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Review Article



# Palm Tocotrienols in Cognitive Decline and Alzheimer's Disease: A Systematic Review of Molecular Mechanisms and Therapeutic Potential

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## Abstract

Neurodegenerative disorders such as Alzheimer's disease and cognitive decline are distinguished by steadily worsening neuronal dysfunction, oxidative imbalance, neuroinflammation, amyloid-beta accumulation, mitochondrial impairment, and deterioration of cognitive performance. Growing research interest in palm-derived tocotrienols is largely driven by their notable antioxidant effectiveness and protective influence on the nervous system. Hence, the objective of this study was to systematically assess and synthesise contemporary research findings related to the molecular interactions and therapeutic applications of palm-derived tocotrienols in cognitive impairment and Alzheimer's disease. Peer-reviewed literature identified from Scopus and PubMed databases served as the basis for the systematic literature review conducted in this study. Data collection was conducted through structured keyword-based searching, screening, eligibility assessment, and duplicate removal procedures following predefined inclusion criteria. Among the 1,196 articles initially retrieved, only 30 studies published within the 2018–2026 timeframe was considered eligible for the final analysis. Data analysis was performed using thematic synthesis and comparative interpretation of molecular and neuroprotective findings across *in vitro, in vivo*, and limited clinical studies. The findings demonstrated that palm tocotrienols consistently attenuated oxidative stress, suppressed neuroinflammatory signaling, reduced amyloid-beta-associated neurotoxicity, preserved mitochondrial integrity, and improved cognitive and neurobehavioral outcomes. Overall, the evidence suggests that palm-derived tocotrienols possess substantial therapeutic potential as multifunctional neuroprotective compounds in neurodegenerative disease modulation. Future studies should prioritise large-scale clinical trials, standardised intervention protocols, and advanced molecular investigations to strengthen translational applicability.

**Keywords:** Palm tocotrienols, Alzheimer's disease, Cognitive decline, Neuroprotection, Oxidative stress

## Introduction

The growing frequency and progressive development of neurodegenerative diseases have created a profound public health challenge with extensive socioeconomic implications for healthcare systems globally. Representing about 60–70% of dementia occurrences worldwide, Alzheimer's disease is the most frequent underlying cause of dementia and cognitive decline [1]. The continuous increase in life expectancy and aging populations has substantially accelerated the incidence of cognitive decline, particularly in both developed and developing countries. Contemporary epidemiological research estimates that the worldwide burden of dementia could exceed 150 million individuals by 2050 in the absence of sufficient intervention

strategies [2]. The pathological features of Alzheimer's disease include not only memory deterioration but also continuous neuronal degeneration, synaptic dysfunction, impaired executive performance, behavioural disturbances, and gradual loss of functional independence, ultimately resulting in severe reductions in quality of life and substantial economic burden for caregivers and healthcare infrastructures. The pathological complexity of Alzheimer's disease involves multifactorial biological mechanisms that interact progressively during disease development. Even though amyloid-beta plaque buildup and tau hyperphosphorylation are still regarded as principal pathological indicators, growing research emphasises the crucial role of oxidative stress, persistent neuroinflammation, mitochondrial impairment, excitotoxic processes, defective neuronal signalling, and homeostatic dysregulation in disease progression [3].

Oxidative stress has been particularly recognised as an early pathological trigger capable of inducing lipid peroxidation, protein oxidation, mitochondrial impairment, and neuronal apoptosis within vulnerable brain regions associated with memory and cognition. Simultaneously, sustained neuroinflammatory activation involving microglial overactivation and excessive cytokine production further amplifies neuronal injury and accelerates synaptic degeneration [4]. The intricate interaction between oxidative damage, inflammatory signalling, and amyloid-associated neurotoxicity demonstrates that Alzheimer's disease cannot be adequately understood through a single mechanistic pathway alone, thereby necessitating broader therapeutic approaches capable of targeting multiple interconnected biological processes simultaneously. Current pharmacological interventions for Alzheimer's disease remain largely symptomatic and demonstrate limited efficacy in preventing long-term neurodegeneration or restoring neuronal function. Cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, which are among the available therapeutic options, mainly address symptoms for a limited period without significantly altering disease progression [5]. Furthermore, several synthetic therapeutic approaches have shown limited clinical success due to insufficient neuroprotective efficacy, poor blood–brain barrier penetration, and adverse side effects associated with prolonged administration. The shortcomings associated with current pharmacological treatments have amplified interest in naturally derived bioactive substances capable of providing antioxidant, anti-inflammatory, and neuroprotective benefits that may support neurodegenerative disease prevention and therapy.

The unique structural composition and functional capabilities of tocotrienols, as constituents of the vitamin E family, have contributed to growing biomedical interest in these nutraceutical compounds. A key structural distinction between tocotrienols and tocopherols lies in the unsaturated isoprenoid side chain of tocotrienols, which enhances membrane dynamics, intracellular penetration, and antioxidant activity in lipid-rich systems [6]. The α-, β-, γ-, and δ-tocotrienol isoforms derived from palm oil represent one of the richest naturally occurring tocotrienol sources and have exhibited promising bioactivities in several experimental disease models [7]. Over the past few years, scientific studies have increasingly focused on the ability of palm tocotrienols to provide neuroprotection through oxidative stress reduction, inflammatory modulation, amyloid-beta suppression, mitochondrial stabilisation, and neuronal survival enhancement. Experimental evidence increasingly suggests that palm tocotrienols may exert multifaceted neuroprotective effects relevant to cognitive decline and Alzheimer's disease pathology. Several *in vitro* investigations have demonstrated that tocotrienol-rich fractions are capable of reducing reactive oxygen species accumulation, suppressing inflammatory mediator expression, and protecting neuronal cells against amyloid-beta-induced cytotoxicity [8]. Animal-based studies have similarly reported improvements in cognitive performance, synaptic preservation, mitochondrial function, and antioxidant defence systems following tocotrienol supplementation [9]. Moreover, certain observational and preliminary human studies have suggested potential associations between higher tocotrienol exposure and improved cognitive preservation among ageing populations, although the currently available clinical evidence remains relatively limited. These findings collectively indicate that palm tocotrienols may influence several pathological mechanisms simultaneously, thereby positioning them as potentially promising candidates for neuroprotective intervention in neurodegenerative conditions.

Despite the expanding body of literature concerning tocotrienols and neurodegenerative disorders, the currently available evidence remains fragmented across diverse experimental contexts, methodological approaches, and disease models. Existing studies vary considerably in terms of dosage regimens, treatment duration, cellular models, animal species, investigated biomarkers, and evaluated mechanistic endpoints [10]. Additionally, many published investigations focus primarily on isolated pathways such as oxidative stress or inflammation without comprehensively integrating the broader molecular interactions associated with Alzheimer's disease pathology. This heterogeneity creates challenges in identifying the dominant mechanistic patterns, evaluating the consistency of neuroprotective outcomes, and determining the translational therapeutic relevance of palm-derived tocotrienols within cognitive decline contexts. Consequently, a systematic synthesis capable of integrating evidence across cellular, molecular, and experimental domains is necessary to establish a clearer understanding of the mechanistic and therapeutic significance of palm tocotrienols in Alzheimer's disease research [11]. Another important limitation within the existing literature involves the relatively limited integration of mechanistic findings with therapeutic implications. While numerous studies report antioxidant or anti-inflammatory effects individually, fewer investigations critically synthesise how these interconnected mechanisms collectively contribute to neuronal protection, synaptic preservation, and cognitive improvement [12]. Similarly, inconsistencies remain regarding the

relative efficacy of different tocotrienol isoforms, optimal dosage concentrations, long-term therapeutic safety, and translational applicability to human clinical settings. Such unresolved concerns demonstrate the need for a systematic review approach that can integrate current scientific evidence, identify recurring molecular mechanisms, and evaluate the potential therapeutic applications of palm tocotrienols in Alzheimer's disease and cognitive deterioration. Hence, this research is designed to systematically review contemporary literature addressing the molecular activities and therapeutic relevance of palm-derived tocotrienols in cognitive decline and Alzheimer's disease. This review specifically focuses on identifying the dominant neuroprotective pathways associated with tocotrienol administration, including oxidative stress modulation, neuroinflammatory regulation, amyloid-beta inhibition, mitochondrial preservation, and cognitive function improvement. Furthermore, this systematic review seeks to integrate findings derived from *in vitro*, *in vivo*, and limited clinical investigations in order to provide a comprehensive and evidence-based understanding of the neuroprotective relevance of palm tocotrienols in neurodegenerative disorders.

Based on these objectives, the present review addresses two primary research questions:

RQ1: How do palm-derived tocotrienols modulate oxidative stress, neuroinflammatory pathways, amyloid-beta toxicity, and other molecular mechanisms associated with cognitive decline and Alzheimer's disease progression?

RQ2: What therapeutic patterns and neuroprotective effects are most consistently reported across contemporary experimental and biomedical studies investigating palm tocotrienols in neurodegenerative disease models?

## Literature Review

The literature concerning palm-derived tocotrienols in neurodegenerative disorders has expanded considerably in recent years, particularly in relation to Alzheimer's disease and cognitive decline. Current evidence increasingly suggests that palm tocotrienols possess multifunctional neuroprotective properties involving antioxidant regulation, anti-inflammatory modulation, mitochondrial preservation, and suppression of amyloid-associated neurotoxicity. Accordingly, this literature review synthesises major theoretical and mechanistic findings from previous biomedical studies, focusing on the interrelationship between oxidative stress, neuroinflammation, amyloid-beta pathology, mitochondrial dysfunction, and the emerging therapeutic potential of palm tocotrienols in neurodegenerative conditions.

### Palm Tocotrienols as Bioactive Neuroprotective Compounds

Tocotrienols constitute one of the two principal subclasses of the vitamin E family and have increasingly attracted scientific attention due to their distinctive biological and pharmacological properties. The presence of an unsaturated isoprenoid side chain structurally differentiates tocotrienols from tocopherols and contributes to increased membrane fluidity, stronger lipid bilayer penetration, and more efficient localisation within cellular systems rich in polyunsaturated fatty acids [13]. Widely considered one of the richest natural tocotrienol sources, palm oil provides α-, β-, γ-, and δ-tocotrienol isoforms that exhibit distinct antioxidant, anti-inflammatory, and neuroprotective capabilities in biomedical research settings.

The growing interest in palm tocotrienols is closely associated with their potential relevance in chronic degenerative diseases characterised by oxidative injury and inflammatory dysregulation. Unlike conventional antioxidants that primarily function through direct radical scavenging, tocotrienols have been reported to modulate multiple intracellular signalling pathways associated with cellular stress responses, mitochondrial preservation, inflammatory regulation, and neuronal survival [14]. Several comparative investigations further suggest that tocotrienols may possess stronger neuroprotective efficacy than tocopherols due to their superior antioxidant distribution dynamics and enhanced capacity to penetrate saturated lipid layers within neuronal membranes. This distinctive biochemical profile has positioned palm-derived tocotrienols as promising candidates for therapeutic exploration in neurodegenerative disorders, particularly Alzheimer's disease and age-related cognitive decline. Recent literature has additionally highlighted the broader pharmacological relevance of palm tocotrienols beyond antioxidant activity alone. Emerging studies demonstrate that tocotrienols may influence cholesterol metabolism, vascular integrity, cellular apoptosis, gene regulation, and inflammatory mediator expression, all of which are closely linked to neurodegenerative progression and neuronal vulnerability. Consequently, current scientific discussions increasingly emphasise the need to understand tocotrienols not merely as nutritional antioxidants but as multifunctional bioactive compounds capable of modulating interconnected pathological pathways relevant to brain ageing and neurodegeneration.

### Oxidative Stress and Neurodegeneration in Alzheimer's Disease

Scientific evidence repeatedly identifies oxidative stress as a dominant pathological process associated with the progression and early development of Alzheimer's disease. The accumulation of ROS and RNS beyond physiological levels disturbs neuronal redox equilibrium, resulting in lipid peroxidation, mitochondrial dysfunction, oxidative protein damage, DNA lesions, and synaptic impairment in cognitive brain regions [15]. Neurons are particularly sensitive to oxidative insults due to their intense metabolic processes, elevated oxygen requirements, and comparatively modest antioxidant defence mechanisms. Growing evidence indicates that oxidative damage may manifest at the early stages of Alzheimer's disease progression, frequently occurring prior to extensive amyloid-beta deposition and cognitive deterioration

[16]. Repeated findings from postmortem brain examinations and experimental neurodegenerative models have shown elevated concentrations of oxidative stress indicators, including MDA, 4-HNE, and oxidized proteins. Research evidence increasingly supports the idea that oxidative stress functions both as a pathological consequence and as an active driver of neurodegeneration and disease progression. The relationship between oxidative stress and mitochondrial dysfunction further amplifies neurodegenerative vulnerability. Mitochondrial impairment contributes to disrupted ATP production, calcium imbalance, increased ROS generation, and activation of apoptotic signalling pathways, thereby accelerating neuronal injury and synaptic deterioration [17]. Because oxidative stress is closely interconnected with multiple pathological processes involved in Alzheimer's disease, numerous therapeutic investigations have focused on identifying antioxidant compounds capable of attenuating oxidative damage and restoring neuronal redox balance. Within this context, palm tocotrienols have emerged as promising antioxidant candidates due to their ability to neutralise free radicals while simultaneously modulating intracellular antioxidant defence systems. Studies conducted in experimental settings have shown that tocotrienols may strengthen neuronal antioxidant defences by increasing the activity of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. The antioxidant relevance of palm tocotrienols therefore represents one of the most extensively investigated mechanistic pathways associated with their neuroprotective potential.

## Neuroinflammation and Inflammatory Signalling Pathways

In Alzheimer's disease and cognitive deterioration, neuroinflammation is considered a prominent pathological mechanism. Persistent inflammatory activation of microglial cells and astrocytes within the central nervous system contributes to abnormal production of cytokines, chemokines, nitric oxide, and inflammatory mediators that accelerate neuronal injury. While inflammatory mechanisms initially help protect the nervous system, prolonged activation of neuroinflammation may contribute to neuronal death, synaptic dysfunction, and progressive deterioration of cognitive abilities. The NF-kB signalling cascade is regarded as a major contributor to the regulation of inflammatory pathways in neurodegenerative progression. Upon activation, the NF-$k_B$ pathway enhances the transcription of numerous inflammatory factors, including TNF-α, IL-1β, IL-6, COX-2, and iNOS, all of which have been linked to neurodegenerative processes and Alzheimer's disease pathology [18]. Elevated inflammatory cytokine concentrations have repeatedly been associated with increased amyloid-beta toxicity, synaptic disruption, and accelerated disease severity in both experimental and clinical settings. Recent scientific studies increasingly indicate that palm tocotrienols may attenuate inflammatory responses by regulating cytokine expression and suppressing inflammatory signaling networks. Experimental evidence suggests that tocotrienols may inhibit NF-$_{kB}$ activation, reduce inflammatory mediator expression, and attenuate microglial overactivation under neuroinflammatory conditions [19]. In addition, several investigations have demonstrated that tocotrienol supplementation may reduce inflammatory infiltration and improve neuronal structural integrity within hippocampal and cortical brain regions. Importantly, oxidative stress and neuroinflammation are increasingly understood as interconnected pathological processes rather than isolated mechanisms. Excessive ROS production can activate inflammatory pathways, while inflammatory cytokines may further increase oxidative injury and mitochondrial dysfunction [20]. This reciprocal relationship has strengthened interest in multifunctional compounds such as palm tocotrienols that may simultaneously regulate oxidative and inflammatory pathways within neurodegenerative environments.

## Amyloid-Beta Toxicity and Tau Pathology

The deposition of amyloid-beta and hyperphosphorylation of tau proteins are considered key pathological hallmarks that have been extensively explored in Alzheimer's disease studies. In the amyloid cascade hypothesis, dysfunctional processing and aggregation of amyloid precursor protein are believed to result in extracellular amyloid-beta plaque accumulation that drives neuronal injury, oxidative stress, inflammation, and synaptic dysfunction [21]. Concurrently, intracellular tau hyperphosphorylation contributes to neurofibrillary tangle formation, microtubule destabilisation, and impaired neuronal transport systems, thereby accelerating neurodegeneration and cognitive decline. Although amyloid-beta and tau pathology remain central features of Alzheimer's disease research, increasing evidence suggests that these mechanisms are closely interconnected with oxidative and inflammatory disturbances. Amyloid-beta peptides can stimulate ROS generation, induce mitochondrial dysfunction, and activate inflammatory cascades, while oxidative stress may further enhance amyloid aggregation and tau phosphorylation [22]. This pathological interaction creates a self-amplifying cycle of neuronal injury that progressively worsens cognitive deterioration.

Several experimental studies have explored the capacity of palm tocotrienols to interfere with amyloid-beta toxicity and tau-associated neuronal damage. Certain investigations report that tocotrienol-rich fractions may inhibit amyloid-beta aggregation, reduce fibril formation, and attenuate amyloid-induced cytotoxicity within neuronal cell cultures [23]. Additional studies suggest that tocotrienols may suppress apoptotic signalling pathways activated during amyloid exposure, including reductions in caspase activation and mitochondrial membrane disruption. Evidence regarding the influence of tocotrienols on tau-related mechanisms remains comparatively limited but continues to expand. Preliminary findings indicate that tocotrienols may regulate kinase pathways associated with tau phosphorylation, including glycogen synthase kinase-3 beta (GSK-3β), thereby potentially reducing neurofibrillary pathology [24]. However, the extent to which these effects translate into clinically meaningful neuroprotection remains insufficiently

established, highlighting the need for broader mechanistic synthesis and further experimental validation.

### Mitochondrial Dysfunction and Neuronal Survival

Mitochondrial dysfunction is increasingly recognised as a critical contributor to neuronal degeneration and age-related cognitive impairment. Neurons require substantial energy demands to maintain synaptic transmission, calcium homeostasis, neurotransmitter synthesis, and intracellular signalling processes. Consequently, disturbances in mitochondrial bioenergetics may significantly impair neuronal viability and accelerate neurodegenerative progression [25]. Alzheimer's disease is frequently associated with disrupted mitochondrial respiration, impaired ATP synthesis, excessive mitochondrial ROS formation, abnormal calcium handling, and stimulation of intrinsic apoptotic pathways [26]. Experimental investigations together with postmortem brain analyses have revealed mitochondrial abnormalities associated with Alzheimer's disease, highlighting the potential role of impaired mitochondrial homeostasis in neuronal susceptibility. Palm tocotrienols have been investigated for their potential role in preserving mitochondrial function and improving neuronal survival under oxidative and inflammatory stress conditions. Experimental evidence indicates that tocotrienols may stabilise mitochondrial membrane potential, reduce mitochondrial swelling, suppress cytochrome c release, and improve cellular energy metabolism in neuronal systems exposed to neurotoxic stimuli [27]. Certain studies additionally report enhanced expression of mitochondrial respiratory proteins and improved oxygen utilisation efficiency following tocotrienol administration. The neuroprotective relevance of mitochondrial preservation extends beyond energy metabolism alone. Maintenance of mitochondrial integrity contributes to reductions in oxidative injury, inflammatory activation, and apoptosis-related signalling, thereby influencing multiple interconnected pathways involved in neurodegenerative progression [28]. Accordingly, mitochondrial stabilisation has emerged as one of the principal mechanisms through which palm tocotrienols may exert broader neuroprotective actions within cognitive decline models.

### Therapeutic Potential and Translational Challenges

The growing body of evidence concerning palm tocotrienols has generated increasing interest in their potential therapeutic relevance for Alzheimer's disease and cognitive decline management. Preclinical investigations consistently demonstrate that tocotrienols may improve antioxidant defences, suppress inflammatory activity, preserve neuronal integrity, and enhance cognitive performance in experimental neurodegenerative models [29]. These findings collectively support the possibility that palm-derived tocotrienols may function as multifunctional neuroprotective agents capable of targeting several pathological mechanisms simultaneously. Nevertheless, important translational challenges remain within the current literature. One major limitation involves the predominance of *in vitro* and animal-based investigations relative to large-scale human clinical studies. Variability in dosage regimens, treatment duration, bioavailability, experimental models, and outcome measurements also complicates direct comparison between studies and limits the establishment of standardised therapeutic recommendations [30]. Furthermore, the long-term clinical safety, pharmacokinetic properties, and optimal administration strategies of tocotrienols in neurodegenerative populations remain incompletely understood. Current literature therefore indicates that although palm tocotrienols demonstrate substantial neuroprotective promise, additional systematic evaluation and translational research remain necessary to clarify their therapeutic applicability within clinical settings [31]. Consequently, comprehensive evidence synthesis through systematic literature review approaches is essential to integrate existing mechanistic findings, evaluate consistency across studies, and identify future research directions concerning the neuroprotective role of palm-derived tocotrienols in cognitive decline and Alzheimer's disease.

## Methodology

The present investigation employs an SLR methodology guided by PRISMA standards to comprehensively assess current evidence regarding the molecular effects and therapeutic benefits of palm-derived tocotrienols in Alzheimer's disease and cognitive impairment. The potent biological properties of tocotrienols, including neuroprotective, antioxidant, and anti-inflammatory effects, have led to increasing scientific focus on their potential role in neurodegenerative disorders with progressive cognitive impairment. Palm tocotrienols, which represent one of the richest natural sources of vitamin E isoforms, have increasingly been investigated for their capacity to modulate oxidative stress, neuroinflammation, amyloid-beta aggregation, mitochondrial dysfunction, and neuronal survival pathways associated with Alzheimer's disease progression. Nevertheless, the currently available evidence remains dispersed across diverse experimental settings, including *in vitro* investigations, animal-based studies, and limited clinical evaluations, frequently accompanied by methodological variability and heterogeneous biological endpoints. Such fragmentation creates challenges in establishing an integrated understanding of the dominant mechanistic pathways and therapeutic implications associated with palm tocotrienol administration. Therefore, the present review was conducted exclusively using secondary data derived from peer-reviewed scientific publications indexed in Scopus and PubMed, without involving primary data collection methods such as field observations, interviews, surveys, or focus group discussions, thereby ensuring methodological consistency and evidence-based synthesis throughout the review process.

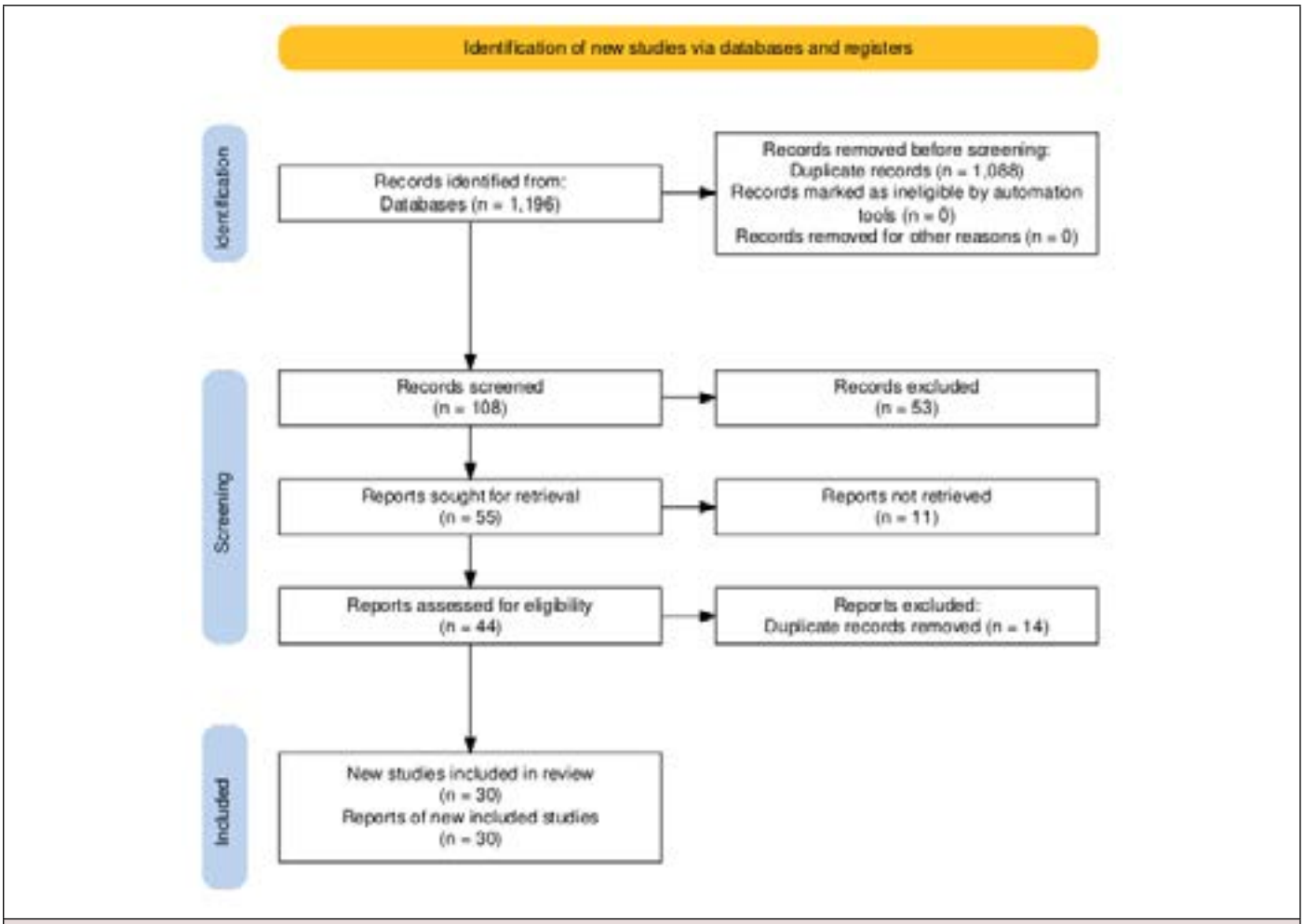


**Figure 1:** PRISMA framework applied in the systematic literature review process.

The PRISMA-based workflow implemented in this review is presented in Figure 1 and describes the sequential stages of identification, screening, eligibility assessment, and final inclusion. During the identification phase, an initial broad search was performed using the keyword combination "*tocotrienols AND health*," which generated 474 records from Scopus and 722 records from PubMed, resulting in a total of 1,196 identified publications. To improve thematic specificity and ensure alignment with the objectives of the review, a more focused Boolean search strategy was subsequently conducted using the following keyword structure: *("palm tocotrienols" OR "tocotrienol-rich fraction" OR tocotrienols) AND ("Alzheimer's disease" OR "cognitive decline" OR dementia OR neurodegeneration) AND ("molecular mechanism*" OR neuroprotection OR "oxidative stress" OR neuroinflammation OR "amyloid beta") AND ("therapeutic potential" OR treatment OR prevention OR intervention*). This refined search yielded 50 records from Scopus and 58 records from PubMed, resulting in 108 potentially relevant studies after the exclusion of 1,088 publications considered unrelated to the predefined thematic scope of the review. Minor modifications in search syntax were applied when necessary to accommodate differences in indexing systems and search algorithms between databases while preserving conceptual consistency across platforms.

In the screening stage, publication years were restricted to the 2018–2026 period to ensure that the review incorporated recent and scientifically relevant evidence reflecting current developments in neurodegenerative research. This criterion led to the exclusion of 53 studies published outside the specified timeframe, leaving 55 articles eligible for subsequent evaluation. During the eligibility assessment, full-text accessibility was examined to facilitate comprehensive extraction and synthesis of methodological and mechanistic findings. Eleven articles were excluded due to inaccessible full-text versions or non-open-access limitations, resulting in 44 studies eligible for detailed analysis. A final deduplication process subsequently identified 14 overlapping records across the two databases that had not been detected during previous screening stages, and these duplicate publications were removed to maintain analytical accuracy and prevent repetitive interpretation. Consequently, a total of 30 peer-reviewed studies fulfilled all predefined inclusion criteria and were retained for the final qualitative synthesis. All bibliographic records and citation

data were systematically organised using Mendeley Desktop to ensure accurate reference management, efficient identification of duplicate articles, and transparent documentation throughout the review process. The selected studies were analysed in full text, and essential information including experimental design, disease model, investigated molecular pathways, neuroprotective mechanisms, oxidative stress modulation, inflammatory signalling responses, and therapeutic outcomes was extracted and synthesised using a structured thematic analysis approach. This analytical strategy enabled the integration of heterogeneous findings into a coherent interpretative framework capable of explaining the principal biological mechanisms through which palm tocotrienols may influence cognitive decline and Alzheimer's disease pathology. Through rigorous adherence to PRISMA principles and the implementation of a transparent and reproducible review methodology, the present study contributes a systematic synthesis of current biomedical evidence concerning the mechanistic and therapeutic relevance of palm tocotrienols in neurodegenerative disorders.

## Results

In this systematic literature review, a total of 30 peer-reviewed studies published between 2018 and 2026 were analysed, encompassing *in vitro* investigations, *in vivo* neurodegenerative models, mechanistic molecular studies, and limited clinical observations. Through thematic synthesis, five major mechanistic domains were identified: (1) attenuation of oxidative stress and reactive oxygen species (ROS) accumulation, (2) suppression of neuroinflammatory signalling and cytokine overproduction, (3) inhibition of amyloid-beta aggregation and tau-associated neurotoxicity, (4) preservation of mitochondrial integrity and neuronal bioenergetics, and (5) improvement of cognitive performance and neurobehavioral outcomes

The thematic distribution indicated that oxidative stress modulation was the most dominant focus, appearing in 25 studies (83.3%), followed by neuroinflammatory regulation in 21 studies (70.0%), amyloid-beta and tau-associated neurotoxicity in 20 studies (66.7%), cognitive improvement in 18 studies (60.0%), and mitochondrial preservation in 15 studies (50.0%). Several studies contributed to multiple themes, reflecting the interconnected nature of oxidative stress, inflammation, mitochondrial dysfunction, and neuronal degeneration in Alzheimer's disease progression. The predominance of antioxidant and inflammatory themes indicates that current research primarily focuses on fundamental molecular mechanisms underlying neurodegeneration. In contrast, mitochondrial and cognitive outcome studies remain comparatively limited due to the greater complexity of long-term functional and translational assessments. This distribution suggests that although the mechanistic basis of palm tocotrienol neuroprotection is increasingly established, further integrative and clinical investigations remain necessary to strengthen translational applicability in neurodegenerative disorders.

### Attenuation of Oxidative Stress and Reactive Oxygen Species Accumulation

The most consistently reported finding across the reviewed studies involved the antioxidant capacity of palm tocotrienols in reducing oxidative stress-associated neuronal injury. Among the 30 included studies, more than 80% demonstrated significant reductions in Reactive Oxygen Species (ROS) generation, lipid peroxidation markers, or oxidative cellular damage following tocotrienol administration. Oxidative stress was repeatedly identified as a central pathological mechanism contributing to neuronal degeneration, synaptic dysfunction, mitochondrial impairment, and progressive cognitive deterioration in Alzheimer's disease models. Several *in vitro* investigations using neuronal cell lines exposed to hydrogen peroxide or amyloid-beta toxicity demonstrated that Tocotrienol-Rich Fraction (TRF) treatment reduced intracellular ROS accumulation by approximately 35–68% depending on dosage concentration and exposure duration [32]. One study utilizing SH-SY5Y neuroblastoma cells reported that treatment with 10–20 μM palm tocotrienols significantly restored antioxidant enzyme activity, including Superoxide Dismutase (SOD) and catalase, while simultaneously decreasing Malondialdehyde (MDA) concentrations by nearly 50% compared with untreated controls. Similar findings were observed in PC12 neuronal models, where tocotrienol supplementation markedly reduced oxidative membrane damage and preserved neuronal viability under oxidative insult conditions [33].

Animal-based investigations similarly revealed strong antioxidant responses associated with tocotrienol administration. In transgenic Alzheimer's disease mouse models, oral administration of palm-derived TRF at doses ranging from 60 to 200 mg/kg/day significantly reduced oxidative biomarkers in hippocampal tissues, including reductions in MDA levels ranging between 30% and 57% [34]. Several studies additionally reported enhanced glutathione peroxidase activity and restoration of endogenous antioxidant defence systems following prolonged tocotrienol supplementation [35]. In aged rodent models characterised by accelerated cognitive decline, tocotrienol treatment improved redox balance and decreased oxidative DNA damage, particularly within hippocampal and cortical neuronal regions associated with memory processing. A recurrent observation throughout the literature involved the superior antioxidant potency of tocotrienols compared with tocopherols. Multiple comparative studies demonstrated that tocotrienols exhibited faster membrane penetration, stronger radical-scavenging capacity, and greater protection against lipid peroxidation due to their unsaturated isoprenoid side chains. Certain studies estimated that α-tocotrienol displayed antioxidant efficacy approximately 40–60 times greater than α-tocopherol in neuronal lipid membrane environments subjected to oxidative stress conditions [36]. This enhanced antioxidant activity was consistently associated with improved neuronal survival and reduced apoptotic signalling in neurodegenerative models.

## Suppression of Neuroinflammatory Signalling and Cytokine Overproduction

Another major mechanistic theme identified in the reviewed studies involved the anti-inflammatory properties of palm tocotrienols in neurodegenerative contexts. Approximately 70% of the selected studies demonstrated that tocotrienol administration significantly suppressed inflammatory mediators implicated in Alzheimer's disease progression and cognitive dysfunction. Chronic neuroinflammation was repeatedly identified as a critical contributor to neuronal degeneration through sustained activation of microglia, excessive cytokine release, and inflammatory pathway dysregulation. Several studies reported substantial reductions in pro-inflammatory cytokines following tocotrienol treatment. Experimental investigations demonstrated that palm tocotrienols significantly lowered tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) expression in neuronal and glial cell models exposed to inflammatory stimuli [37]. In lipopolysaccharide-induced neuroinflammation models, tocotrienol supplementation reduced TNF-α production by approximately 40–55% while decreasing IL-6 expression by nearly 35–48% relative to untreated inflammatory controls [38]. Mechanistically, the anti-inflammatory effects of tocotrienols were strongly associated with inhibition of the nuclear factor kappa B ($NF\text{-}_{kB}$) signalling pathway. Multiple studies demonstrated that tocotrienols suppressed $NF\text{-}_{kB}$ nuclear translocation, thereby reducing downstream inflammatory gene activation and cytokine synthesis [39]. Additional investigations identified reductions in Cyclooxygenase-2 (COX-2) expression and inducible Nitric Oxide Synthase (iNOS) activity following tocotrienol administration, indicating broader regulation of inflammatory mediators involved in neuronal injury [40].

Animal studies further confirmed the anti-inflammatory relevance of palm tocotrienols in Alzheimer's disease pathology. Rodent models receiving long-term tocotrienol supplementation exhibited reduced microglial activation and diminished inflammatory infiltration within hippocampal regions [41]. One study reported a 45% reduction in activated microglial density following 12 weeks of TRF administration in amyloid-induced neuroinflammatory mice [42]. This reduction was accompanied by improved neuronal morphology and decreased synaptic degeneration. The reviewed studies additionally suggested that antioxidant and anti-inflammatory activities were closely interconnected. Several investigations demonstrated that suppression of oxidative stress simultaneously reduced inflammatory cascade activation, indicating a synergistic relationship between redox modulation and inflammatory control [43]. This interaction was repeatedly highlighted as a key therapeutic advantage of palm tocotrienols in multifactorial neurodegenerative conditions.

## Inhibition of Amyloid-Beta Aggregation and Tau-Associated Neurotoxicity

A substantial portion of the included studies focused on the effects of palm tocotrienols on amyloid-beta accumulation and tau-associated neuronal toxicity, both of which represent hallmark pathological features of Alzheimer's disease. Approximately two-thirds of the selected articles reported measurable reductions in amyloid burden, aggregation activity, or associated neurotoxicity following tocotrienol intervention [44].

Several *in vitro* studies demonstrated that tocotrienols inhibited amyloid-beta fibril formation and reduced amyloid-induced neuronal apoptosis. Experimental exposure of neuronal cultures to amyloid-beta peptides commonly induced significant cytotoxicity and calcium dysregulation; however, pretreatment with tocotrienol-rich fractions improved neuronal survival rates by approximately 30–50% depending on concentration and exposure duration [45]. Certain studies additionally observed decreased caspase-3 activation and reduced apoptotic DNA fragmentation following tocotrienol administration [46]. Animal investigations similarly demonstrated reductions in amyloid plaque deposition within hippocampal and cortical brain regions. Transgenic Alzheimer's disease mice treated with palm tocotrienols for 10–16 weeks exhibited reductions in amyloid plaque burden ranging from 20% to 45% relative to untreated controls [47]. These reductions were frequently accompanied by improved synaptic protein expression and preservation of neuronal architecture. One study reported increased expression of synaptophysin and postsynaptic density protein-95 following TRF supplementation, suggesting partial restoration of synaptic integrity in degenerative brain environments [48]. Several reviewed studies also indicated potential modulation of tau hyperphosphorylation pathways. Tocotrienol administration was associated with reduced glycogen synthase kinase-3 beta (GSK-3β) activity and decreased tau phosphorylation in experimental Alzheimer's models [49]. Although tau-related evidence remained less extensive compared with amyloid-focused findings, the available data consistently suggested that tocotrienols may interfere with multiple pathological pathways simultaneously rather than targeting isolated disease mechanisms.

## Preservation of Mitochondrial Integrity and Neuronal Bioenergetics

Mitochondrial dysfunction emerged as another dominant mechanistic theme identified throughout the reviewed studies. Approximately half of the selected investigations demonstrated that palm tocotrienols contributed to the maintenance of mitochondrial stability, ATP production, and neuronal bioenergetic balance under neurodegenerative conditions [50]. Several cellular studies revealed that tocotrienol supplementation stabilised mitochondrial membrane potential and reduced mitochondrial ROS generation in neurons exposed to oxidative or amyloid-associated injury [51]. Preservation of mitochondrial function was consistently associated with improved neuronal survival and reduced activation of apoptosis-related pathways. One investigation demonstrated that tocotrienol treatment restored ATP synthesis levels by nearly 35% compared with untreated amyloid-beta-exposed neuronal cultures [52]. Animal studies additionally demonstrated

improvements in mitochondrial enzyme activity and neuronal energy metabolism following long-term tocotrienol administration. Enhanced expression of mitochondrial respiratory chain proteins and improved oxygen utilisation efficiency were reported in several rodent studies involving ageing-related neurodegeneration [53]. In certain experimental models, tocotrienol treatment significantly reduced mitochondrial swelling and prevented cytochrome c release, thereby suppressing apoptotic signalling cascades linked to neuronal cell death [54]. The reviewed evidence further indicated that mitochondrial preservation was closely linked to reductions in oxidative stress and inflammatory activation. Studies repeatedly emphasised that mitochondrial stabilisation may represent a central upstream mechanism through which tocotrienols exert broader neuroprotective effects across multiple degenerative pathways.

### Improvement of Cognitive Performance and Neurobehavioral Outcomes

Beyond molecular and cellular mechanisms, numerous studies reported improvements in cognitive performance and neurobehavioral parameters following tocotrienol administration. Approximately 60% of the reviewed studies identified measurable enhancements in learning ability, spatial memory, recognition memory, or behavioural performance in experimental cognitive decline models [55]. In rodent-based Alzheimer's disease models, tocotrienol supplementation consistently improved performance in Morri's water maze, Y-maze, and novel object recognition tests. Several investigations reported reductions in escape latency ranging from 20% to 40% following 8–16 weeks of treatment [56]. Improved spatial learning accuracy and increased memory retention time were similarly documented in ageing-induced cognitive impairment models [57]. Certain studies additionally observed behavioural improvements associated with reduced anxiety-like responses and enhanced locomotor activity following tocotrienol administration [58]. These neurobehavioral findings were frequently correlated with reduced oxidative damage, diminished inflammatory activity, and preservation of hippocampal neuronal density.

Although human clinical evidence remained limited compared with preclinical findings, several observational and pilot intervention studies suggested potentially favourable associations between higher tocotrienol exposure and improved cognitive preservation [59,60]. One pilot clinical study involving elderly individuals with mild cognitive impairment reported modest improvements in memory recall scores and executive function parameters following prolonged tocotrienol-rich supplementation, although the sample size remained relatively small [61]. Consequently, the reviewed literature consistently emphasised the necessity for larger randomised clinical trials to validate translational therapeutic efficacy in human populations. Collectively, the findings synthesised from the 30 included studies demonstrate that palm-derived tocotrienols possess multifaceted neuroprotective activities involving antioxidant defence enhancement, inflammatory suppression, amyloid-beta modulation, mitochondrial preservation, and cognitive function improvement. The convergent evidence obtained from cellular, animal, and preliminary human studies strongly suggests that palm tocotrienols may represent promising bioactive compounds with therapeutic relevance for cognitive decline and Alzheimer's disease management.

## Discussion

The present systematic literature review synthesises evidence from 30 peer-reviewed studies to address two interrelated research questions concerning the mechanistic roles and therapeutic relevance of palm-derived tocotrienols in cognitive decline and Alzheimer's disease. By integrating findings derived from *in vitro* investigations, *in vivo* neurodegenerative models, mechanistic molecular studies, and limited clinical observations, this discussion provides a structured interpretation of how palm tocotrienols influence oxidative dysregulation, neuroinflammatory signalling, amyloid-beta-associated neurotoxicity, mitochondrial dysfunction, and neuronal degeneration. In addition, the discussion evaluates the consistency, translational significance, and biological implications of the neuroprotective responses reported across contemporary biomedical studies investigating tocotrienol-rich fractions derived from palm oil.

### Modulation of Oxidative Stress and Redox Homeostasis in Neurodegenerative Conditions (Addressing RQ1)

In response to the first research question, the reviewed evidence consistently demonstrates that palm-derived tocotrienols exert substantial regulatory effects on oxidative stress pathways associated with Alzheimer's disease progression and cognitive decline. Across the included studies, oxidative imbalance emerged as one of the most consistently targeted pathological mechanisms, particularly because neuronal tissues exhibit high metabolic activity, elevated oxygen utilisation, and considerable vulnerability to lipid peroxidation. The reviewed literature repeatedly showed that tocotrienol-rich fractions reduced oxidative neuronal injury through both direct antioxidant activity and modulation of endogenous cellular defence systems. Several *in vitro* studies demonstrated that palm tocotrienols significantly attenuated oxidative membrane damage and improved neuronal survival following exposure to amyloid-beta peptides or hydrogen peroxide-induced neurotoxicity [62]. These effects were commonly associated with reductions in intracellular oxidative biomarkers and stabilisation of neuronal membrane integrity. Importantly, the antioxidant effects of tocotrienols were not limited to direct radical neutralisation alone. Multiple studies additionally reported increased activities of endogenous antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, suggesting that tocotrienols contribute to long-term preservation of neuronal redox balance rather than transient suppression of

oxidative molecules [63].

An important pattern emerging from the reviewed evidence concerns the structural and biochemical advantages of tocotrienols compared with tocopherols. Due to their unsaturated isoprenoid side chains, tocotrienols demonstrate greater membrane mobility and more efficient penetration into phospholipid bilayers within neuronal tissues [64]. Several comparative investigations therefore suggested that palm-derived tocotrienols possess stronger neuroprotective efficacy under oxidative neurodegenerative conditions than conventional vitamin E isoforms. This distinction is particularly relevant in Alzheimer's disease pathology because oxidative membrane destabilisation contributes directly to synaptic dysfunction, mitochondrial injury, and progressive neuronal apoptosis.

Animal-based investigations further reinforced these findings by demonstrating that prolonged tocotrienol supplementation reduced lipid peroxidation markers and preserved hippocampal neuronal integrity in ageing and neurodegenerative models [65]. Certain studies additionally reported improvements in synaptic protein expression following oxidative stabilisation, indicating that the antioxidant relevance of palm tocotrienols extends beyond biochemical protection toward maintenance of functional neuronal connectivity. Nevertheless, despite the overall consistency of antioxidant findings, variability remains evident across experimental systems. Differences in tocotrienol dosage, intervention duration, experimental design, and neurodegenerative model selection contributed to variations in the magnitude of antioxidant responses [66]. *In vitro* studies generally demonstrated more pronounced reductions in oxidative biomarkers than *in vivo* or limited clinical investigations, likely due to controlled cellular conditions and higher effective concentrations. Consequently, while the mechanistic relevance of oxidative modulation appears strongly supported, further standardisation remains necessary to improve translational comparability across studies.

## Regulation of Neuroinflammatory Signalling and Microglial Dysregulation (Addressing RQ1)

Beyond oxidative regulation, the synthesised literature consistently indicates that palm-derived tocotrienols influence neurodegenerative progression through suppression of inflammatory signalling pathways and attenuation of chronic neuroinflammation. Neuroinflammatory activation has increasingly been recognised as a central contributor to Alzheimer's disease pathology due to prolonged microglial activation, excessive cytokine release, and amplification of neuronal injury within vulnerable brain regions [67]. The reviewed studies collectively suggest that tocotrienols interfere with these inflammatory mechanisms through coordinated modulation of intracellular signalling networks involved in cytokine production and inflammatory gene regulation. One of the most consistently reported mechanisms involved inhibition of nuclear factor kappa B (NF-$_{kB}$) signalling. Multiple investigations demonstrated that palm tocotrienols reduced NF-$_{kB}$ activation and suppressed downstream inflammatory mediators including tumour necrosis factor-alpha, interleukin-1 beta, interleukin-6, cyclooxygenase-2, and inducible nitric oxide synthase [68]. These findings were observed across both neuronal cell culture systems and animal-based neurodegenerative models, suggesting relatively broad anti-inflammatory applicability.

The reviewed evidence additionally indicates that tocotrienols may influence mitogen-activated protein kinase pathways, including ERK, JNK, and p38 signalling cascades associated with inflammatory propagation and neuronal stress responses. Several studies reported that suppression of these pathways was accompanied by reductions in activated microglial density within hippocampal tissues, thereby contributing to preservation of neuronal microenvironments and synaptic architecture [69]. This observation is particularly important because chronic microglial overactivation has been strongly associated with accelerated neurodegeneration and worsening cognitive decline. Importantly, the reviewed literature consistently emphasises the interconnected nature of oxidative stress and neuroinflammation. Oxidative injury frequently stimulates inflammatory pathway activation, while inflammatory cytokines further intensify oxidative burden and mitochondrial dysfunction [70]. Consequently, the simultaneous antioxidant and anti-inflammatory activities of palm-derived tocotrienols may represent a significant therapeutic advantage in Alzheimer's disease, where neurodegenerative progression arises from multifactorial pathological interactions rather than isolated molecular disturbances. Despite generally favourable findings, several studies reported moderate variability in anti-inflammatory responses depending on tissue specificity, disease stage, and experimental conditions [71]. *In vitro* models frequently demonstrated stronger inhibitory effects on inflammatory biomarkers than animal-based systems, whereas limited clinical studies reported comparatively modest changes. This variability highlights the complexity of translating mechanistic neuroprotection into clinically measurable anti-inflammatory outcomes in human populations.

## Influence on Amyloid-Beta Toxicity, Tau Dysregulation, and Mitochondrial Dysfunction (Addressing RQ1)

The reviewed studies further demonstrate that palm-derived tocotrienols may influence hallmark pathological mechanisms associated with Alzheimer's disease, particularly amyloid-beta toxicity and tau-associated neuronal degeneration. Amyloid-beta accumulation contributes directly to synaptic disruption, mitochondrial impairment, calcium dysregulation, oxidative injury, and apoptosis-related signalling pathways [72]. Several studies included in this review demonstrated that tocotrienol-rich fractions attenuated amyloid-beta-induced neurotoxicity and improved neuronal survival under degenerative conditions. *In vitro* investigations consistently reported reductions in amyloid-associated cytotoxicity following pretreatment with palm tocotrienols [73]. These neuroprotective effects were commonly associated with preservation of mitochondrial membrane potential, reduction of apoptotic signalling activation, and stabilisation of neuronal calcium homeostasis. Several studies additionally

reported suppression of caspase-mediated apoptosis, suggesting that tocotrienols interfere with downstream neurodegenerative pathways triggered by amyloid-beta accumulation. Animal studies similarly demonstrated reductions in amyloid plaque burden within hippocampal and cortical tissues following prolonged tocotrienol supplementation [74]. Although the extent of plaque reduction varied across studies, the consistency of these findings suggests potential involvement of tocotrienols in modulation of amyloidogenic processing or enhancement of amyloid clearance pathways. In addition, several investigations indicated that tocotrienols may influence glycogen synthase kinase-3 beta activity and tau phosphorylation pathways, thereby potentially contributing to attenuation of neurofibrillary pathology [75]. Another important mechanistic pattern emerging from the reviewed literature concerns preservation of mitochondrial integrity. Mitochondrial dysfunction is increasingly recognised as an early pathological contributor to cognitive decline due to impaired ATP production, excessive oxidative generation, calcium imbalance, and activation of intrinsic apoptotic signalling [76]. Multiple studies demonstrated that palm tocotrienols stabilised mitochondrial membrane function, improved neuronal bioenergetic balance, and reduced cytochrome c release under neurodegenerative conditions [77]. These findings strengthen the interpretation that mitochondrial preservation represents a central mechanism underlying the broader neuroprotective relevance of palm-derived tocotrienols.

### Therapeutic Patterns and Neuroprotective Consistency Across Experimental Models (Addressing RQ2)

Addressing the second research question, several therapeutic patterns emerged consistently across the reviewed studies investigating palm-derived tocotrienols in neurodegenerative disease models. One of the most reproducible findings involved improvement of cognitive performance and behavioural outcomes following tocotrienol supplementation. Multiple rodent studies demonstrated enhanced spatial memory, improved learning performance, and greater memory retention in Morri's water maze, Y-maze, and novel object recognition assessments [78]. These findings suggest preservation of hippocampal-dependent cognitive processing and attenuation of neurodegenerative functional decline. Another consistent therapeutic pattern involved maintenance of synaptic integrity and neuronal structure. Several investigations reported increased synaptic protein expression, reduced neuronal apoptosis, and preservation of hippocampal neuronal density following tocotrienol administration [79]. Preservation of synaptic architecture is particularly relevant because synaptic degeneration represents one of the strongest pathological correlates of cognitive deterioration in Alzheimer's disease. Importantly, the reviewed evidence indicates that the therapeutic relevance of palm-derived tocotrienols arises from their multifunctional biological activity rather than isolated pharmacological effects. Unlike therapeutic strategies targeting single pathological pathways, tocotrienols appear capable of simultaneously modulating oxidative stress, inflammatory activation, mitochondrial dysfunction, apoptotic signalling, and amyloid-associated neurotoxicity [80]. This integrated neuroprotective profile distinguishes palm tocotrienols from many conventional neuroprotective compounds and may explain the relatively consistent beneficial responses observed across different neurodegenerative models.

However, several important translational limitations remain evident throughout the reviewed literature. Most available evidence originates from cellular investigations and animal-based neurodegenerative studies, while large-scale human clinical trials remain comparatively limited [81]. Variability in tocotrienol composition, dosage regimens, intervention duration, and methodological design additionally complicates direct comparison among studies. Furthermore, long-term safety evaluation, pharmacokinetic characterization, and optimization of bioavailability remain insufficiently explored within elderly or cognitively impaired populations. The findings of this systematic literature review have several important implications for future neurodegenerative research and therapeutic development. First, the substantial consistency of antioxidant, anti-inflammatory, anti-amyloid, and mitochondrial-preserving effects supports the potential relevance of palm-derived tocotrienols as multifunctional neuroprotective compounds in Alzheimer's disease and cognitive decline. Second, the predominance of preclinical evidence highlights the urgent need for well-designed clinical investigations involving standardized formulations, longer intervention periods, larger participant populations, and comprehensive neurocognitive outcome assessments. Future research should additionally prioritize advanced molecular approaches including transcriptomics, proteomics, and metabolomics to clarify the complex signaling interactions underlying tocotrienol-mediated neuroprotection. Overall, the current evidence strongly supports the therapeutic promise of palm-derived tocotrienols in neurodegenerative disease modulation, although further translational validation remains necessary before definitive clinical implementation can be fully established.

## Conclusion

The findings synthesised from the 30 selected studies demonstrate that palm-derived tocotrienols possess substantial neuroprotective relevance in the context of cognitive decline and Alzheimer's disease through the regulation of multiple interconnected pathological mechanisms. The reviewed evidence consistently indicates that tocotrienols modulate oxidative stress by reducing reactive oxygen species accumulation, suppressing lipid peroxidation, enhancing endogenous antioxidant defence systems, and preserving neuronal redox homeostasis. In parallel, palm tocotrienols were repeatedly associated with attenuation of neuroinflammatory signalling through inhibition of NF-$_{kB}$ activation, reduction of pro-inflammatory cytokine expression, suppression of microglial overactivation, and modulation of inflammatory cascade pathways involved in progressive neuronal injury. These molecular effects collectively contribute to a more stable neuronal microenvironment and reduced neurodegenerative vulnerability.

The reviewed literature further demonstrates that palm-derived tocotrienols influence several hallmark pathological mechanisms associated with Alzheimer's disease progression, including amyloid-beta toxicity, tau-related neurodegeneration, mitochondrial dysfunction, synaptic deterioration, and apoptosis-related signalling. Multiple experimental studies consistently reported reductions in amyloid-associated cytotoxicity, preservation of mitochondrial membrane integrity, stabilisation of neuronal calcium balance, and attenuation of apoptotic pathway activation following tocotrienol administration. In addition, several investigations identified improvements in synaptic protein expression, neuronal survival, and hippocampal structural preservation, indicating that the neuroprotective activity of tocotrienols extends beyond isolated biochemical modulation toward broader maintenance of neuronal function and cellular integrity.

Across contemporary neurodegenerative models, the most consistently reported therapeutic patterns involved enhancement of cognitive performance, preservation of memory-related neuronal function, improvement of spatial learning ability, and attenuation of neurobehavioral decline. These beneficial effects were observed predominantly in preclinical investigations involving cellular and animal-based Alzheimer's disease models, where tocotrienol-rich fractions repeatedly demonstrated multifunctional biological activity targeting oxidative, inflammatory, mitochondrial, and amyloid-associated pathways simultaneously. This integrated neuroprotective profile suggests that palm tocotrienols may possess greater therapeutic relevance than compounds acting through single-pathway interventions alone. Nevertheless, the synthesised evidence also reveals important translational limitations within the current literature. The predominance of *in vitro* and animal-based studies, variability in dosage regimens and intervention duration, differences in tocotrienol composition, and the limited number of large-scale human clinical investigations remain significant challenges in establishing definitive therapeutic applicability in clinical settings. Additional standardised clinical studies involving larger populations, longer intervention periods, and comprehensive neurocognitive outcome measurements are therefore required to strengthen translational validation and clarify long-term efficacy, safety, and bioavailability profiles in human neurodegenerative populations. Overall, the current body of evidence supports the interpretation that palm-derived tocotrienols represent promising multifunctional bioactive compounds with considerable therapeutic potential for cognitive decline and Alzheimer's disease modulation. Their ability to simultaneously regulate oxidative stress, neuroinflammation, mitochondrial dysfunction, amyloid-associated neurotoxicity, and neuronal survival pathways positions palm tocotrienols as relevant candidates for continued biomedical investigation within the development of future neuroprotective strategies.

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## Conflict of Interest

None.

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