocin-induced diabetic rats found that oral TRF supplementation protected against retinal degenerative changes, increased retinal layer thickness, reduced retinal cell apoptosis, and lowered VEGF expression, whereas topical TRF was less effective. This finding is relevant because it suggests that systemic delivery may be necessary to achieve meaningful retinal neuroprotection [57]. A study in late 2023 reported that TRF reduced retinal inflammation and angiogenesis in diabetic rats and protected against the development of diabetic retinopathy. Together, these studies support the view that tocotrienols can act on both the neuronal and vascular components of retinal injury, which is especially valuable in DR, where these processes are tightly interwoven [16]. Human translational evidence has also begun to emerge. A 2021 pilot phase II clinical trial investigated Tocovid, a palm oil-derived tocotrienol-rich vitamin E preparation, in patients with type 2 diabetes and diabetic retinopathy. Participants receiving 200 mg twice daily for 8 weeks were studied for ocular and diabetic outcomes, indicating early clinical movement in this field. Although the available summary does not establish definitive long-term retinal efficacy, the trial demonstrates feasibility and clinical interest in palm-derived tocotrienol formulations for diabetic neurovascular complications [61].

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is among the most frequent chronic complications of diabetes and is characterised by oxidative stress, microvascular injury, inflammation, axonal degeneration, sensory dysfunction, and neuropathic pain. Because tocotrienols possess antioxidant, anti-inflammatory, and neuroprotective properties, they have been explored as adjunctive therapy in DPN [62-65]. A randomised clinical trial published before 2020 already suggested that oral mixed tocotrienols could improve neuropathic outcomes in DPN, helping establish the translational basis for later work. More recently, a 2025 review highlighted the potential of palm TRF to halt or mitigate DPN severity, emphasising the central role of oxidative stress in diabetic nerve injury and proposing tocotrienols as plausible disease-modifying supplements. Additional reports summarised by bibliographic databases indicate improvements in nerve conduction parameters with tocotrienol-rich vitamin E preparations such as Tocovid SupraBio, although comprehensive final trial reporting remains limited in the currently accessible record [47,62,64,66-68]. The DPN literature remains less mature than the DR or VaD literature, but it illustrates a key point: palm oil-derived tocotrienols are being investigated not only in classical neurodegeneration, but also in metabolic neuropathies where oxidative stress and microvascular dysfunction are central [57,62,66,68].

Stroke, Cerebrovascular Protection, and Related Human Evidence

Cerebrovascular injury shares key mechanisms with other neurodegenerative disorders, including oxidative stress, excitotoxicity, inflammation, platelet dysfunction, endothelial damage, and neuronal apoptosis. A long-standing interest in tocotrienols as neuroprotective agents in ischemic injury has now evolved toward more formal clinical assessment [50,69-72]. The SATURN trial was designed as a phase III randomised, double-blind, placebo-controlled study evaluating oral mixed tocotrienol 200 mg twice daily for 6 months in patients with moderate ischemic stroke, with endpoints including lesion volume, functional recovery, and cognitive performance. Although the trial registry demonstrates strong translational intent, definitive efficacy outcomes published in the accessible material remain limited [72-74]. A 2020 phase II clinical trial in patients with prior ischemic stroke or transient ischemic attack evaluated 400 and 800 mg tocotrienol daily for one year and investigated platelet function. The existence of this trial is important because it suggests that tocotrienols may have clinically relevant vascular and thromboregulatory effects in

patients with cerebrovascular disease, adding another dimension to their neuroprotective profile [75]. Taken together, the stroke-related evidence indicates that palm oil-derived tocotrienols have moved beyond purely laboratory investigation and into structured human studies, although high-quality outcome data on disability reduction, lesion progression, and long-term cognition are still needed [11,12,72,76,77]. The disease-specific evidence landscape for palm oil-derived tocotrienols across neurodegenerative, neurovascular, retinal, peripheral nerve, and cerebrovascular conditions is summarised in Figure 2.

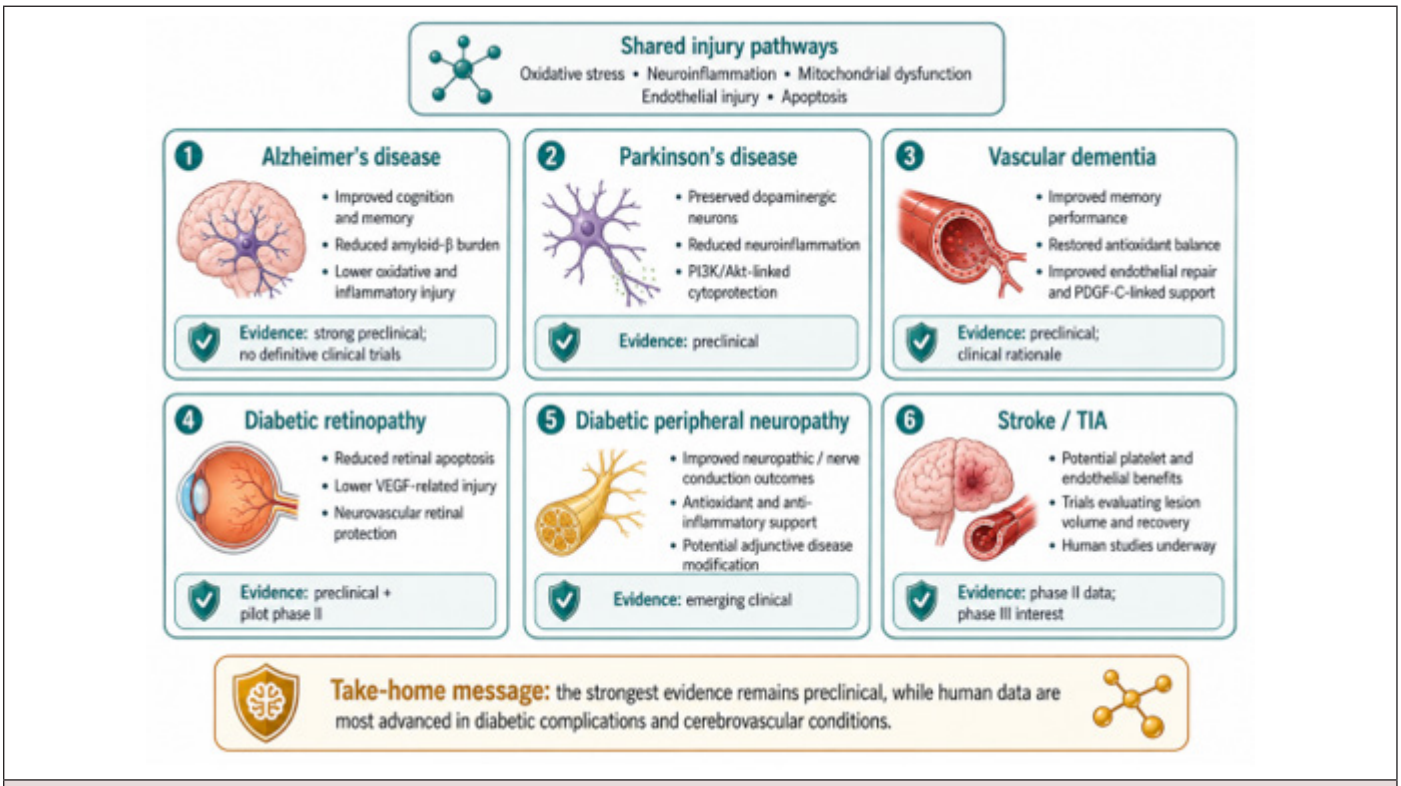

Figure 2: Disease- Specific Evidence Landscape for Palm Oil-Derived Tocotrienols.

Figure 2 summarises the current disease-specific evidence landscape for palm oil-derived tocotrienols. Across Alzheimer's disease, Parkinson's disease, vascular dementia, diabetic retinopathy, diabetic peripheral neuropathy, and stroke/TIA, the figure highlights shared injury pathways including oxidative stress, neuroinflammation, mitochondrial dysfunction, endothelial injury, and apoptosis. It also distinguishes the relative maturity of evidence across conditions, showing that the strongest support remains preclinical, while human data are most advanced in diabetic complications and cerebrovascular conditions.

Bioavailability, Formulation, and Translational Barriers

A recurring challenge in tocotrienol research is bioavailability. Tocotrienols are lipophilic, and oral absorption, tissue distribution, and central nervous system delivery can be variable. Reviews published since 2021 emphasise that improving extraction, formulation, and delivery is crucial for translation to clinical neuroprotection. Nano-enabled delivery systems and lipid-based approaches are increasingly discussed as strategies to improve stability, tissue targeting, and blood-brain barrier penetration [24,50,78-81]. Another limitation is the heterogeneity of formulations. Studies use TRF, purified isomers, and branded preparations such as Tocovid, often at different doses and durations, complicating cross-study comparisons. Preclinical models also differ markedly in disease induction, exposure period, and outcome measures [82,83]. The translational pathway from palm oil-derived tocotrienol source to clinical neuroprotective outcomes, together with key bioavailability barriers and proposed formulation solutions, is summarised in Figure 3.

Figure 3 illustrates the translational pathway for palm oil-derived tocotrienols, beginning with the palm oil source and extraction of mixed TRF or individual tocotrienol isomers, followed by formulation, oral absorption, systemic distribution, blood–brain barrier delivery, engagement of neural and neurovascular targets, and eventual clinical outcomes. The figure also highlights major barriers to translation, including variable oral absorption, limited CNS penetration, heterogeneous formulations and doses, short study duration, and the lack of large randomised trials. Potential solutions include nano-enabled delivery, lipid-based or self-

emulsifying systems, standardised formulations, longer trials with robust endpoints, and direct comparison of TRF versus individual isomers. The paucity of large randomised trials with hard neurological endpoints additionally constrains clinical translation. Reviews consistently note that while preclinical evidence is strong, evidence in human AD and PD remains insufficient. Even in DR, DPN, and stroke, the emerging human studies are promising but not yet definitive [84-88].

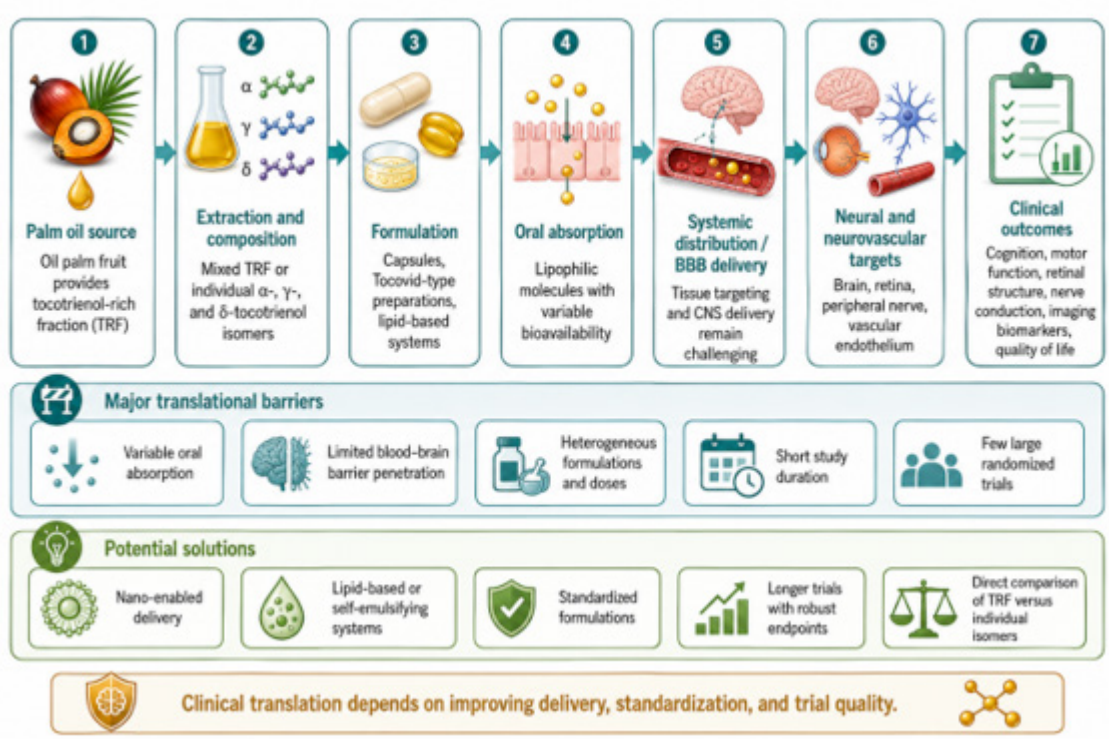

Figure 3: Translational Pathway, Bioavailability Challenges, and Solutions.

Safety Profile

One of the strengths of palm oil-derived tocotrienols is their generally favourable safety profile. The 2020 systematic review specifically addressed safety alongside neuroprotective efficacy and did not identify major toxicity concerns in the preclinical evidence reviewed. Human trials in diabetic and cerebrovascular settings also indicate practical tolerability sufficient for medium-term supplementation studies [6,11,13, 68,89]. This safety profile matters for neurodegenerative disease because candidate agents often require prolonged administration, possibly for months or years. A compound with broad antioxidant, anti-inflammatory, and vasculoprotective activity but poor long-term tolerability would have limited preventive or adjunctive utility. In contrast, palm-derived tocotrienol formulations appear sufficiently safe to warrant larger, longer-term studies, provided that dose standardisation and careful monitoring are maintained [6,20,24,45].

Future Directions

Future research should prioritise several areas. First, randomised controlled trials in Alzheimer's disease, Parkinson's disease, vascular cognitive impairment, and diabetic neuropathies are needed, with clinically meaningful endpoints such as cognition, motor function, retinal structure, nerve conduction, quality of life, and imaging biomarkers. Second, studies should directly compare TRF with individual isomers to clarify whether α-tocotrienol, γ-tocotrienol, or mixed formulations are optimal for specific neurological conditions. Third, formulation science deserves special emphasis. If inadequate CNS delivery limits efficacy, lipid nanoparticles, advanced emulsions, and other nanotechnological systems may be required to unlock the full therapeutic potential of tocotrienols. Fourth, mechanistic studies should continue to investigate interactions with amyloid processing, tau biology, microglial activation, endothelial signalling, mitochondrial metabolism, and neurovascular repair pathways. The current evidence strength and future research roadmap for palm oil-derived tocotrienols in neuroprotection are summarised in Figure 4.

Figure 4 presents a roadmap of evidence strength and future research needs for palm oil-derived tocotrienols. It shows that current evidence is strongest at the cellular, mechanistic, and animal-model levels, while pilot and phase II human studies

provide emerging but still limited clinical signals in diabetic retinopathy, diabetic neuropathy, stroke, and vascular biomarkers. The figure emphasises that definitive phase III efficacy data remain limited and that routine neuroprotective use is not yet established. It also identifies key priorities, including standardisation of TRF and isomer formulations, improved bioavailability and CNS delivery, longer randomised trials, clinically meaningful neurological endpoints, and studies addressing mixed vascular-metabolic pathology. Finally, future studies should consider that many patients have mixed pathology rather than a single isolated disease. Palm oil-derived tocotrienols may be especially useful in overlapping conditions such as diabetes-associated cognitive decline, vascular-metabolic dementia, or diabetic retinopathy with concurrent neuropathy, because their mechanisms span oxidative, inflammatory, vascular, and neuronal domains.

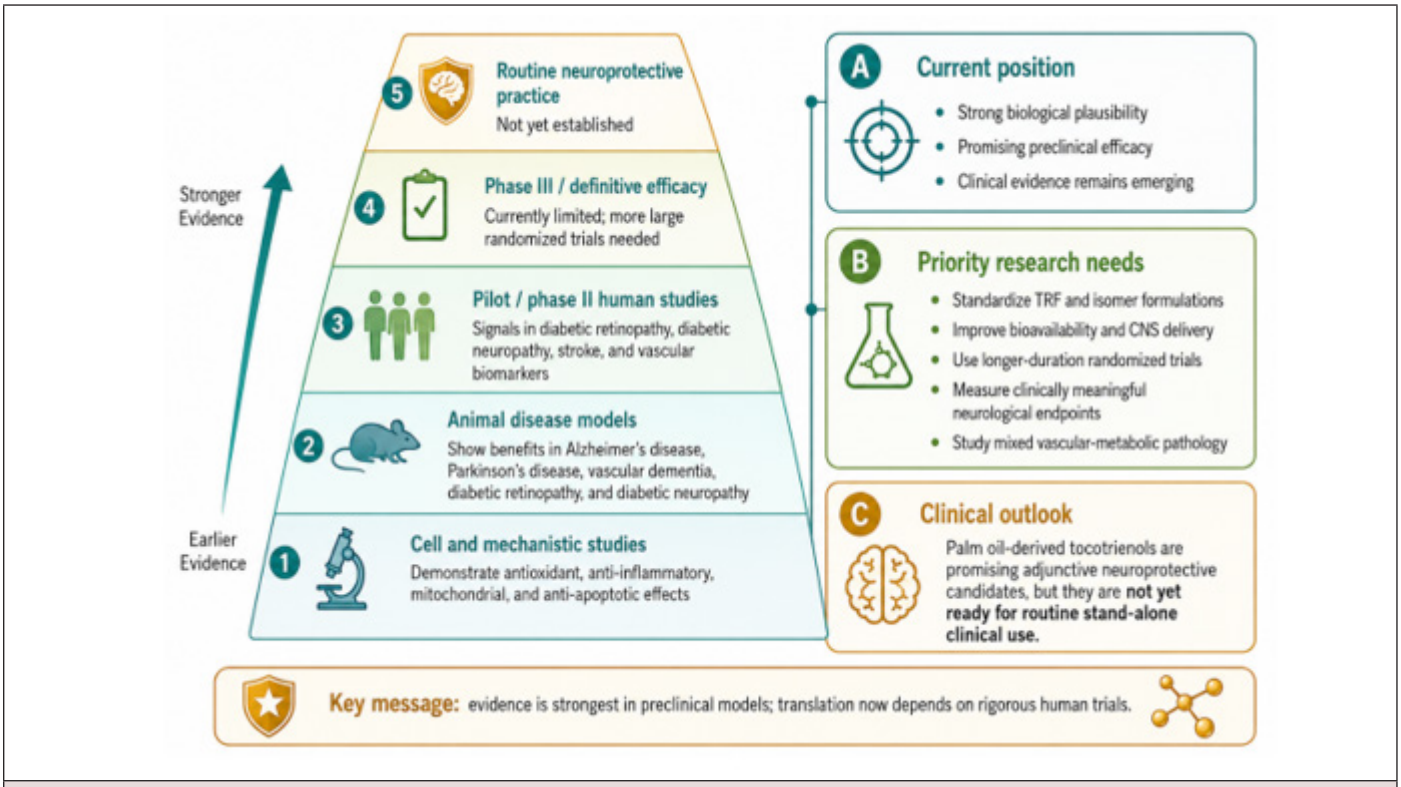

Figure 4: Evidence Strength and Future Research Roadmap.

Conclusion

Palm oil-derived tocotrienols are among the most promising nutraceutical neuroprotective candidates currently under investigation. Evidence published since 2020 shows that TRF and individual tocotrienol isomers can improve cognition, protect retinal neurons, preserve dopaminergic pathways, ameliorate vascular dementia, and modulate multiple mechanisms central to neurodegeneration, including oxidative stress, neuroinflammation, apoptosis, mitochondrial injury, and endothelial dysfunction. The strongest data currently come from preclinical models, but emerging human studies in diabetic retinopathy, diabetic peripheral neuropathy, stroke, and broader ageing-related health research suggest that clinical translation is feasible. At present, the evidence is not yet sufficient to support routine clinical use of palm oil-derived tocotrienols as established therapy for Alzheimer's disease, Parkinson's disease, or vascular dementia. Nevertheless, their combination of mechanistic breadth, relative safety, and growing translational interest makes them attractive candidates for adjunctive prevention and disease-modifying research. If future trials can confirm efficacy using standardized, bioavailable formulations and robust neurological endpoints, palm oil-derived tocotrienols may become valuable components of a multi-target strategy for neurodegenerative and neurovascular disorders.

Acknowledgement

None.

Conflict of Interest

None.

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