Targeting Oxidative Stress in Neurodegenerative Diseases: Advances and Challenges in Antioxidant Therapy

This systematic review provides researchers and medical-affairs teams with actionable insights into antioxidant-based therapeutic strategies for neurodegenerative diseases. Three illustrative findings are highlighted below, drawn from a comprehensive 494-page analysis; additional insights are provided in the full review.

- **TG15-132**, a selective Nox2 inhibitor, reduces ROS and inflammatory gene expression while penetrating the brain effectively—making it a strong candidate for oxidative stress–linked neurodegeneration.
- **ApoE4** expression impairs neuronal mitochondria, reducing ATP and elevating ROS, suggesting the need for mitochondrial-targeted interventions to counteract ApoE4-related cognitive decline.
- **Antioxidant therapy** in MS patients cut ROS by 15% and reduced lipid peroxidation and DNA oxidation by 41% and 32%, respectively—supporting clinical use to manage oxidative injury and inflammation.

6603	784	Jan 2018–Mar 2025
Records screened	Full-text studies included	Coverage window

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1. Methods

The search strategy was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [1]. The systematic literature review was automatically generated on demand using the Synthory.AI service. All components listed below were identified, extracted, assessed, and analyzed automatically as part of the review process. The review was created for research purposes.

Go to Annex 1: Methods

2. Results

2.1. Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's: Therapeutic Insights

2.1.1. Mitochondrial Dysfunction and Oxidative Stress

Selected findings

- The study by Jiang S et al. (2018) demonstrates that conditional knockout of Mfn2 in the forebrain leads to mitochondrial dysfunction, oxidative stress, neuroinflammation, and severe neuronal degeneration in the hippocampus and cortex. This finding underscores the importance of Mfn2 in maintaining mitochondrial and neuronal integrity, offering a potential target for therapeutic strategies aiming to mitigate oxidative stress and neurodegeneration in Alzheimer's disease.
- Quintanilla RA et al. (2020) revealed that caspase-cleaved tau expression in neuronal cells induces mitochondrial fragmentation, bioenergetic deficits, and impaired mitochondrial transport, marked by reduced TRAK2 expression and increased oxidative stress. These findings highlight the mechanistic link between tau pathology and mitochondrial dysfunction, suggesting a therapeutic opportunity to target tau-induced mitochondrial impairments in Alzheimer's disease.
- Peng W et al. (2024) identified that iron-induced ferroptosis exacerbates oxidative damage, mitochondrial dysfunction, and neuronal impairment in Alzheimer's-like pathologies, which were mitigated by ferroptosis inhibitors and antioxidants. This discovery positions ferroptosis as a critical pathway in Alzheimer's disease progression and highlights the potential of ferroptosis inhibitors as a therapeutic strategy to counteract oxidative stress and mitochondrial dysfunction.
- Iron-induced ferroptosis exacerbates oxidative damage, mitochondrial dysfunction, and neuronal impairment in Alzheimer's disease-like pathologies, with paralysis and mitochondrial ROS levels showing marked increases. The mitigation of these effects by ferroptosis inhibitors (e.g., Ferrostatin-1) and antioxidants (e.g., NAC) highlights a promising therapeutic strategy to counteract

ferroptosis-driven neurodegeneration in AD.

- Dysregulated sphingolipid metabolism, marked by elevated ceramide and sphingosine levels, impairs mitochondrial oxygen consumption and disrupts oxidative phosphorylation in both 5xFAD mice and AD patients. Targeting sphingolipid pathways could provide a novel therapeutic avenue to restore mitochondrial function and slow AD progression.
- Long-term mitochondrial stress leads to Tau dimerization and aggregation, driven by elevated ROS levels, independently of Tau phosphorylation. The reversal of Tau aggregation by ROS scavengers such as NAC and MitoQ suggests potential antioxidant-based interventions for mitigating proteinopathy in AD.
- SkQThy treatment effectively reduces oxidative stress, mitigates mitochondrial fragmentation, and improves cell viability in a model of Aβ42-induced mitochondrial dysfunction. These findings support SkQThy's potential as a mitochondrial-targeted therapeutic for addressing early mitochondrial impairments in AD.

Table 1. Mitochondrial Dysfunction and Oxidative Stress

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome	Secondary outcome
Jiang S et al. (2018)		Mfn2 cKO mice, ages 4 to 78 weeks, total 18 participants	Age-matched mice without Cre+ expression, total 18 participants	Knockout of neuronal Mfn2 in hippocampus and cortex using CAMKII promoter	Genetic engineering of transgenic mice, CAMKII promoter for neuronal Mfn2 knockout, constitutive expression study across ages 4–78 weeks, standard housing conditions, approved protocol by Case Western Reserve University IACUC board	Progression of neurodegeneration via mitochondrial morphological changes, leading to severe neuronal death in the hippocampus and cortex	Oxidative stress response, inflammatory changes, loss of MAP2 in dendrites, hippocampal size reduction, cortical size reduction, mitochondrial oxygen consumption rate changes

Go to Annex 2: Table 1. Mitochondrial Dysfunction and Oxidative Stress

Oxidative stress and mitochondrial dysfunction are increasingly recognized as interconnected drivers of Alzheimer's disease, contributing to neuronal damage, cognitive decline, and neuroinflammation. Disruptions in mitochondrial bioenergetics, reactive oxygen species homeostasis, and impaired antioxidant defenses exacerbate neurodegeneration, underscoring the complex interplay of these pathological mechanisms. Recent studies have explored therapeutic strategies aimed at mitigating oxidative damage and restoring mitochondrial function, with antioxidant-based interventions showing promise. However, challenges remain in translating these findings into effective clinical therapies, highlighting the need for further research to address these limitations and advance treatment options for Alzheimer's disease.

Previous studies have highlighted the critical role of oxidative stress and mitochondrial dysfunction in Alzheimer's Disease (AD) pathogenesis, with preclinical evidence supporting the therapeutic potential of mitochondrial-targeted antioxidants, mTOR pathway modulators, and compounds like melatonin in mitigating amyloid β accumulation, tau phosphorylation, and cognitive deficits. However, clinical translation remains limited due to challenges in drug bioavailability, blood-brain barrier penetration, and the lack of robust human studies, while existing FDA-approved treatments only manage symptoms without addressing disease progression [23]. These findings underscore the need for innovative therapeutic strategies that effectively target mitochondrial dysfunction and oxidative stress while overcoming translational barriers.

The role of mitochondrial dysfunction in neurodegeneration is further elucidated by examining the impact of Mfn2 deficiency on neuronal and mitochondrial integrity. The study demonstrates that conditional knockout of Mfn2 in the forebrain leads to mitochondrial dysfunction, including reduced basal and maximal oxygen consumption rates and respiratory control ratio ($p < 0.05$), as well as mitochondrial fragmentation and ultrastructural damage (Jiang S et al. 2018). This is accompanied by increased oxidative stress, evidenced by elevated protein carbonyls ($p < 0.05$), and neuroinflammation, marked by GFAP-positive astrocyte accumulation and microglial activation ($p < 0.001$). Additionally, cytoskeletal disruptions, such as dendritic MAP2 loss and tau hyperphosphorylation, were observed alongside severe neuronal degeneration in the hippocampus and cortex, with a significant reduction in NeuN-positive neurons ($p < 0.001$). These findings highlight the role of Mfn2 in maintaining mitochondrial and neuronal integrity, aligning with therapeutic strategies aimed at mitigating oxidative stress, neuroinflammation, and cytoskeletal abnormalities in Alzheimer's Disease.

Mitochondrial dysfunction emerges as a converging factor in neurodegeneration, as evidenced by distinct molecular mechanisms involving Mfn2 deficiency and caspase-cleaved tau expression. Caspase-cleaved tau expression in neuronal cells induces mitochondrial fragmentation, reduces TRAK2 expression ($p < 0.05$), increases mitochondrial localization in the soma, and impairs bioenergetics, evidenced by mitochondrial depolarization and decreased ATP production ($p < 0.05$) (Quintanilla RA et al. 2020). These effects collectively lead to disrupted mitochondrial transport and dynamics, characterized by reduced movement and altered functionality. Despite no observed changes in the expression of motor proteins or adaptors, the combination of reduced TRAK2 levels and bioenergetic deficits, including increased ROS production ($p < 0.05$),

highlights significant mitochondrial impairments.

Mitochondrial dysfunction, characterized by bioenergetic deficits and elevated ROS levels, emerges as a shared mechanism underlying diverse pathological processes, including those induced by BMAA exposure. BMAA at 3 mM significantly impairs mitochondrial function by reducing oxygen consumption rates (OCR), ATP production, and glycolytic capacity ($p < 0.05$, $p < 0.01$, $p < 0.001$), alongside a decrease in mitochondrial membrane potential, as reported by Silva DF et al. (2020). These changes are accompanied by increased mitochondrial ROS production ($p < 0.05$) and cardiolipin exposure, which activate innate immune pathways through elevated TLR3 and TLR4 expression, NF-κB nuclear translocation ($p < 0.05$), and NLRP3 inflammasome activation. This immune activation is associated with higher caspase-1 activity ($p < 0.05$) and IL-1β release ($p < 0.01$), contributing to the progression of Alzheimer's disease pathology through increased Tau phosphorylation at Thr181 ($p < 0.05$) and intracellular Aβ oligomer accumulation ($p < 0.05$).

Genetic variants such as those in mitochondrial-related genes may contribute to the oxidative stress and mitochondrial dysfunction observed in Alzheimer's Disease patients. The study by Liou CW et al. (2021) identifies heightened oxidative stress and mitochondrial dysfunction in Alzheimer's Disease (AD) patients, evidenced by elevated TBARS levels (1.62 ± 0.73 μmol/L vs. 1.54 ± 0.86 μmol/L, $p = 0.003$), reduced antioxidative thiols (1.64 ± 0.46 μmol/L vs. 1.71 ± 0.39 μmol/L, $p < 0.001$), and lower mitochondrial DNA copy number (2.34 ± 0.21 vs. 2.46 ± 0.28, $p < 0.001$) compared to controls. Cholinesterase inhibitor therapy, particularly with rivastigmine and galantamine, is shown to reduce TBARS levels ($p < 0.05$) and increase mitochondrial DNA copy number ($p < 0.05$) in AD patients. Additionally, the APOE4 allele is associated with greater oxidative stress (TBARS ptrend = 0.003), reduced antioxidative thiols (ptrend = 0.008), and lower mitochondrial DNA copy number (ptrend < 0.001), further linking genetic predisposition to mitochondrial impairment in AD.

These findings on oxidative stress and mitochondrial dysfunction in Alzheimer's Disease provide a framework for examining population-specific variations in mitochondrial oxidative damage and their genetic underpinnings. Reid DM et al. (2022) Mexican Americans show significantly higher mtDNA 8oxoG mutational load than non-Hispanic whites (mean = 7.46 vs. 5.96, $p < 0.0001$), with a significant population-by-sex interaction indicating the highest burden in Mexican American females ($p = 0.01458$). Mitochondrial haplogroups A and C are associated with increased 8oxoG counts ($p = 0.004545$ and $p = 0.0186$, respectively), while haplogroups I and K are associated with reduced counts ($p = 8.127E{-}05$ and $p = 0.004681$, respectively). Haplogroup L is protective in Mexican Americans ($p = 0.0294$), while haplogroup H is linked to increased oxidative damage in non-Hispanic whites ($p = 0.04796$). Years of education show a significant positive association with oxidative damage in Mexican Americans ($p = 0.008$). No significant associations are observed with age, diabetes, or cognition, and oxidative hotspot analysis does not reveal consistent trends.

The reversible modulation of mitochondrial NADH levels under oxidative conditions complements findings on ALDH2 dysfunction, further elucidating mechanisms of mitochondrial impairment and therapeutic strategies in Alzheimer's disease. Reduced ALDH2 activity (approximately 25% of control levels) in Alzheimer's disease patient-derived fibroblasts with ALDH2*2 mutation or ApoE ε4 allele is associated with a five-fold increase in 4-HNE levels, elevated mitochondrial ROS, and decreased ATP production, with ethanol exposure further intensifying these effects (Joshi AU et al. 2019). Pharmacological activation of ALDH2 using Alda-1 restores mitochondrial function, reduces oxidative stress, and mitigates aldehydic load, addressing key aspects of mitochondrial dysfunction. Additionally, ALDH2*2 mutation contributes to increased amyloid-β42 levels, tau phosphorylation, and neuroinflammation, with Alda-1 demonstrating significant potential to mitigate these pathological features.

Insights into ALDH2-related mitochondrial dysfunction and therapeutic restoration align with evidence of abnormal mitochondrial dynamics as early biomarkers of Alzheimer's Disease. Abnormal mitochondrial dynamics, characterized by increased Drp1 levels ($p = 0.012$ in mPFC; $p = 0.013$ in HIPP) and decreased ATP5A levels ($p = 0.012$ in mPFC; $p = 0.017$ in HIPP), along with a reduced mitochondrial aspect ratio ($p = 0.014$ in mPFC; $p = 0.002$ in HIPP), were found to correlate with neuronal alterations such as reduced dendritic morphology ($p < 0.01$ in mPFC; $p < 0.001$ in HIPP) and impaired social interaction memory (discrimination index, $p < 0.001$) in 4–5-month-old APP/PS1 mice (Misrani A et al. 2021). These findings support the role of mitochondrial dysfunction as an early biomarker of Alzheimer's disease and provide a foundation for exploring targeted interventions such as Mdivi-1, though further evidence is required to evaluate its specific efficacy.

Building on NRF1's role in modulating mitochondrial dynamics, presenilin-1 mutations further illustrate the critical link between mitochondrial dysfunction and Alzheimer's disease pathology. Familial Alzheimer's disease-linked presenilin-1 mutations are associated with mitochondrial dysfunction, as evidenced by increased fragmentation ($p < 0.05$, $p < 0.01$, $p < 0.001$), elevated ER-mitochondria colocalization ($p < 0.05$, $p < 0.01$, $p < 0.001$), enhanced reactive oxygen species (ROS) production ($p < 0.05$, $p < 0.01$), reduced complex I activity ($p < 0.05$), compromised membrane potential ($p < 0.001$, $p < 0.0001$), and decreased ATP levels ($p < 0.05$, $p < 0.01$) (Han J et al. 2021). These findings align with evidence supporting the role of mitochondrial impairments in Alzheimer's disease pathology. Additionally, ATL2 expression is significantly upregulated in AD brains ($p < 0.05$), 3xTg-AD mouse hippocampi ($p < 0.0001$), and PS1 mutant-induced cell lines, correlating with increased ER-mitochondria interactions and mitochondrial dysfunction. Knockdown of ATL2 mitigates abnormal colocalization and partially rescues mitochondrial impairments, highlighting its involvement in these processes.

The role of mitochondrial dysfunction in Alzheimer's pathology extends to oxidative stress mechanisms, where NOX4-mediated alterations exacerbate cellular damage. Elevation of NOX4 significantly exacerbates mitochondrial dysfunction and oxidative stress in astrocytes by increasing mitochondrial ROS production, lipid peroxidation markers (4-HNE, MDA), and iron accumulation ($p < 0.01$), while suppressing mitochondrial respiration, ATP production, and antioxidant processes such as the GSH/GSSG ratio and NRF2 signaling ($p < 0.01$) (Park MW et

al. 2021). These alterations contribute to ferroptosis-dependent cytotoxicity, with significant morphological and biochemical evidence ($p < 0.01$), highlighting a mechanistic link between oxidative stress, mitochondrial impairment, and cellular damage in Alzheimer's disease.

Oxidative stress and ferroptosis further illustrate the interplay between mitochondrial dysfunction and neuronal damage in Alzheimer's disease. Iron-induced ferroptosis significantly exacerbates oxidative damage, mitochondrial dysfunction, and neuronal impairment in Alzheimer's disease-like pathologies, as reported by Peng W et al. (2024), with paralysis and mitochondrial ROS levels showing marked increases ($p < 0.0001$ and $p = 0.0001$, respectively). Lipid peroxidation was also elevated, but these effects were effectively mitigated by ferroptosis inhibitors like Ferrostatin-1 ($p < 0.0001$) and antioxidants such as NAC ($p < 0.0001$). Furthermore, DMT1 knockout in C. elegans reduced iron uptake, leading to a significant decrease in paralysis ($p < 0.0001$) and restoration of swimming rates to wild-type levels under both basal and iron-induced conditions, demonstrating the potential for addressing mitochondrial dysfunction and oxidative stress in Alzheimer's disease.

In addition to ferroptosis, dysregulated sphingolipid metabolism emerges as a critical factor influencing mitochondrial function in Alzheimer's disease. Abnormal sphingolipid metabolism, marked by elevated ceramide species such as Cer24:1, Cer24:0, Cer20:0, and Cer22:0, alongside increased sphingosine levels, contributes to mitochondrial dysfunction in 5xFAD mice and Alzheimer's Disease patients (Crivelli SM et al. 2024). This is evidenced by impaired oxygen consumption ($p < 0.05$), dysregulated mitochondrial proteins involved in oxidative phosphorylation and ATP synthesis, and pathway enrichment of respiratory chain components ($\log10\ p > 2$). Dysregulation of sphingolipid composition, including early and age-related accumulation of long-chain ceramides, occurs in mitochondria during Alzheimer's pathogenesis in 5xFAD mice, with synaptic mitochondrial oxygen consumption significantly impaired at 3 months ($p < 0.05$) and proteins linked to respiratory electron transport and ATP synthesis exhibiting notable dysregulation.

Downstream consequences of mitochondrial dysfunction include the promotion of Tau aggregation, linking metabolic stress to proteinopathy in Alzheimer's disease. Samluk L et al. (2022) long-term mitochondrial stress leads to a 1.5-fold increase in Tau dimerization at 100 nM rotenone treatment and a 2-fold increase at 200 nM rotenone treatment, driven by elevated ROS levels ($p < 0.05$, $p < 0.01$, $p < 0.001$). This aggregation process occurs independently of Tau phosphorylation but is partially modulated by ISR inhibition. The use of ROS scavengers, such as NAC (1 mM) and MitoQ, significantly reverses Tau dimerization, as shown by normalized Venus fluorescence fold changes and statistical significance ($p < 0.05$, $p < 0.01$, $p < 0.001$). Additionally, ISR activators, including salubrinal, guanabenz, and sephin1, partially mitigate the effects of mitochondrial stress on Tau aggregation.

Mitochondrial dysfunction and oxidative stress, as highlighted in Tau aggregation, also emerge as critical factors in cellular responses to environmental exposures. Exposure to ultrafine particles (A0 and A20) significantly disrupts mitochondrial function in primary human olfactory mucosa cells derived from individuals with Alzheimer's disease, as evidenced by a 29% reduction in ATP production for A0 ($p < 0.01$) and a 39% reduction for A20 ($p < 0.001$), alongside elevated ROS levels (76%, $p < 0.001$) and a 185% increase in the NAD+/NADH ratio ($p < 0.05$) (Mussalo L et al. 2024). These findings highlight mitochondrial dysfunction, oxidative stress, and redox imbalance, aligning with the broader understanding of mitochondrial pathways as critical factors in Alzheimer's disease pathology.

Similar disruptions in mitochondrial function are observed in Alzheimer's disease models, where altered OXPHOS protein expression correlates with cognitive impairments. Significant reductions in nuclear-encoded OXPHOS protein ATP5H (−1.18-fold in mitochondria, −1.43-fold in nuclei) were observed in the hippocampus of 3xTg-AD mice, correlating with spatial memory impairments (Yu H et al. 2018). These impairments were quantified through decreased time spent and distance traveled in the correct quadrant during Morris Water Maze tests ($p < 0.05$, $p < 0.01$). Additionally, differential expression of dynamin-1 (DYN1) and ATP5H in hippocampal mitochondria and nuclei was identified, suggesting their involvement in synaptic function, apoptosis, and energy metabolism.

Mitochondrial-targeted approaches, such as SIRT3 modulation, parallel the therapeutic potential of SkQThy in restoring mitochondrial function and reducing oxidative stress. Epremyan KK et al. (2023) found that the study identified mitochondrial dysfunction in *Yarrowia lipolytica* cells expressing Aβ42, marked by a 25% reduction in ATP production ($p < 0.01$), elevated hydrogen peroxide generation ($p < 0.001$), and increased oxidative stress, leading to impaired energy metabolism and cell death. Treatment with 250 nM SkQThy effectively reduced oxidative stress ($p < 0.001$), mitigated mitochondrial fragmentation, and improved cell viability ($p < 0.01$), suggesting its role in restoring mitochondrial structure and function. These findings align with prior evidence on mitochondrial-targeted interventions, providing quantitative support for their potential in addressing Alzheimer's disease-related mitochondrial impairments.

Mitochondrial dysfunction as a hallmark of Alzheimer's pathology is further underscored by APP-CTFs accumulation, which disrupts mitochondrial morphology and function. Vaillant-Beuchot L et al. (2021), APP-CTFs accumulation disrupts mitochondrial morphology, as evidenced by a reduction in class I mitochondria (29% vs. 86% in controls, $p < 0.0001$), cristae disorganization, and increased mitochondrial size. This accumulation elevates ROS production ($p < 0.01$) and induces mitophagy failure, marked by an altered LC3-II/LC3-I ratio, unchanged p62 levels, and reduced lysosomal targeting in cellular, animal, and human AD models. In 3xTgAD mice, functional mitochondria were significantly reduced (class I: 19% vs. 79% in WT, $p < 0.0001$), with elevated p62 levels and reduced mitophagy priming markers (PINK1 and Parkin, $p < 0.05$), correlating strongly with Alzheimer's pathology.

Mitochondrial dysfunction, as seen in Iso-Aβ42's effects, also emerges as a critical hallmark in SIRT6-deficient brains, with broader implications for metabolic and transcriptional regulation. In SIRT6-deficient brains, mitochondrial dysfunction is marked by significantly reduced mitochondrial gene expression (e.g., mt-Co3, FDR p-value = 3.8×10^{-18}), a 1.21-fold decrease in mitochondrial membrane potential (FDR p-value = 0.0006), elevated ROS production ($p < 0.0001$), and a 21.8% reduction in mitochondrial mass ($p = 0.0087$). These disruptions are

accompanied by dysregulated TCA cycle metabolites, with 92 out of 235 metabolomic features significantly altered, including reduced NAD+ levels. The transcriptional downregulation of mitochondrial genes (>91%, FDR $p < 0.05$) further underscores the impact on oxidative phosphorylation and energy metabolism. Partial restoration of mitochondrial function through SIRT3 and SIRT4 reactivation highlights their critical role in counteracting these impairments and aligns with observed pathways linked to neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and ALS (FDR p-values < 0.0169) as reported by Smirnov D et al. (2023).

In addition to miRNA-mediated pathways, mitochondrial dysfunction is exacerbated by mTORC1 hyperactivation, which disrupts proteostasis and autophagy in neurodegenerative contexts. Hyperactivation of mTORC1, driven by increased mitochondrial calcium influx, exacerbates proteostasis and neurodegenerative defects, including reduced autophagosome formation ($p < 0.001$) and increased Q35 protein aggregates ($p < 0.01$) (Ryan KC et al. 2021). Inhibition of mTORC1 restores autophagy, as evidenced by increased GFP::LGG-1 puncta and lipidated GFP::LGG-1-PE levels ($p < 0.01$, $p < 0.001$), reduces proteostasis defects, and improves neuronal function. These effects are dependent on autophagy induction, as RNAi knockdown of autophagy-related genes (lgg-1 and bec-1) abolishes the benefits ($p < 0.05$). Improvements include reductions in polyQ aggregate counts ($p < 0.001$) and alleviation of neurodegenerative phenotypes such as neuronal morphology and soft touch response ($p < 0.001$).

The protective effects of ECS on mitochondrial function align with findings that mitochondrial dysfunction plays a critical role in Alzheimer's disease, particularly in platelet-mediated amyloid-beta aggregation and oxidative stress. Donner L et al. (2021) The study identifies mitochondrial dysfunction in platelets as a significant factor in Alzheimer's disease, with findings showing increased reactive oxygen species (ROS) production ($p < 0.01$), reduced mitochondrial transmembrane potential ($p < 0.01$), and impaired mitochondrial respiration ($p < 0.0001$). These dysfunctions are linked to enhanced amyloid-beta (Aβ) aggregate formation, mediated by oxidative stress, which is significantly reduced by antioxidant treatment with vitamin C ($p < 0.001$). Additionally, Aβ40 exposure exacerbates mitochondrial dysfunction by increasing ROS and mitochondrial superoxide production ($p < 0.01$, $p < 0.05$), decreasing mitochondrial membrane potential ($p < 0.01$), and reducing oxygen consumption rate ($p < 0.0001$, $p < 0.01$, $p < 0.05$). These effects are shown to be mediated through GPVI-dependent ROS production, which enhances integrin αIIbβ3 activation ($p < 0.001$, $p < 0.01$, $p < 0.05$), further linking oxidative stress and mitochondrial dysfunction to platelet-mediated Aβ aggregation in Alzheimer's disease.

2.1.2. Therapeutic Interventions

Selected findings

- P110 treatment in 5XFAD Alzheimer’s disease mouse models significantly reduced amyloid β accumulation, restored ATP levels by 40%, and alleviated oxidative stress markers. This finding highlights the potential of targeting mitochondrial dysfunction to address key pathological features of Alzheimer’s disease, advancing therapeutic strategies for oxidative stress-related neurodegeneration.
- Restoration of mitochondrial function through modulation of ER-mitochondria calcium dynamics in *sel-12* mutants normalized mitochondrial calcium levels, reduced ROS, and prevented neurodegeneration. This approach underscores the importance of targeting calcium homeostasis to mitigate mitochondrial dysfunction and oxidative stress in neurodegenerative diseases.
- The combination treatment of SS31 and Mdivi1 demonstrated synergistic effects by improving mitochondrial function, increasing ATP production, and reducing amyloid β levels in mutant AβPP cells. These results suggest that multi-targeted therapies addressing mitochondrial bioenergetics and oxidative stress may offer enhanced neuroprotection in Alzheimer’s disease models.
- Luteolin significantly ameliorates cognitive impairment, reduces amyloid β generation, repairs mitochondrial damage, and enhances mitochondrial biogenesis in Alzheimer’s disease models (He Z et al. 2023). These findings suggest luteolin’s potential as a therapeutic agent targeting oxidative stress and mitochondrial dysfunction via the PPARγ pathway.
- Aerobic exercise improves mitochondrial quality, reduces oxidative stress, decreases β-amyloid plaque deposition, and enhances cognitive performance in 5×FAD mice (Cai J et al. 2025). This study highlights the importance of CD38 signaling in astrocytic-neuronal mitochondrial transfer, offering insights into non-pharmacological interventions for neurodegeneration.
- NRF1 overexpression restores mitochondrial dynamics, reduces oxidative stress, and mitigates neuronal apoptosis and neurite shortening in Aβ1-42-exposed SH-SY5Y cells (Massaro M et al. 2025). This research underscores NRF1’s role in enhancing mitochondrial biogenesis and oxidative phosphorylation as a therapeutic target in Alzheimer’s disease.
- Urolithin A significantly reduces mitochondrial calcium influx, mtROS accumulation, amyloid beta production, and Tau phosphorylation, mitigating cognitive deficits in diabetes-associated Alzheimer’s disease models. This finding highlights the therapeutic potential of targeting mitochondria-ER interactions and oxidative stress pathways to address Alzheimer’s disease-related neurodegeneration.
- PL171 restores mitochondrial function and reduces oxidative stress by enhancing SIRT3 expression and activity via the AMPK/PGC-1α pathway in Aβ42 oligomer-treated neuroblastoma cells. This mechanism provides a promising avenue for developing therapies aimed at mitochondrial homeostasis and cellular senescence in Alzheimer’s disease.
- Luteolin ameliorates cognitive impairments in Alzheimer’s disease models by reducing amyloid β generation, repairing mitochondrial

damage, and enhancing mitochondrial biogenesis through the PPARγ pathway. These results suggest a pathway-specific intervention that could improve mitochondrial dynamics and antioxidant defenses in neurodegenerative conditions.

- NRF1 overexpression significantly improved mitochondrial function, reduced oxidative stress, and mitigated neuronal apoptosis in Aβ1-42-exposed SH-SY5Y cells, with enhanced mitochondrial biogenesis and dynamics. This highlights NRF1's therapeutic potential in addressing mitochondrial dysfunction and oxidative damage in Alzheimer's disease, aligning with strategies to restore neuroprotection and cognitive function.
- Cycloastragenol administration demonstrated reductions in oxidative stress and neuroinflammation, while enhancing neurogenic markers and cognitive performance in Aβ-injected mice. These findings suggest its potential to mitigate oxidative stress and inflammation in Alzheimer's disease, supporting its development as a therapeutic agent targeting mitochondrial dysfunction and neurodegeneration.
- Rhein treatment in APP/PS1 mice reduced amyloid β burden, oxidative stress, and neuroinflammation, while promoting mitochondrial biogenesis via the SIRT1/PGC-1α pathway. This underscores its potential as a therapeutic approach to enhance mitochondrial function and counteract Alzheimer's disease-related pathology.
- XE-991 demonstrated significant neuroprotective effects by restoring mitochondrial function, reducing oxidative stress, and mitigating Alzheimer’s-associated pathologies in experimental models. This finding highlights the potential of XE-991 as a promising therapeutic agent for targeting mitochondrial dysfunction and oxidative stress in Alzheimer’s disease treatment.
- SUL-138 treatment improved synaptic plasticity, reduced amyloid plaque load, and rescued mitochondrial bioenergetics in APP/PS1 mice. These results emphasize the therapeutic potential of SUL-138 in enhancing mitochondrial function and addressing oxidative stress in Alzheimer’s disease models.
- Mitotherapy significantly improved cognitive performance, activated autophagy, and restored mitochondrial function in Alzheimer’s disease model mice. This approach offers a novel avenue for addressing mitochondrial dysfunction and oxidative stress in neurodegenerative diseases through mitochondrial replacement strategies.
- MST1 inhibition reduced oxidative stress, improved mitochondrial function, and mitigated cognitive decline in Alzheimer’s disease models. These findings identify MST1 as a potential therapeutic target for addressing mitochondrial dysfunction and oxidative stress in neurodegeneration.

Table 2. Therapeutic Interventions

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome	Secondary outcome
Gao C et al. (2018)	30 min preincubation, unspecified duration of NaN3 treatment	Rat pheochromocytoma PC12 cells	Control cultures maintained in DMEM under normoxic conditions	Preincubation of PC12 cells with NaHS prior to NaN3 treatment	NaHS dissolved in saline, freshly prepared immediately prior to use, stock solutions directly added to bath solution to achieve final concentration, preincubation for 30 min prior to NaN3 treatment, maintained throughout the experiment	Neuroprotective effect of H2S against NaN3-induced neurotoxicity, demonstrated by improved cell viability	Suppression of ROS production, attenuation of apoptosis, decreased mitochondrial membrane potential, increased lipid peroxidation (MDA levels), increased caspase-3 protein expression

Go to Annex 3: Table 2. Therapeutic Interventions

Population-linked mitochondrial oxidative damage highlights the importance of exploring therapeutic agents, such as H2S, that mitigate oxidative stress and preserve mitochondrial function in experimental neurotoxicity models. H2S, administered as NaHS at concentrations of 100–200 μmol/l, significantly improves mitochondrial function and reduces oxidative stress in PC12 cells exposed to NaN3-induced neurotoxicity (30 mmol/l for 12 hours) (Gao C et al. 2018). This is evidenced by increased cell viability ($p < 0.05$), reduced reactive oxygen species (ROS) accumulation ($p < 0.05$), restored mitochondrial membrane potential ($p < 0.05$), and decreased lipid peroxidation (MDA levels, $p < 0.05$). Additionally, NaHS modulates apoptosis-related protein expression by lowering caspase-3 levels and enhancing Bcl-2 expression ($p < 0.05$), with optimal effects observed at 200 μmol/l pretreatment, supporting its role in preserving mitochondrial integrity and promoting neuroprotection.

Therapeutic strategies targeting mitochondrial dysfunction, such as P110 treatment, offer promising avenues for mitigating neurodegenerative processes associated with Alzheimer's disease. Joshi AU et al. (2018) P110 treatment demonstrated significant therapeutic effects in the 5XFAD Alzheimer's disease mouse model, including a marked improvement in behavioral deficits such as nesting ability and memory recall ($p < 0.05$). Biochemically, it reduced amyloid β40 and β42 accumulation as measured by ELISA ($p < 0.05$), restored ATP levels by approximately

40% ($p < 0.05$), and alleviated oxidative stress through reductions in lipid peroxidation and hydrogen peroxide production ($p < 0.05$).

Restoration of mitochondrial function can also be achieved by modulating ER-mitochondria calcium dynamics, highlighting the interplay between calcium homeostasis and oxidative stress in neurodegeneration. Reducing ER calcium release or mitochondrial calcium uptake in *sel-12* mutants effectively restores mitochondrial function, normalizes mitochondrial calcium levels ($p < 0.0001$), reduces ROS levels ($p < 0.0001$), and prevents neurodegeneration, as reported by Sarasija S et al. (2018). These interventions significantly improve neuronal morphology and mechanosensation, with the behavioral response to light touch increasing from 48.4% to 77.7% compared to 83.1% in wild type ($p < 0.0001$). Targeted approaches, such as CRT-1 or UNC-68 mutations to reduce ER calcium release, MCU-1 mutations to limit mitochondrial calcium uptake, or MitoTEMPO treatment to scavenge mitochondrial superoxides ($p < 0.0001$ for all), demonstrate substantial efficacy in addressing disruptions in ER-to-mitochondria calcium transfer and oxidative stress, which are linked to neurodegenerative processes.

Protective agents like berberine further emphasize the potential of targeting mitochondrial dysfunction and oxidative stress to counteract Aβ-induced neurotoxicity. Berberine pretreatment (1 μM) demonstrates significant efficacy in preserving mitochondrial function and axonal mitochondrial dynamics in hippocampal neurons under Aβ1-42-induced stress, as reported by Zhao C et al. (2019). This includes preventing mitochondrial membrane potential loss (~42.0% recovery, $p < 0.01$), mitigating ATP level decline (~37.5% restoration, $p < 0.05$), and rescuing axonal mitochondrial density (~51.5%, $p < 0.05$). Additionally, berberine reduces oxidative stress (~85.0% attenuation of ROS increase, $p < 0.01$) and protects against synaptic loss (~59.4% restoration, $p < 0.01$). These findings align with mechanisms addressing mitochondrial dysfunction, oxidative stress, and synaptic health, highlighting berberine's role in mitigating Aβ1-42-induced neurotoxicity.

Mitochondrial dysfunction and oxidative stress remain central targets, as demonstrated by SkQ1's modulation of gene expression and neuroprotective effects in Alzheimer's disease models. Stefanova NA et al. (2019) found that SkQ1 treatment in OXYS rats resulted in a 48% reduction in differentially expressed genes in the hippocampus, decreasing from 1,159 to 598 (padj < 0.05), and restored 76% of mitochondrial-related gene expression changes (93 out of 122 DEGs). Oxidative stress markers were modulated, including upregulation of Gsr ($p < 0.03$) and downregulation of Cat ($log2FC = -0.52$, $p < 0.015$) and Ptgs2 ($log2FC = -0.68$, $p < 0.0005$). These changes were accompanied by improvements in mitochondrial organization, neuronal loss, synaptic damage, amyloid-β 1-42 levels, and tau hyperphosphorylation, reflecting a significant mitigation of Alzheimer's disease-like pathology.

Extending the focus on mitochondrial therapies, combination treatments such as SS31 and Mdivi1 demonstrate complementary mechanisms to enhance mitochondrial function and reduce neurodegeneration. The combination treatment of SS31 and Mdivi1 demonstrates significant improvements in mitochondrial function, including increased mtDNA copy number ($p = 0.002$), cytochrome c oxidase activity ($p = 0.004$), and ATP production ($p = 0.004$), as well as reductions in Aβ42 levels ($p = 0.002$), apoptotic cell death ($p = 0.001$), hydrogen peroxide production ($p = 0.004$), and GTPase Drp1 activity ($p = 0.004$) (Reddy PH et al. 2018). These synergistic protective effects enhance cell survival ($p = 0.001$) and outperform the efficacy of individual treatments in mutant AβPP cells.

Compounds such as D5L5U5 and DHA further expand on strategies to mitigate mitochondrial dysfunction and oxidative stress in Alzheimer's disease models. The study demonstrates that D5L5U5, DHA, Luteolin, and Urolithin A effectively counteract Aβ1–42-induced mitochondrial dysfunction by reducing ROS levels (e.g., D5L5U5: 101.6 ± 6.6%, $p < 0.001$), restoring ATP production with significant increases observed at 48–72 hours ($p = 0.001$ to $p < 0.001$), and enhancing mitochondrial fusion through increased OPA1 expression ($p < 0.05$ to $p < 0.001$) (Jayatunga DPW et al. 2021). Additionally, these compounds promote mitophagy via upregulation of key markers such as p62, NDP52, OPTN, and PINK1 ($p < 0.05$ to $p < 0.001$) and induce mitochondrial biogenesis by elevating PGC1-α levels (e.g., DHA: $p < 0.001$). In contrast, resveratrol increases ROS levels (159.8 ± 1.4%, $p < 0.001$) and inhibits mitophagy entirely. These findings underscore the therapeutic potential of these compounds, particularly D5L5U5, which shows significant improvements across multiple mitochondrial parameters, including ROS reduction (101.6 ± 6.6%, $p < 0.001$), S-OPA1-mediated fusion ($p < 0.05$), NDP52-dependent mitophagy ($p < 0.001$), and PGC1-α-driven biogenesis ($p < 0.05$).

Quercetin exemplifies another therapeutic approach aimed at mitigating oxidative damage and enhancing mitochondrial biogenesis in neurodegenerative contexts. Ho CL et al. (2022) Quercetin exhibits neuroprotective effects by significantly reducing reactive oxygen species (ROS) production, apoptosis, and β-site amyloid precursor protein cleaving enzyme 1 (BACE1) expression, while enhancing mitochondrial biogenesis-related proteins (SIRT1, PGC-1α, TFAM), ATP production, and ADMA-10 expression in SH-SY5Y cells subjected to H2O2-induced oxidative stress. These findings underscore its role in mitigating oxidative damage and promoting mitochondrial function, aligning with therapeutic strategies that target mitochondrial dysfunction and oxidative stress in Alzheimer's disease models.

Similarly, sulforaphane has been shown to counteract oxidative stress and mitochondrial dysfunction by activating the Nrf2 pathway in Alzheimer's disease models. Villavicencio-Tejo F et al. (2022) found that sulforaphane (SFN) treatment at 10 μM for 24 hours effectively mitigates mitochondrial dysfunction and oxidative stress in Alzheimer's disease models by activating the Nrf2 pathway. This leads to restored mitochondrial morphology ($p < 0.001$), improved membrane potential ($p < 0.05$), enhanced ATP production ($p < 0.0001$), reduced ROS levels ($p < 0.0001$), and increased expression of antioxidant genes and proteins such as NQO1 and HO-1 ($p < 0.001$). These findings support the therapeutic potential of SFN in addressing mitochondrial abnormalities and oxidative damage associated with Alzheimer's disease.

Building on the focus on mitochondrial dysfunction and oxidative stress in Alzheimer's disease, luteolin emerges as another compound with promising therapeutic effects mediated through distinct molecular pathways. He Z et al. (2023) Luteolin demonstrates a statistically significant

ability to ameliorate memory and cognitive impairments in Alzheimer's disease models by reducing amyloid β generation ($p < 0.01$), repairing mitochondrial damage ($p < 0.01$), and enhancing mitochondrial biogenesis ($p < 0.001$). Additionally, it reduces oxidative stress ($p < 0.001$) and prevents neuronal apoptosis ($p < 0.001$) through activation of the PPARγ pathway. These effects are supported by enhanced PPARγ expression and activity, with a binding affinity of $KD = 9.69 \times 10^{-6}$ M. The findings highlight improvements in mitochondrial dynamics and antioxidant defenses, as well as modulation of apoptosis-related markers, with all key results achieving statistical significance ($p < 0.05$, $p < 0.01$, $p < 0.001$).

Mitochondrial health and oxidative stress modulation remain central themes in exploring therapeutic approaches, as demonstrated by alternative compounds and signaling pathways. The administration of LIG-LPs (10 or 30 mg/kg for 6 months) demonstrated a significant reduction in oxidative stress markers, including ROS levels, MDA, and PCO ($p < 0.001$), alongside decreased β-amyloid deposition ($p < 0.05$ and $p < 0.001$) and improved cognitive performance as assessed by NOR and MWM tests ($p < 0.05$, $p < 0.01$, and $p < 0.001$) according to Zhang Q et al. (2024). These outcomes were achieved through the modulation of mitochondrial dynamics, particularly via the PKA/AKAP1 signaling pathway, which preserved hippocampal mitochondrial structure, enhanced ATP production ($p < 0.001$), and regulated mitochondrial fission and fusion. The treatment also alleviated mitochondrial dysfunction in APP/PS1 mice, reflecting improvements in neuroprotection and cognitive function consistent with previously noted therapeutic strategies targeting mitochondrial health in Alzheimer's disease.

Building on the role of mitochondrial dynamics and oxidative stress in Alzheimer's disease, aerobic exercise emerges as another intervention with comparable effects on mitochondrial health and cognitive function. Cai J et al. (2025): Aerobic exercise demonstrated significant improvements in mitochondrial quality within astrocytes and neurons, reduced oxidative stress with decreased ROS levels and increased SOD2 levels ($p < 0.05$, $p < 0.01$, $p < 0.001$), decreased β-amyloid plaque deposition, and enhanced cognitive performance in 5×FAD mice. The findings also revealed the importance of CD38 signaling in astrocytic-neuronal mitochondrial transfer, which supports reductions in oxidative stress and Aβ accumulation ($p < 0.05$, $p < 0.001$) while improving cognitive function. CD38 knockdown impaired these benefits, leading to increased hippocampal ROS levels ($p < 0.01$) and neurodegeneration.

Building on the role of mitochondrial regulation in mitigating oxidative stress and neurodegeneration, NRF1 emerges as another key modulator with therapeutic implications in Aβ-induced neuronal dysfunction. NRF1 overexpression enhanced mitochondrial function and neuronal health in Aβ1-42-exposed SH-SY5Y cells, as indicated by a 4.4-fold increase in NRF1 expression, a 1.8-fold increase in TFAM levels ($p < 0.05$), and improved oxidative phosphorylation, demonstrated by a higher OCR/ECAR ratio and increased intracellular ATP levels ($p < 0.005$) (Massaro M et al. 2025). Additionally, oxidative stress was reduced, with decreased mtROS and preserved mitochondrial membrane potential ($p < 0.05$). Neuronal apoptosis was significantly mitigated, with apoptotic cells reduced from ~20% to ~8% ($p < 0.005$), and neurite shortening was counteracted ($p < 0.0001$). Restoration of mitochondrial dynamics was achieved through modulation of fusion (OPA1, MFN2) and fission (Drp1, Fis1) markers, alongside reduced membrane depolarization and oxidative damage ($p < 0.05$), highlighting the therapeutic potential of NRF1 in addressing Aβ1-42-induced neurodegeneration.

Given the mitochondrial impairments associated with presenilin-1 mutations, therapeutic approaches such as photobiomodulation provide insights into addressing these dysfunctions in Alzheimer's disease models. Photobiomodulation (PBM) therapy demonstrates quantifiable improvements in cognitive and memory functions in Alzheimer's disease-like models, with significant reductions in escape latency during spatial memory testing ($p = 0.00751$) and enhancements in short-term working memory ($p = 0.0224$) (Yang L et al. (2022)b). Additionally, PBM treatment effectively decreases amyloid plaque accumulation in the hippocampus ($p = 0.0004$) and tau hyperphosphorylation in both the cortex ($p = 0.0047$) and hippocampus ($p = 0.0038$). Neuronal injury markers, such as MAP2 intensity in the hippocampus ($p = 0.04826$), and apoptotic cell counts, as indicated by TUNEL staining in the cortex and hippocampus ($p < 0.001$ for both), are also significantly ameliorated. Synaptic integrity and spine density are preserved, with notable improvements in spinophilin levels in the cortex ($p < 0.001$) and reductions in spine damage in both the cortex and hippocampus ($p < 0.001$ for both). These metrics underscore the therapy's role in addressing mitochondrial dysfunction and associated neuropathological features.

Complementing photobiomodulation's therapeutic effects, Nobiletin demonstrates efficacy in targeting mitochondrial dysfunction through biochemical pathways. Amarsanaa K et al. (2021) Nobiletin demonstrates significant efficacy in addressing mitochondrial dysfunction by reducing mitochondrial ROS levels (101.0±2.1%, $p < 0.01$), restoring neuronal viability (91.4±1.6%, $p < 0.01$), and enhancing ATP-linked oxygen consumption rates (573.1±9.9, $p < 0.05$). It further suppresses apoptotic signaling by reducing AIF translocation (nAIF to 86.0±9.4%, $p < 0.01$) and promotes antioxidant defense mechanisms, as indicated by increased expression of Nrf2 (173.2±4.1%, $p < 0.01$) and HO-1 (151.5±0.2%, $p < 0.01$). Additionally, it upregulates complex I activity in a dose-dependent manner (253±1.0%, $p < 0.01$), aligning with therapeutic strategies targeting oxidative stress and mitochondrial homeostasis.

Nobiletin's ability to restore mitochondrial homeostasis aligns with DCBEI's neuroprotective strategies in mitigating neurodegeneration and oxidative stress. DCBEI treatment enhances HT22 cell viability by over 20% ($p < 0.01$) and reduces apoptosis by over 9.5% ($p < 0.01$), demonstrating its protective effects against L-Glu-induced neuroexcitation toxicity (Qu Y et al. 2021). It preserves mitochondrial function by significantly decreasing caspase activity, including reductions of 37.5% in caspase-3/7, 78.3% in caspase-8, and 64.2% in caspase-9 ($p < 0.01$ or $p < 0.001$). In APP/PS1 mice, DCBEI improves cognitive performance, as shown by reduced escape latency in the Morris water maze (30.50 ± 7.84 s [160 mg/kg, $p < 0.05$] and 19.33 ± 5.64 s [320 mg/kg, $p < 0.01$] compared to 51.67 ± 10.54 s in untreated mice) and lowers hippocampal Aβ1-42 levels by 17.1% and 14.8% ($p < 0.01$). Additionally, DCBEI modulates apoptotic pathways by decreasing pro-apoptotic protein expression (e.g., Bax, Bid, Bad) and increasing anti-apoptotic protein expression (e.g., Bcl-2, Bcl-xL), while reducing phospho-Tau levels

($p < 0.01$) and alleviating oxidative stress through elevated SOD, CAT, and GSH-Px levels ($p < 0.05$).

Extending DCBEI's protective effects, PITRM1 overexpression underscores the importance of mitochondrial function and synaptic restoration in Alzheimer's disease models. Overexpression of PITRM1 in advanced-age Alzheimer's disease mouse models demonstrated a ~40% improvement in mitochondrial complex IV activity and ATP levels ($p < 0.01$), a ~4-fold reduction in reactive oxygen species ($p < 0.01$), and significant restoration of synaptic proteins (40–50% for Synapsin 1 and PSD95, $p < 0.01$), alongside reductions in synapse loss and cognitive deficits ($p < 0.01$) (Du F et al. (2021)b). Additionally, PITRM1 overexpression significantly reduced mitochondrial and cerebral amyloid β accumulation ($p < 0.01$), suppressed proinflammatory cytokines ($p < 0.01$), and enhanced synaptic plasticity and density, underscoring its role in mitigating mitochondrial and synaptic dysfunction in Alzheimer's disease.

Building on the role of PITRM1 in restoring mitochondrial function, D-AKAP1/PKA signaling further exemplifies the potential of targeted interventions to improve neuronal health and connectivity. Restoration of D-AKAP1/PKA signaling demonstrates measurable improvements in neuronal health, including increased dendrite length (indicative of enhanced connectivity), improved mitochondrial morphology (reflecting better structural integrity), and reduced apoptosis (indicating decreased cell death) (Banerjee TD et al. 2021). These findings directly address the pathophysiological features associated with Alzheimer’s disease and provide quantitative evidence supporting the potential of targeted mitochondrial interventions to mitigate neurodegeneration.

Continuing the exploration of mitochondrial-targeted strategies, PL171 emerges as another promising compound for mitigating oxidative stress and restoring cellular homeostasis. Li Y et al. (2020), PL171 demonstrates efficacy in mitigating Aβ42 oligomer-induced mitochondrial dysfunction and oxidative stress, evidenced by a 26% reduction in mitochondrial ROS ($p < 0.01$), restoration of ATP production and respiration ($p < 0.05$), and normalization of senescence markers, including a complete reduction in SA-β-gal-positive cells to control levels ($p < 0.001$). Additionally, PL171 enhances SIRT3 expression and activity via the AMPK/PGC-1α pathway, leading to a 36% increase in mitochondrial SIRT3 expression and reductions in acetylation of MnSOD and OSCP by 20% and 36%, respectively ($p < 0.05$). These findings highlight the compound's capacity to restore cellular and mitochondrial homeostasis under conditions of Aβ42 oligomer-induced stress.

Shifting focus to alternative therapeutic approaches, cannabinoid agents like URB597 highlight additional pathways for addressing neurodegeneration and oxidative stress. The study highlights that cannabinoid agents, particularly URB597, exhibit significant neuroprotective effects in hippocampal neurons exposed to GLU + Aβ1–42-induced toxicity (Elmazoglu Z et al. 2020). Key outcomes include up to 26% recovery in cell viability ($p \leq 0.05$), reductions in reactive oxygen species by approximately 25% to 38% ($p \leq 0.01$), maximal recovery of mitochondrial membrane potential at 100 nM ($p \leq 0.001$), and decreases in inflammatory markers such as iNOS, IL-1β, and TNF-α ($p \leq 0.05$–$p \leq 0.001$). URB597 demonstrated the most consistent efficacy, reducing ROS formation by 45% to 55% ($p \leq 0.001$) and mitigating amyloid aggregation and inflammation while preserving cell survival. Its effects were partially mediated through the Nrf2 pathway, despite lacking intrinsic antioxidant scavenging activity.

Urolithin A exhibits mitochondrial protective effects by mitigating oxidative stress and calcium-related dysfunction in Alzheimer's disease models. According to Lee HJ et al. (2021), Urolithin A significantly reduces mitochondrial calcium influx, mtROS accumulation, amyloid beta production, Tau phosphorylation, and cognitive deficits in diabetes mellitus-associated Alzheimer's disease models. These therapeutic effects are linked to the suppression of TGM2 expression, disruption of the AIP–AhR complex, and inhibition of mitochondria-ER interactions. Experimental evidence, both in vitro and in vivo, demonstrates reduced LDH release, decreased amyloid beta levels, lower Tau phosphorylation, and improved cognitive function ($p < 0.05$). Additionally, Urolithin A inhibits TGM2-dependent MAM formation and IP3R1-VDAC1 interactions, effectively preventing neuronal degeneration by suppressing mitochondrial calcium influx and amyloidogenesis under high glucose and amyloid beta conditions ($p < 0.05$).

These findings resonate with observations in tau−/− mice, where improved mitochondrial function and reduced oxidative damage are critical for preserving cognitive health. In aged tau−/− mice, mitochondrial function is improved with significantly reduced oxidative damage (4HNE levels, $p < 0.05$), increased ATP production ($p < 0.05$), and reduced sensitivity to mitochondrial permeability transition pore (mPTP) opening due to decreased CypD levels ($p < 0.05$) (Jara C et al. 2020). These changes are associated with preserved hippocampal-dependent memory, while CypD overexpression negates these benefits, leading to mitochondrial dysfunction, reduced ATP production ($p < 0.05$), impaired calcium buffering ($p < 0.05$), and memory deficits. The findings emphasize a CypD-dependent mechanism underlying tau-related mitochondrial and cognitive impairments in aging.

In parallel, Se-Met enhances mitochondrial biogenesis and dynamics, further underscoring the importance of targeting mitochondrial dysfunction in Alzheimer's disease. Chen C et al. (2021) Se-Met treatment enhances mitochondrial function in Alzheimer's disease models by increasing mitochondrial count ($p < 0.05$, $n = 6$), promoting mitogenesis via NRF1 upregulation ($p < 0.05$, $n = 4$ for N2a-SW cells; $p < 0.05$, $n = 3$ for AD mice), improving ATP synthesis ($p < 0.05$, $n = 6$), elevating mitochondrial membrane potential ($p < 0.05$, $n = 4$), reducing ROS levels ($p < 0.05$, $n = 6$), and decreasing apoptosis rates ($p < 0.05$, $n = 6$). Additionally, it restores mitochondrial dynamics by enhancing fusion (increased Mfn2, $p < 0.05$, $n = 4$; decreased OPA1, $p < 0.01$, $n = 4$; decreased Drp1, $p < 0.05$, $n = 4$) and upregulating SELENO O ($p < 0.05$, $n = 3$), aligning with previously observed therapeutic strategies targeting mitochondrial dysfunction.

Exercise training complements mitochondrial-targeted therapies by improving synaptic integrity, reducing oxidative stress, and alleviating neuroinflammation. Long-term exercise training in TgF344-AD rats demonstrates significant therapeutic effects, including improved escape

latency, quadrant occupancy, and field entries in the Barnes maze test ($p < 0.05$), alongside reductions in anxiety and depression-related behaviors as measured by the elevated plus maze and sucrose preference tests ($p < 0.05$) (Yang L et al. 2022). Additionally, exercise significantly attenuates amyloid-β deposition ($p < 0.05$), reduces tau hyperphosphorylation ($p < 0.05$), preserves synaptic integrity, mitigates neuronal damage and degeneration, reduces oxidative stress, and suppresses neuroinflammation ($p < 0.05$). These findings provide detailed evidence of both behavioral and molecular improvements, complementing prior observations of exercise's role in Alzheimer's disease models.

The protective effects of exercise on mitochondrial function are consistent with the ability of ECS to restore mitochondrial homeostasis and dynamics in Alzheimer's disease models. Cheng D et al. (2021b) demonstrated that ECS improves mitochondrial function and dynamics, as evidenced by enhanced cell viability, normalization of mitochondrial ultrastructure and ATP levels, increased mitochondrial membrane potential (MMP), and reductions in reactive oxygen species (ROS) and intracellular calcium ion concentrations ($p < 0.01$). Additionally, ECS regulates mitochondrial dynamics-related proteins, including Drp1 and the p-Drp1/Drp1 ratio ($p < 0.05$). These findings support therapeutic strategies aimed at mitigating mitochondrial dysfunction and maintaining homeostasis in Alzheimer's disease.

Building on the link between mitochondrial dysfunction and oxidative stress, SIL treatment demonstrates targeted improvements in mitochondrial function and cellular metabolism in neurodegenerative models. Esselun C et al. (2021)b SIL exhibits significant protective effects on mitochondrial function in a neurodegenerative disease model, rescuing ATP levels ($p = 0.0002$), reducing ROS (~20–33%, $p = 0.035$; $p = 0.0002$), attenuating calcium-induced mitochondrial swelling ($p < 0.0001$), and enhancing membrane fluidity ($p < 0.0004$). These findings align with the therapeutic focus on oxidative stress and mitochondrial dysfunction, highlighting targeted improvements in cellular metabolism, as evidenced by reduced pyruvate concentrations ($p = 0.0004$) without altering mitochondrial respiration or content.

These protective mechanisms resonate with the therapeutic potential of Vitamin B12 supplementation, which similarly mitigates mitochondrial dysfunction and oxidative stress through metabolic pathway modulation. Vitamin B12 supplementation mitigates mitochondrial dysfunction by delaying Aβ-induced paralysis in *C. elegans* (Lam AB et al. 2021). This is achieved through improvements in mitochondrial morphology, evidenced by enhanced mitochondrial length, and functionality, with increased ATP levels and reduced oxidative stress markers, including H_2O_2 and O_2^-. These effects align with the therapeutic potential of targeting mitochondrial pathways, such as the methionine/S-adenosylmethionine (SAMe) cycle, as demonstrated by comparable benefits from methionine (13.4 mM) and choline (10 mM) supplementation.

Expanding on the role of oxidative stress and mitochondrial dysfunction, Cycloastragenol showcases additional therapeutic benefits, including neuroinflammation reduction and cognitive enhancement in Alzheimer's disease. Ikram M et al. (2021) found that Cycloastragenol demonstrated significant reductions in oxidative stress markers, including lipid peroxidation (LPO) and reactive oxygen species (ROS), and restored antioxidant responses through increased expression of Nrf2 and HO-1. It enhanced neurogenic markers such as BDNF, p-TrkB, p-CREB, and NeuN while mitigating apoptosis by modulating Bax, Caspase-3, Bim, and Bcl-2. Additionally, it reduced neuroinflammation by decreasing p-JNK, p-p38, TNF-α, and IL-1β levels. Cognitive improvements were observed in the Morris Water Maze test, with reduced latency ($p < 0.05$), increased time spent in the target quadrant ($p < 0.05$), and increased platform crossings ($p < 0.05$). These outcomes highlight Cycloastragenol's potential in addressing oxidative stress, neuroinflammation, and memory impairment in Alzheimer's disease models.

These findings are complemented by research on VDAC1 modulation, which addresses tau-induced impairments and highlights mitochondrial and synaptic restoration as therapeutic strategies. Partial reduction of VDAC1 in symptomatic-transgenic TAU mice significantly alleviates tau-induced behavioral impairments, including motor coordination and spatial memory deficits, while restoring mitochondrial morphology and increasing synaptic density, dendritic spine number, and length ($p < 0.05$ to $p < 0.0001$), as reported by Vijayan M et al. (2022). Enhanced mitophagy and autophagy were observed, with elevated markers such as PARKIN ($p < 0.0001$), PINK1 ($p < 0.0001$), LC3B ($p < 0.0001$), and ATG5 ($p < 0.01$). Synaptic protein levels, including PSD95 ($p < 0.01$) and SNAP25 ($p < 0.0001$), were significantly increased, alongside improvements in dendritic spine density ($p < 0.0001$) and mitochondrial length ($p < 0.0001$). Additionally, reductions in mitochondrial number ($p < 0.0001$) and phosphorylated tau levels ($p < 0.0001$) further demonstrate the therapeutic potential of VDAC1 modulation.

Building upon the role of mitochondrial and synaptic restoration, the focus shifts to autophagy enhancement as a therapeutic strategy. Ubisol-Q10 treatment enhances autophagy by upregulating autophagy-related genes, including beclin-1 and MAPK8/JNK1, and proteins in PS-1 mutated Alzheimer's Disease fibroblasts and transgenic AD mice, restoring expression levels to those observed in healthy controls (Vegh C et al. 2019). Continuous supplementation with Ubisol-Q10 restores autophagy-related protein expression, reduces oxidative stress, and prevents premature senescence in PS-1 mutated fibroblasts and double transgenic AD mice. Withdrawal of the treatment or inhibition of autophagy reverses these benefits, demonstrating the necessity of sustained supplementation to maintain therapeutic efficacy.

The emphasis on sustained supplementation transitions to interventions targeting oxidative neurotoxicity and apoptotic pathways. The study demonstrated that treatments with GSH, TRPM2 antagonists, and ACA significantly reduced Aβ-induced oxidative stress and apoptosis in hippocampal neurons and TRPM2WT mice (nar R et al. 2023). These interventions mitigated Ca^{2+} and Zn^{2+} influx, ROS generation (cytosolic and mitochondrial), lipid peroxidation (MDA), and apoptotic markers (caspase-3, caspase-9, Bax), while enhancing antioxidant defenses (GSH, GSH-Px) and cell viability. The results were statistically significant with $p \leq 0.05$, indicating effective modulation of oxidative neurotoxicity and apoptotic pathways in the context of Alzheimer's disease.

Continuing the focus on oxidative stress and cellular protection, the discussion moves to mechanisms involving amyloid β reduction and mitochondrial biogenesis. Yin Z et al. (2022) Rhein demonstrated a significant therapeutic impact on cognitive and memory functions in APP/PS1 mice, with improvements in nesting scores and novel object recognition test performance ($p < 0.01$, $p < 0.001$). These outcomes

were achieved through mechanisms involving reduced amyloid β burden ($p < 0.01$), decreased neuroinflammation ($p < 0.01$), and oxidative stress ($p < 0.001$), alongside enhanced mitochondrial biogenesis and neuronal protection. The activation of the SIRT1/PGC-1α pathway was identified as a key mediator of these effects, contributing to mitochondrial dynamics and neuroprotection.

The connection between mitochondrial dysfunction and neurodegenerative features progresses to the impact of APP overexpression on oxidative metabolism and therapeutic modulation. Pahrudin Arrozi A et al. (2021) found that APP overexpression influences mitochondrial oxidative metabolism, as indicated by increased respiratory capacity, enhanced membrane potential, and elevated complex IV enzyme activity in APP WT and APP Swe cells, contrasted by impairments in APP Swe/Ind cells. Treatment with ATF (100 μM) and GTF (80 μM) demonstrated a dose-dependent improvement in these parameters, with respiratory capacity, membrane potential, and complex IV activity showing statistically significant enhancements ($p < 0.05$ to $p < 0.001$) in APP-overexpressing cells.

Building on the therapeutic modulation of mitochondrial function, minocycline demonstrates efficacy in alleviating Alzheimer's disease-related pathologies through similar mitochondrial-targeted mechanisms. Minocycline at a dose of 870 μM demonstrated significant therapeutic effects in Aβ42-overexpressing transgenic flies, including restored mitochondrial function ($p < 0.001$), normalized apoptotic protein expression (p-JNK: $p < 0.001$; cleaved caspase 3: $p < 0.001$), reduced Aβ42 protein levels ($p < 0.001$), and decreased acetylcholinesterase activity ($p < 0.001$). Behavioral improvements were observed in climbing ($p < 0.01$) and jumping ($p < 0.05$) assays, alongside increased survival rates, with 75% of flies surviving after 30 days ($p < 0.05$). These findings align with observed benefits of mitochondrial-targeted interventions in mitigating Alzheimer’s disease pathologies (Khatoon R et al. 2022).

The therapeutic potential of targeting mitochondrial dysfunction is further exemplified by alpha lipoic acid's effects on oxidative stress and energy metabolism in cellular models. Dieter F et al. (2022) found that alpha lipoic acid (ALA) at 100 μM demonstrated improvements in mitochondrial function, including increased basal ATP levels ($p < 0.0417$), enhanced mitochondrial membrane potential ($p = 0.0127$), and elevated respiratory chain complex activities such as coupled respiration of complex I ($p < 0.0436$). It also reduced oxidative stress in SH-SY5Y-MOCK ($p = 0.0064$) and SH-SY5Y-APP ($p < 0.0006$) cells, with differential effectiveness based on concentration and cell type. Notably, 100 μM ALA was more effective in reducing ROS levels in SH-SY5Y-MOCK cells ($p = 0.0064$) compared to 1 mM ALA ($p = 0.0316$), while 1 mM ALA showed greater efficacy in SH-SY5Y-APP cells ($p = 0.0006$ vs. $p = 0.0437$ for 100 μM). Despite these benefits, ALA's protective effects were limited under rotenone-induced mitochondrial stress and did not affect mitochondrial content, highlighting nuanced cellular responses to oxidative stress and mitochondrial dysfunction.

Therapeutic strategies addressing mitochondrial dysfunction are exemplified by XE-991, which restores mitochondrial integrity and reduces oxidative stress in Alzheimer's models. Piccirillo S et al. (2022) found that XE-991 exhibited robust neuroprotective effects by restoring mitochondrial function and reducing oxidative stress in Alzheimer's disease experimental models. It fully restored superoxide dismutase (SOD) activity in RA-differentiated SH-SY5Y cells and primary rat cortical neurons ($p < 0.01$, $p < 0.001$), significantly reduced mitochondrial ROS production ($p < 0.0001$), restored mitochondrial membrane potential ($\Delta\Psi m$) ($p < 0.001$), and increased intracellular ATP levels ($p < 0.0001$). Additionally, XE-991 reversed elevated cytoplasmic and mitochondrial $Ca2+$ levels ($p < 0.001$), decreased amyloid-β (Aβ) and hyperphosphorylated tau protein (pTau) levels ($p < 0.0001$), and modulated the AMPK/mTOR pathway ($p < 0.001$), demonstrating its antioxidant defense mechanisms independent of Kv7 channel activity.

These findings align with subsequent therapeutic approaches, such as SUL-138 treatment, which also target amyloid pathology and mitochondrial bioenergetics. de Veij Mestdagh CF et al. (2022) SUL-138 treatment demonstrates significant improvements in synaptic plasticity ($p = 0.0463$ in wildtype; $p = 0.0421$ in APP/PS1), restoration of hippocampal and contextual fear memory deficits in APP/PS1 mice ($p = 0.0261$), and enhancements in contextual fear memory in wildtype mice ($p = 0.0022$). It reduces amyloid plaque load by 54% in number ($p = 0.0203$) and 30% in size ($p = 0.0042$), alongside rescuing 66 dysregulated proteins (12.0% of APP/PS1-affected proteins). These effects are linked to improved mitochondrial bioenergetics, including decreased ROS, increased ATP production, and upregulation of proteins associated with fatty acid oxidation, glycolysis, and amino acid metabolism (e.g., ETFA and ETFB), contributing to reduced oxidative stress and alleviation of Alzheimer’s-associated pathology.

Building on these observations, NFP treatment further highlights the interplay between mitochondrial pathways and protein regulation in Alzheimer’s disease. NFP treatment in 5XFAD mice significantly modulates 111 proteins (28 upregulated, 83 downregulated; FDR < 0.05), primarily linked to synaptic and mitochondrial pathways, while restoring mitochondrial beta-oxidation and carnitine shuttle pathways, as reported by Kim S et al. (2023). Protein alterations include Ywhag, Ywhah, and YME1L1, with metabolic flux changes observed in L-carnitine and (13Z)-octadecenoic acid, suggesting alignment with WT levels and potential therapeutic relevance for Alzheimer's disease.

Similarly, dietary compound interventions underscore the potential of targeting mitochondrial function to mitigate Alzheimer’s-related pathology. The combination of dietary compounds (SC) demonstrated a measurable enhancement of mitochondrial function in SH-SY5Y-APP695 cells, with a significant increase in ATP levels ($p = 0.0031$, $N = 11$) and endogenous respiration ($p = 0.0314$, $N = 16$) (Babylon L et al. 2023). Additionally, SC treatment significantly reduced Aβ1-40 levels ($p = 0.0217$, $N = 9$), complementing strategies aimed at mitigating amyloid β accumulation. No significant changes were observed in ROS, lactate, or pyruvate levels, indicating a specific effect on mitochondrial function and amyloid-related processes.

Extending these findings, NCX3 silencing demonstrates additional strategies to address oxidative stress and mitochondrial dysfunction in

Alzheimer's models. Preziuso A et al. (2023) NCX3 silencing in GA-challenged RA-differentiated SH-SY5Y cells resulted in significant improvements in cell viability ($p < 0.001$), intracellular ATP levels ($p < 0.01$), and reductions in mitochondrial ROS production ($p < 0.001$), Aβ accumulation ($p < 0.0001$), and pTau levels ($p < 0.001$). Additionally, NCX reverse-mode activity was normalized, recovering towards control values, demonstrating its role in addressing oxidative stress, mitochondrial dysfunction, and cellular damage characteristic of Alzheimer's disease-like conditions.

The modulation of mitochondrial function and inflammation through SDH inhibition complements approaches like mitotherapy, which restore mitochondrial health and cognitive performance in Alzheimer's models. Yang X et al. (2023) found that mitotherapy significantly improved cognitive performance in Alzheimer's disease model mice, evidenced by reduced escape latency ($p < 0.01$) and increased time spent in the target quadrant ($p < 0.01$) during the Morris water maze test. Additionally, mitotherapy activated autophagy via the NAD+/SIRT1 pathway, decreased oxidative stress and ROS levels, reduced Aβ aggregation, eliminated damaged mitochondria, restored mitochondrial function, elevated BDNF production and ERK phosphorylation, and enhanced neuronal health and oxidative balance, contributing to improved cognitive function in Alzheimer's disease models ($p < 0.01$).

The restoration of mitochondrial function and oxidative balance through mitotherapy parallels the neuroprotective effects of Prx1 expression in mitigating Alzheimer's-like pathology. Park J et al. (2024) Prx1 expression demonstrates significant neuroprotective effects in STZ-induced AD-like pathology in HT-22 cells by reducing neuronal apoptosis markers (cleaved caspase-3 and PARP, $p < 0.05$ to $p < 0.001$), preserving synaptic proteins (PSD95, $p < 0.001$), attenuating tau phosphorylation (p-Tau(S262) and AT8(S202/T205), $p < 0.001$), and improving mitochondrial parameters, including ATP levels ($p < 0.001$) and mitochondrial length ($p < 0.001$). These effects are achieved through the suppression of oxidative stress, intracellular $Ca2+$ accumulation, and modulation of calpain/Cdk5/Drp1 signaling pathways, aligning with established roles of mitochondrial-targeted approaches and oxidative stress reduction in AD models.

The mitochondrial preservation and tauopathy reduction achieved by Prx1 expression are consistent with the neuroprotective effects of polyphenol-rich sorghum extracts in Alzheimer's disease models. Rezaee N et al. (2025), the polyphenol-rich extracts from six varieties of sorghum demonstrated significant neuroprotective effects by reducing Aβ42-induced taupathies, including total tau levels by 28% ($p \leq 0.01$) and phosphorylated tau levels (pS199 by 31%, $p \leq 0.01$; pT231 by 27.6%, $p \leq 0.01$), while also mitigating mitochondrial dysfunction by preserving mitochondrial membrane potential ($\Delta\psi m$) by 39.8% ($p \leq 0.01$) and restoring ATP levels by 37.7% ($p \leq 0.01$) in a dose-dependent manner. The varieties QL33 and QL12 exhibited the most pronounced protective effects.

Mitochondrial dysfunction emerges as a critical target, further explored through MST1 inhibition strategies in Alzheimer's disease models. Cui D et al. (2024): In Alzheimer's disease models, MST1 knockdown or inactivation improves mitochondrial function and reduces oxidative stress, aligning with evidence supporting therapeutic strategies targeting mitochondrial dysfunction. Enhanced spatial memory and reduced neuronal apoptosis observed in 5xFAD mice and Aβ-induced SH-SY5Y cells underscore the role of mitochondrial biogenesis in mitigating cognitive decline ($p < 0.05$). Furthermore, MST1 inhibition through pharmacological intervention, such as XMU-MP-1, demonstrates significant reductions in mitochondrial damage and oxidative stress, reinforcing the connection between mitochondrial-targeted therapies and improved neuronal outcomes.

Building on mitochondrial-targeted interventions, Givinostat treatment offers additional insights into cognitive and synaptic restoration in Alzheimer's pathology. Gao QC et al. (2024) Givinostat treatment demonstrates significant improvements in cognitive functions, synaptic plasticity, and mitochondrial function in Alzheimer's disease models. Quantitative outcomes include enhanced spatial learning and memory ($p < 0.05$, $p < 0.01$), reduced hippocampal Aβ plaque levels (Thio S staining $p < 0.01$, 6E10 staining $p < 0.05$), and restored synaptic protein levels (PSD-95 $p < 0.05$, SYN $p < 0.01$). Additionally, mitochondrial function and biogenesis are improved, as evidenced by normalized membrane potential, reduced ROS levels ($p < 0.01$), increased ATP production ($p < 0.01$), and activation of the PGC-1α/NRF-1/TFAM pathway ($p < 0.05$). Enhanced cerebral glucose metabolism (FDG uptake $p < 0.05$) further supports its role in mitigating Alzheimer's disease-related pathologies.

2.1.3. Molecular Mechanisms and Biomarkers

Selected findings

- SIRT3 dysfunction was identified as a major contributor to mitochondrial and neuronal damage in AD, with its overexpression restoring mitochondrial function and preventing neuronal apoptosis. This finding highlights SIRT3 as a promising therapeutic target to mitigate oxidative stress and mitochondrial dysfunction in neurodegenerative diseases.
- miR-1273g-3p was significantly elevated in early-stage AD patients and shown to impair mitochondrial function by downregulating key mitochondrial genes, promoting oxidative stress and amyloid-beta production. Its potential as a biomarker for early AD diagnosis positions it as a critical tool for staging and therapeutic targeting of mitochondrial dysfunction.
- Orexin-A exacerbated oxidative stress, mitochondrial dysfunction, and amyloid pathology in AD models via the p38 MAPK pathway, with these effects reversed by the p38 MAPK inhibitor SB203580. This mechanistic insight underscores the therapeutic potential of targeting p38 MAPK to alleviate mitochondrial and oxidative stress-related damage in AD.
- Mitochondrial Complex III dysfunction in CIIIKO-AD mice significantly reduces Aβ42 toxic fragment levels and amyloid plaque

numbers while inducing mild oxidative stress and altering amyloid precursor protein clearance (Pinto M et al. 2022). This finding suggests that modulating mitochondrial function could directly impact amyloid pathology and oxidative stress, offering a potential therapeutic avenue for Alzheimer's Disease.

- The N-terminal region of SSH1 impairs mitochondrial respiration, while its C-terminal domain inhibits mitophagy by suppressing p62-mediated autophagy, contributing to synaptic deficits and mitochondrial abnormalities in Alzheimer's models (Cazzaro S et al. (2023)b). Targeting SSH1 domains may provide a novel therapeutic strategy to restore mitochondrial function and synaptic integrity in neurodegenerative diseases.

Table 3. Molecular Mechanisms and Biomarkers

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome
Csaban D et al. (2021)		Patients diagnosed with Alzheimer's Disease, 46 participants (5 male and 6 female post-mortem brain tissue analysis; 2 male and 11 female blood samples analyzed by WES-NGS; 6 male and 16 female analyzed by Sanger sequencing)	134 individuals (72 male, 62 female), including 55 healthy and 79 without neurological disorders; 9 post-mortem brain tissues (3 male, 6 female)	Genetic analysis of αKGDHc subunits, post-mortem brain tissue analysis, blood sample sequencing	Brain tissue collected post-mortem within 2–6 h, several brain regions analyzed for rare variants and somatic mutations, DNA isolated from blood samples using QIAamp DNA blood kit, bidirectional Sanger sequencing performed using ABI Prism 3500 DNA Sequencer, DNA library preparation for WES using SureSelect QXT library preparation kit, NGS performed on Illumina HiSeq 2500 system	Association of rare damaging variants in αKGDHc subunit genes, specifically the R263H mutation in the DLD gene, with Alzheimer's Disease

Go to Annex 4: Table 3. Molecular Mechanisms and Biomarkers

Mitochondrial dysfunction, as highlighted earlier, aligns with emerging genetic insights, such as the identification of mutations in mitochondrial enzyme subunits linked to Alzheimer's Disease. The R263H mutation in the DLD gene, a subunit of αKGDHc, was identified in an Alzheimer's Disease patient and absent in controls (Csaban D et al. 2021). Predictive tools suggest its pathogenicity, and it has been previously associated with Congenital Lactic Acidosis. However, its classification as a variant of uncertain significance underscores the need for further research to clarify its role in Alzheimer's Disease.

Regulatory mechanisms, such as SIRT3, play a pivotal role in mitigating mitochondrial dysfunction and preserving neuronal integrity. SIRT3 dysfunction is identified as a key contributor to mitochondrial and neuronal damage in Alzheimer's Disease, according to Lee J et al. (2018)b, with reduced ND2 and ND4 expression ($p < 0.05$, $n = 6$), impaired mitochondrial oxygen consumption ($p < 0.005$, $n = 5$), increased ROS levels ($p < 0.01$, $n = 5$), and elevated p53 occupancy on mitochondrial DNA ($p < 0.05$, $n = 6$). Overexpression of SIRT3 significantly restores ND2 and ND4 mRNA levels ($p < 0.05$), enhances oxygen consumption ($p < 0.05$), decreases ROS accumulation ($p < 0.01$), and prevents neuronal apoptosis ($p < 0.05$), demonstrating its role in addressing mitochondrial dysfunction and neurodegeneration.

Building upon the role of mitochondrial dysfunction, Orexin-A emerges as a critical factor exacerbating oxidative stress and amyloid pathology through specific signaling pathways. The study demonstrates that Orexin-A significantly exacerbates cytotoxicity, mitochondrial dysfunction, oxidative stress, and amyloid pathology in APPswe-transfected SH-SY5Y cells through activation of the p38 MAPK pathway (Li M et al. 2020). This is supported by increased Aβ1–40/Aβ1–42 levels ($p < 0.01$), reduced cell viability and proliferation ($p < 0.01$), impaired mitochondrial morphology and function ($p < 0.01$), and elevated ROS levels ($p < 0.01$). Importantly, these detrimental effects are reversed by the p38 MAPK inhibitor SB203580, which restores cell viability ($p < 0.05$), proliferation ($p < 0.01$), mitochondrial morphology and function ($p < 0.05$ to $p < 0.01$), and reduces ROS levels ($p < 0.01$). These findings highlight the mechanistic role of Orexin-A in mitochondrial and oxidative stress-related pathways and suggest the potential of targeting the p38 MAPK pathway in therapeutic interventions.

The mechanistic insights into mitochondrial impairments are extended by examining the effects of the PS1E280A mutation, which alters autophagic flux and mitochondrial function. The PS1E280A mutation induces cellular stress vulnerability by impairing autophagic flux, as indicated by an increased LC3B-II/I ratio ($p < 0.05$), and mitochondrial function, evidenced by accelerated mitochondrial permeability transition pore opening ($p < 0.001$) and elevated mitochondrial calcium levels ($p < 0.01$) (Rojas-Charry L et al. 2020). These disruptions occur independently of Aβ pathology, with autophagy impairment being γ-secretase-independent and MPTP modulation showing γ-secretase dependency. Additionally, the mutation does not significantly influence ER stress responses.

Therapeutic interventions targeting mitochondrial dysfunction are exemplified by the effects of ATF and GTF treatments in cellular models of Alzheimer's disease. Pahrudin Arrozi A et al. (2020) ATF (5–100 μM) and GTF (5–80 μM) treatments significantly reduced Aβ42 levels ($p < 0.05$), mitochondrial ROS levels ($p < 0.05$), cytochrome c release ($p < 0.05$), and apoptosis markers such as the BAX/Bcl-2 ratio ($p < 0.05$) in SH-SY5Y cells expressing wild-type or mutant APP genes. Both compounds improved mitochondrial complex V activity ($p < 0.05$), while GTF uniquely increased ATP production ($p < 0.05$) and reduced pro-caspase-3 expression ($p < 0.05$), demonstrating superior effects compared to

ATF in certain contexts.

Animal studies further reveal the interplay between mitochondrial regulation and Alzheimer's pathology, as demonstrated in Sgo1−/+ mice with cerebral amyloid-β accumulation. Middle-aged Sgo1−/+ mice (15-18 months) exhibit cerebral amyloid-β accumulation linked to GSK3 inactivation, characterized by increased phosphorylated GSK3α (S21) and GSK3β (S9), Wnt signaling activation indicated by nuclear β-catenin localization, and ARC/Arg3.1 accumulation (Rao CV et al. 2020). Aged Sgo1−/+ mouse brains reveal misregulation of 25 proteins, including mitochondrial and antioxidant proteins relevant to Alzheimer's disease, along with neuroinflammation marked by significant upregulation of IFN-γ ($p < 0.0001$), co-localizing with amyloid-β accumulation.

Mitochondrial dysfunction in Alzheimer's disease is further influenced by miRNA dysregulation, as exemplified by miR-1273g-3p and its downstream effects on energy metabolism and neuronal health. miR-1273g-3p is significantly elevated in the plasma and cerebrospinal fluid of early-stage Alzheimer's disease (AD) patients ($p < 0.05$ to $p < 0.001$) (Kim SH et al. 2021). It upregulates BACE1 through oxidative stress and JNK signaling, facilitating amyloid-beta production ($p < 0.01$). Furthermore, miR-1273g-3p impairs mitochondrial function by downregulating genes such as TIMM13, GLRX5, and MTCH1 ($p < 0.001$), leading to energy deprivation, oxidative stress, and neuronal degeneration. TIMM13 expression is significantly reduced in AD hippocampi ($p < 0.001$), correlating with disease pathogenesis. Diagnostic analysis reveals miR-1273g-3p as a potential biomarker for AD, with an AUC > 0.75.

Mitochondrial dysfunction, as a central feature of neurodegenerative pathologies, is further highlighted by the protective mechanisms associated with AnxA2 in Alzheimer's Disease. Ye L et al. (2024) AnxA2 plays a protective role in mitigating key pathological processes in Alzheimer's Disease, including oxidative stress, mitochondrial dysfunction, apoptosis, inflammation, and autophagy inhibition. Knockdown of AnxA2 significantly increases ROS levels (20.72%-69.75%, $p < 0.01$) and apoptosis (103.54%-213.92%, $p < 0.01$), while reducing ATP production (26.99%-31.57%, $p < 0.01$) and cell migration ($p < 0.05$). Furthermore, it exacerbates Aβ42-induced cytotoxicity by impairing autophagy-related gene expression, such as Stx-17, Vamp8, and Lc3-II ($p < 0.01$), and modulating inflammatory responses. These findings emphasize its critical role in addressing mitochondrial dysfunction and related pathologies.

Insights into mitochondrial dysfunction are further enriched by proteomic analyses, revealing altered proteins linked to energy metabolism and oxidative stress in Alzheimer's disease models. Proteomic and bioinformatics analyses revealed 232 differentially expressed proteins (DEPs) in mitochondrial, synaptosomal, and myelin fractions of 3×Tg-AD mice at 6 months of age, with 32, 11, and 23 DEPs consistently altered in mitochondria, synaptosomes, and myelin, respectively ($p < 0.05$) (Shen L et al. 2022). These DEPs were linked to mitochondrial dysfunction, synaptic impairment, decreased energy metabolism, and disrupted amino acid pathways, including oxidative phosphorylation and TCA cycle disruptions. Validation of key DEPs such as Lrpprc, Nefl, and Sirpa across 2, 4, and 6 months indicated these as early pathological events ($p < 0.017$ after Bonferroni correction). Additionally, the subcellular fractionation approach identified 2424 unique proteins across mitochondrial, synaptosomal, and myelin fractions, with 833, 273, and 150 proteins detected in each respective fraction using iTRAQ-based mass spectrometry, enabling detailed analysis of subcellular dysfunction in Alzheimer's disease.

Further exploring mitochondrial dysfunction, Complex III deficiency demonstrates a role in modulating amyloid pathology and oxidative stress in Alzheimer's models. Mitochondrial Complex III dysfunction in CIIIKO-AD mice results in a ~66% reduction in Aβ42 toxic fragment levels ($p < 0.05$) and a decrease in amyloid plaque numbers, as reported by Pinto M et al. (2022). Additionally, mild oxidative stress induced by Complex III deficiency correlates with altered amyloid precursor protein clearance, as evidenced by increased 20S proteasome activity, elevated SOD2 levels, protein carbonylation, and fewer amyloid plaques compared to AD controls ($p < 0.05$).

This focus on mitochondrial and synaptic mechanisms is complemented by the identification of SSH1 as a contributor to these dysfunctions. Cazzaro S et al. (2023)b The study identifies the N-terminal region of SSH1 as a contributor to mitochondrial dysfunction and synaptic integrity loss, marked by impaired mitochondrial membrane potential ($\Delta\Psi m$, $p < 0.05$, $p < 0.005$, $p < 0.0005$, $p < 0.0001$) and respiratory capacity ($p < 0.0005$). Additionally, the C-terminal p62-binding domain (residues 549–649) inhibits mitophagy by suppressing p62-mediated autophagy, as observed in HT22 cells, primary neurons, and APP/PS1 mouse models. SSH1 knockdown improves mitochondrial function, synaptic integrity, and mitophagy, aligning with therapeutic strategies that target mitochondrial dysfunction and mitophagy modulation in Alzheimer's disease.

The normalization of NCX reverse-mode activity underscores the broader role of mitochondrial regulation, which is further explored through the genetic interactions of the APOE locus in Alzheimer's disease. Upregulation of APOE locus genes (APOE, APOC1, NECTIN2, TOMM40) and markers of mitochondrial dysfunction, including reduced mitochondrial membrane potential (MMP) and altered mitochondrial DNA copy number (mtDNA CN), were identified in oxidative stress-induced models and Alzheimer's disease postmortem brains (Lee EG et al. 2023). A significant interaction ($p = 0.027$) between the APOE SNP rs429358 (ε4 allele) and mtDNA CN in AD brains underscores the connection between APOE locus regulation and mitochondrial dysfunction in the context of oxidative stress. Additionally, ε4 carriers exhibit higher mtDNA copy numbers in AD brains, with coordinated upregulation of APOE locus genes suggesting a relationship between APOE genetics and mitochondrial regulation in Alzheimer's disease.

The interplay between APOE genetics and mitochondrial dysfunction aligns with therapeutic strategies targeting bioenergetic balance and inflammation, such as SDH inhibition in microglia. Sangineto M et al. (2023) Inhibition of succinate dehydrogenase (SDH) using dimethyl malonate (DMM) demonstrates significant reductions in pro-inflammatory cytokines (IL-1β, TNF-α, $p < 0.05$), normalization of the iNOS/Arg1 ratio ($p < 0.01$), and restoration of metabolic balance by mitigating glycolysis and mitochondrial dysfunction in microglia. These effects, observed in LPS-stimulated HMC3 cells and 3xTg-AD mice, align with strategies aimed at modulating mitochondrial function and bioenergetic

profiles. Additionally, DMM reduces LPS-induced mitochondrial biogenesis and circulating LPS levels while improving mitochondrial function, with reductions in pro-inflammatory cytokines and bioenergetic dysfunction across in vitro and in vivo models ($p < 0.05$ to $p < 0.0001$).

The exploration of mitochondrial dynamics and cognitive improvements leads to the investigation of Rlip haploinsufficiency and its neurodegenerative implications. Awasthi S et al. (2021) Rlip+/− mice display significant cognitive impairments, including reduced Morris Water Maze performance (latency, $p = 0.0433$) and motor coordination deficits (Rotarod performance time, $p = 0.0009$), alongside reduced synaptic protein levels such as synaptophysin ($p = 0.048$). Mitochondrial dysfunction is evident through reduced mitochondrial length in hippocampal regions ($p = 0.0005$) and altered dynamics, including increased Drp1 ($p = 0.0210$) and reduced Mfn1 ($p = 0.0217$). Oxidative stress markers, such as GPx activity, are significantly reduced ($p < 0.001$), further contributing to the observed neurodegenerative features. These metrics establish a mechanistic connection between Rlip haploinsufficiency and pathophysiological processes associated with Alzheimer's Disease.

The findings delineate the molecular aspects of oxidative stress and mitochondrial dysfunction in Alzheimer’s disease, contributing to the characterization of these processes.

2.2. Therapies Targeting Oxidative Stress in Parkinson’s Disease: Mechanisms and Neuroprotection

2.2.1. Improvement of mitochondrial function and oxidative stress mechanisms

Selected findings

- Nitrite administration improves mitochondrial respiration, redox balance, and dopaminergic neuron preservation in Parkinson’s disease models, with mechanisms involving Complex I S-nitrosation and Nrf2 activation. This finding supports the development of nitrite-based therapies targeting oxidative stress and mitochondrial dysfunction in neurodegenerative diseases.

2.2.2. Motor function and behavioral improvements in Parkinson's disease models

Selected findings

- Simvastatin significantly reduced oxidative stress markers, inhibited apoptosis, suppressed inflammation, and improved motor function in Parkinson's disease models (Tong H et al. 2018). This multifaceted mechanism highlights its potential as a scalable therapeutic candidate for addressing oxidative stress and neurodegeneration in Parkinson’s disease.

2.2.3. Neuroprotection and anti-inflammatory mechanisms

Selected findings

- ICA mitigates dopaminergic neurotoxicity and glial-mediated neuroinflammation via Nrf2-dependent mechanisms, showing improved motor behavior and DA neuronal survival in WT mice but no protection in Nrf2 KO or neuron-only cultures. This finding underscores the critical role of Nrf2 activation in antioxidant therapies for Parkinson’s disease, providing a targeted pathway for therapeutic development.

2.2.4. Antioxidant pathways and oxidative stress reduction

Selected findings

- Gracilin A derivatives significantly upregulate antioxidant gene expression (e.g., CAT, SOD1, Nrf2) and reduce pro-inflammatory cytokines (e.g., IL-1β, ROS) in cellular models of oxidative stress, with compound 3 demonstrating the highest efficacy. These findings highlight the potential of transcriptional pathway modulation as a novel therapeutic strategy for reducing oxidative and inflammatory damage in Parkinson’s disease.

2.2.5. Specific compounds and therapeutic interventions

Selected findings

- The intranasal administration of vitamin E-loaded naringenin nanoemulsion significantly improved motor function and oxidative stress markers in a 6-OHDA-induced Parkinson's disease rat model (Gaba B et al. 2019). This innovative delivery system highlights the potential for targeted antioxidant therapies to address both motor deficits and neurodegeneration through oxidative stress mitigation.

2.2.6. Negative or neutral findings

Selected findings

- The combination of NAC and HA-1077 exacerbated dopaminergic neuronal loss and increased neuroinflammatory markers in aged MPTP-treated mice, as evidenced by significant increases in Iba-1+ and GFAP+ cell expression in the substantia nigra pars compacta and striatum. This finding highlights potential risks of combining antioxidant therapies with kinase inhibitors, urging caution in therapeutic development for Parkinson's disease.

2.3. Redox Dysregulation and Mitochondrial Dysfunction: Therapeutic Strategies for Neurodegeneration

Selected findings

- Nox2-derived ROS was identified as a key driver of oxidative stress and neuroinflammation, with significant increases in ROS production, microglial activation, and inflammatory markers in aging brains and Aβ42-stimulated BV2 cells. This finding highlights the potential of targeting Nox2 pathways to mitigate redox-driven neuroinflammation, offering a promising avenue for therapeutic intervention in neurodegenerative diseases.

2.4. Innovative Therapies for Oxidative Stress in Alzheimer’s Disease: Mechanisms and Outcomes

2.4.1. Oxidative Stress and Neuroprotection

Selected findings

- Shikonin demonstrated dose-dependent neuroprotection in Aβ1–42-treated PC12 cells by improving cell viability, reducing oxidative stress and apoptosis, and stabilizing mitochondrial membrane potential. This finding highlights Shikonin's potential as a therapeutic agent targeting oxidative stress and mitochondrial dysfunction in Alzheimer's disease.

2.4.2. Amyloid-Beta Aggregation and Pathology

Selected findings

- The SiO_2–cyclen nanochelator effectively inhibits metal-induced Aβ aggregation, reduces reactive oxygen species (ROS) generation, and alleviates neurotoxicity, while demonstrating blood-brain barrier permeability in vivo. This finding highlights its potential as a scalable nanotherapeutic for targeting oxidative stress and metal dyshomeostasis in Alzheimer's disease.

2.4.3. Cognitive Improvement and Behavioral Studies

Selected findings

- Urolithin A ameliorates brain aging and cognitive deficits by targeting the miR-34a/SIRT1/mTOR signaling pathway, reducing oxidative stress, and restoring autophagy. This finding underscores the potential of autophagy-modulating antioxidants for Alzheimer's disease therapy.

2.4.4. Neuroinflammation and Synaptic Function

Selected findings

- Ψ-GSH treatment significantly restored glyoxalase-1 activity, reduced oxidative stress markers, attenuated neuroinflammation, and mitigated late-stage Alzheimer's pathology, including insoluble Aβ42 levels and cortical TH+ afferent loss. This multi-target therapeutic strategy offers promising avenues for addressing advanced neurodegeneration and oxidative stress in Alzheimer's disease models.

2.4.5. Iron Dysregulation and Metal Toxicity

Selected findings

- Chaudhary S et al. (2021) demonstrated significant transcriptional upregulation of hepcidin in Braak stage III–VI Alzheimer's brains, correlating with decreased ferroportin expression and iron accumulation alongside inflammatory markers such as IL-6 and Iba1. This finding highlights the mechanistic role of iron dysregulation and inflammation in Alzheimer's progression, providing potential targets for therapeutic interventions addressing metal homeostasis.

2.5. Mitochondrial Dysfunction and Oxidative Stress in Neurodegenerative Diseases: Therapeutic Strategies

2.5.1. Mitochondrial Dysfunction and Oxidative Stress

Selected findings

- Mitochondrial dysfunction in ApoE4-expressing neuronal cells is characterized by reduced ATP production, increased reactive oxygen species, and metabolic rewiring impairing energy demands (Orr AL et al. 2019). These findings highlight ApoE4's role in oxidative stress and suggest targeting mitochondrial pathways could mitigate neurodegeneration in Alzheimer's disease.

2.5.2. Mechanisms of Neuronal Degeneration

Selected findings

- Mitochondrial dysfunction in astrocytes leads to lipid droplet accumulation, oxidative stress, neuroinflammation, synaptic loss, and cognitive impairment, as demonstrated in Alzheimer's Disease-like models (Mi Y et al. 2023). This finding underscores the importance of targeting astrocytic mitochondrial pathways to mitigate systemic neurodegenerative processes and improve therapeutic strategies.

2.5.3. Therapeutic Interventions

Selected findings

- Honokiol treatment significantly reduces oxidative stress, enhances mitochondrial bioenergetics, and decreases amyloidogenic processes in cellular models of Alzheimer's disease. These findings suggest a promising therapeutic strategy through the activation of the AMPK-CREB-PGC1α pathway for mitigating mitochondrial dysfunction and oxidative stress in neurodegenerative diseases.

2.6. Therapies Targeting Mitochondrial Dynamics and Oxidative Stress in Neurodegeneration

2.6.1. Mitochondrial Dynamics and Dysfunction

Selected findings

- SC9 significantly reduces mitochondrial fragmentation, oxidative stress, and metabolic collapse by inhibiting Drp1-mediated effects, with improvements in survival and sepsis severity in vivo. This finding highlights SC9's potential as a scalable therapeutic intervention targeting mitochondrial dysfunction and oxidative stress in neurodegenerative diseases.

2.6.2. Protein Aggregation and Neurodegeneration

Selected findings

- Intramitochondrial protein homeostasis significantly regulates the aggregation of α-synuclein and amyloid-β, with increased aggregation observed upon inhibition of mitochondrial proteases and protein import mechanisms, while HtrA2 overexpression reduces aggregation. This finding underscores the therapeutic potential of targeting mitochondrial proteostasis to mitigate protein aggregation in neurodegenerative diseases.

2.6.3. Parkinson's Disease Mechanisms and Models

Selected findings

- Inhibition of c-Abl phosphorylation using STI 571 reduces oxidative stress and enhances PHB2-mediated mitophagy, providing neuroprotection by mitigating dopaminergic neuron loss in Parkinson's disease models. This finding offers a dual-targeted therapeutic strategy to address oxidative stress and mitochondrial dysfunction in neurodegeneration.

2.6.4. Mitophagy and Autophagic Processes

Selected findings

- PRKN mutant neurons exhibit reduced basal mitophagy, elevated ROS levels, ATP deficits, and mitochondrial fragmentation, highlighting severe impairments in mitochondrial dynamics and oxidative phosphorylation. This finding underscores the critical role of mitophagy in neurodegenerative diseases and emphasizes the need for targeted therapeutic strategies to restore mitochondrial function.

2.6.5. Oxidative Stress and Neuroprotection

Selected findings

- Drp1 knockout prevents ferroptosis by preserving mitochondrial integrity, reducing mitochondrial ROS and lipid peroxidation, stabilizing bioenergetics, and maintaining redox homeostasis. This finding highlights Drp1 as a critical therapeutic target for addressing oxidative stress and ferroptosis in neurodegenerative diseases.

2.7. Oxidative Stress Mechanisms and Antioxidant Therapies in Neurodegenerative Diseases

2.7.1. Mechanisms of Oxidative Stress and Neurodegeneration

Selected findings

- PM2.5 exposure induces dose-dependent neurodegeneration-like changes in mice, including cognitive deficits, neuronal loss, and protein aggregation, while Vitamin E administration mitigates these effects by reducing oxidative stress and inflammation. This finding underscores the translational potential of antioxidant therapies in addressing environmental risk factors contributing to neurodegenerative diseases.

2.7.2. Neuroprotective Interventions and Treatments

Selected findings

- The elimination of SSH1 significantly reduced tau pathology by approximately 60% and amyloid-β accumulation by 40%, along with marked decreases in oxidative injury, neuroinflammation, and neurodegeneration (Cazzaro S et al. 2023). This finding underscores the therapeutic potential of targeting SSH1 to modulate oxidative stress and neurodegenerative processes in Alzheimer’s disease and related conditions.

2.7.3. Behavioral and Cognitive Improvements

Selected findings

- Astaxanthin demonstrated significant neuroprotective effects in LPS-induced models by reducing oxidative stress, inflammation, and amyloidogenic proteins, while improving cognitive performance. This finding highlights its potential as a therapeutic candidate for targeting oxidative stress and inflammation in neurodegenerative diseases.

2.8. Mitochondrial Dysfunction and Oxidative Stress: Mechanisms and Therapies in Neurodegenerative Diseases

2.8.1. Mitochondrial Dysfunction and Oxidative Stress in Neurodegeneration

Selected findings

- Manganese exposure significantly worsens mitochondrial dysfunction and exacerbates motor deficits, striatal dopamine depletion, and oxidative stress in a MitoPark mouse model of Parkinson's disease (Langley MR et al. 2018). This finding underscores the

critical role of environmental toxins in accelerating neurodegenerative processes and highlights the need for targeted interventions to mitigate oxidative damage in vulnerable populations.

2.8.2. Neuroprotective Strategies and Therapeutic Interventions

Selected findings

- PTZ administration significantly reduced TH+ neuron loss by ~71%, normalized oxidative stress markers (e.g., SS/SH ratios, 3-NT, 4-HNE), and restored NADH/NAD+ balance in Parkinson's disease models (Tapias V et al. 2019). This finding highlights PTZ's therapeutic potential in addressing oxidative stress and mitochondrial dysfunction, with implications for developing neuroprotective strategies targeting Parkinsonian pathology.

2.8.3. Molecular Pathways and Mechanisms in Parkinson's and Alzheimer's Disease

Selected findings

- DJ-1 missense mutations (D149A and M26I) disrupt mitochondrial homeostasis by altering interactions with DJBP and SUMO-1, leading to mitochondrial fragmentation, dysregulated mitophagy, and increased susceptibility to dopamine toxicity. These mutation-specific mechanisms offer insights into targeted therapies addressing mitochondrial dysfunction in Parkinson's disease.

2.9. Preclinical Strategies for Oxidative Stress and Cellular Dysfunction in Traumatic Brain Injury

2.9.1. Oxidative Stress and Mitochondrial Function

Selected findings

- SS-31 administration significantly improved mitochondrial function and neuroprotection in TBI models by reducing oxidative stress, restoring antioxidant activity, and promoting mitochondrial biogenesis. This finding highlights the potential of SS-31 as a therapeutic agent targeting mitochondrial dysfunction and oxidative stress in neurodegenerative conditions, including TBI.

2.9.2. Neuroprotection and Neurological Recovery

Selected findings

- Mitophagy was shown to promote recovery in TBI models by reducing neuronal apoptosis, lesion volume, and behavioral deficits, with cardiolipin externalization identified as a key mechanism (Chao H et al. 2019). This finding highlights the therapeutic potential of targeting mitochondrial quality control processes to mitigate secondary brain injury and enhance recovery.

2.9.3. Therapeutic Interventions

Selected findings

- EP treatment significantly reduced metabolite alterations following traumatic brain injury (TBI), with only 5 metabolites altered in EP-treated rats compared to over 100 in vehicle-treated controls, highlighting its impact on glutathione metabolism and energy pathways. This finding underscores the potential of EP to modulate oxidative stress and metabolic dysfunction, offering a promising avenue for

neuroprotective strategies in TBI management.

2.9.4. Mechanistic Insights

Selected findings

- Krishnan Muthaiah VP et al. (2025) identified significant modulation of the PARP1-SIRT-NRF2 axis in glial cells post-BOP exposure, with oxidative stress, mitochondrial dysfunction, and proinflammatory responses as key outcomes. This mechanistic insight highlights molecular targets for antioxidant therapy and offers a foundation for developing interventions to mitigate cellular dysfunction in TBI.

2.10. Oxidative Stress and Mitochondrial Dysfunction in ALS: Mechanisms and Therapies

2.10.1. Molecular Mechanisms of Oxidative Stress in ALS

Selected findings

- Post-translational modifications of NGF, including glycation and nitration under oxidative stress, lead to oligomerization that induces motor neuron death via the RAGE/p75NTR signaling pathway (Kim MJ et al. 2018). This finding highlights a novel therapeutic target for disrupting neurotoxic signaling cascades in ALS.

2.10.2. Mitochondrial Dysfunction and Ferroptosis in ALS

Selected findings

- FUS-ALS motor neuron models exhibit heightened vulnerability to ferroptosis due to mitochondrial dysfunction, reduced xCT and FSP1 expression, and increased lipid peroxidation. This finding highlights ferroptosis as a therapeutic target and suggests the potential of inhibitors like deferoxamine and Ru265 to mitigate oxidative damage and improve neuronal survival.

2.10.3. Therapeutic Strategies and Antioxidant Interventions

Selected findings

- α-Tocopherol modulates transcriptional activity, affecting 34 genes in the Classical MAP kinase pathway and 12 genes in the JNK and p38 MAP kinase pathway, enhancing motor neuron survival and reducing oxidative stress-induced damage. This highlights its potential for therapeutic strategies targeting oxidative stress and transcriptional dysregulation in ALS.

2.10.4. Preclinical and Clinical Outcomes in ALS Models

Selected findings

- Overexpression of GPX4 or ferrostatin-1 treatment significantly improved motor function, reduced oxidative stress markers, and maintained phospholipid redox balance in ALS mouse models. These findings suggest promising therapeutic avenues for targeting lipid peroxidation and oxidative damage in ALS pathology.

2.11. Mechanisms and Therapies for Mitigating Oxidative Stress in Neurodegenerative Diseases

2.11.1. Oxidative Stress and Antioxidant Mechanisms

Selected findings

- Graphene oxide quantum dots (GOQDs) significantly reduced ROS levels in zebrafish brains by 90.6%, ameliorated neurotoxicity, and improved locomotive activity by 77%. This finding highlights the potential of nanomaterials in targeting oxidative stress and developing innovative therapies for neurodegenerative diseases.

2.11.2. Neuroprotection in Disease Models

Selected findings

- Nrf2 activation via pharmacological agents such as CDDO-TFEA improves sensorimotor and cognitive functions while reducing brain tissue loss in ischemic stroke models, with benefits abolished in Nrf2 knockout mice. This finding reinforces the central role of Nrf2 in oxidative stress tolerance and highlights its potential as a therapeutic target for neurodegeneration.

2.11.3. Cellular and Molecular Mechanisms of Neuroprotection

Selected findings

- Low ascorbate supplementation increases susceptibility to kainic acid-induced seizures, impairs spatial learning, and accelerates cognitive decline in Alzheimer's disease models by altering glutamatergic gene expression and EEG patterns. This finding underscores the critical interplay between oxidative stress and excitotoxicity, highlighting the potential for antioxidant therapies to mitigate seizure susceptibility and cognitive impairment in neurodegenerative contexts.

2.11.4. Cognitive and Behavioral Improvements

Selected findings

- ERGO treatment in 5XFAD mice led to significant cognitive improvements and a 4- to 5-fold reduction in Aβ aggregation, alongside marked decreases in neuroinflammatory markers and oxidative stress. These findings underscore the potential of targeting oxidative stress and neuroinflammation as therapeutic strategies for Alzheimer's disease and related neurodegenerative conditions.

2.12. Flavonoids as Therapeutic Agents in Neurodegenerative Diseases: Mechanisms and Outcomes

2.12.1. AChE and BChE Inhibition

Selected findings

- The methanol extract of *E. papillosum* demonstrated dose-dependent inhibition of AChE and BChE, alongside significant antioxidant activity, positively correlated with its phenolic content. This finding underscores the therapeutic potential of plant-derived flavonoids in mitigating oxidative stress and cholinesterase-related dysfunctions in neurodegenerative diseases.

2.12.2. Antioxidant Activity and Oxidative Stress

Selected findings

- Quercetin demonstrates dual roles in oxidative stress modulation, enhancing neuronal viability under moderate stress while exacerbating damage under severe conditions through concentration-dependent antioxidant and prooxidant mechanisms. This finding underscores the need for precise dosing strategies in antioxidant therapy to optimize neuroprotection in neurodegenerative diseases.

2.12.3. Neuroprotection and Cognitive Improvement

Selected findings

- Fisetin significantly reduced neuroinflammatory markers, oxidative stress, and apoptotic pathways while enhancing BDNF expression and hippocampal neuronal density in vascular dementia models. This highlights its robust neuroprotective potential and provides a foundation for clinical exploration targeting cognitive deficits and neuronal degeneration.

2.12.4. Therapeutic Interventions in Specific Models

Selected findings

- Quercetin-cinnamic acid amide (quercetin-CA) demonstrated superior neuroprotective efficacy by reducing oxidative stress and reversing cognitive impairments in Alzheimer's Disease mouse models at low doses. This highlights its potential for therapeutic application and improved drug stability in neurodegenerative disease interventions.

2.13. Therapies Targeting Oxidative Stress and Tau Pathology: Mechanisms and Preclinical Insights

Selected findings

- Sodium selenate treatment reversed hippocampal-dependent cognitive impairments and reduced tau aggregation and neuroinflammation in aged 3xTg-AD mice (Van der Jeugd A et al. 2018). This finding highlights sodium selenate as a potential therapeutic agent targeting tau pathology and oxidative stress, with implications for mitigating neurodegenerative processes.

2.14. Antioxidant Strategies for Oxidative Stress in Neurodegenerative Disorders: Mechanisms and Innovations

2.14.1. Oxidative Stress and Mitochondrial Protection

Selected findings

- Melatonin co-treatment significantly mitigates oxidative stress, cognitive impairment, and neurodegeneration induced by high-LET carbon ion irradiation by restoring mitochondrial Complex I activity (~1.6-fold increase, *P < 0.05*) and activating NRF2 and PINK1 signaling pathways. This highlights its potential as a targeted antioxidant therapy for radiation-induced neurodegenerative effects and underscores the importance of mitochondrial protection in antioxidant strategies.

2.14.2. Cognitive and Behavioral Improvements

Selected findings

- Crocin significantly ameliorated memory and behavioral deficits in rats with Aβ1-42-induced neurodegeneration, demonstrating improvements in escape latency, target quadrant time, and hippocampal mitochondrial function, including reductions in reactive oxygen species and lipid peroxidation. These findings highlight crocin's potential as a therapeutic candidate for mitigating oxidative stress and neurodegeneration, warranting further exploration in clinical models of Alzheimer's disease.

2.14.3. Mechanistic Pathways and Cellular Studies

Selected findings

- Melatonin significantly mitigates oxidative stress and neuronal degeneration in traumatic brain injury models by regulating p-AMPK/p-CREB and p-NF-κB signaling pathways. This finding supports melatonin's potential as a therapeutic agent for oxidative stress-related neurodegenerative conditions, emphasizing its role in energy homeostasis and neuroinflammation modulation.

2.14.4. Disease-Specific Neuroprotection

Selected findings

- Siracusa R et al. (2020) demonstrated that Hidrox® significantly mitigates dopaminergic neuron loss, reduces oxidative stress, and modulates neuroinflammation in a rotenone-induced Parkinson's disease mouse model. This highlights the potential of natural antioxidants in addressing multifactorial neurodegenerative mechanisms and supports further translational research into Parkinson’s disease therapies.

2.15. Natural Bioactives for Oxidative Stress and Neuroinflammation in Neurodegenerative Diseases

2.15.1. Neuroinflammation and oxidative stress

Selected findings

- Catechin and procyanidin A2 from LSF significantly reduced pro-inflammatory cytokines (TNF-α, IL-1β, IL-6; $p<0.001$) and apoptosis markers in Aβ(1-42)-induced BV-2 cells (Tang Y et al. 2018). This finding highlights their potential for therapeutic development targeting neuroinflammation and apoptotic pathways in Alzheimer's disease models.

2.15.2. Neuroprotection and memory improvement

Selected findings

- Quercetin treatment reduced neuroinflammation and neurodegeneration in LPS-induced mouse models, while enhancing synaptic protein expression and improving memory performance in behavioral tests. These findings suggest quercetin may serve as a promising candidate for antioxidant therapy targeting neuroinflammatory pathways in neurodegenerative diseases.

2.15.3. Cellular and molecular mechanisms

Selected findings

- HDAC3 inhibition enhanced GLUT4 expression up to eightfold and increased neuronal CREB/ICER content by 245%, while TNF-induced inflammation reduced GLUT4 and neuronal function-related gene expression by ~25%. This suggests that targeting HDAC3 and GLUT4 may provide a novel therapeutic strategy for addressing metabolic and neuroinflammatory dysfunctions in neurodegenerative diseases.

2.16. Oxidative Stress and Mitochondrial Dysfunction in Epilepsy: Experimental Therapeutic Insights

Selected findings

- Upregulation of UCP2 significantly reduced oxidative stress, inhibited apoptosis, and enhanced neuronal survival in pilocarpine-induced epilepsy models, while its silencing exacerbated oxidative damage, inflammation, and neuronal loss. This finding underscores the potential of targeting UCP2 pathways for mitigating mitochondrial dysfunction and oxidative stress in epilepsy, offering a promising avenue for therapeutic intervention.

2.17. Mesenchymal Stem Cell Therapies for Oxidative Stress and Neuroprotection

2.17.1. Oxidative Stress and MSC Mechanisms

Selected findings

- Progressive multiple sclerosis-derived MSCs exhibit reduced secretion and activity of key antioxidant enzymes (SOD1, GSTP1) and diminished expression of antioxidant regulators (Nrf2, PGC-1α), correlating negatively with disease duration and leading to increased susceptibility to nitrosative stress and cellular senescence. This finding underscores the need to address oxidative stress-induced dysfunction in MSCs to improve their therapeutic efficacy in neurodegenerative diseases.

2.17.2. Parkinson's Disease and MSC-Based Therapies

Selected findings

- MSC transplantation in ROT-induced Parkinson's disease rats restored motor function, normalized dopamine levels, reduced oxidative stress and inflammatory markers, and protected the nigrostriatal system (Essawy Essawy A et al. 2024). This finding highlights the therapeutic potential of MSCs in addressing oxidative stress and neuroprotection, with intrastriatal delivery showing slightly superior outcomes compared to intravenous administration.

2.17.3. Neurodegeneration, Retinal and Cognitive Improvements

Selected findings

- The combined therapy of PVA-coated selenium nanoparticles (SeNPs) and mesenchymal stem cell (MSC) transplantation significantly improved cognitive performance and memory reacquisition while enhancing antioxidant capacity and reducing oxidative damage in Alzheimer’s disease models. This synergistic approach highlights a promising avenue for developing combinatorial therapies targeting oxidative stress and neurodegeneration.

2.18. Probucol's Therapeutic Strategies for Oxidative Stress and Neurodegeneration

Selected findings

- Huang JL et al. (2019) demonstrated that probucol significantly alleviated cognitive impairments and hippocampal neuronal loss in a D-galactose-induced aging model by activating the Keap1/Nrf2 pathway and enhancing antioxidant enzyme activities. This highlights its potential as a therapeutic agent for mitigating oxidative stress and cognitive decline in neurodegenerative conditions.

2.19. Targeting Oxidative Damage in ALS: Mechanisms and Therapeutic Advances

Selected findings

- Repeated intramuscular transplantation of hUCB-MSCs significantly improved motor function, delayed disease onset, and reduced oxidative stress in ALS mouse models. This finding supports the potential of stem cell therapy as a scalable approach to mitigate oxidative damage and neuromuscular degeneration in ALS.

2.20. Ferroptosis and Iron Dysregulation in Parkinson's Disease: Mechanistic Therapies

2.20.1. Pathological Mechanisms in Parkinson's Disease

Selected findings

- The study by Agostini F et al. (2023) highlights that ferroptosis exacerbates α-synuclein-induced neurotoxicity in *Drosophila* models, leading to reduced lifespan, dopaminergic neurodegeneration, impaired locomotor function, and enhanced protein aggregation. This finding underscores the therapeutic relevance of ferroptosis inhibitors like NAC and DEF in mitigating α-synuclein-driven neurodegeneration, potentially guiding the development of targeted interventions for Parkinson's disease.

2.20.2. Ferroptosis and Iron Dysregulation in Parkinson's Disease

Selected findings

- Stress-induced ferroptosis mediated by the ALOX15/PEBP1 pathway exacerbates dopaminergic neuron loss and motor impairments in Parkinson's disease models, with pharmacological interventions like ferrostatin-1 and leonurine effectively mitigating these effects. This finding underscores the therapeutic potential of targeting ferroptosis-related oxidative stress to preserve dopaminergic neurons and improve motor outcomes in Parkinson's disease.

2.20.3. Neuroprotective Interventions in Parkinson's Disease Models

Selected findings

- ACSL4 knockdown or inhibition significantly reduces lipid ROS accumulation, protects dopaminergic neurons, and ameliorates motor deficits in MPTP-induced Parkinson's disease models. This finding highlights a promising therapeutic target for mitigating oxidative stress and ferroptosis-related damage in neurodegenerative diseases.

2.21. Antioxidative and Therapeutic Properties of SA-2 in Retinal Ganglion Cell Degeneration

Selected findings

- SA-2 significantly reduced apoptosis, decreased ROS levels, and enhanced RGC survival in in vitro and ex vivo models of retinal degeneration, demonstrating robust antioxidative and neuroprotective effects. These findings suggest SA-2 as a promising candidate for addressing oxidative stress-driven neurodegeneration, warranting further investigation in preclinical and clinical settings.

Table 63. Antioxidative and Therapeutic Properties of SA-2 in Retinal Ganglion Cell Degeneration

2.22. Mitochondrial Oxidative Stress and Amyloid β in Alzheimer's: Mechanisms and Therapies

Selected findings

- The mitochondria-targeted antioxidant SS31 significantly reduces mitochondrial oxidative stress caused by amyloid β plaques and soluble oligomers in APP/PS1 transgenic mice. This finding supports the potential of mitochondria-targeted antioxidants in mitigating oxidative damage in Alzheimer's disease, though their inability to reduce amyloid β plaque burden highlights limitations in addressing the broader pathology.

Table 64. Mitochondrial Oxidative Stress and Amyloid β in Alzheimer's: Mechanisms and Therapies

3.1. Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's: Therapeutic Insights

Selected findings

- Mitochondrial dysfunction, characterized by reduced ATP production, ΔΨm depolarization, and Cytochrome c release, is a central feature of oxidative stress in AD. This highlights the critical need for therapies targeting mitochondrial pathways to mitigate neurodegeneration.

3.2. Therapies Targeting Oxidative Stress in Parkinson's Disease: Mechanisms and Neuroprotection

Selected findings

- Reduction in Reactive Oxygen Species (ROS) levels was consistently observed with treatments like simvastatin and curcumin, demonstrating their efficacy in mitigating oxidative stress. This finding supports the therapeutic strategy of targeting ROS as a central mechanism in neuroprotection for Parkinson's Disease.

3.3. Redox Dysregulation and Mitochondrial Dysfunction: Therapeutic Strategies for Neurodegeneration

Selected findings

- Nox2-derived ROS were identified as key mediators of microglial activation and neuroinflammation, with enzyme inhibition or knockout significantly reducing oxidative stress and inflammatory markers. This finding underscores the therapeutic potential of

targeting Nox2 to mitigate neuroinflammation in neurodegenerative diseases.

3.4. Innovative Therapies for Oxidative Stress in Alzheimer's Disease: Mechanisms and Outcomes

Selected findings

- Recent evidence underscores the dual targeting of Aβ aggregation and oxidative stress by antioxidant therapies, with novel mechanisms like metal ion chelation and nanoparticle-based approaches showing therapeutic promise. This paradigm shift highlights the potential for multi-target strategies to address AD pathology more comprehensively, opening new research avenues for drug development.

3.5. Mitochondrial Dysfunction and Oxidative Stress in Neurodegenerative Diseases: Therapeutic Strategies

Selected findings

- Elevated ROS levels are consistently linked to neuronal damage, particularly in the presence of amyloid-beta (Aβ) peptides, though therapeutic responses to ROS modulation vary. This underscores the need for targeted antioxidant strategies that account for the complexity of ROS-related pathways in neurodegenerative disease progression.

3.6. Therapies Targeting Mitochondrial Dynamics and Oxidative Stress in Neurodegeneration

Selected findings

- Pharmacological activation of mitofusins has been shown to delay ALS progression and improve neuromuscular function, emphasizing the therapeutic potential of enhancing mitochondrial fusion. This finding highlights a promising avenue for developing targeted therapies aimed at restoring mitochondrial dynamics in neurodegenerative diseases.

3.7. Oxidative Stress Mechanisms and Antioxidant Therapies in Neurodegenerative Diseases

Selected findings

- Protein carbonyls have emerged as a critical biomarker of oxidative damage, with studies linking their accumulation to cellular dysfunction and broader oxidative stress mechanisms in neurodegenerative diseases. This finding enhances the potential for protein carbonyls to serve as reliable indicators of oxidative stress severity, advancing biomarker development and enabling more precise therapeutic targeting.

3.8. Mitochondrial Dysfunction and Oxidative Stress: Mechanisms and Therapies in Neurodegenerative Diseases

Selected findings

- ΔΨm depolarization is a hallmark of mitochondrial dysfunction in neurodegenerative diseases, with antioxidant treatments demonstrating efficacy in mitigating this effect under oxidative stress. This finding underscores the therapeutic potential of targeting ΔΨm to restore mitochondrial function, although discrepancies in ΔΨm changes across studies highlight the need for standardized protocols to enhance reproducibility.

3.9. Preclinical Strategies for Oxidative Stress and Cellular Dysfunction in Traumatic Brain Injury

Selected findings

- Targeted antioxidants such as SS-31 and TPP-D-NAC significantly reduced mitochondrial ROS levels and improved mitochondrial function in preclinical TBI models. This underscores the therapeutic potential of mitochondrial-targeted antioxidants in addressing oxidative stress and neurodegeneration.

3.10. Oxidative Stress and Mitochondrial Dysfunction in ALS: Mechanisms and Therapies

Selected findings

- Conventional antioxidant therapies have shown limited efficacy in counteracting lipid peroxidation, whereas targeted approaches like GPX4 overexpression have demonstrated success in preserving motor neuron viability. This highlights the need for precision-targeted therapeutic strategies that address specific oxidative damage pathways in ALS.

3.11. Mechanisms and Therapies for Mitigating Oxidative Stress in Neurodegenerative Diseases

Selected findings

- Reactive Oxygen Species (ROS) levels play a pivotal role in neurodegenerative disease pathology, with interventions like GOQDs demonstrating significant reductions in oxidative stress across multiple models. This finding underscores the therapeutic potential of targeted antioxidant therapies and provides a foundation for developing ROS-modulating drugs for neurodegenerative conditions.

3.12. Flavonoids as Therapeutic Agents in Neurodegenerative Diseases: Mechanisms and Outcomes

Selected findings

- Flavonoids, such as quercetin and apigenin, exhibit consistent β-amyloid inhibitory effects, reducing aggregation associated with Alzheimer's disease pathology. This finding strengthens their therapeutic potential in neurodegenerative diseases and highlights the need for controlled clinical trials to confirm efficacy in human-relevant models.

3.13. Therapies Targeting Oxidative Stress and Tau Pathology: Mechanisms and Preclinical Insights

Selected findings

- Reactive oxygen species (ROS) production is exacerbated by tau aggregation and tau-metal ion interactions, contributing to neurodegeneration through NADPH oxidase and mitochondrial dysfunction. Antioxidant therapies targeting ROS, such as SG-Tang and vitamin K2, show promise in mitigating oxidative stress, although their clinical applicability requires further validation.

3.14. Antioxidant Strategies for Oxidative Stress in Neurodegenerative Disorders: Mechanisms and Innovations

Selected findings

- Antioxidants such as melatonin, crocin, and EUK-134 consistently demonstrated efficacy in reducing ROS levels and lipid peroxidation markers like MDA in neurodegenerative models. These findings highlight their potential to mitigate oxidative damage, a central feature of neurodegenerative diseases, and inform the development of targeted antioxidant therapies.

3.15. Natural Bioactives for Oxidative Stress and Neuroinflammation in Neurodegenerative Diseases

Selected findings

- Natural bioactives, including catechin and resveratrol, consistently suppress TNF-α and ROS levels by modulating NF-κB and MAPK signaling, reducing apoptosis and oxidative stress. This finding strengthens the evidence for targeting TNF-α as a key inflammatory mediator in antioxidant therapy for neurodegenerative diseases.

3.16. Oxidative Stress and Mitochondrial Dysfunction in Epilepsy: Experimental Therapeutic Insights

Selected findings

- Reactive Oxygen Species (ROS) levels are consistently elevated in pathological conditions, and interventions like NAC have demonstrated efficacy in reducing ROS, highlighting the therapeutic potential of antioxidants. However, the dual role of ROS as both a damaging agent and a signaling molecule necessitates nuanced approaches in antioxidant therapy, particularly in neurodegenerative diseases.

3.17. Mesenchymal Stem Cell Therapies for Oxidative Stress and Neuroprotection

Selected findings

- Mesenchymal stem cell (MSC) therapies significantly reduce reactive oxygen species (ROS) levels in multiple neurodegenerative models, while also illustrating ROS's dual role as both a therapeutic target and pathological driver. This finding advances our understanding of oxidative stress modulation and opens new avenues for precision-targeted MSC therapies in neurodegenerative diseases.

3.18. Probucol’s Therapeutic Strategies for Oxidative Stress and Neurodegeneration

Selected findings

- Probucol activates the Keap1/Nrf2 pathway, increasing antioxidant enzyme activity and reducing ROS and MDA levels in pathological models of oxidative stress. This finding underscores the potential for antioxidant therapies targeting oxidative stress pathways in neurodegenerative diseases.

3.19. Targeting Oxidative Damage in ALS: Mechanisms and Therapeutic Advances

Selected findings

- NRF2/ARE signaling pathways in ALS models show activation of protective genes like HO-1 and NQO1 but fail to fully counteract oxidative damage. This finding challenges the adequacy of targeting NRF2 alone and may redirect research toward combination strategies that address oxidative stress comprehensively.

3.20. Ferroptosis and Iron Dysregulation in Parkinson's Disease: Mechanistic Therapies

Selected findings

- Iron dysregulation exacerbates α-synuclein aggregation and dopaminergic neurodegeneration in PD models. Targeting iron metabolism may offer a direct approach to reducing oxidative stress and preventing protein aggregation-related neurotoxicity.

3.21. Antioxidative and Therapeutic Properties of SA-2 in Retinal Ganglion Cell Degeneration

Selected findings

- SA-2 significantly reduces ROS levels and apoptosis in oxidative stress-induced models, with reductions of 51.1% in TBHP-induced ROS and 99.99% in apoptosis, demonstrating robust antioxidative effects. This finding provides strong evidence for SA-2 as a potential therapeutic agent targeting oxidative stress, a key driver in neurodegenerative diseases.

3.22. Mitochondrial Oxidative Stress and Amyloid β in Alzheimer's: Mechanisms and Therapies

Selected findings

- Mitochondria-targeted antioxidant SS31 significantly reduces ROS levels and alleviates neurotoxic effects caused by Aβ, but it does not influence Aβ plaque burden. This finding underscores the therapeutic potential of targeting mitochondrial oxidative stress while highlighting the need for complementary approaches to address plaque pathology and long-term disease progression.

4.1. Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's: Therapeutic Insights

4.2. Therapies Targeting Oxidative Stress in Parkinson's Disease: Mechanisms and Neuroprotection

4.3. Innovative Therapies for Oxidative Stress in Alzheimer's Disease: Mechanisms and Outcomes

4.4. Mitochondrial Dysfunction and Oxidative Stress in Neurodegenerative Diseases: Therapeutic Strategies

4.5. Therapies Targeting Mitochondrial Dynamics and Oxidative Stress in Neurodegeneration

4.6. Oxidative Stress Mechanisms and Antioxidant Therapies in Neurodegenerative Diseases

4.7. Mitochondrial Dysfunction and Oxidative Stress: Mechanisms and Therapies in Neurodegenerative Diseases

4.8. Preclinical Strategies for Oxidative Stress and Cellular Dysfunction in Traumatic Brain Injury

4.9. Oxidative Stress and Mitochondrial Dysfunction in ALS: Mechanisms and Therapies

4.10. Mechanisms and Therapies for Mitigating Oxidative Stress in Neurodegenerative Diseases

4.11. Flavonoids as Therapeutic Agents in Neurodegenerative Diseases: Mechanisms and Outcomes

4.12. Therapies Targeting Oxidative Stress and Tau Pathology: Mechanisms and Preclinical Insights

4.13. Antioxidant Strategies for Oxidative Stress in Neurodegenerative Disorders: Mechanisms and Innovations

4.14. Natural Bioactives for Oxidative Stress and Neuroinflammation in Neurodegenerative Diseases

4.15. Oxidative Stress and Mitochondrial Dysfunction in Epilepsy: Experimental Therapeutic Insights

4.16. Mesenchymal Stem Cell Therapies for Oxidative Stress and Neuroprotection

4.17. Probucol’s Therapeutic Strategies for Oxidative Stress and Neurodegeneration

4.18. Targeting Oxidative Damage in ALS: Mechanisms and Therapeutic Advances

4.19. Ferroptosis and Iron Dysregulation in Parkinson’s Disease: Mechanistic Therapies

4.20. Antioxidative and Therapeutic Properties of SA-2 in Retinal Ganglion Cell Degeneration

4.21. Mitochondrial Oxidative Stress and Amyloid β in Alzheimer’s: Mechanisms and Therapies

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Annex 1: Methods

1.1 Approach

The search strategy was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [1]. The systematic literature review was automatically generated on demand using the Synthory.AI service. All components listed below were identified, extracted, assessed, and analyzed automatically as part of the review process. The review was created for research purposes.

1.2 Criteria of Inclusion and Exclusion

Inclusion criteria

- Publications available in PubMed and PubMed Central™.
- Publications related to neurodegenerative diseases, targeting, antioxidant therapy, oxidative stress, limitations, promise, and associated aspects.
- Primary research studies, including randomized controlled trials, cohort studies, and qualitative research.

Exclusion criteria

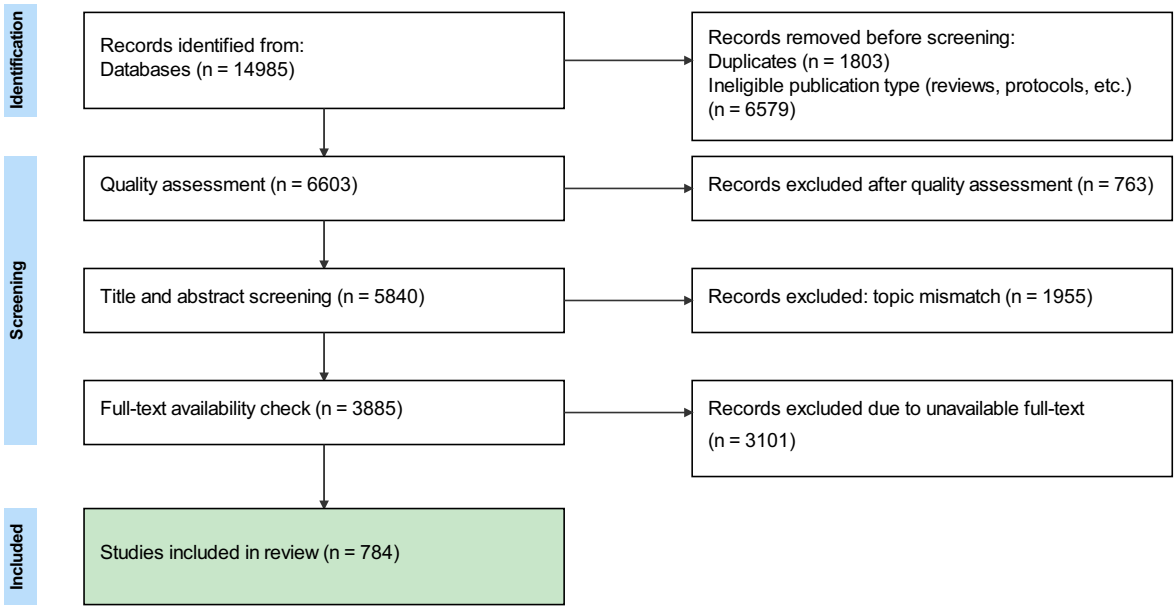
- Articles published before 2018/01.
- Systematic literature reviews, case series, case reports, expert opinions, study protocols, and any unidentified study types.
- Studies without full-text availability in PubMed or PubMed Central™.
- Articles that have been previously included and analyzed in existing reviews within the defined focus areas, to avoid duplication and ensure the inclusion of novel research findings.

1.3 Search Strategy and Screening Process

The topic of the request was 'Targeting Oxidative Stress in Neurodegenerative Diseases: Promise and Limitations of Antioxidant Therapy'. The search employed 70 keywords. The search was conducted across the PubMed and PubMed Central™ databases, covering the publication period from 2018/01 to 2025/03.

1. Identification: 14985 records were retrieved from PubMed using the inclusion criteria.
2. Screening:
   a. Articles were excluded based on the criteria.
   b. Articles of low quality risk were excluded following an Article Quality Assessment.
3. Eligibility: Assessment of alignment with defined topics.

Figure 1. PRISMA 2020 Flow Diagram



A total of 784 articles were included in the final review, based on the inclusion and exclusion criteria.

- Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's: Therapeutic Insights – 79
- Therapies Targeting Oxidative Stress in Parkinson's Disease: Mechanisms and Neuroprotection – 64

- Redox Dysregulation and Mitochondrial Dysfunction: Therapeutic Strategies for Neurodegeneration – 4
- Innovative Therapies for Oxidative Stress in Alzheimer's Disease: Mechanisms and Outcomes – 86
- Mitochondrial Dysfunction and Oxidative Stress in Neurodegenerative Diseases: Therapeutic Strategies – 44
- Therapies Targeting Mitochondrial Dynamics and Oxidative Stress in Neurodegeneration – 18
- Oxidative Stress Mechanisms and Antioxidant Therapies in Neurodegenerative Diseases – 59
- Mitochondrial Dysfunction and Oxidative Stress: Mechanisms and Therapies in Neurodegenerative Diseases – 114
- Preclinical Strategies for Oxidative Stress and Cellular Dysfunction in Traumatic Brain Injury – 24
- Oxidative Stress and Mitochondrial Dysfunction in ALS: Mechanisms and Therapies – 37
- Mechanisms and Therapies for Mitigating Oxidative Stress in Neurodegenerative Diseases – 77
- Flavonoids as Therapeutic Agents in Neurodegenerative Diseases: Mechanisms and Outcomes – 42
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- Antioxidant Strategies for Oxidative Stress in Neurodegenerative Disorders: Mechanisms and Innovations – 46
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- Oxidative Stress and Mitochondrial Dysfunction in Epilepsy: Experimental Therapeutic Insights – 15
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- Targeting Oxidative Damage in ALS: Mechanisms and Therapeutic Advances – 6
- Ferroptosis and Iron Dysregulation in Parkinson's Disease: Mechanistic Therapies – 22
- Antioxidative and Therapeutic Properties of SA-2 in Retinal Ganglion Cell Degeneration – 1
- Mitochondrial Oxidative Stress and Amyloid β in Alzheimer's: Mechanisms and Therapies – 1

1.4 Data extraction

Key study characteristics were extracted from the included articles. A predefined data extraction table was used to document details such as study design and key findings.

1.5 Quality Assessment

The quality of the included articles was assessed as follows:

1. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of non-randomized and cohort studies [2].
2. The risk of bias assessment was used for randomized trials [3].

1.6 Analysis

The analysis proceeded in three phases:

- Phase 1: Identification of potential topics.
- Phase 2: Data extraction from relevant articles.
- Phase 3: Analysis of the relevance of new findings.

A hybrid generative and causal method was employed for data analysis and review generation, with OpenAI™ serving as the generative component. This method combines generative modeling with causal analysis, enhancing both the reliability and interpretability of the outcomes by accounting for underlying cause-effect relationships.

The approach facilitated the integration of various evidence types into a coherent summary. The review process included summarizing and interpreting findings, as well as discussing the limitations identified in the included articles.

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Annex 2: Table 1. Mitochondrial Dysfunction and Oxidative Stress

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome	Secondary outcome
Jiang S et al. (2018)		Mfn2 cKO mice, ages 4 to 78 weeks, total 18 participants	Age-matched mice without Cre+ expression, total 18 participants	Knockout of neuronal Mfn2 in hippocampus and cortex using CAMKII promoter	Genetic engineering of transgenic mice, CAMKII promoter for neuronal Mfn2 knockout, constitutive expression study across ages 4–78 weeks, standard housing conditions, approved protocol by Case Western Reserve University IACUC board	Progression of neurodegeneration via mitochondrial morphological changes, leading to severe neuronal death in the hippocampus and cortex	Oxidative stress response, inflammatory changes, loss of MAP2 in dendrites, hippocampal size reduction, cortical size reduction, mitochondrial oxygen consumption rate changes
Quintanilla RA et al. (2020)	72 hours	Hippocampal neuronal cultures from Sprague–Dawley rats at embryonic day 18		Transfection of neuronal cells with tau constructs tagged with GFP	Transfection using Lipofectamine 2000 diluted in OptiMEM, tau constructs include GFP-full-length tau and GFP-cleaved tau, media changed 24 h post-transfection, analysis conducted 48 h post-transfection for CN1.4 cells and 15 days in vitro for hippocampal neurons, GFP plasmid expression verified with live-cell imaging, transfection efficiency observed at 40% for CN1.4 cells and 8% for hippocampal neurons	Mitochondrial fragmentation, reduced Opa1 expression, decreased number of moving mitochondria, mitochondrial accumulation in soma, bioenergetic deficits (depolarization, oxidative stress, reduced ATP production), reduced TRAK2 expression	Role of mitochondrial protein adaptors (TRAK2, RhoT1/T2, syntaphilin) and motor proteins (kinesin 1, dynein) in mitochondrial transport failure
Silva DF et al. (2020)	6, 24, 48 hours	Neurons from embryonic days 15–16 C57BL/6 mice and human neuroblastoma SH-SY5Y cells		Treatment of cultured neurons and SH-SY5Y cells with BMAA, LPS, CCCP, and FDU	Cultured neurons treated in vitro, compounds added to culture medium, poly-l-lysine-coated dishes used, Neurobasal medium supplemented with B-27, fetal bovine serum, penicillin, and streptomycin used, medium refreshed before treatment, BMAA applied for 6, 24, or 48 hours, LPS and CCCP applied for 48 hours, FDU applied the day after seeding, cultures maintained at 37°C in a humidified atmosphere of 5% CO2 and 95% air	Reduced O2 consumption rates and glycolytic rates in isolated mitochondria and primary cortical cultures, indicating mitochondrial dysfunction	Increased TLR expression, NF-κB nuclear translocation, NLRP3 and pro-IL-1β expression, elevated caspase-1 activity, higher IL-1β levels, increased Tau phosphorylation, elevated Aβ peptide production

Liou CW et al. (2021)		Patients diagnosed with Alzheimer's Disease, average age 76.4 years, total 600 participants	Newly diagnosed AD patients with no history of medication	Cholinesterase inhibitor therapy using donepezil, rivastigmine, galantamine	Administered as medication therapy, duration of use recorded for each medication type, patients divided into subgroups based on medication usage and type	Higher oxidative TBARS, lower antioxidative thiols, and lower mitochondrial DNA copy number observed in Alzheimer's Disease patients compared to controls	Associations between APOE4 allele and oxidative stress biomarkers and mtDNA copy number, potential benefits of cholinesterase inhibitor therapy in attenuating oxidative stress and manipulating mtDNA copy number
Reid DM et al. (2022)		Aging subjects diagnosed with AD, MCI, or normal cognition, total 560 participants		Annual standardized assessments	Conducted at one of five original participating sites, included medical evaluation, neuropsychological testing, interview, blood draw, conducted annually	Higher mtDNA 8oxoG mutational load in Mexican Americans compared to non-Hispanic whites, with differential impact on MA females, identification of mtDNA haplotypes conferring increased oxidative damage risk	Relationship between 8oxoG variant count and cognition, sex, age, education, diabetes, identification of oxidative hotspots in at least 25 participants
Joshi AU et al. (2019)	12 weeks	Male ALDH2*2/*2 knock-in mice of C57BL/6 N background, AD patient-derived fibroblasts screened for ALDH2*2 mutation, primary neuron and astrocyte cultures derived from ALDH2*2/*2 mice	8–10-week-old mice, vehicle-alone group	Administration of Alda-1 dissolved in vehicle using osmotic pumps, ethanol challenge via intraperitoneal injection	Alda-1 dissolved in 50% PEG-400 and 50% DMSO, delivered subcutaneously using Alzet osmotic pumps (#1004) at 10 mg/kg/day, pumps replaced every 4 weeks for up to 12 weeks, ethanol administered intraperitoneally at 1 g/kg/day (20% v/v in normal saline) for 11 weeks, pumps surgically implanted under general anesthesia with wounds closed using metal clips removed after 10–14 days, consistent cell culture conditions including poly-D-lysine-coated plates, Neurobasal medium, DMEM/F12, fetal bovine serum, and CO2-controlled humidified chambers	Increased mitochondrial dysfunction, oxidative stress, and aldehydic load in fibroblasts of AD patients with ALDH2*2 mutation or ApoE ε4 allele, exacerbated by ethanol exposure	Elevated amyloid-β levels, increased neuroinflammation in ALDH2*2/*2 mice, contribution of ethanol-derived acetaldehyde metabolism to AD pathology

Misrani A et al. (2021)	1 hour	APP/PS1 double transgenic mice derived from the B6C3-Tg (APPswe, PSEN1dE9) 85Dbo/J strain, both male and female, aged 1 to 18 months	WT littermate mice	Use of Drp1 inhibitor Mdivi-1 to test prevention of neuronal functional alterations	Brain slices incubated with Mdivi-1 or DMSO for 1 hour, Mdivi-1 prepared as 10 mM stock and diluted to 10 µmol/L with DMSO before use, continuous perfusion of DMSO or Mdivi-1-containing aCSF during recording	Abnormal mitochondrial dynamics identified as a biomarker of early-stage AD, correlating with social deficits and neuronal functional alterations	Testing of Mdivi-1 for prevention of neuronal functional alterations, improvement in mitochondrial function
Han J et al. (2021)	5 days	Seven-month-old PS1M146V knock-in male mice, seven and twelve-month-old 3xTg-AD mice, three AD patients from the University of Kentucky Alzheimer's Disease Center	Wild-type littermates of PS1M146V knock-in mice and 3xTg-AD mice, age-matched human control subjects	Use of genetically engineered H4 glioblastoma cell lines inducibly expressing wild-type PS1 or PS1 mutants	Cultured in DMEM supplemented with 10% fetal bovine serum, 50 µg/ml Zeocin, and 2.5 µg/ml Blasticidin, treated with 100 ng/ml tetracycline for 5 days to induce PS1 expression, passaged and plated on Nunc Lab-Tek Chambered coverglass 24 h before imaging	Deleterious effects of five familial Alzheimer's disease-linked presenilin-1 mutations on mitochondrial functions, including fragmentation, increased MAMs formation, ROS production, impaired enzymatic activities, compromised membrane potential, and reduced ATP levels	Upregulation of Atlastin 2 expression levels, rescue of abnormally elevated ER-mitochondria interactions, increased ATL2 expression in AD brains
Park MW et al. (2021)	24-48 hours	Donors with Alzheimer's disease, brain tissues from The Netherlands Brain Bank	Four normal brain tissue donors, geographic location Minneapolis, MN, USA	Overexpression of human NOX4 in cultured human astrocytes through transduction with pCMV6-AC-GFP constructs	Human astrocytes cultured in Gibco™ Astrocyte Medium with N-2 Supplement, DMEM, FBS, penicillin, and streptomycin, transduced with pCMV6-AC-GFP constructs or pCMV6-AC-GFP vector, plated on XF96 microplates, mitochondrial function and ATP production assays conducted using Seahorse XF96e bioanalyzer with XF Mito Stress Test Kit and XF Real-Time ATP Rate Assay Kit, incubation duration 24 h or 48 h, manufacturer's instructions followed for assays	Elevation of NOX4 promotes ferroptosis in astrocytes by oxidative stress-induced lipid peroxidation through mitochondrial dysfunction in Alzheimer's disease	Increased mitochondrial ROS production, mitochondrial fragmentation, inhibition of antioxidant processes, ferroptosis-dependent cytotoxicity

Peng W et al. (2024)		Synchronized L4 *C. elegans* worms, exposed to 35 μM iron		Exposure of synchronized L4 worms to iron (0 or 35 μM)	Delivered by transferring synchronized L4 worms individually to seeded plates every 24 h, grown on HB101 with iron for 3 days, swimming rate assessed after acclimatization period of 30 s, worms exposed to 1.25 μM BODIPY 581/591 C11 for 60 min before imaging, anesthetized on 2% agarose pad with 0.1% tetramisole	Iron-induced ferroptosis drives oxidative damage, energetic imbalance, and neuronal dysfunction in Alzheimer's disease-like pathologies	DMT1 knockout abolishes neuronal Aβ-associated pathologies by reducing iron uptake, suppressing phenotypic measures of Aβ toxicity
Crivelli SM et al. (2024)	3 months, 7 months	Mice aged 3 and 7 months, balanced for sex, studied in a laboratory setting in Lexington, Kentucky, genotype WT and 5xFAD		Isolation and functional assessment of non-synaptic and synaptic mitochondria from mouse brain cortices	Brain cortices homogenized using Potter-Elvehjem homogenizer, centrifugation and Ficoll gradient used for mitochondria isolation, nitrogen cell disruptor applied for synaptic mitochondria rupture, functional assessment conducted with Seahorse XFe96 Extracellular Flux Analyzer, Seahorse Standard XFe96 assay plates used for loading mitochondria	Abnormal sphingolipid metabolism contributes to mitochondrial dysfunction, evidenced by diminished oxygen consumption, altered oxidative phosphorylation proteins, increased ceramides in 5xFAD mice, and elevated sphingosine levels in 5xFAD mice and AD patients	Dysregulation of sphingolipid composition in mitochondria occurs early in AD pathogenesis, with age-related accumulation of long-chain ceramides in 5xFAD mice
Samluk L et al. (2022)	24 h, 48 h, 68 h, 72 h	HEK293T wild-type and NDUFA11 knockout cells, SH-SY5Y cells differentiated	Untreated HEK293T and SH-SY5Y cells	Treatment with rotenone, ISRIB, salubrinal, guanabenz, sephin1, NAC, MitoQ, antimycin A, okadaic acid, differentiation with retinoic acid, transfection with plasmids encoding Tau protein variants	Treatments applied to HEK293T and SH-SY5Y cells in culture dishes, differentiation for 72 h in RA-containing medium, transfection with GeneJuice Transfection Reagent following 15 min DNA incubation, treatments applied for 24 h, 48 h, or 68 h as indicated, plasmids encoding Tau protein variants transfected for 72 h	Induction of Tau dimerization as an early step in protein aggregation caused by long-term mitochondrial stress	Partial reversal of Tau dimerization by ISR activation, reduction of ROS and Tau dimerization by ROS scavengers
Mussalo L et al. (2024)	24-h, 72-h	Individuals diagnosed with Alzheimer's disease, biopsies obtained at Kuopio University Hospital, Finland	Vehicle-treated cells with 10% v/v sterile DMSO in sterile water	Exposure of OM cells to three different UFPs	UFPs prepared in sterile DMSO and water, particles sonicated in ultrasonic water bath for 30 min, exposure delivered in culture medium, cells cultured in DMEM/F-12 with 10% FBS and 1% penicillin-streptomycin, incubated at 37 °C and 5% CO2, exposure duration of 24-h or 72-h, protocol for UFP preparation referenced from previous studies	Impairment of mitochondrial functions, hampered oxidative phosphorylation, disturbed redox balance, and increased oxidative stress in primary human OM cells	AD-related alterations in OM cells, differential effects of fuels and engine technologies

Yu H et al. (2018)	5 days	Male triple transgenic AD mice harboring human mutations APPSwe, PS1M146V, TauP301L	Wild-type mice from the same genetic background	Training in water maze to locate submerged platform, memory evaluation after training	Placed in one of four quadrants facing pool wall, submerged platform hidden 2 cm below water surface, guided to platform if not found within 60 s, kept on platform for 30 s, training conducted for 5 consecutive days, memory evaluation performed 6 days post-training, platform removed during memory test, mice allowed to swim for 120 s	Perturbations in hippocampal mitochondrial energy metabolism-related proteins, especially nuclear-encoded OXPHOS proteins, correlated with cognitive deficits in a murine AD model	Behavioral impairments in spatial learning and memory, potential biomarkers identified (respiratory chain-related proteins and DYN1)
Epremyan KK et al. (2023)	1 hour	Yarrowia lipolytica Po1f cells, genetically modified with plasmid constructs		Preincubation with SkQThy, transfection of cells by electroporation, mitochondria staining with MitoTracker Red CmxRos	Preincubation with 250 nM SkQThy for 1 hour, SkQThy consisting of triphenylphosphonium linked via a C10 aliphatic chain to thymoquinone, transfection by electroporation, mitochondria staining with 200 nM MitoTracker Red CmxRos for 30 minutes in 50 mM PBS at pH 5.5	Mitochondrial dysfunction caused by Aβ42 expression, indicated by loose coupling of respiration and phosphorylation, decreased ATP production, increased hydrogen peroxide formation, elevated ROS production, and cell death	Mitigation of Aβ42-induced effects by low concentrations of SkQThy, mitochondrial fragmentation suggested as a biomarker for the earliest preclinical stage of AD
Vaillant-Beuchot L et al. (2021)	1 month	5-month-old female 3xTgAD mice treated with γ-secretase inhibitor	Vehicle-treated 5-month-old 3xTgAD and WT female mice, placebo control group	Treatment with γ-secretase inhibitor (ELND006), β-secretase inhibitor, deferiprone (DFP), CCCP, induction of C99 expression with doxycycline	γ-secretase inhibitor administered by oral gavage daily for 1 month (30 mg/kg), cells treated with ELND006 (5 μM for 20 h), β-secretase inhibitor (30 μM for 20 h), deferiprone (1 mM for 20 h), CCCP (1 μM for 6 h), C99 expression induced with doxycycline (10 μg/ml for 48 h), animals sacrificed 6 h after the last administration	APP-CTFs accumulation triggers mitochondrial morphology alterations, increased reactive oxygen species production, and mitophagy failure	Validation of mitochondrial dysfunction and mitophagy failure in vivo in 3xTgAD mice and human post-mortem AD brains, correlation of APP-CTFs accumulation with Alzheimer's pathology
Smirnov D et al. (2023)		Brain-specific SIRT6-KO mice, genetically modified		RNA extraction from brain hemispheres, mitochondrial mass measurement using staining and flow cytometry, protein analysis via western blotting	RNA extracted using NucleoSpin RNA Plus kit and RNeasy MinElute Cleanup Kit, cells stained with MitoTracker Green, viability dye, TMRE, and MitoSOX™, flow cytometry performed using CytoFLEX S Flow Cytometer, proteins separated on Tris-Glycine polyacrylamide gel and blotted to nitrocellulose membranes, incubation with primary antibodies overnight, chemiluminescence reagent used for blot development	Mitochondrial dysfunction in SIRT6-deficient brains, including reduced mitochondrial gene expression, increased ROS production, reduced mitochondrial number, impaired membrane potential, and partial rescue by restoring SIRT3 and SIRT4 levels	Association of reduced SIRT6 levels with neurodegenerative diseases, metabolomic changes in TCA cycle byproducts

Ryan KC et al. (2021)	1 day (rapamycin, doxycycline, bortezomib), approximately 3 days (metformin)	*C. elegans* nematodes, synchronized by bleaching gravid worms, analyzed as Day 1 adults	Equivalent DMSO on control plates	RNAi feeding with HT115 bacteria expressing lgg-1 or bec-1 dsRNA, drug treatments with rapamycin, doxycycline, bortezomib, and metformin	RNAi delivered by feeding as per Timmons & Fire (1998), HT115 bacteria expressing lgg-1 or bec-1 dsRNA verified by PCR and DNA sequencing, RNAi specificity confirmed by GFP::lgg-1 reduction, drug treatments delivered to L4 animals on treated plates overnight, metformin added to agar plates with heat-killed OP50 bacteria, L1 animals grown on metformin or control plates until day 1 of adulthood	Hyperactivation of mTORC1 caused by elevated mitochondrial calcium influx exacerbates proteostasis and neurodegenerative defects in SEL-12 mutants, with improvements requiring autophagy induction	Reduction in proteostasis defects and neurodegenerative phenotypes with mTORC1 inhibition, changes in positive response rates, body bend counts, polyQ aggregate counts, fluorescence intensity, oxygen consumption rate
Donner L et al. (2021)	3 days, 24 hours, 90 minutes, 1 hour, 15 minutes, 4 hours	Healthy volunteers, ages 18 to 50 years	Solvent control (0.0015% EtOH)	Platelet stimulation with synthetic Aβ40, Aβ16, antimycin A, thrombin, Vitamin C, and collagen-related peptide (CRP)	Platelets isolated from human/murine sources, incubated with Aβ40 (various concentrations) and other agents in DMEM medium, incubation at 37 °C (5% CO2 or room temperature), pre-incubation with fluorescent dyes (MitoSOX™ Red, TMRM, MitoTracker™ green FM) in the dark, stimulation with thrombin, CRP, or Aβ40 for specific durations (15 min, 30 min, 1 h, 2 h, 4 h), platelets seeded in Cell-Tak coated XFe96 microplates for adhesion, centrifugation at 143×g and 213×g for 1 min each, Seahorse XF DMEM medium used for resuspension, incubation in non-CO2 incubator at 37 °C for 30 min	Mitochondrial dysfunction in platelets contributes to enhanced Aβ aggregate formation in Alzheimer's disease	Increased ROS and superoxide production, reduced mitochondrial membrane potential and oxygen consumption rate, enhanced integrin αIIbβ3 activation via GPVI-mediated ROS production

Back to 2.1.1. Mitochondrial Dysfunction and Oxidative Stress

Annex 3: Table 2. Therapeutic Interventions

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome	Secor
Gao C et al. (2018)	30 min preincubation, unspecified duration of NaN3 treatment	Rat pheochromocytoma PC12 cells	Control cultures maintained in DMEM under normoxic conditions	Preincubation of PC12 cells with NaHS prior to NaN3 treatment	NaHS dissolved in saline, freshly prepared immediately prior to use, stock solutions directly added to bath solution to achieve final concentration, preincubation for 30 min prior to NaN3 treatment, maintained throughout the experiment	Neuroprotective effect of H2S against NaN3-induced neurotoxicity, demonstrated by improved cell viability	Suppr produ attenu apopt mitoch memb increa peroxi levels) caspa expres
Joshi AU et al. (2018)	3 months	5XFAD transgenic mice		Administration of P110-TAT47–57 or related peptides	Delivered via Alzet osmotic pumps for animals at 3 mg/Kg/day, pumps implanted every 28 days until 6 months of age, SH5YSY cells treated with P110, vehicle, or inactive analog at 1 μM for 24 hours with or without Aβ42, N2a cells treated with P110 at 1 μM daily in serum-free media, patient-derived fibroblasts treated with TAT or P110-TAT peptides at 1 μM daily	Improvement in behavioral deficits, reduction in Aβ accumulation, energetic failure, and oxidative stress in the AD mouse model (5XFAD) through P110 treatment	
Sarasija S et al. (2018)	3 days	Synchronized L1 larvae, glp-1(e2141) mutants and wild-type counterparts		Exposure to mitoTEMPO, TPP, doxycycline, Compound E, FUDR, RNAi bacteria	Animals moved to NGM plates containing specific compounds or seeded with bacteria, gravid adults bleached and progeny moved as eggs, synchronized L1 larvae grown on unseeded or seeded NGM plates, L4 stage animals sterilized with FUDR, RNAi bacteria carrying empty vector or drp-1 RNAi used for experiments	Rescue of mitochondrial metabolic defects and prevention of neurodegeneration in sel-12 mutants	Reduc Ca2+ mitoch uptake superc produ into m linking mutati mitoch dysfur

Zhao C et al. (2019)	24 hours, 25 hours	One-day-old male C57BL/6 mice	No treatment control group	Treatment of neurons with berberine and oligomeric Aβ1-42	Neurons treated in vitro, preincubation with berberine (0.1, 0.3, or 1μM) for 1 hour, addition of oligomeric Aβ1-42 (0.5μM) for 24 hours, poly-D-lysine precoated plates used, MTT assay and other biochemical assays performed to evaluate viability, mitochondrial function, ROS, and axonal mitochondrial dynamics	Preservation of mitochondrial function and axonal mitochondrial dynamics in hippocampal neurons under Aβ-induced stress	Impro viabilit Aβ-inc cytoto
Stefanova NA et al. (2019)	6 months	Male OXYS rats	Wistar rats	Daily oral administration of SkQ1	SkQ1 supplement added to dried bread slices, delivered daily, dosage of 250 nmol/kg body weight	Reduction in AD-like pathology markers, including neuronal loss, synaptic damage, amyloid-β 1-42 protein levels, and tau hyperphosphorylation, alongside a twofold decrease in differentially expressed genes in OXYS rats.	Altere expres mitoch functi and sy immur cerebr syster degra apopt activit pathwa intrac proce
Reddy PH et al. (2018)	6 hrs	N2a mouse neuroblastoma cells, transfected with mutant AβPP cDNA, treated with SS31 peptide and Mdivi1	Untreated N2a cells	Treatment of N2a cells with SS31, Mdivi1, and their combination (SS31+Mdivi1)	SS31 peptide at 0.25 nM, Mdivi1 at 20 μM, delivered to mutant AβPP cDNA-transfected N2a cells, single 6-hour treatment, concentrations optimized via serial dilutions, 4 independent cell cultures and transfections (n=4)	Synergistic protective effects of SS31+Mdivi1 on mitochondrial function, Aβ levels, and cell survival in mutant AβPP cells	Reduc mitoch dysfur in GTI activit mtDN
Jayatunga DPW et al. (2021)	24 hours pre-treatment, 16 hours exposure	Human neuroblastoma BE(2)-M17 cells		Pre-treatment with compound combination D5L5U5 and individual compounds, followed by treatment with oligomeric Aβ1–42	Pre-treatment duration: 24 h, exposure duration: 16 h, BE(2)-M17 cells seeded at 1 × 10^6 cells per T25 flask, grown for 24 h prior to intervention, concentrations selected based on previous studies, appropriate Aβ1–42–treated and vehicle-treated controls included	Inhibition of Aβ1-42-induced toxicity through mitochondrial protection, including minimizing oxidative stress, increasing ATP levels, and inducing mitophagy and mitobiogenesis	Poten of D5I preve for Alz Disea further vivo ir

Ho CL et al. (2022)	48 hours	SH-SY5Y human neuroblastoma cell line		Incubation of cells with quercetin (QE) and exposure to H2O2	QE at 0, 2.5, 5, 7.5, 10 μM, H2O2 at 40 μM, sirtinol at 50 μM, QE incubation for 24 hours followed by 24-hour H2O2 incubation, sirtinol pre-treatment for 1 hour before QE exposure, experiments conducted at 80% cell confluence	Reduction in amyloid beta (Aβ) accumulation via stimulation of mitochondrial biogenesis-related proteins (SIRT1, PGC-1α, TFAM), protection against oxidative stress in SH-SY5Y cells	Reduc oxyge (ROS) apopt amylo protei enzym expre ADAM
Villavicencio-Tejo F et al. (2022)	24 hours	Conditionally immortalized cortical neurons (CN1.4), transiently transfected with plasmids		Treatment with 10 μm SFN	Cells transiently transfected with GFP, GFP-T4, and GFP-T4C3 plasmids, treated with 10 μm SFN, duration of treatment 24 hours	Prevention of mitochondrial dysfunction and oxidative damage by SFN treatment in Alzheimer's disease models	Reduc levels, mitoch abnor increa of Nrf antiox
He Z et al. (2023)	8 weeks	Female 8-month-old 3 × Tg-AD mice	Wild-type (WT) mice, female, 8-month-old	Intraperitoneal administration of luteolin	Administered via intraperitoneal injections for 8 consecutive weeks, neuron treatments with luteolin (2.5 and 5 μM) or Aβ (10 μM) for 24 hours, behavioral tests conducted post-treatment with 3-day intervals between tests	Amelioration of memory and cognitive impairment in 3 × Tg-AD mice, inhibition of Aβ generation, repair of mitochondrial damage	Reduc apopt oxidat PPAR mecha
Zhang Q et al. (2024)	6 months, 30 days	Male C57BL/6 mice, aged 4 months, body weight 22–26 g, treated with LPs or LIG-LPs	Male C57BL/6 mice, aged 4 months, body weight 22–26 g, no treatment control group	Intraperitoneal injection of LPs or LIG-LPs at doses of 10 mg/kg and 30 mg/kg	Delivered via intraperitoneal injection, administered daily for 6 months or 30 days depending on group, random assignment to groups, housed individually in cages with corncob bedding and paper, behavioral testing conducted during the intervention	Reduction of oxidative stress, β-amyloid (Aβ) deposition, and cognitive impairment in APP/PS1 mice	Prese hippoc mitoch structu of mit fissior upregu PKA/A signali allevia mitoch dysfur

Cai J et al. (2025)	4 weeks	Male 5×FAD mice with a C57BL/6 background, five- and six-month-old, genetically modified for Alzheimer's disease	Culture medium with DMSO	Aerobic exercise on a treadmill, CD38 silencing using siRNA mixture injection	Treadmill inclined at 10 degrees, initial adaptation period of 2 days at speeds of 8 m/min and 10 m/min for 30 min each, daily training speed increased from 10 m/min to 13 m/min over 20-min intervals, total exercise duration of 90 min/day with 1-min breaks every 5 min, bilateral hippocampal catheter implantation for siRNA delivery, 2-μL siRNA mixture injected every 3 days using Elite Fect-I siRNA In vivo Transfection Kit	Improvement in mitochondrial quality in astrocytes and neurons, reduction in oxidative stress, β-amyloid plaque deposition, and cognitive dysfunction in 5×FAD mice through aerobic exercise	Role c astroc mitoch transf CD38 exerci increa oxyge genera atroph ATP l cognit discri
Massaro M et al. (2025)	24 hours	SH-SY5Y cells, subline of SK-N-SH neuroblastoma cell line, used in neurodegenerative studies involving Alzheimer's Disease	Non-treated SH-SY5Y cells	Treatment with 2 μM Aβ1-42, mRNA transfection using Lipofectamine™ Messengermax™	Cells seeded and treated with resuspended Aβ1-42, mRNA transfected using Lipofectamine™ Messengermax™ at 1 μg/ml in 2 % FBS for 24 h, stained with MitoTracker™ Deep Red FM for 15 min, washed with PBS, fixed with 4 % PFA, analyzed using Seahorse XFe96 Analyzer	Improvement of mitochondrial function, evidenced by increased mitochondrial mass, enhanced oxidative phosphorylation, increased ATP production, reduced oxidative stress, and decreased neuronal death and neurite disruption	Balanc mitoch dynam fissior preser mitoch memb

Yang L et al. (2022)b	16 months	Two-month-old male TgF344-AD and wild-type Fischer 344 rats	Sham laser treatment control group	Non-contact transcranial photobiomodulation (PBM) treatment using 808 nm continuous-wave low-level laser	Performed on shaved scalp, animals restrained in transparent plastic cone, eyes covered with aluminum foil, laser tip placed 35 cm from scalp to generate 1.5 cm² laser spot, irradiance on scalp 350 mW/cm² (fluence 42 J/cm²), irradiance on cortex 25 mW/cm² (fluence 3 J/cm²), administered 2 minutes/session, 3 times/week (Monday, Wednesday, Friday), for 16 months, procedure aligned with prior studies	Improvement in cognitive dysfunction in Alzheimer's disease rats	Reduc loss, a plaque hyperp neuron degen damag loss
Amarsanaa K et al. (2021)	48 hours	Primary cortical neurons prepared from cerebral cortices of 1-day-old Sprague Dawley rats		Treatment of isolated mitochondria with nobiletin and other mitochondrial reagents	Primary cortical neurons prepared from neonatal SD rats, mitochondria isolated from rat brain cortices, mitochondria incubated in mitochondrial assay buffer at 37°C, treated with nobiletin and reagents (ADP, oligomycin, FCCP, rotenone, antimycin A), OCR measured using Seahorse XF-24 extracellular flux analyzer, reagents added sequentially per manufacturer protocol	Reduction in mitochondrial ROS, inhibition of apoptotic signaling, enhancement of ATP production, restoration of neuronal viability under CI inhibition	Downr AIF tra upregu activit expres antiox Nrf2 a
Qu Y et al. (2021)	28 days	APP/PS1 double transgenic male mice, 8 months old, 45–50 g, 30 participants	APP/PS1 mice, 15 participants, no treatment control group	Intraperitoneal injection of DCBEI (160 mg/kg and 320 mg/kg), saline injection	Random assignment to groups, delivered via intraperitoneal injection, DCBEI solution and saline used, daily administration for 28 days, euthanization post-experiment using 1.5% pentobarbital solution	Reduction in L-Glu-dependent neuroexcitation toxicity, maintenance of mitochondrial function, attenuation of AD-like behaviors in APP/PS1 mice	Reduc apopt expres in anti- protei reduct neurof depos in pho

Du F et al. (2021)b	8 days	Male and female transgenic mice, age 19–24 months	mPitrm1 mice with an inactive mutant PITRM1, male and female mice, age 19–24 months	Increasing neuronal PITRM1 activity/expression in aged PITRM1/Aβ-producing Alzheimer's Disease mice	Overexpression of neuronal PITRM1 achieved via Thy-1 promoter, transgenic and double transgenic mice models used, Morris Water Maze training conducted for 7 consecutive days with 4 trials per day followed by a probe trial on day 8, investigators blinded to genotype, experiments performed under IACUC approval and NIH guidelines	Restoration of mitochondrial respiration, suppression of reactive oxygen species, improvement in synaptic function, reduction in synapse loss in advanced-age AD mouse models	Failure loss to mitoch synap neces activit clearа protec mitoch synap
Banerjee TD et al. (2021)	72 hours, 48 hours, 24 hours	Primary cortical neurons prepared from E17 wild-type C57BL/6 mice, 32 million cells plated	Primary cortical neurons transfected with non-targeting control siRNA	Transfection of primary cortical neurons with plasmids or siRNAs, treatment with β amyloid (Aβ42) and estrogen	Transfection using Lipofectamine at 0.07% concentration, plasmids (0.75µg/well) or siRNAs (20–30 pmols/well) delivered on LabTekII slides, treatment with estrogen (30nM for 48 hours) and Aβ42 (10µM for 24 hours), fixed with 4% PFA, blocked with 1% goat serum, permeabilized with PBS containing 0.1% Triton X-100, immunostaining for GFP and cleaved caspase-3 using rabbit-anti GFP (1:500) and mouse anti-caspase 3 (1:1000), imaging performed at 25°C using EVOS-FL microscope	Reversal of neurodegeneration and mitochondrial fragmentation in neurons through restoration of D-AKAP1/PKA signaling	Reduc retract in apo phosp Drp1 r protec

Li Y et al. (2020)	24 h, 4 h + 24 h, 72 h	SK-N-SH cells, human-derived neuroblastoma cell line		Treatment of cells with PL171 and/or Aβ42O	PL171 and Aβ42O at indicated concentrations, pretreatment with PL171 for 4 h followed by Aβ42O for 24 h, Aβ42O treatment for 72 h, staining with DCFH-DA for 30 min, incubation in nonbuffered bicarbonate-free DMEM with glucose, glutamax, and sodium pyruvate for 45 min, SA-β-gal staining following manufacturer's guidelines	Rescue of Aβ42O-induced oxidative stress, mitochondrial dysfunction, and cell senescence via upregulation of SIRT3	Upreg SIRT3 suppre mitoch acetyl of neu senes
Stojakovic A et al. (2021)	14 months	Mice selected based on age and genotype	Female transgenic APP/PS1 and non-transgenic littermates, 16–21 per group	CP2 treatment through drinking water or oral gavage	Administered in drinking water (0.1% PEG) ad lib or via oral gavage (20% PEG 400 and 5% dextrose water in PEG), concentration adjusted weekly based on weight and water consumption, oral gavage applied at 0, 4, 24, 48, and 72 hours, glucose uptake measured using FDG-PET	Neuroprotective effects in APP/PS1 mice, including improved energy homeostasis, synaptic activity, cognitive function, proteostasis, and reduced oxidative stress and inflammation	Valida therap using NMR, and al mouse transc pathw
Elmazoglu Z et al. (2020)	6 h pretreatment, 48 h glucose, 24 h amyloid beta-peptide	Primary hippocampal neurons isolated from embryonic day 18–19 (E18-E19) Wistar albino rat fetuses		Treatment with cannabinoid agents, glucose, and amyloid beta-peptide	Increased concentrations of cannabinoids (10–1000 μM) administered to cultured neurons, pretreatment with cannabinoids for 6 hours, co-treatment with 150 mM glucose for 48 hours, amyloid beta-peptide (500 nM) added after 24 hours of glucose exposure for 24 hours, sequential treatment maintained for consistency	Neuroprotective effects of cannabinoid agents against GLU + Aβ1-42-induced toxicity, preserving cell viability, mitochondrial membrane potential, and reducing oxidative stress, inflammation, and related damage	Differe of can agents showi effica recruit antiox and N regula

Lee HJ et al. (2021)	8 weeks, 3 days	Nine-week-old male CrljOri:CD1(ICR) mice, streptozotocin (STZ)-induced diabetic models	Placebo control group, citrate buffer (0.05 M) and 0.5 mM NaOH administered	Daily intraperitoneal injections of urolithin A	Urolithin A dissolved in 0.5 mM NaOH, delivered via intraperitoneal injections, daily for 8 weeks, randomized controlled trial with single-blind design, housed under controlled specific pathogen-free conditions (22 °C, 70% relative humidity, 12 h light:dark cycle), monitored twice daily	Alleviation of high glucose-induced mitochondrial calcium influx, mtROS accumulation, amyloid beta (Aβ) production, Tau phosphorylation, and cognitive impairment in a diabetes mellitus-associated Alzheimer's disease model	Reduc depen forma of IP3 interac preve neuro degen
Jara C et al. (2020)	3 weeks	18-month-old tau-knockout (tau−/−) mice, both male and female	WT C57BL/6J mice, active control group with sham injection	Bilateral intrahippocampal administration of Lenti ORF particles (GFP-tagged)-mouse peptidylprolyl isomerase D via stereotaxic injection	Anesthetized with isoflurane, placed in stereotaxic frame, boreholes made above hippocampal CA1 (coordinates: 2.46 mm anterior to bregma, 1.0 mm lateral, 1.5 mm relative to dura mater), 1 µl lentiviral vector (108TU/ml) injected per site	Prevention of cognitive impairment and improvement of mitochondrial function in aged tau−/− mice, evidenced by reduced oxidative damage, increased ATP production, and reduced mPTP opening	Role c mitoch perme calciu effect overe mitoch and m
Chen C et al. (2021)	12 weeks	3xTg-AD mice, 8 months of age, expressing mutant PS1M146V, APPswe, and tauP301L transgenes	3xTg-AD mice, no treatment control group	Treatment with Se-Met in drinking water, incubation with Se-Met for primary neurons	6 µg/ml Se-Met in drinking water, provided ad libitum, duration of 12 weeks, primary neurons incubated with 10 µM Se-Met for 24 hours	Improvement in mitochondrial function, including increased mitochondrial count, enhanced membrane potential, reduced ROS levels, decreased apoptosis, and improved mitochondrial energy metabolism in AD models	Increa NRF1 compl and c activit levels Drp1, SELE
Yang L et al. (2022)	8 months	Male TgF344-AD rats, 2 months old, genetically engineered with Alzheimer's disease traits	Male WT rats, no treatment control group	Treadmill exercise training	Adaptive training stage with progressive intensity and duration, treadmill used for delivery, constant intensity at 18 m/min for 45 min during exercise training stage, performed three times a week	Alleviation of learning and memory dysfunction, reduction in anxious-depressive-like behaviors in AD rats	Attenu amylo reduct hyperp preser densit and pr vesicl neuro apopt degen

Cheng D et al. (2021)b	24 hours	HT22 mouse hippocampal neuronal cells exposed to Aβ25-35 and H2O2 to mimic Alzheimer's disease		Pretreatment and co-culture of HT22 cells with ECS, Aβ25–35, and H2O2	HT22 cells seeded at 5×10^3 cells/well in 96-well plates, ECS applied at 20–800 μg/mL for 2 hours, co-cultured with Aβ25–35 and H2O2 for 22 hours, cells fixed in 2.5% glutaraldehyde at 4°C overnight, stained with Fluo-4-AM at 2.5 μM for 30 minutes in darkness, washed with PBS and DPBS three times	Protective effects of ECS on mitochondrial function and dynamics in AD models	
Esselun C et al. (2021)b	24 hours	PC12APPsw cells with Swedish double mutation of human AβPP	DMSO solvent control, cyclosporin A	SIL exposure to cells	Incubation with SIL or DMSO control, SNP incubation for nitrosative stress assessment, R123 fluorescence dye incubation, washing with HBSS buffer, centrifugation, storage at −80 °C, thawing and heating before assay, 24-well and 96-well plates, Greiner flasks, incubation durations of 48 hours pre-treatment and 24 hours SIL exposure	Protective effects of SIL on mitochondrial function, rescuing ATP levels, reducing ROS, improving basal ATP levels	No ef mitoch respira reduce conce

Lam AB et al. (2021)		C. elegans, wild-type Bristol N2 and eat-2(ad465) and pek-1 mutants		Dietary shifts with B12 supplementation or deprivation, temperature upshift to 25°C	Animals grown on nutrient-supplemented NGM plates, transferred at late L4 stage to plates with or without B12, plates supplemented with glucose, fatty acids, methylcobalamin, methionine, choline chloride, and homocysteine, supplements added to autoclaved media at 55°C, plates stored at 4°C and covered with foil for fatty acids, animals shifted to 25°C for 24 hours, paralysis assays conducted every 2 hours post-upshift	Delay in Aβ-induced paralysis through alleviation of mitochondrial fragmentation, bioenergetic defects, and oxidative stress, mediated via the methionine/S-adenosylmethionine (SAMe) cycle	Impro mitoch functi ATP p oxidat mitiga therap applic B12 fo
Ikram M et al. (2021)	6 weeks	Male C57BL/6N mice, average age 10 weeks, 32 participants	Saline injected mice	Cycloastragenol administration at a dose of 20 mg/kg/day	Administered orally using curved dosing cannula, 20–25 gauge × 1.5 inches cannula, daily for 6 weeks	Reduction in oxidative stress, enhancement of neurogenic markers (BDNF, p-TrKB), mitigation of apoptosis and memory dysfunction in Aβ-injected mice co-treated with Cycloastragenol	Downr MAP I p-P38 impro water perfor (reduc increa crossi time ir quadra
Vijayan M et al. (2022)		VDAC1+/−/TAU double mutant mice	TAU mice with human Tau P301L mutation	Partial reduction of VDAC1 protein through genetic crossbreeding	Achieved through genetic crossbreeding of VDAC1+/- and TAU mice, mice bred and housed under a standard 12-hour light–dark cycle, protocols approved by TTUHSC-IACUC	Reduction of behavioral impairments and mitochondrial/synaptic toxicities in symptomatic-transgenic TAU mice through partial reduction of VDAC1	Increa autoph synap levels, dendri reduce numbe mitoch
Vegh C et al. (2019)	18 months	Male double transgenic APP/PS-1 mice, model for Alzheimer's disease, University of Windsor, Canada	Water supplemented with PTS carrier or regular drinking water	Ubisol-Q10 supplementation in drinking water at a concentration of 200µg/mL	Delivered through drinking water, fresh water provided weekly, PSAF grown in medium supplemented with Ubisol-Q10 or PTS carrier, Ubisol-Q10 withdrawn during 48-hour period for autophagy inhibition experiments	Activation of autophagy by Ubisol-Q10 treatment evidenced by increased expression of autophagy-related genes beclin-1 and JNK1 in AD fibroblasts and transgenic AD mice	Reduc oxidat preve prema senes mutat requir contin Q10 s to mai and pr senes pheno

nar R et al. (2023)	24 h, 30 min, 24 h + 30 min, 24 h + 2 h	Newborn C57BL/6j black mice, aged 1–3 days, obtained from Burdur Mehmet Akif University, Turkey	Neurons in cell culture conditions without treatments	Treatments with Aβ, ACA, and GSH	Incubation of neurons with Aβ (20 μM for 24 h), ACA (25 μM for 30 min), GSH (10 mM for 2 h), cultured in DMEM medium with low glucose, use of T25 and T75 flasks, sterile conditions maintained, additional experiments with 2/APB (100 μM)	Reduction in oxidative neurotoxicity and apoptosis in hippocampal neurons caused by Aβ through GSH and TRPM2 antagonist treatments	Decre apopt hippo death, Zn2+, ROS, caspa peroxi cytos ACA, and P. inhibit
Yin Z et al. (2022)	1 month	Six-month-old male APP/PS1 mice with C57BL/6 background	WT mice, no treatment control group	Rhein administration to APP/PS1 mice via intravenous injection	Rhein (20 mg/kg body weight) for APP/PS1+rhein group, PBS for WT and APP/PS1 groups, delivered via intravenous injection, every two days for one month, behavior tests during third week, therapeutic evaluation after one month	Amelioration of cognitive impairment in APP/PS1 mice	Reduc burde neuroi revers stress neuro oxidat assoc apopt of mit biogen SIRT1 pathw superc activit ROS, mitoch mitoch inhibiti produ electr chain
Pahrudin Arrozi A et al. (2021)	24 hours	SH-SY5Y cells stably transfected with wild-type and variants of the APP gene		Tocopherol treatment using isomers at working concentrations	Isomers incubated overnight with FBS at 37°C, diluted sequentially with CCM and ethanol to prepare stock solutions (0.1 M, 0.025 M, 0.005 M, 0.004 M, and 0.00025 M), working concentrations prepared from respective stock solutions, final concentrations of ethanol and FBS maintained at 0.1% and 0.027%	Modulation of mitochondrial oxidative metabolism in APP-overexpressing cells, including increased respiratory capacity, enhanced membrane potential, and elevated complex IV enzyme activity	

Khatoon R et al. (2022)		Two-days-old male flies expressing human Aβ42 in the brain		Minocycline administration via food	Mixed into conventional Drosophila feed with agar, maize, sugar, and yeast, supplemented with additional yeast suspensions, fresh protectant solutions prepared daily in maize meals, administered daily, three replicates conducted for each treatment and control	Alleviation of Alzheimer's disease-related symptoms, including lifespan decline, locomotion deficit, memory loss, impaired mitochondrial membrane potential, and increased apoptotic protein expression, by minocycline in transgenic flies	Impro mitoch functi apopt expre JNK, impro chang AchE
Dieter F et al. (2022)		SH-SY5Y-APP695 neuroblastoma cells transfected with amyloid-precursor protein 695, used as a model for early Alzheimer's disease	Vector-transfected SH-SY5Y-MOCK cells, ethanol solvent control group	Incubation with aminolevulinic acid (ALA) in various concentrations, ethanol as control, rotenone exposure	Seeded into 24-well plates (MMP assay) or 96-well plates (ATP assay), incubated in reduced DMEM medium (2% FBS), ALA or ethanol exposure for 24 hours, rotenone exposure 1 hour after ALA or ethanol treatment, standardized rotenone concentration (25 µM)	Improvement in mitochondrial function, evidenced by increased ATP production, enhanced mitochondrial membrane potential, and respiratory chain complex activities	Reduc oxyge
Piccirillo S et al. (2022)	24 hours, 16 hours	Cortical neurons isolated from the cortex of Wistar rat pups (P2–P4)	No interventions or treatments	Exposure to 10 µM all-trans retinoic acid (RA) for neuronal differentiation, glyceraldehyde (GA) treatment to induce AD-like phenotype, addition of Ret (30 µM), XE-991 (300 nM–10 µM), and ICA-27243 (30 µM) to culture medium	RA delivered via culture medium for 6 days, GA exposure for 24 hours, XE-991 pretreatment for 1 hour followed by GA exposure for 16 hours, compounds added directly to culture medium, cells cultured in polystyrene dishes in humidified incubator at 37 °C and 5% CO2, medium renewed every 48 h or twice a week	Neuroprotective action of XE-991 through the resumption of superoxide dismutase (SOD) activity compromised during GA challenge	Reduc Ca2+ decre mitoch produ modul AMPK pathw mitoch memb (ΔΨm intrac conte amylo hyper tau pr levels

de Veij Mestdagh CF et al. (2022)	~12 weeks	Male APP/PS1 mice, 3 months ± 2 weeks of age, bred locally at Amsterdam Animal Research Center (AARC)	Placebo control group	Feeding mice with SUL-138 containing food pellets to achieve 30 mg/kg/day oral dose	Food pellets sprayed with SUL-138 dissolved in ethanol and diluted with water, final ethanol concentration of 0.015%, vehicle food prepared with ethanol-water solution without SUL-138, delivered ad libitum based on weight and food intake	SUL-138-induced improvements in synaptic plasticity, hippocampal memory, and long-term potentiation	Reduc amylo rescue dysreg mitoch expres protei acid m glycol acid m pathw
Kim S et al. (2023)		Male 5XFAD mice with AD-related pathogenesis, 3.5 months old	Vehicle-treated 5XFAD mice	Administration of NFP	NFP dissolved in saline, administered intragastrically, daily for 3 weeks, dose of 100 mg/kg	Therapeutic mechanisms of NFP associated with synaptic- and mitochondrial-related pathways, 111 proteins significantly affected, flux changes in mitochondrial carnitine shuttle and beta-oxidation pathways observed	
Babylon L et al. (2023)	24 hours	Human SH-SY5Y-APP695 cells, model of early Alzheimer's disease		Incubation of cells with a cocktail containing hesperetin, magnesium orotate, folic acid, caffeine, cafestol, and kahweol	Mixture of hesperetin 10 µM, magnesium orotate 200 µM, folic acid 10 µM, caffeine 50 µM, cafestol 1 µM, kahweol 1 µM, delivered via incubation	Improvement in mitochondrial function evidenced by increased endogenous mitochondrial respiration and ATP levels	Reduc levels, and py
Preziuso A et al. (2023)	6 days	SH-SY5Y cell line derived from human neuroblastoma, exposed to 10 µM all-trans retinoic acid for 6 days		Induction of differentiation using all-trans retinoic acid, siRNA-mediated silencing, treatment with GA and SN6	RA exposure for 6 days, siRNA incubation for 48 hours with transfection reagents, GA treatment for 24 hours, SN6 treatment for 24 hours, sequential protocol involving RA differentiation followed by silencing and compound treatments	NCX3 silencing ameliorated cell viability, increased intracellular ATP production, reduced oxidative damage, prevented Aβ and pTau enhancement, normalized NCX reverse-mode activity	Impro increa mitoch reduce restor Ca2+
Yang X et al. (2023)	7 days	Healthy male C57BL/6 mice, weight 25–30 g, AD model mice constructed by microinjection of Aβ1−42	Sham group receiving an equal dose of saline, placebo control group	Mitochondria injection through caudal vein	Mitochondria at dose of 3 × 10^6/0.2 mL, delivered via caudal vein injection, administered continuously for 4 days	Improvement in cognitive ability of AD model mice assessed by reduced escaping time and increased time spent in the target quadrant in the Morris water maze test	Activa autopl in ROS elimin damag mitoch protei BDNF phosp levels

Park J et al. (2024)	30 minutes	HT-22 cells derived from HT-4 cells, immortalized from primary mouse hippocampal neuronal culture		Pretreatment with BAPTA-AM and NAC, incubation with STZ	Cells maintained at 37 °C in DMEM with high glucose supplemented with 10% FBS, 100 U/ml penicillin, and 100 µg/ml streptomycin, incubated in a humidified atmosphere with 5% CO2, pretreatment with BAPTA-AM (0.5 µM) and NAC (5 mM) for 30 minutes, incubation with STZ (10 mM)	Protection against STZ-induced AD-like pathology, including neuronal apoptosis, synaptic loss, tau phosphorylation, and mitochondrial dysfunction	Suppr intrace accum inhibiti Ca2+/ media mitoch dysfur regula phosp mitoch
Rezaee N et al. (2025)	72 hours	Human neuroblastoma BE (2)-M17 cells, treated with sorghum extracts (750 µg/mL, 1000 µg/mL, 2000 µg/mL) and 10 µM Aβ, seeded at 105 cells/well	Cells treated with treatment media (DMEM/F12 supplemented with 1% (v/v) FBS) and the equivalent amount of DMSO and NPR f12 (without Aβ42, without extracts), negative control group	Application of sorghum extracts and Aβ42 to cell cultures	Cells plated and attached for 24 hours, growth media replaced by treatments, FCCP added for 10 minutes to control wells, TMRE staining performed, treatments incubated for 72 hours, CellTiter Glo reagent added for ATP measurement	Attenuation of beta amyloid-induced phospho-tau levels, total tau levels, and mitochondrial dysfunction in neuronal cells	Reduc mitoch memb (Δψm in ATF
Cui D et al. (2024)	1 month	4- and 7-month-old 5xFAD male mice, simulating early and middle stages of Alzheimer's Disease in a specific pathogen-free facility	Placebo control group	AAV injection into the hippocampus, intraperitoneal administration of XMU-MP-1, pre-treatment with PI3K-Akt pathway activator and inhibitor, plasmid transfection of SH-SY5Y cells	Stereotaxic injection of AAV using microinjector at 0.2 µL/min, anesthetized with pentobarbital sodium (50 mg/kg), hippocampal injection coordinates based on mouse brain atlas, needle held in place for 5 min, XMU-MP-1 administered intraperitoneally at 1 mg/kg daily for 1 month, PI3K-Akt activator (740 Y-P, 25 µM) and inhibitor (LY294002, 20 µM) pre-treatment for 1 h, plasmid transfection using Lipofectamine™ 3000 following manufacturer's instructions	Reduction in cognitive decline, neuronal degeneration, and mitochondrial dysfunction through MST1 knockdown and inactivation	Regula mitoch transc interac PGC1 of oxi throug ROS p identif MST1 therap Alzhei

Gao QC et al. (2024)	44 days	Male APP/PS1 double transgenic mice, 8 months old, 16 participants	WT and APP/PS1 mice, placebo control group	Givinostat administration via intraperitoneal injection	Givinostat (10 mg/kg) or vehicle, intraperitoneal injection daily, administered for 30 consecutive days prior to behavioral experiments, continued during testing, maintained for 2 additional weeks	Improvement in cognitive behavior and brain pathology in APP/PS1 mouse models treated with Givinostat	Enhan hippoc plastic mitoch memb reduce oxyge increa conter mitoch morph quanti brain g metab improv sponta and ex (open short-t memo improv spatia memo water

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Annex 4: Table 3. Molecular Mechanisms and Biomarkers

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome
Csaban D et al. (2021)		Patients diagnosed with Alzheimer's Disease, 46 participants (5 male and 6 female post-mortem brain tissue analysis; 2 male and 11 female blood samples analyzed by WES-NGS; 6 male and 16 female analyzed by Sanger sequencing)	134 individuals (72 male, 62 female), including 55 healthy and 79 without neurological disorders; 9 post-mortem brain tissues (3 male, 6 female)	Genetic analysis of αKGDHc subunits, post-mortem brain tissue analysis, blood sample sequencing	Brain tissue collected post-mortem within 2–6 h, several brain regions analyzed for rare variants and somatic mutations, DNA isolated from blood samples using QIAamp DNA blood kit, bidirectional Sanger sequencing performed using ABI Prism 3500 DNA Sequencer, DNA library preparation for WES using SureSelect QXT library preparation kit, NGS performed on Illumina HiSeq 2500 system	Association of rare damaging variants in αKGDHc subunit genes, specifically the R263H mutation in the DLD gene, with Alzheimer's Disease
Lee J et al. (2018)b		Human brain samples from individuals with Alzheimer's Disease, donated post-mortem		Therapeutic modulation of SIRT3 activity to address mitochondrial pathology and neurodegeneration in AD	Mouse cortical primary neurons cultured in Neurobasal medium with B-27 and L-glutamine supplements, 293T cells, SH-SY5Y cells, and DOXY-inducible mito-p53 cells cultured in DMEM with fetal bovine serum and penicillin/streptomycin, humidified atmosphere of 5% CO2 at 37°C, immunogold labeling and TEM performed with modified protocols	SIRT3 dysfunction leads to p53-mediated mitochondrial and neuronal damage in Alzheimer's Disease, with SIRT3 overexpression restoring ND2 and ND4 expression and improving mitochondrial oxygen consumption
Li M et al. (2020)	24 hours	Human neuroblastoma SH-SY5Y cells stably transfected with vector carrying APPswe		Orexin-A treatment, with or without SB203580	Delivered to cell cultures, serum-deprived for 24 hours, incubated with CCK-8 for 4 hours, incubated with BrdU for 4 hours, incubated with H2DCFDA for 20 minutes, fixed in 2.5% glutaraldehyde overnight followed by 1-hour osmium fixation, homogenized in lysis buffer on ice and centrifuged at 12,000 rpm for 15 minutes at 4 °C, washed with PBS, harvested, and pooled	Aggravation of cytotoxicity, mitochondrial dysfunction, and activation of the p38 MAPK pathway by Orexin-A in SH-SY5Y cells transfected with APPswe, contributing to Alzheimer's disease pathogenesis
Rojas-Charry L et al. (2020)	16 hours	Murine Neuroblastoma N2a cells stably transfected with pcDNA 3.1 Zeo + vector; PS KO−/− MEFs stably transfected with wildtype or mutated (E280A) human PS1	Cells treated with DMSO or only culture medium	Transfection of Murine Neuroblastoma N2a cells with plasmids, exposure to cellular stress inducers	Plasmids transfected using LipofectamineTM2000, stress inducers dissolved in DMSO and added at defined concentrations, stress inducers included tunicamycin, calcimycin, antimycin, serum starvation, Aβ 1–42 oligomers, incubation for 16 hours, tandem LC3B fluorescent construct transfected using LipofectamineTM2000, cells cultured in DMEM with 10% FBS	Intrinsic cellular vulnerability to stress in PS1 mutants associated with altered autophagic and mitochondrial function independent of Aβ pathology

Pahrudin Arrozi A et al. (2020)		SH-SY5Y cells stably expressing wild-type (WT), Swedish (Swe), or Swedish/Indiana (Swe/Ind) APP gene	Non-transfected SH-SY5Y cells	Treatment of cells with tocopherol isomers (ATF and GTF) at working concentrations of 5, 80, and 100 μM	Prepared in ethanol, incubated overnight with FBS at 37 °C, diluted with CCM and ethanol to achieve final concentrations, delivered in culture media, final ethanol and FBS concentrations of 0.1% and 0.027% maintained, treatment duration of 24 hours	Reduction in Aβ levels, modulation of mitochondrial function, and reduction of apoptosis markers in SH-SY5Y cells expressing wild-type or mutant APP gene
Rao CV et al. (2020)		Sgo1−/+ mice, 15- and 18-month-old, both genders, genetically modified population	Wild-type mice, 12-month-old and 24-month-old, no treatment control group	Study of cerebral amyloid-β accumulation in Sgo1−/+ brain tissue samples	Brain tissues extracted in RIPA buffer with protease inhibitors, processed with SDS and BSA internal standard, immunoblots and immunofluorescence conducted per Rao et al. (2018) protocol, immunohistochemistry performed with SuperPicture 3rd gen IHC kit following manufacturer's protocol	Initial cerebral amyloid-β accumulation in middle-aged Sgo1−/+ mice associated with GSK3 inactivation, Wnt signaling activation, and ARC/Arg3.1 accumulation
Kim SH et al. (2021)	4 days	Participants aged 65–90 years, diagnosed with amnestic MCI or Alzheimer's Disease	Cognitively normal controls	Transfection of miR-1273g-3p mimic, miR-1273g-3p inhibitor, TIMM13 siRNA, plasmids into H4-APPswe and SH-SY5Y cells	Transfected using DharmaFECT 1 reagent and Lipofectamine 3000, plated at densities of 25,000/cm² (H4-APPswe) and 40,000/cm² (SH-SY5Y), maintained in DMEM with supplements (10% FBS, 1x Antibiotic-Antimycotic, geneticin for H4-APPswe), media replaced with Seahorse XF DMEM after 24 h, supplemented with glucose, sodium pyruvate, and Glutamax	Identification of miR-1273g-3p as an AD-associated miRNA elevated in early-stage AD patients, contributing to Aβ production and mitochondrial impairments
Ye L et al. (2024)	48 hours	Female participants, age 79.3 ± 12.3 years with Alzheimer's Disease	Age-matched female healthy controls	Manipulation of AnxA2 and P11 gene expression in SH-SY5Y cells secreting Aβ42	Transfection of pcDNA3.1 plasmids expressing secretable Aβ42, AnxA2, or siRNA targeting AnxA2, medium replaced with Opti-MEM 2 h before transfection, cells transfected for 5 h followed by DMEM medium with 10% FBS and antibiotics, G418 added 24 h post-transfection for positive selection, siRNA diluted to 10 μM combined with Lipofectamine 2000 pre-incubated at room temperature for 15 min, incubation at 37 °C for 4 h, medium replaced with DMEM containing 5% FBS and antibiotics, cells seeded into 96-well plates at 5 × 10^3 cells per well	Identification of AnxA2 as a critical gene in Alzheimer's Disease pathophysiology, influencing mitochondrial function and cellular processes
Shen L et al. (2022)		Male 3×Tg-AD mice, 2-, 4-, and 6-month-old	Male WT mice (strain: B6129SF2/J)	Extraction and separation of subcellular brain components from pooled brain tissues	Pooled brain tissues homogenized in isolation buffer, centrifuged sequentially at 1500×g, 21,000×g, and 31,000×g, fractionated using 24%/40% Percoll gradient, components collected and washed, resuspended in lysis buffer, sonicated 10 times with 10-second pauses, stored at −80°C	Identification of differentially expressed proteins (DEPs) associated with mitochondrial damage, synaptic dysfunction, decreased energy metabolism, and abnormal amino acid metabolism as early events in Alzheimer's disease

Pinto M et al. (2022)	5 days	Female mice, 5 months old, C57Bl/6J genetic background	8-month-old C57Bl/6J females, wild-type (WT)	Intraperitoneal injection of tamoxifen	Prepared by dissolving tamoxifen powder in ethanol and mixing with corn oil to achieve 20 mg/ml concentration, delivered via IP injection, administered once daily for 5 consecutive days	Mitochondrial Complex III dysfunction does not promote amyloid beta accumulation, as evidenced by decreased amyloid plaque number and decreased Aβ42 toxic fragment in CIIIKO-AD mice.
Cazzaro S et al. (2023)b	15 days, 2 months	Hippocampal primary neurons from P0 mouse pups, APP/PS1 mice with Swedish APP and PS1 ΔE9 mutations		Use of rAAV9 viruses for transduction of primary neurons and stereotaxic injection into mouse brains	Transduced to neurons on DIV3, transient transfection using Lipofectamine 2000 and Opti-MEM I media, media replaced 4–6 h post-transfection, neurons cultured until DIV18, cells grown for 48 h post-transfection, recombinant AAV9 viruses generated by co-transfection in HEK293 cells, stereotaxic injection into anesthetized mice with Hamilton syringe and 26-gage needle, injection coordinates specified, mice sacrificed 2 months post-injection	Negative regulation of mitochondrial health and respiration by the N-terminal region of SSH1, impairment of mitophagy by the C-terminal p62-binding domain of SSH1
Lee EG et al. (2023)	24-72 hours	AD patients confirmed postmortem by neuropathological analysis	Untreated cells	Hydrogen peroxide (H2O2) treatment to induce oxidative stress in U87, HMC3, and SH-SY5Y cell lines	H2O2 added at 600 μM (U87), 400 μM (HMC3), 100 μM (SH-SY5Y), incubated for 24 h at 37 °C, 5% CO2, cells seeded at 70–80% density on 6-well or 96-well plates, recovery phases with fresh media for 24 h ("c2") or 48 h ("c3"), MMP assay performed with 2 μM JC-1 dye after washing, 3–6 independent experiments conducted	Upregulation of APOE locus genes and changes in mitochondrial function markers in oxidative stress-induced models and AD postmortem brains
Sangineto M et al. (2023)	3 days, 10 days, 24 hours	6- and 18-month-old male 3xTg-AD mice with 3 mutant human genes	Dulbecco's Phosphate Buffered Saline (PBS)	Dimethyl malonate (DMM) administration as a succinate dehydrogenase (SDH) inhibitor	HMC3 cells treated with DMM (10 mM), LPS (1 μg/mL), TAK-242 (1 μM), PX-478 (10 μM), and Succ (5 mM); LPS exposure for 24 h or 10 days +/- DMM on the last day; DMM intraperitoneally injected into mice at 160 mg/kg daily for 3 days; materials used include reagents from Sigma-Aldrich and Cayman chemical	Modulation of pro-inflammatory cytokine expression (IL-1β, TNF-α), normalization of iNOS/Arg1 ratio, reduction in inflammation, and metabolic rewiring in microglia to prevent Alzheimer's disease onset
Awasthi S et al. (2021)		10-month-old Rlip+/- mice	WT mice, 10-month-old	Behavioral tests including Open Field Test, water maze training, rotating rod test	Acclimation to testing room for 60 min, Open Field Test in dimly lit apparatus (20–30 lux, 44 cm × 44 cm × 30 cm) for 10 min, water maze training in galvanized steel pool (160 cm diameter, 62 cm high, 26 ± 1 °C water, hidden platform 10 cm diameter, 1.5 cm below surface), maximum trial time of 60 s, rotating rod test at 18 RPM for maximum running time of 5 min	Cognitive decline in Rlip+/- mice resembling AD, assessed by behavioral tests and hippocampal function measurements

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