



# Exploring the Mechanisms and Therapeutic Approaches of Mitochondrial Dysfunction in Alzheimer's Disease: An Educational Literature Review

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## Abstract

Alzheimer's disease (AD) presents a significant challenge to global health. It is characterized by progressive cognitive deterioration and increased rates of morbidity and mortality among older adults. Among the various pathophysiologies of AD, mitochondrial dysfunction, encompassing conditions such as increased reactive oxygen production, dysregulated calcium homeostasis, and impaired mitochondrial dynamics, plays a pivotal role. This review comprehensively investigates the mechanisms of mitochondrial dysfunction in AD, focusing on aspects such as glucose metabolism impairment, mitochondrial bioenergetics, calcium signaling, protein tau and amyloid-beta-associated synapse dysfunction, mitophagy, aging, inflammation, mitochondrial DNA, mitochondria-localized microRNAs, genetics, hormones, and the electron transport chain and Krebs cycle. While lecanemab is the only FDA-approved medication to treat AD, we explore various therapeutic modalities for mitigating mitochondrial dysfunction in AD, including antioxidant drugs, antidiabetic agents, acetylcholinesterase inhibitors (FDA-approved to manage symptoms), nutritional supplements, natural products, phenylpropanoids, vaccines, exercise, and other potential treatments.

**Keywords** Mitochondrial Dysfunction · Alzheimer's Disease · Therapeutic Modalities

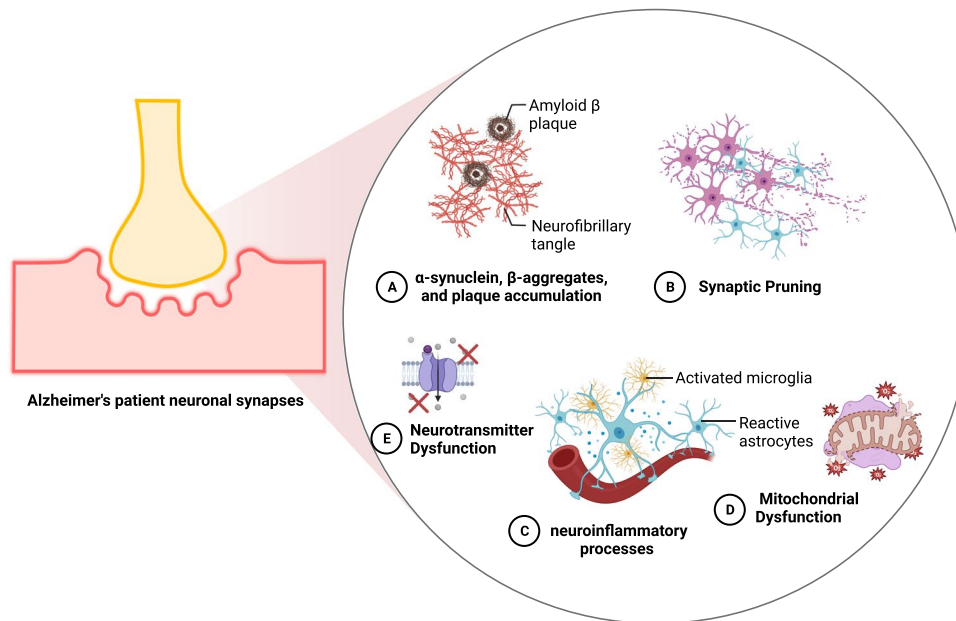
## Introduction

Alzheimer's disease (AD) is the leading cause of dementia and presents a substantial challenge to healthcare systems worldwide [1, 2]. It is distinguished by a gradual deterioration in cognitive function, leading to impairment in daily activities and a rise in morbidity and mortality among older people [1, 2]. FDA-approved AD medications encompass both symptom management and disease treatment. Symptom management drugs include brexpiprazole, donepezil, galantamine, memantine, a combination of memantine and donepezil, and rivastigmine [3]. For disease treatment, lecanemab, a disease-modifying immunotherapy, is used. It treats mild cognitive impairment or mild AD by removing abnormal beta-amyloid to help reduce the number of plaques in the brain [3, 4].

The pathophysiology of AD is complex and involves multiple factors [5–12]. Mitochondria, essential for cellular energy metabolism, can impair neuronal function when dysfunctional [8, 13]. Synapses, the connections between neurons, are critical for communication and signal transmission in the brain. Several mechanisms contribute to synapse dysfunction in AD, including amyloid beta peptide (A $\beta$ ) and tau protein [14], synaptic pruning [15, 16], inflammatory processes [17], mitochondrial dysfunction, and cholinergic signaling, particularly acetylcholinesterase [18–21] (Fig. 1).

Research suggests that mitochondrial dysfunction plays a central role in the progression of AD [22, 23]. This literature review aims to highlight and provide up-to-date information on the mechanism of mitochondrial dysfunction and the therapeutic modalities for mitigating mitochondrial dysfunction in AD.

## Synaptic Mechanisms in Alzheimer's Disease



**Fig. 1** Synaptic mechanisms in Alzheimer's disease (AD). **A** AD is characterized by the accumulation of tau protein tangles and amyloid beta ( $A\beta$ ) plaques in the brain, disrupting synapses' normal functioning. The regular operation of synapses is compromised due to the interference of oligomers with neurotransmitter action. Microtubules, which are essential for maintaining the structure and function of synapses, are adversely affected by tau protein tangles that disrupt their typical structure and function [14]; **B** synaptic pruning is a process through which the brain eliminates redundant or underused synapses. This process is essential for the normal functioning of the brain. However, it may be implicated in AD. In AD, synaptic pruning is excessively activated, leading to a reduction in functional synapses. Consequently, the brain ends up with fewer synapses, which could contribute to the cognitive decline associated with AD [15, 16]; **C** microglia, the brain's immune cells, can become activated due to persistent inflammation. While microglia are necessary for removing  $A\beta$

plaques, they may also contribute to synaptic dysfunction. The pro-inflammatory cytokines secreted by activated microglia can impair synaptic function. Additionally, the activation of astrocytes, another type of brain cell, can release inflammatory substances that exacerbate synaptic dysfunction [17]; **D** the onset of AD has been linked to mitochondrial dysfunction. When mitochondria fail, they produce reactive oxygen compounds that can disrupt proteins, lipids, and DNA. This oxidative stress may play a role in the loss of functional connections, a characteristic feature of AD [13], and **(E)** neurotransmitters are chemical messengers essential for transmitting signals between neurons. AD is characterized by decreased neurotransmitters, such as acetylcholine, which plays a crucial role in memory and learning. The dysfunction of synapses caused by this neurotransmitter deficiency may contribute to the cognitive decline associated with AD [18]

## Mechanism of Mitochondrial Dysfunction in Alzheimer's Disease

### Glucose Metabolism Impairment and AD

Despite accounting for only 2% of body weight, the brain consumes 25% of the body's oxygen and 25% of its glucose. These demonstrated how vulnerable our brains are to energy metabolism abnormalities, to the point that a minor change in energy metabolism is significantly associated with a disturbance in the functioning of the nervous system. Impaired energy metabolism is one of the early and most persistent symptoms of AD [24]. The primary necessary substrate for the adult human brain and its cerebral endothelial cells is glucose [25]. A 55-kDa isoform

of glucose transporter 1 (GLUT1) imports glucose into cerebral endothelial cells [26]. After that, glucose travels through glycolysis, followed by the pentose-phosphate route, lactate fermentation, or mitochondrial metabolism [25].

A growing amount of data points to decreased glucose consumption as an early and persistent characteristic of AD, occurring up to decades before the disease's onset [27–30]. When comparing AD brains (especially the hippocampus and cortex) to individuals without dementia, fluoro-2 deoxyglucose positron-emission tomography (FDG-PET) was used to discover a greater decline in glucose consumption. Furthermore, in the early stages of AD, the posterior cingulate cortex was shown to be the most metabolically damaged of all brain areas [27]. Moreover, people with moderate cognitive decline, a prodromal phase of AD, show glucose

hypometabolism but to a lower extent in terms of quantity or geographic distribution. This suggests low glucose metabolism affected the disease's onset [29]. Apolipoprotein E (ApoE  $\epsilon$ 4) allele is recognized as a risk factor for AD and moderate cognitive decline. Indeed, it is frequently mentioned as the primary genetic factor of AD [31–36]. In their 84-month longitudinal FDG PET investigation, Paranjpe et al. [31] showed that patients with moderate cognitive decline had an ApoE  $\epsilon$ 4-associated brain region-specific glucose metabolism pattern. Decades before dementia may manifest, in their 20 s, young persons with the ApoE  $\epsilon$ 4 gene were found to have glucose hypometabolism in the brain regions that are susceptible to it [37].

Furthermore, in patients with AD, the amount and geography of glucose underutilization reflected the distribution of diminished synaptic function and density in distinct brain areas, coinciding with the severity of symptoms [38, 39]. These days, cerebral glucose hypometabolism is recognized as a characteristic of the illness, and measuring it with FDG-PET is turning it into a biomarker for early AD identification and entirely accurate and sensitive moderate cognitive decline to AD conversion prediction [40, 41].

The relationship between amyloid plaque formation and glucose low metabolism has been examined using amyloid PET biomarkers and FDG PET. Longitudinal A depositions (the predominant type of amyloid) were found in practically every cortical area in carriers of autosomal-dominant AD mutations 15–25 years before the expected age of beginning, which appeared before glucose hypometabolism in specific cortical regions approximately 5–10 years later. In these circumstances, glucose underutilization may arise due to A depositions in AD development [30, 42, 43]. Diminished local glucose consumption was linked to worldwide amyloidosis. Comparing the same patients revealed weak correlations between regional amyloid pathology and regional glucose hypometabolism (just one location out of 404 showed a negative correlation between glucose metabolism and amyloid plaque deposition) [44]. These findings might imply that glucose underutilization is vital in defining the clinical manifestations of the illness, even if it happens incidentally in autosomal-dominant AD carriers. Given this, as well as the recurrent failures of A-centered clinical studies, one may argue that it is too late to target A in AD or even those with moderate cognitive decline after years of amyloid pathology launching deadly cascades of events. Impaired energy metabolism, on the other hand, may afford a wider window for therapeutic intervention [24].

### Mitochondrial Bioenergetics in AD

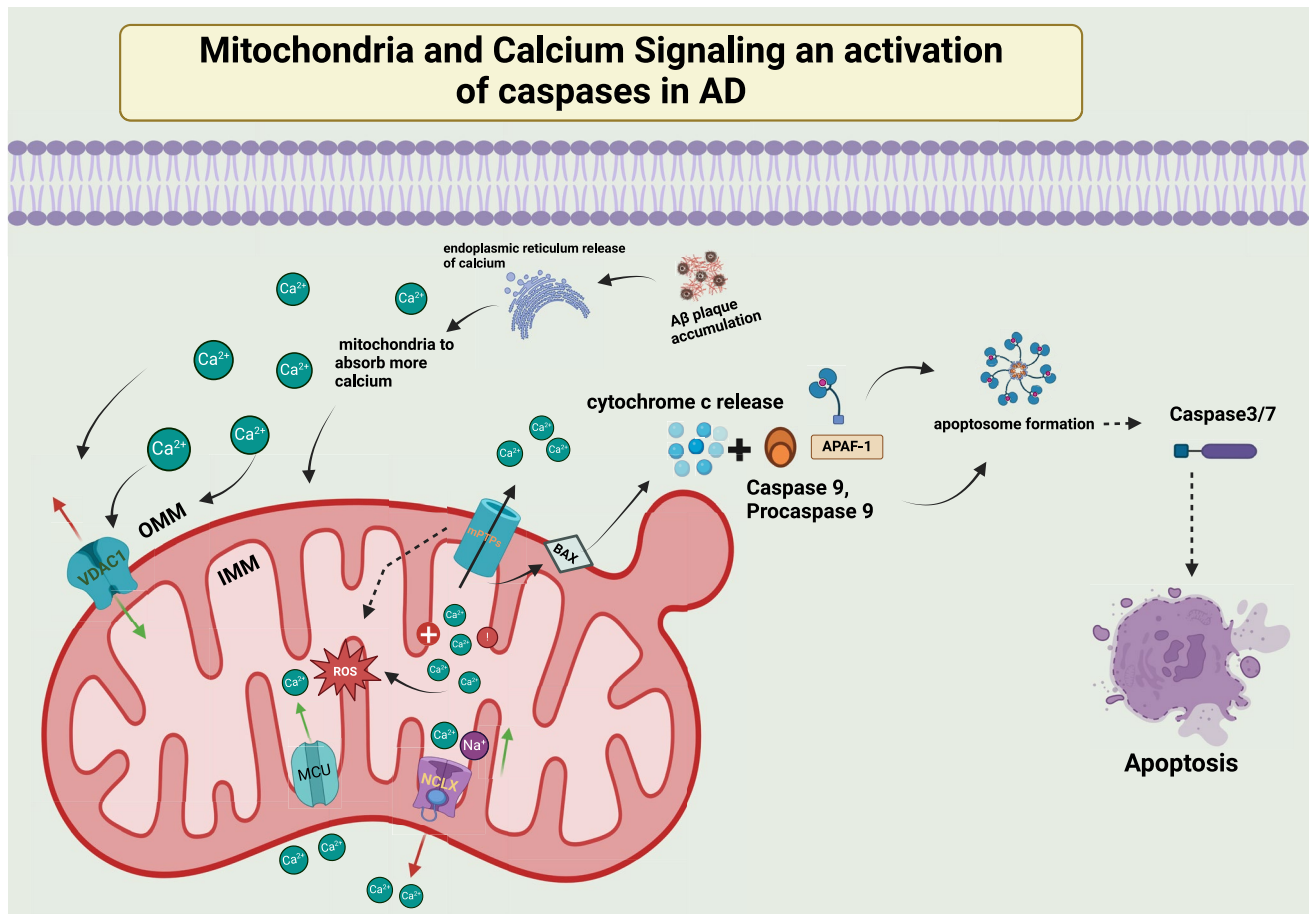
Several studies have identified abnormalities in mitochondrial-related metabolic processes associated with AD through gene expression analyses, providing compelling

evidence of dysfunctional mitochondrial bioenergetics in patients with AD [45–49]. Liang et al. [46] conducted a genome-wide transcriptome study using postmortem brains of patients with AD and controls from various brain regions, focusing on the activity of 80 metabolically relevant nuclear genes in non-tangle-bearing neurons obtained through laser-capture microdissection. Their findings revealed a significant decrease in the expression of nuclear genes encoding components of the mitochondrial electron transport chain in patients with AD's posterior cingulate cortex, hippocampus CA1, and middle temporal gyrus, with reductions of 70%, 65%, and 61%, respectively. In contrast, the visual cortex exhibited only a 16% decrease in expression, indicating relative protection from metabolic deficits in aging and AD [47, 48].

Another study utilized postmortem human hippocampus tissues to analyze the expression of mRNA transcripts involved in glucose metabolism in patients with AD, revealing substantial downregulation of 15 out of 51 members associated with pathways related to oxidative phosphorylation (OXPHOS), glycolysis, and the TCA cycle [49]. Mastroeni et al. [45] investigated hippocampal specimens from healthy controls, individuals with amnesic mild cognitive impairment, and AD cases, confirming a significant reduction in OXPHOS genes in AD, particularly those expressed by the nucleus. Interestingly, individuals with mild cognitive impairment exhibited higher levels of these genes compared to both patients with AD and healthy controls.

### Mitochondria and Calcium Signaling

The active transport of calcium ions ( $\text{Ca}^{2+}$ ), triggered by the action potential, is essential for neuronal development and function [50]. It functions as a messenger, activating the calcium channel to transfer depolarization calcium ions to the neuron's presynaptic end. This releases neurotransmitters via exocytosis, which gives the postsynaptic neuron the action potential [51, 52]. The presynaptic zone has an increase in calcium concentrations due to this mechanism [51]. Calcium homeostasis is one of the most critical functions performed by mitochondria and the endoplasmic reticulum [53, 54]. It reduces calcium concentrations by transferring calcium ions out of the mitochondria and into the matrix via the voltage-dependent anion-selective channel 1 (VDAC1) on the outer membrane, the  $\text{Na}^+$ -dependent mitochondrial calcium efflux transporter (NCLX), and the mitochondrion calcium uniporter (MCU) on the inner membrane of the mitochondria [55–58]. When the mitochondria are overloaded with calcium ions, the inner membrane's permeability of mitochondria transition pores (mPTPs) opens, releasing cytochrome c from the cells and triggering caspases in the cytoplasm, triggering apoptosis [59] (Fig. 2). A $\beta$  plaque



**Fig. 2** Illustration of calcium ions ( $\text{Ca}^{2+}$ ) signaling in mitochondrial dysfunction-associated neuronal apoptosis in Alzheimer's disease (AD). The buildup of  $\text{A}\beta$  in cortical neurons is associated with releasing calcium from the endoplasmic reticulum, leading to increased cytosolic calcium ion levels and enhanced mitochondrial calcium absorption. Mitochondria and the endoplasmic reticulum play a crucial role in maintaining calcium homeostasis by transferring calcium

ions out of the mitochondria and into the matrix via various channels and transporters [voltage-dependent anion-selective channel 1 (VDAC1); the  $\text{Na}^{+}$ -dependent mitochondrial calcium efflux transporter (NCLX), and the mitochondrion calcium uniporter (MCU)]. Overloading mitochondria with calcium ions triggers the opening of mitochondrial transition pores (mPTPs), releasing cytochrome c, activating caspase activation, and initiating apoptosis [50–54, 59]

accumulation in synaptic mitochondria plays a significant role in calcium dyshomeostasis in AD [59].

Furthermore, it is hypothesized that the accumulation of  $\text{A}\beta$  in cortical neurons instigates calcium release from the endoplasmic reticulum. This event elevates the levels of cytosolic calcium ions, thereby prompting mitochondria to absorb more calcium [60, 61]. The subsequent rupture of the mitochondrial membrane can be attributed to the high calcium concentrations within the mitochondria. This phenomenon can be elucidated by activating pro-apoptotic proteins, opening mPTPs, and augmentation in ROS [59]. Notably, this dysregulation of calcium at the mitochondrial level has been observed in the brains of patients diagnosed with AD [62, 63].

### **$\text{A}\beta$ , Protein Tau, and Associated Synapse Dysfunction**

An accumulation has been associated with synaptic dysfunction and neurotoxicity. It obstructs anterograde mitochondrial transport to the synapses, neurotransmitter release, and synaptic vesicle renewal [64–68]. Furthermore, it was demonstrated that  $\text{A}\beta$  promoted and inhibited long-term depression and N-methyl-D-aspartate (NMDA)-dependent long-term potentiation in synaptic connections [69, 70]. In a similar vein, tau has been linked to synaptic impairment in patients with AD. Through its interaction with Synaptogyrin-3, it was discovered to limit synaptic vesicles' mobility and diminish neurotransmitters' release from vesicles [64, 71, 72]. Furthermore, tau has been linked to reduced



mitochondrial axonal transport movement by interfering with microtubules, which in turn interferes with dynein and kinesin binding, diminishing neurotransmission [73, 74]. Interestingly, increased synaptic activity has been linked to increased tau diffusion to synapses, exacerbating synaptic dysfunction [75]. It was discovered that interactions between dynamin-related protein 1 (Drp1) and a rise in hyperphosphorylated tau mitochondrial fission, which in turn reduces the amount of functional mitochondria present in the synapse [11]. Memory impairment and cognitive impairment caused by AD are triggered by slower and disrupted neurotransmission as a result of progressive synaptic dysfunction. Individuals with AD experience dementia, and the condition proceeds as a result of synaptic degradation and subsequent neuronal death in their brains [76].

### Mitophagy and Autophagy

Mitophagy is a particular type of autophagy through which mitochondria are attacked and degraded. These cellular processes play a crucial role in energy conservation, cellular destruction, and preventing the accumulation of damaged organic molecules [77]. Many studies revealed that mitophagy processes are deformed in AD [78–81].

Most studies report the Pink–Parkin mitophagy pathway; however, cardiolipin-induced mitophagy has been reported in mouse models with AD [82]. Mitophagy markers increase with the disease progression, as reported in postmortem brain tissue and animal models. Yet, the cytosolic Parkin concentration is decreased, reducing its availability for mitophagy [83]. The cause of the accumulated mitochondria that are targeted for mitophagy is unclear. However, some studies reported that cells with presenilin-1 (PSEN1) mutations [84] or cells expressing the apoE4 gene [85] exhibit lysosomal dysfunction.

It is unknown what is generating the increased recruiting of Parkin to mitochondria; it might be due to mitochondrial membrane potential depolarization, which is produced by amyloid interlinkage with mitochondria. Furthermore, amyloid contributes to ROS generation, signaling mitophagy's start by boosting Parkin accumulation [77]. However, studies using animal and cell models have demonstrated that tau can either boost the recruitment of Parkin to mitochondria [79] or prevent its movement from the cytoplasm [80, 81].

The preparedness of a mitochondrion for mitophagy can be influenced by several factors, including the formation of ROS and its breakdown of mitochondrial membrane potential. The permeability of the mPTP is a transmembrane protein found in the inner mitochondrial layer that is critical in determining the degree of cellular death and mitophagy [86]. It has been reported that the mPTP function may be disturbed in AD, as a study showed a further constant activation of the pore in cells compared to healthy controls [87].

### Aging

Because of accumulating damage and limited self-repair, old age is a substantial contributory factor for many neurodegenerative illnesses. As we age, our mitochondria's shape and function alter substantially. Several studies, for example, found age-related changes in the structure of mitochondrial membranes, including the loss of cristae and inner membrane vesicles. Apoptogens are released into the cytoplasm because of the outer membrane breach caused by the division of adenosine triphosphate (ATP) synthase dimers into monomers. Furthermore, vesiculations of the membrane's inner layer and the breaking of ATP synthase dimers cause a considerable decrease in ATP [88].

According to research, age-related synaptic mitochondria aggregation disrupts synaptic activities such as ATP synthesis and calcium equilibrium, which are required for efficient depolarization-evoked neurotransmitter vesicle formation and plasticity. As a result, cognitive function and memory are impaired. Nonsynaptic mitochondria are less sensitive to age-dependent alterations and the accumulation of A aggregates [89, 90].

Aging is the leading risk factor for the beginning of sporadic AD; prevalence increases with age, from 2% in those 65–69 to 25% in those 90+ [91]. Numerous cohort studies indicate that age must be considered when evaluating AD treatments' safety and possible efficacy [92]. The accumulation of free radicals may accelerate aging in addition to metabolic decline.

Oxidative damage to mitochondrial macromolecules, especially mtDNA, would be most severe as mitochondria are the cell's primary source of free radical production [93]. Reduced activity of antioxidant enzymes such as glutathione reductase, catalase, superoxide dismutase, and glutathione peroxidase is also associated with chronic free radical accumulation in the AD brain [94, 95].

Moreover, reports indicate that a decline in proteasome activity brought on by aging may facilitate the deposition of A $\beta$  and tau [96, 97]. Consequently, these aging-related mechanisms establish an endless loop that leads to advanced mitochondrial dysfunction as well as the buildup of A $\beta$  and tau, the two main pathogenic characteristics of AD.

### Inflammation

Pathogen-associated molecular patterns (PAMPs) originate from pathogens or exogenous ligands, while damage-associated molecular patterns (DAMPs) are endogenously produced molecules released into the extracellular environment following tissue damage. Pattern recognition receptors identify PAMPs and DAMPs, subsequently triggering intracellular signal transduction pathways that enhance innate immune responses. Due to the similarities

between mitochondria and bacteria, when mitochondrial material escapes into the cytosol or extracellular environment, it activates pattern recognition receptors signaling by serving as a PAMP or DAMP [98]. As a result, mitochondria control the signals that cause inflammation.

DAMPs and PAMPs in the central nervous system induce pro-inflammatory immune responses in glial cells, resulting in chronic neuroinflammation and speeding up the etiology of neurodegenerative diseases such as AD [99, 100]. There is evidence that mtDNA causes *in vivo* neuroinflammation, as when mtDNA or mitochondrial lysates are injected into the hippocampus dentate gyri, pro-inflammatory signaling is triggered [101].

The introduction of mitochondria or mtDNA into the hippocampus area phosphorylates NF- $\kappa$ B, increases TNF mRNA synthesis, and lowers myeloid cells 2 (TREM2) expression, all of which are markers of AD pathogenesis [102, 103] and are included in phagocytic and anti-inflammatory pathways [104, 105]. Notably, mitochondrial lysates likewise increase endogenous APP and A $\beta$  [101].

### Mitochondrial DNA (mtDNA)

mtDNA is susceptible to oxidative damage due to its proximity to generating ROS, the absence of protective histones, and limited repair mechanisms [106]. In the brains of patients with AD, mtDNA exhibits approximately ten times more oxidized bases and three times more oxidative damage than nuclear DNA, potentially leading to mutations impairing mitochondrial function, cell death, and disease progression [107]. Mutations in mtDNA have been associated with cognitive impairments and are implicated in the onset of AD [106]. Specific maternally inherited genetic changes, known as mtDNA single nucleotide polymorphisms and haplogroups, have been linked to an increased risk of AD [108–110]. Notably, mtDNA accumulates mutations during aging, the primary risk factor for AD [111]. Furthermore, alterations in mtDNA, such as elevated 5-methylcytosine levels in the D-loop region in AD pathology brain samples with and reduced D-loop region methylation in peripheral blood mtDNA from patients with late-onset AD, can impact mtDNA transcription and function [112, 113].

ROS or the autophagic/lysosomal system may release mtDNA, initiating or exacerbating AD development by triggering a pro-inflammatory response. While this phenomenon has been observed in other conditions, such as cardiomyopathy and systemic inflammation, the specific mechanisms underlying the effects of released mtDNA in AD remain unclear and require additional investigation [114].

### Mitochondria-Localized microRNAs (mitomiRs)

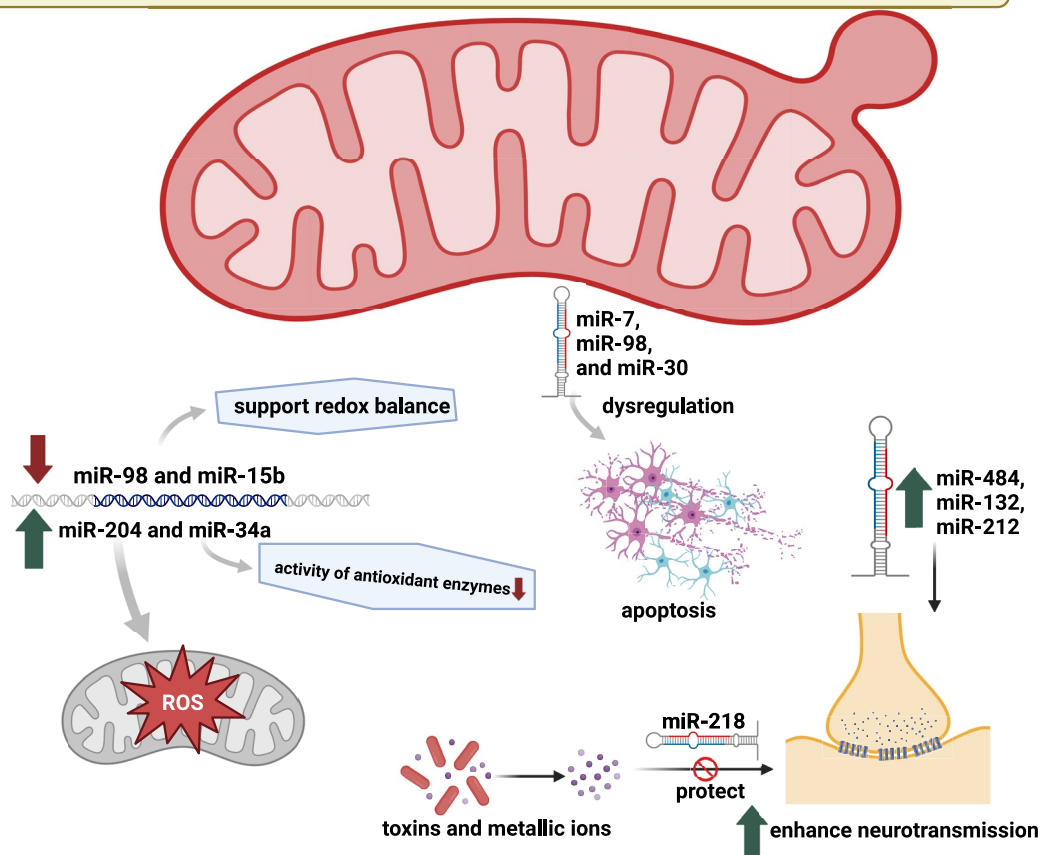
The pathogenesis of AD has been linked to mitochondrial miRNAs, which play a crucial role in regulating mitochondrial function. Dysfunctional miRNAs in neurons, often due to oxidative stress, can lead to increased production of ROS by mitochondria [115]. Specific mitochondrial miRNAs, such as miR-98 and miR-15b, have been shown to support redox balance, while miR-204 and miR-34a have been found to elevate ROS generation and impede the activity of antioxidant enzymes [116–119]. Dysregulation of these miRNAs can lead to neuronal death due to heightened oxidative stress in AD, while reduced levels of miR-98 and miR-15b can increase ROS production and oxidative damage. The transmission of synaptic information and plasticity heavily relies on mitochondrial function. Specific mitochondrial miRNAs, including miR-484, miR-132, and miR-212, have been demonstrated to enhance neurotransmission [120, 121].

Additionally, miR-218 has been identified as playing a role in protecting neurons from toxins and metallic ions that can induce synaptic toxicity [122]. The dysregulation of miRNAs involved in synaptic plasticity, such as miR-132 and miR-484, is likely to contribute to the observed synaptic dysfunction in AD [117, 121]. Programmed cell death, or apoptosis, is a fundamental mechanism for regulating the survival and death of neurons, particularly in the context of AD. Dysregulation of mitochondrial miRNAs implicated in apoptosis, such as miR-7, miR-98, and miR-30, has been observed, potentially leading to increased apoptosis and neuronal death [118, 123, 124]. Extensive neuronal death disrupts pathways associated with learning and memory, further exacerbating the cognitive deficits seen in AD [125]. Therefore, the dysregulation of mitochondrial miRNAs in AD will likely contribute to various aspects of the condition, including oxidative damage, synaptic dysfunction, and neuronal death. Overall, research on mitochondrial miRNAs and their role in neurodegenerative diseases holds promise for developing novel diagnostic and therapeutic approaches for AD and other neurodegenerative disorders (Fig. 3).

### Genetics

Genetic variations in mitochondrial regulatory pathways can lead to a gradual decline, ultimately resulting in compromised mitochondrial integrity and mtDNA damage, leading to mtDNA alteration dysfunction and disease [126]. Genetics can influence mitochondrial dysfunction and increase the risk of developing AD through various mechanisms. Aberrations in genes responsible for encoding mitochondrial proteins can disrupt mitochondrial function, resulting in the accumulation of oxidative damage and a decrease in energy production. Some of these mutations are associated with the production and metabolism of

## Mitochondria-localized microRNAs pathways in Alzheimers disease



**Fig. 3** The role of mitochondrial miRNAs in the pathogenesis of Alzheimer's disease (AD). Dysregulation of specific miRNAs, often due to oxidative stress, can lead to increased production of ROS and neuronal death. Specific miRNAs, such as miR-98 and miR-15b, support redox balance, while others, like miR-204 and miR-34a, elevate ROS generation. The figure also highlights the role of miRNAs in synaptic information transmission and plasticity, with miR-484, miR-132, and

miR-212 enhancing neurotransmission. Dysregulation of these miRNAs can contribute to synaptic dysfunction in AD. The figure further depicts the role of miRNAs in apoptosis, a mechanism regulating neuronal survival and death. Dysregulation of miRNAs implicated in apoptosis, such as miR-7, miR-98, and miR-30, can lead to increased apoptosis and neuronal death, disrupting learning and memory pathways [115–125]

A $\beta$ , which are known to aggregate in the brains of individuals with AD. Early-onset, autosomal dominant familial AD has been linked to mutations in the amyloid precursor protein (APP), PSEN1, and PSEN2 genes, typically manifesting in the fifth or sixth decade of life [126]. However, exceptions exist, and generally, if an individual develops AD after the age of 60 and does not have a parent who was affected by the disease before the age of 60, genetic testing is unlikely to reveal an autosomal dominant mutation in the APP, PS1, or PS2 genes. Individuals who develop sporadic AD at a younger age are thought to have a higher genetic predisposition for the disease. The presence of the APOE4 allele is frequently observed in these patients, indicating that APOE4 may be a risk factor for the early onset of AD in individuals carrying this allele [127].

## Hormones

Several studies have indicated sex-specific differences in mitochondrial dysfunction in the brain and that age-related declines in sex hormone levels may play a role in such dysfunction due to the critical regulatory role of hormones in mitochondrial activity [128]. Moreover, research has shown that ovulation significantly reduces mitochondrial respiration, suggesting that female sex hormones like progesterone and estrogen have a more pronounced impact on mitochondrial activity than testosterone [129]. Estradiol, the primary estrogen in humans, has been found to enhance OXPHOS activity, reduce the generation of ROS, and preserve mitochondrial membrane potential [130]. A postmenopausal mouse model investigation revealed that cognitive decline

associated with estrogen deficiency coincides with abnormal mitochondrial biogenesis, disrupted mitochondrial dynamics, reduced mitophagy, and mitochondrial dysfunction [131]. Similarly, progesterone has been shown to decrease oxidative stress and increase mitochondrial energy production [132]. Additionally, studies have suggested that testosterone deficiency may potentially impair brain substantia nigra mitochondria by increasing oxidative stress and reducing the activity of complex I, underscoring the potential influence of testosterone on mitochondrial dysfunction in the brain [133]. Furthermore, it has been proposed that the age-related decline in sexual steroid production could contribute to the deterioration of brain mitochondria [128].

### Electron Transport Chain and Krebs Cycle

Numerous studies have highlighted alterations in the electron transport chain (ETC) and tricarboxylic acid (TCA) cycle, the two paramount metabolic pathways within mitochondria. Researchers have reported a decrease of 30–40% in the activity of complex IV [134–137] and alpha-ketoglutarate dehydrogenase (αKGDH) [138–140], both crucial components of these metabolic pathways. Recent studies on human donor livers have provided evidence that the activity of the mitochondrial respiratory chain (complexes I, II, III, IV) and Krebs cycle enzymes (aconitase, citrate synthase) does not significantly differ before and after a 4-h preservation period across all study groups ( $p > 0.05$ ) [141]. Interestingly, low-risk livers that were clinically viable ( $n = 8$ ) exhibited lower activities of complexes II–III following 4-h perfusion compared to high-risk livers (73 nmol/mg/min vs. 113 nmol/mg/min,  $p = 0.01$ ). Applying actively oxygenated and air-equilibrated end-ischemic hypothermic machine perfusion (HMP) did not induce oxidative damage to aconitase, and the integrity of the respiratory chain complexes was maintained. This suggests that mitochondria likely adapt their respiratory function in response to varying oxygen levels in the perfusate during end-ischemic HMP. Given these findings, the activities of complexes II–III warrant further investigation as potential biomarkers for viability [141].

A more exhaustive screening of the activities of TCA cycle enzymes in AD [142] revealed a heterogeneous response: some enzymes exhibited decreased activity (e.g., pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, isocitrate dehydrogenase), others showed increased activity (e.g., succinate dehydrogenase and malate dehydrogenase), while the activity of the remaining four enzymes remained unchanged (e.g., aconitase). These alterations are presumed to result in a decline in succinyl-CoA, an intermediate of the TCA cycle produced by alpha-ketoglutarate dehydrogenase and utilized in the subsequent reactions catalyzed by succinate dehydrogenase and malate dehydrogenase. Succinyl-CoA serves as a precursor for heme synthesis

[143, 144]; thus, a decrease in succinyl-CoA levels would be expected to lead to a decline in heme production [145, 146].

### Therapeutic Modalities for Mitigating Mitochondrial Dysfunction in Alzheimer's Disease

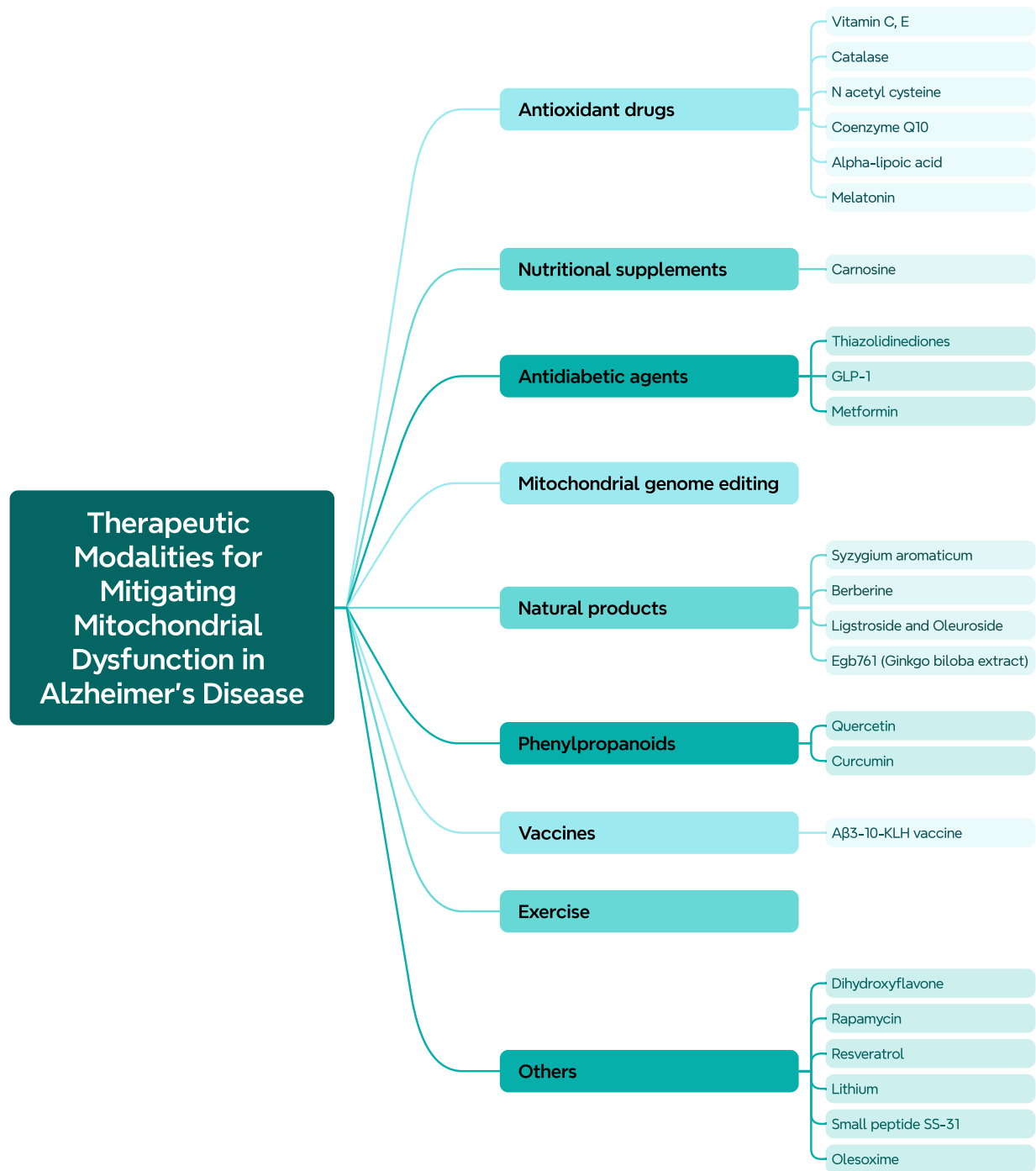
Numerous studies have connected mitochondrial dysfunction to the etiology of AD, involving oxidative stress, faulty electron transport chain, mtDNA damage, and improper mitochondrial dysfunction (Fig. 4). The following section highlights potential therapeutics for AD in preclinical (catalase, N-acetylcysteine, Coenzyme Q10, melatonin, exenatide, metformin, carnosine, clove, berberine, ligstroside and oleuroside, Egb761, quercetin, dihydroxyflavone, nilotinib, rapamycin, resveratrol, Aβ3-10-KLH vaccine, and olesoxime), and clinical models (vitamin C and E, alpha-lipoic acid, thiazolidinediones, curcumin, lithium, and small peptide SS-31). Table 1 summarizes the mechanisms of proposed therapeutic modalities [106–126, 147–153].

### Antioxidant Drugs

#### Vitamin C, E

Exogenous antioxidants, such as vitamins C and E, which can reduce ROS-induced damage, are one strategy to enhance mitochondrial function and halt disease development (Fig. 5). Unfortunately, clinical trials have not proved these antioxidants' usefulness since they cannot localize into mitochondria or cross the blood–brain barrier. Researchers added a novel group of naturally occurring antioxidants termed triphenylphosphonium to the mix to circumvent this barrier. This lipophilic cation boosts the efficiency of antioxidants in restoring mitochondrial health due to its capacity to localize to the negatively charged mitochondrial membrane. One example is MitoVitE, a vitamin E molecule connected to a triphenylphosphonium cation. This enables its rapid uptake into mitochondria, and it has been found to reduce mitochondrial damage induced by oxidative stress and protect against loss of mitochondrial membrane potential in rats [154]. On the other hand, individuals with AD who participated in a 1-year open clinical study received daily supplements containing 1000 mg of vitamin C and 400 IU of vitamin E. Antioxidant vitamins in cerebral fluid increased due to the treatment. However, the progression of AD was not significantly affected [155]. Furthermore, a meta-analysis of vitamin C, E, and carotene levels found that in patients with AD, vitamin E levels were considerably lower than in the control group; however, little difference was seen for vitamin C or carotene [156]. These findings





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**Fig. 4** Summary of therapeutic modalities for mitigating mitochondrial dysfunction in Alzheimer's disease. Preclinical models (catalase, N-acetylcysteine, Coenzyme Q10, melatonin, exenatide, metformin, carnosine, clove, berberine, ligstroside, and oleuroside,

Egb761, quercetin, dihydroxyflavone, nilotinib, rapamycin, resveratrol, Aβ3-10-KLH vaccine and olesoxime), and clinical models (vitamin C and E, alpha-lipoic acid, thiazolidinediones, curcumin, lithium and small peptide SS-31)

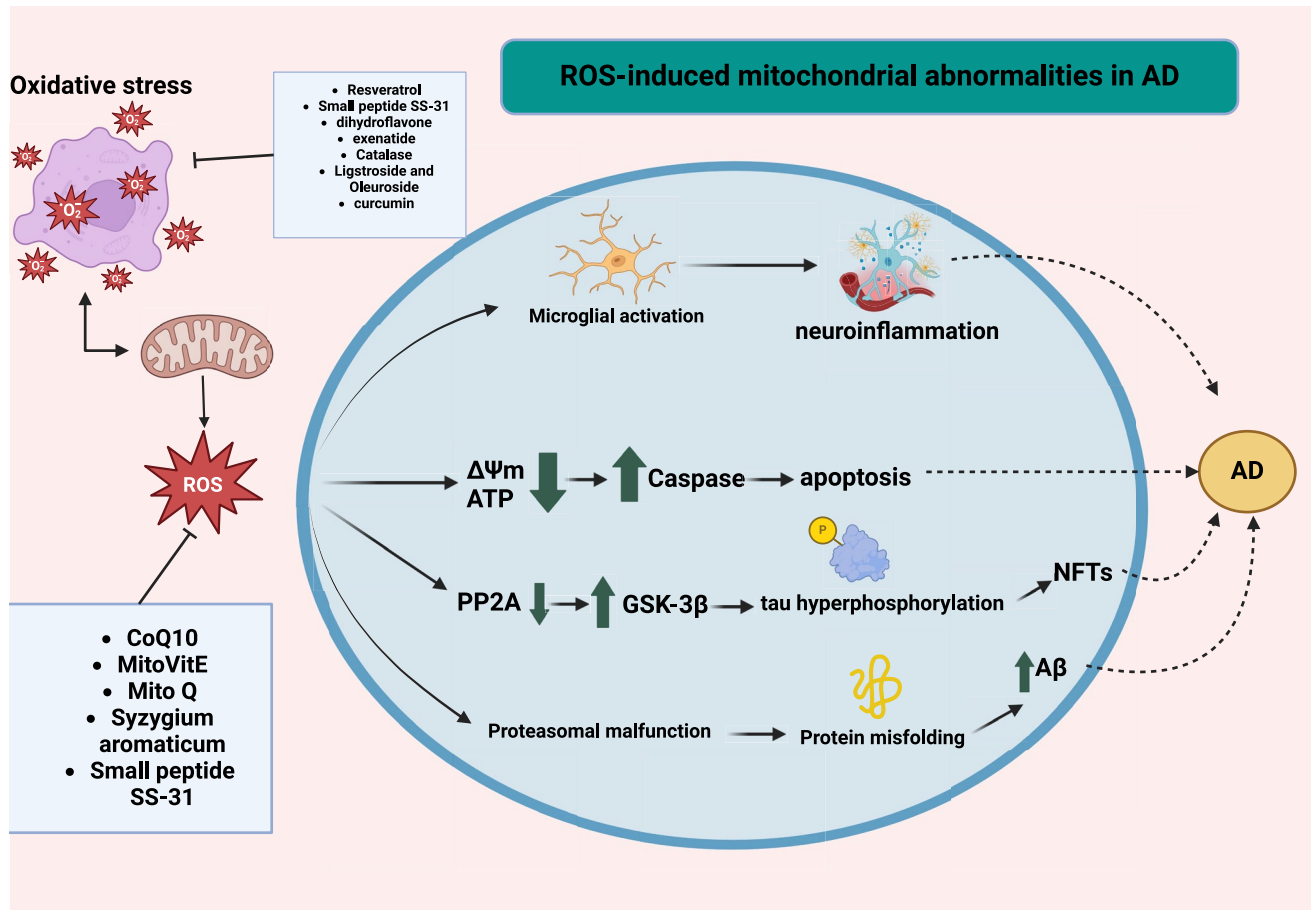
**Table 1** Summary of the proposed agents targeting mitochondrial dysfunction in Alzheimer's disease

Treatment	Proposed mechanism	Ref
<b>Antioxidant agents</b>		
Vitamins C and E	Scavenges ROS and reduces lipid peroxidation	[106, 107]
Catalase*	Decreased BACE activity, lessened aberrant APP processing, decreased oligomeric A $\beta$ buildup, and defense against oxidative damage	[108]
<i>N</i> -acetylcysteine*	Influencing the levels of energy- and mitochondria-related proteins	[109]
Coenzyme Q10*	CoQ10 reduces oxidative stress and amyloid pathology and improves behavioral performance	[110]
<i>alpha-lipoic acid</i>	Improve mitochondria function by enhancing different respiratory complexes and ATP levels	[111]
Melatonin*	Improve mitophagy, restore mitochondrial function, attenuate A $\beta$ pathology	[112]
<b>Mitochondria genome editing*</b>		
Using mitochondria-specific mitoCas9 and the clustered regularly interspaced short palindromic repeats (CRISPR) method		[147]
<b>Antidiabetic agents</b>		
Thiazolidinediones	Induces mitochondrial biogenesis, improves memory, lowers A $\beta$ burden, and lowers phospho- $\tau$	[113]
GLP1 (exenatide)*	Enhancing OXPHOS activity, reducing oxidative stress, and improving mitochondrial biogenesis	[114]
Metformin*	Mitophagy is induced by activating SIRT1, AMPK, and Parkin and suppressing the activities of complex 1 and mTOR	[115, 118, 119]
<b>Nutritional supplements</b>		
Carnosine*	Prevent intracellular Zn <sup>2+</sup> + dyshomeostasis and intraneuronal A $\beta$ deposition	[116]
<b>Natural products</b>		
<i>Syzygium aromaticum</i> *	Anti-oxidative capacity and can scavenge ROS, activate SIRT1, and downregulate $\gamma$ -secretase level	[117]
Berberine*	Modulate mitochondrial bioenergetics and glutathione metabolism pathways	[120]
Ligstroside and oleuroside*	Restore brain ATP level and enhance the capacity of respiratory chain complexes	[149]
Egb761 ( <i>Ginkgo biloba</i> extract)*	Suppress the JNK signaling pathway	[150]
<b>Phenylpropanoids</b>		
Quercetin*	Increase in mitochondrial biogenesis and reduction in free radicals	[121]
Curcumin	Modulates mitochondria stress response, a potent antioxidant, and regulates mitochondria redox balance	[122]
<b>Others</b>		
Dihydroflavone*	Reducing oxidative stress, mitochondrial dysfunction, and insulin resistance	[124]
Nilotinib*	Increases the clearance of amyloid beta (A $\beta$ ) by promoting mitophagy mediated by Parkin	[125]
Rapamycin*	Alleviates AD-like behaviors and synaptic plasticity deficits in APP/PS1 mice by correcting mitophagy	[126]
Resveratrol*	- The impact of A $\beta$ on mitochondrial oxidative stress, neuro-protection, and antiaging - Elevation of COX levels autophagic and mitophagies' stimulation	[123]
A $\beta$ 3-10-KLH vaccine*	Induce a high level of anti-A $\beta$ antibodies	[151]
Lithium	Selective inhibitory effect on GSK-3 $\beta$	[152]
Small peptide SS-31	Inhibits oxidative stress and restores normal mitochondrial function	[153]

**Table 1** (continued)

Treatment	Proposed mechanism	Ref
Olesoxime*	Enhancing the activity of respiratory chain complexes and reversing complex IV activity	[148]

\*Preclinical models



**Fig. 5** Reactive oxygen species (ROS)-induced mitochondrial abnormalities in Alzheimer's disease (AD). The overproduction of ROS or an impaired antioxidant system can shift the cellular redox balance towards oxidative imbalance. ROS, generated during cellular respiration, can harm mitochondria and neuronal function. An increase in ROS can lead to a reduction in mitochondrial membrane potential ( $\Delta\Psi_m$ ) and ATP generation, negatively impacting mitochondrial

energy stores, disrupting energy metabolism, and compromising dynamics and mitophagy. Furthermore, ROS can increase caspase activity, initiating apoptosis. Overproduction of ROS can also inhibit phosphatase 2A (PP2A), which activates glycogen synthase kinase (GSK) 3 $\beta$ , leading to tau hyperphosphorylation and the accumulation of neurofibrillary tangles [157]

suggest that increasing the intake of vitamin E-rich foods may be beneficial in preventing AD.

### Catalase

Catalase is an enzyme that aids in breaking hydrogen peroxide, a poisonous byproduct of cellular metabolism linked to mitochondrial malfunction and AD pathology. A study discovered that the mitochondria-targeted antioxidant catalase can prevent aberrant APP processing, lower A levels,

and increase A-degrading enzymes in AD mice, showing its promise as a treatment strategy [158].

### N-acetyl cysteine

N-acetyl cysteine is the primary source of glutathione, an antioxidant vital in avoiding oxidative stress and mitochondrial dysfunction. According to research on an AD animal model, N-acetyl cysteine treatment improved A $\beta$ -induced abnormalities in mitochondria and synaptic degeneration, reduced

oxidative stress, and increased mitochondrial function [159]. However, more investigation is needed to determine the ideal dosage and length of N-acetyl cysteine therapy to address mitochondrial dysfunction in patients with AD.

### Coenzyme Q10 (CoQ10)

AD and other neurodegenerative illnesses may benefit from Coenzyme Q10 (CoQ10) as a treatment [160]. Although CoQ10 may have neuroprotective properties, research on in vitro and animal models has shown conflicting findings in AD clinical trials [160]. Patients with AD exhibited equivalent serum/plasma CoQ10 levels to controls, according to a comprehensive review and meta-analysis of studies evaluating tissue CoQ10 levels in patients with dementia and controls [161]. Human investigations have produced conflicting outcomes, although CoQ10 has demonstrated significant neuroprotective effects in laboratory models of AD and other dementias [161].

### Alpha-lipoic Acid

Alpha-lipoic acid has been shown to have various beneficial effects on pathogenic pathways of dementia, including reducing oxidative stress, inflammation, and mitochondrial dysfunction [162]. A study investigated the impact of alpha-lipoic acid treatment (600 mg/day) on cognitive performance in patients with AD with and without diabetes mellitus and found that alpha-lipoic acid therapy may be effective in slowing cognitive decline in patients with AD with insulin resistance [163]. Furthermore, a review article suggests that alpha-lipoic acid may have potential therapeutic benefits in preventing several diseases, including AD, due to its antioxidant and anti-inflammatory properties [164].

### Melatonin

Melatonin's antioxidant properties and sleep–wake cycle modulation are only two of its numerous roles. Melatonin is widely known for protecting against aging, neurological ailments, and mitochondrial diseases. However, its effect on mitophagy in AD is unknown. An experiment on an AD-prone mouse model indicated that oral melatonin treatment increased mitophagy, restored mitochondrial function, decreased A pathology, and improved cognitive performance, hinting that it might be used as a therapeutic alternative for managing AD [165].

### Antidiabetic Agents

#### Thiazolidinediones

Thiazolidinediones are a family of insulin-sensitizing drugs that have been identified to have potential therapeutic

benefits in treating AD due to their unique agonists of the gamma receptor for peroxisome proliferator (PPAR). They have also been proposed as innovative and potentially effective treatments for neurodegenerative illnesses. In preclinical studies, rosiglitazone treatment had positive effects. Rodent studies show that rosiglitazone reduces the quantity of phosphorylated tau protein, improves cognition, boosts mitochondria biogenesis, and lowers A burden [166]. Furthermore, in a Phase 2 human study, rosiglitazone-treated patients with AD (ApoE 4 non-carriers) displayed enhanced cognitive performance [167]. Advantages were not shown in later phase 3 trials [168].

#### GLP-1

GLP-1 agonists have been licensed to heal type 2 diabetes, including exenatide. It has also been postulated that these agents may have neuroprotective effects due to their impact on mitochondrial activity [169]. GLP-1 analogs have been shown to improve mitochondrial function by increasing OXPHOS activity, decreasing oxidative stress, increasing glucose uptake and utilization, and boosting mitochondrial biogenesis. Exenatide, a GLP-1 receptor agonist, has shown promise in lowering mitochondrial dysfunction and cognitive decline in 5xFAD transgenic mice, implying that it might one day be utilized to prevent mitochondrial damage in AD [170]. Furthermore, the research looked at the impact of subcutaneous liraglutide (25 nmol/kg/qd for 8 weeks) in 5 FAD mice and A-treated astrocytes. Liraglutide was discovered to increase neuronal support, reduce neuronal death, and alleviate mitochondrial dysfunction in the brain by activating the cyclic adenosine 3',5'-monophosphate (cAMP)/phosphorylate protein kinase A (PKA) pathway. Furthermore, GLP-1 reduced mitochondrial fragmentation in A-treated astrocytes, enhanced mitochondrial failure, ROS excessive production, mitochondrial membrane potential collapse, and cell toxicity [171].

#### Metformin

Metformin, a treatment for type 2 diabetes mellitus, has demonstrated potential in managing conditions such as AD [172]. Clinical studies have indicated that metformin is associated with enhanced cognitive function and a reduced risk of developing AD; however, these effects may be influenced by variables such as APOE-ε4 status and diabetes status [172]. Mechanistic investigations have revealed the impact of metformin on AD etiology and pathophysiology, encompassing neuronal loss, neural dysfunction, tau phosphorylation, Aβ deposition, chronic neuroinflammation, insulin resistance, altered glucose metabolism, and mitochondrial dysfunction [172]. Recent research suggests that metformin prevents mitochondrial-mediated apoptosis



and diminishes the generation of ROS in mitochondrial respiratory-chain complex 1 [173]. Metformin has been shown to delay aging and mitigate the progression of aging-related diseases, including AD, by targeting critical aging-related events, such as mitochondrial dysfunction [174]. Furthermore, metformin activates SIRT1, AMPK, and Parkin while inhibiting complex 1 and mTOR activities, thereby inducing mitophagy [175]. Additionally, promising results of metformin have been observed in disease models, including increased lifespan in mice, reduced hyperphosphorylated  $\tau$  in a diabetes mouse model, and reversal of AD features in APP/PS1 [176].

### Acetylcholinesterase Inhibitors/NMDA-Receptor Antagonist

The only pharmacological treatments approved for AD are acetylcholinesterase inhibitors (ChEIs) and the NMDA receptor antagonist memantine [177]. Despite their seemingly modest benefits [178, 179], a substantial body of evidence supports their efficacy in enhancing cognition and cost-effectiveness [180–190]. One of the earliest pathological findings in AD is the degeneration of basal forebrain cholinergic neurons, which precedes the onset of dementia [180, 190]. The progression of AD correlates more closely with dysfunction in the cholinergic system than with the amyloid plaque load [191]. Furthermore, a reduction in the volume of the basal forebrain precedes changes in the volume of the hippocampus and predicts the cortical spread of AD pathology [192].

ChEIs function by maximizing the availability of endogenous acetylcholine in the brain [193]. However, few randomized clinical trials have investigated the efficacy of ChEIs in AD following 1 year of treatment [194–198] or have conducted patient follow-ups beyond this point [197]. Studies examining long-term cognitive decline are complicated due to high attrition rates and loss of follow-up [197]. Some follow-up studies of cohorts treated with ChEIs for Alzheimer's dementia have demonstrated minor cognitive benefits at 2, 3, and over 10 years [199–201]. A positive short-term response to ChEIs can also delay admission to nursing homes [202].

Xu et al. [203] emphasized that ChEIs are associated with modest cognitive benefits that persist over time and with a reduced risk of mortality, which could be partially attributed to their cognitive effects. Among all ChEIs, only galantamine has demonstrated a significant reduction in the risk of progressing to severe dementia. Other studies have reported associations between the use of ChEIs and a decreased risk of myocardial infarction, stroke, and death in patients with AD [204–207].

### Nutritional Supplements

AD is known by zinc ( $\text{Zn}^{2+}$ ) dyshomeostasis with the pathological accumulation of A $\beta$  and tau protein in the brain [208]. A study investigated the potential impact of carnosine, a dipeptide, on zinc ( $\text{Zn}^{2+}$ ) chelation and AD-like cognitive deficits in 3xTg-AD mice [209]. The findings demonstrated that carnosine effectively chelates intracellular  $\text{Zn}^{2+}$  and reduces intraneuronal A $\beta$  deposition in the hippocampus. However, it was ineffective in addressing tau pathology in the brain [208]. The administration of carnosine at a concentration of 20 mM during acute and intense  $\text{Zn}^{2+}$  rises allowed for examining its chelating properties [208]. The supplementation of carnosine exhibited a favorable trend towards improved cognitive performance in 3xTg-AD mice, as evidenced by the reduced latency to locate the platform [208]. The study suggests that carnosine may serve as a potential dietary supplement for mitigating intracellular  $\text{Zn}^{2+}$  dyshomeostasis and intraneuronal A $\beta$  deposition, which are significant contributors to the onset and progression of AD [208].

### Natural Products

#### *Syzygium aromaticum* (Clove)

Shekhar et al. [210] investigated the impact of *Syzygium aromaticum* (or clove) on sirtuin (SIRT1) and the oxidative balance in the context of A $\beta$ -induced toxicity to determine whether clove could modulate the oxidative pathway. The findings revealed that clove exhibits anti-oxidative properties, which can scavenge ROS, activate SIRT1, and down-regulate secretase levels [210]. These results suggest that clove may offer a holistic approach to treating neurodegenerative diseases, potentially leading to the development of innovative therapeutics for AD. Given its high oxygen radical absorbance capacity value and ability to balance Vata while stimulating nerves, clove may also serve as a potential anti-aging agent [211].

#### Berberine

Chinese medicinal herbs, such as berberine, have a long history of use in treating various illnesses, including AD [212]. berberine has been associated with numerous neuroprotective benefits that may enhance the brain's energy state in the early stages of AD [213]. A recent study revealed that berberine mitigates abnormalities in crucial energy and glutathione metabolism pathways in AD cells and modulates mitochondrial bioenergetics, slowing basal respiration and reducing the production of pro-inflammatory cytokines from activated microglial cells [214]. These findings suggest that berberine may benefit from disrupted metabolic pathways in

the early stages of AD development [214]. Additionally, the study investigated the synergistic effects of berberine and pioglitazone, a PPAR agonist. It indicated that both drugs may have comparable potential benefits for AD, as they bind to the PPAR protein with similar affinities [214].

### Ligstroside and Oleuroside

Two secoiridoids, ligstroside and oleuroside, are bioactive chemicals in olive oil [215], which may play an essential role in preventing AD due to their capacity to increase mitochondrial activity [216]. Grewal et al. studied the effects of two metabolites and ten distinct pure phenolic secoiridoids at deficient concentrations on mitochondrial activity in early AD cellular model SH-SY5Y-APP695 cells [149]. The studied secoiridoids markedly raised these cells' baseline ATP levels. The compounds that significantly impacted ATP levels were ligstroside, oleacein, oleuroside, and oleocanthal. They were also tested for their effects on mitochondrial respiration. The only substances that may increase the respiratory chain complexes' capability were ligstroside and oleocanthal [149].

To investigate the underlying molecular mechanisms of these activities, qRT-PCR was utilized to assess the expression of genes associated with respiration, anti-oxidative ability, and mitochondrial biogenesis. Only ligstroside increased mRNA expression of complex I, GPx1, SIRT1, and CREB1 [149]. Additionally, oleocanthal, not ligstroside, reduced A $\beta$ 1–40 levels in SH-SY5Y-APP695 cells. To assess the in vivo effects of pure secoiridoid, the two most promising compounds, oleocanthal, and ligstroside, were tested in an aging mouse model [217]. Female NMRI mice were fed a diet supplemented with 50 mg/kg of ligstroside or oleocanthal for 6 months. Compared to aged control animals, mice administered with ligstroside exhibited significantly prolonged lifespan, improved spatial working memory, and restored brain ATP levels [149]. These findings indicate that pure ligstroside significantly enhances mitochondrial bioenergetics in early AD and brain aging models through pathways that may not affect A $\beta$  production. Furthermore, ligstroside enhances cognitive function and extends the lifespan of aged mice [149]. Therefore, ligstroside holds promise as a potential therapeutic agent for the prevention and treatment of AD.

### Egb761 (*Ginkgo biloba* Extract)

Flavonoids and terpenoids are among the bioactive substances found in Egb761, a standardized extract made from *Ginkgo biloba* leaves [218]. The possible therapeutic effects of Egb761 on brain function have been assessed in clinical studies; its impact on age-related dementias and AD has received particular attention [219].

In recent work, researchers used an in vitro cell culture model and an in vivo AD rat model to evaluate the regulation of A-induced necroptosis by Egb761 and associated roles in AD pathogenesis [150]. They showed that Egb761 may suppress the JNK signaling pathway in vitro and in vivo. This could explain why it may avoid A-induced tissue morphogenesis, cell death, and necroptosis in BV2 cells and enhance cognitive performance. These findings support the potential therapeutic effects of plant extracts like Egb761 in treating neurodegenerative illnesses like Alzheimer's [150].

Randomized double-blind trials were carried out in the study, requiring a minimum of 22 weeks of treatment for Egb761 at a dose of 240 mg/day and 12 weeks for ChEIs or memantine [220]. The study assessed how Medicare enrollees with dementia or moderate cognitive impairment were managed clinically with amyloid PET imaging. This multisite longitudinal trial, called the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study, aimed to determine whether amyloid PET imaging was associated with changes in clinical care after that [220, 221].

### Phenylpropanoids

Phenylpropanoids are a class of natural chemicals found in plants with a wide range of biological actions [222]. Because of their anti-inflammatory, antioxidant, and neuroprotective qualities, they have been examined for their potential therapeutic implications in mitochondrial dysfunction associated with AD. Among the phenylpropanoids, quercetin and curcumin have been widely studied for their potential advantages in treating mitochondrial dysfunction in AD [223].

### Quercetin

Quercetin, a naturally occurring flavonoid, has been demonstrated to have protective benefits in animal models of AD. It is being studied for its efficacy in treating mitochondrial dysfunction in AD [224]. Studies on the effect of quercetin on mitochondrial function have yielded promising results. Quercetin treatment boosted mitochondrial biogenesis, decreasing free radicals in neuronal SH-SY5Y cells [225]. Chronic oral quercetin therapy decreased  $\alpha$ -amyloidosis and tauopathy in a triple transgenic AD mouse model, leading to cognitive functional recovery [226]. A meta-analysis of 14 research found that quercetin had neuroprotective benefits in multiple AD models, including the potential to ameliorate mitochondrial abnormalities [224]. Moreover, a study exploring the effects of quercetin liposomes administered nasally demonstrated improved cognitive behavior and reduced oxidative stress markers in the hippocampus of an AD animal model [227].

## Curcumin

Curcumin, a natural chemical found in turmeric, has received interest for its possible neuroprotective and cognitive-enhancing qualities in treating or preventing neurodegenerative illnesses such as AD [228, 229]. Several studies have investigated curcumin's potential in addressing mitochondrial dysfunction in AD. Notably, one study demonstrated curcumin's ability to suppress A $\beta$ -induced oxidative damage, improve memory impairment, and enhance microglial labeling near A $\beta$  [229]. Additionally, a review article explored curcumin's effects on cognition and proposed strategies to overcome current limitations and improve its efficacy [230]. Studies in vitro and in vivo have shown that curcumin can decrease A $\beta$  production, inhibit A $\beta$  aggregation, and promote A $\beta$  clearance [231]. Its mechanism of action involves attenuating amyloid precursor protein maturation, suppressing beta-secretase 1 expression, and binding to A $\beta$  peptides to prevent aggregation [232].

Additionally, curcumin activates the Wnt/ $\beta$ -catenin and PERK/eIF2/ATF4 pathways, leading to BACE-1 inhibition and accelerated A $\beta$  clearance [233]. Moreover, a study discussed using curcumin nanoformulations as theranostic agents to optimize its pharmacokinetic properties alongside other bioactive compounds [234]. However, a systematic review evaluating the efficacy of curcumin in patients with AD, encompassing dosages ranging from 100 mg to 4 gm/day, indicated inconsistent results likely attributed to limitations such as small sample sizes and short study durations, underscoring the necessity for further research in this field [228].

## Vaccines

The A $\beta$ 3-10-KLH vaccine has been developed as a potential treatment for AD by stimulating an immune response against A $\beta$  [235]. This vaccine includes A $\beta$ 3-10, a fragment of the protein believed to be highly immunogenic. In a study on a mouse model of AD [151], the A3-10-KLH vaccination induced a high level of anti-A antibodies in mice, improving cognitive and learning abilities. The vaccination reduced A plaques and oligomers in the cortex and hippocampus of mice, which are areas of the brain most affected by AD [151]. Additionally, the vaccination inhibited neuron loss and apoptosis, which are significant pathogenic factors in AD. Moreover, the immunization increased the levels of Preps, a protein that may degrade A in brain mitochondria. Consequently, the A3-10-KLH vaccination shows promise as a therapy for AD, potentially enhancing cognitive performance while reducing pathogenic markers associated with the condition [151].

## Exercise

It has been proposed that physical activity may help enhance cognitive abilities among people with AD. According to a recent investigation conducted on APP/PS1 transgenic mice [236], high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) workouts were found to increase memory and exploratory behavior. In the Morris water maze test [237], both workouts increased navigation and swimming distance, with no significant difference between the two activities [236]. In the spatial probe test, both workouts enhanced the frequency of platform crossings and the percentage of platform quadrant distance, improving memory capacity. Furthermore, both workouts enhanced exploratory behavior in the open field test, as indicated by the number of probing, total time in the center region, and total distance in the central area. Body weight did not differ considerably across groups; however, the HIIT and MICT groups increased their exercise capacity significantly. These data demonstrate that independent of body weight, HIIT and MICT may improve cognitive performance in patients with AD [236].

## Others

### Dihydroxyflavone

In a study using a rat model, it was observed that 7,8-dihydroxyflavone (7,8-DHF), a naturally occurring flavonoid present in certain plants, enhanced cognitive function and decreased neurodegeneration by mitigating oxidative stress, mitochondrial dysfunction, and insulin resistance. These findings suggest that 7,8-DHF holds promise as a potential therapeutic intervention for AD in humans. Additionally, the study demonstrated that 7,8-DHF restored cognitive impairment in a rat AD model by addressing oxidative imbalance and dysfunction of mitochondrial enzymes [238].

### Rapamycin

Rapamycin, a pharmacological agent, has emerged as a promising intervention for enhancing healthy aging and longevity in animals. Its potential use in treating mitochondrial disorders in AD has also been investigated. According to a study, rapamycin therapy increased mitochondrial activity and reduced oxidative stress in a mouse model of AD [239]. Another study revealed that even in the absence of detectable improvements in mitochondrial dysfunction, low-dose oral rapamycin was sufficient to prolong the lifespan of a mouse model with authentic mtDNA disease resulting from a mutation in the thymidine kinase 2 (TK2) [240].

## Resveratrol

Grapes, apples, blueberries, plums, and peanuts produce natural non-flavonoid polyphenol resveratrol. It exists naturally as a phytoalexin [241]. Numerous bioactivities of resveratrol have been demonstrated, such as anti-aging, anti-inflammatory, cardiovascular protection, anti-cancer, anti-diabetes mellitus, anti-obesity, and neuroprotective properties [242]. In rats, resveratrol at doses of 20 and 40 mg/kg/day was beneficial in lowering the expression of pro-inflammatory markers and mitigating the memory and learning deficits caused by A $\beta$  [243]. Rats with vascular dementia showed enhanced learning and memory when resveratrol (25 mg/kg) was given intragastrically daily. Moreover, it raised glutathione levels, superoxide dismutase activity, and malondialdehyde levels in vascular dementia-affected rats' hippocampal and cerebral cortex [244].

## Lithium

Lithium, a treatment for psychiatric illnesses, has been found to have the potential to treat neurodegenerative disorders, including AD, due to its neuroprotective and neurotrophic properties [245]. GSK-3 $\beta$ , a kinase protein implicated in multiple physiological processes related to neurodegeneration, is selectively inhibited by lithium. Its inhibitory action on GSK-3 $\beta$  has been demonstrated to lessen A $\beta$  generation, stop tau phosphorylation, and make it easier to induce long-term potentiation in AD-affected mice [152]. Human studies have also shown a substantial positive correlation between long-term lithium medication and a lower incidence of dementia in elderly bipolar illness patients [246]. Additionally, long-term subtherapeutic lithium medication has raised levels of brain-derived neurotrophic factor, lowered AD-related CSF fluid biomarkers [247], and slowed the deterioration in cognitive and functional abilities in patients with amnesic mild cognitive impairment [248]. The neuroprotective mechanisms of lithium may also be related to its regulation of energy metabolism and mitochondrial efficiency, including the activation of the Wnt signaling pathway [249].

## Small Peptide SS-31

SS-31, a mitochondrial peptide, has shown promise as a possible therapy for AD [250]. The peptide belongs to the Szeto-Schiller family of tiny cell-permeable peptides and binds to the inner mitochondrial membrane without requiring mitochondrial membrane potential or energy [251]. Elamipretide, MTP-131, and Bendavia are the brand names for these drugs. SS-31 is more effective than standard antioxidants like vitamin E [153]. It inhibits oxidative stress and restores normal mitochondrial function. Mitochondria oversee glucose homeostasis, and mitochondrial failure is

linked to oxidative stress and malfunction. These have been connected to the development of metabolic and neurological diseases. The usage of MT-targeted drugs like SS-31 can aid in the reduction of oxidative stress and mitochondrial damage [251]. SS-31 has been found to have neuroprotective effects by protecting the synapses, reducing A $\beta$  accumulation, and preventing mitochondrial dysfunction [250]. The peptide has shown promise in preclinical studies for treating AD, indicating its potential as a novel therapeutic agent.

## Olesoxime

Olesoxime (TRO19622) is a medication tested in AD animal models to see how it affects mitochondrial dysfunction and amyloid precursor protein processing [252]. TRO19622 was given to 3-month-old mice with AD-like features and wild-type mice for 15 weeks in research [148]. In dissociated brain cells and brain tissue homogenates, the drug's effects on mitochondrial membrane potential, adenosine triphosphate levels, respiration, citrate synthase activity, A $\beta$  levels, and malondialdehyde levels were studied. The results showed that TRO19622 alleviated mitochondrial dysfunction by increasing respiratory chain complex activity and reversing complex IV activity and mitochondrial membrane potential [148]. Furthermore, the medication protected dissociated brain cells against complex I activity inhibition. TRO19622, on the other hand, was shown to enhance the levels of A1-40 in the brains of mice and HEKsw cells. This study reveals that while TRO19622 may have mitochondrial advantages, the increased production of A1-40 may have negative consequences. More studies are needed to determine TRO19622's potential as a feasible therapy for AD [148].

## Future Research Directions and Potential Roadblocks

The development of therapeutic drugs that specifically target mitochondrial dysfunction is an increasing focus in AD management. An ideal drug may enhance mitochondrial function, reduce oxidative stress, and prevent neuronal death [157, 253]. We have highlighted the latest scientific progress toward developing such medications in Table 2. However, the development of formulations targeting mitochondria faces explicitly numerous challenges.

First, the precise mechanisms of action of these drugs are still not fully understood, and further research is needed to elucidate these mechanisms and optimize the efficacy of these drugs, particularly those with promising results in preclinical models such as CoQ10 [161], melatonin [165], olesoxime [148], SS-31 [250, 251], lithium [152, 245, 248],



**Table 2** Latest proposed mitochondrial drugs in the treatment of Alzheimer's disease

NCT	Status	Interventions	Enrollment	Location
NCT03514875	Withdrawn	MitoQ	12	United States
NCT02142777	Completed	S -Equol (AUS-131)	15	United States
NCT04842552	Recruiting	Hydralazine hydrochloride	424	Iran
NCT02711683	Completed	DL-3-n-butylphthalide	92	China
NCT00675623	Completed	Dimebon	598	United States
NCT00951834	Completed	Epigallocatechin-gallate	21	Germany
NCT03999879	Recruiting	Measure of OxPhos upregulation	45	United States
NCT04740580	Recruiting	Glycine, N-acetylcysteine, alanine	52	United States
NCT04044131	Completed	Metabolic cofactor, sorbitol	120	Turkey
NCT00678431	Completed	Resveratrol with glucose, and malate	27	United States
NCT04701957	Recruiting	Ketogenic diet	70	France
NCT04018092	Recruiting	Active NIR-PBM, Sham NIR-PBM	168	United States
NCT04430517	Recruiting	Nicotinamide riboside	50	United States
NCT05040048	Completed	Clinical, biological, and imaging assessment	220	France, Germany, Spain, Sweden
NCT02062099	Completed	[18F]DPA-714 PET/ [18F]AV-45 PET/neuropsychological assessment	25	France
NCT03860792	Recruiting	Ketogenic diet, therapeutic lifestyles changes diet	80	United States
NCT05040321	Recruiting	MIB-626	50	United States
NCT03859245	Unknown	Ketogenic diet, photobiomodulation	30	United States
NCT05383833	Recruiting	Creatine monohydrate	20	United States
NCT05591027	Recruiting	Centella asiatica product	48	United States
NCT03702816	Enrolling by invitation	GE180 PET scan	70	United States
NCT00829374	Completed	Dimebon	1003	United States
NCT05343611	Recruiting	Combination of high protein diet and physical exercise protocol, HPP Choko, HPP/VE Choko	75	Italy
NCT01388478	Completed	R-pramipexole	20	United States
NCT02460783	Completed	Boost (R) 5–2 diet, healthy living diet	129	United States
NCT05617508	Recruiting	Nicotinamide riboside 1000 mg daily in total, nicotinamide riboside dose escalation (up to 3000 mg daily in total)	80	Norway
NCT03101085	Completed	S-equol	40	United States
NCT01498263	Completed	Not provided	682	United States

249], vaccines [151, 235], berberine, and pioglitazone [212–214].

Second, there is difficulty in diagnosing the extent of mitochondrial functioning and dysfunction and determining the drug dose required to produce the desired modulation in mitochondrial functioning [77, 254, 255]. Available AD diagnosis includes cognitive testing, imaging of A $\beta$  and tau pathology in various brain parts, and cerebrospinal fluid assays [256]. However, these techniques have disadvantages, including limited availability, high cost, and invasive procedures employed with their results and integrity under question. Technological advancement has led to researchers speculating novel biomarkers involved in the disorder's pathogenesis, such as 5-methylcytosine levels in patients with late-onset AD [112, 113], complexes II–III

in ETC, and Krebs cycle [141] and mtDNA [106–113]. Developing mitochondrial biomarkers could be an excellent approach, as mitochondrial functions are standard in various cell types and present in sporadic and familial AD. However, identifying common metabolic deficits in most AD patients is undoubtedly required before producing the mitochondrial function as a clinically useful biomarker.

Third, achieve tissue selectivity for the drug to reach mitochondria by penetrating the blood–brain barrier to minimize other side effects. Some proposed ways to attain this include selective activation of pro-drug by enzymes, combined delivery of more than one active compound targeting mitochondria that react with each other after reaching mitochondria, or radiotherapeutic approaches [255, 257, 258].

## Conclusion

Understanding mitochondrial function in AD is challenging due to the complex nature of the mitochondrial network and its interactions with other cellular components. Some therapeutic modalities have shown promising results in pre-clinical models, including antioxidants, CoQ10, melatonin, olesoxime, small peptide SS-31, lithium, vaccines, berberine, and pioglitazone. However, it is crucial to acknowledge that current animal and human cell models do not fully replicate AD or the complexity of the human brain. Furthermore, AD's varied potential causes and progression paths add another layer of complexity to the research. Future work should prioritize understanding the progression of AD and the mitochondria-associated biomarkers at each stage. This knowledge can then be used to develop formulations targeting these biomarkers in mitochondria while optimizing tissue selectivity. Meanwhile, it is essential to optimize the use of current FDA-approved medications to manage the symptoms of AD, tailoring them to the specific needs of patients.

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**Data Availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethical Approval** Not applicable, and all data are available on the internet.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Competing Interests** The authors declare no competing interests.

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