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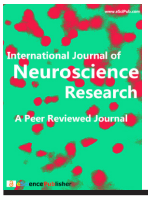

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The Influence of Mitochondria in Alzheimer Disease and Possible Alternative Therapies

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ABSTRACT

The epidemiology of Alzheimer's disease (AD) is notable. North America and Western Europe have the most expressive rates of disease (6.4% and 5.4% at age 60), followed by Latin America (4.9%) and, finally China (4%). The most important fact is that head trauma increases the deposition of amyloid βeta (Aβ) and the expression of neuronal tau as well as diabetes. Obesityand trans fats also increase the risk of AD. However, virtually no current pharmacotherapy is approved for agitation / excitation caused by AD, the only purpose is maintaining the memory of those affected by this disease. There is substantial evidence that some dysfunctions in the mitochondria are involved in AD.Mitochondria are essential for neuronal function because the limited glycolytic metabolism of these cells makes them highly dependent on aerobic oxidative phosphorylation (OXPHOS) for their energy needs. Increased concentrations of ROS are known to result in molecular damage to the site where they are produced, triggering what science calls oxidative stress. Another no less important pathophysiological process in neurological disease is mitochondrial membrane cholesterol. New evidence indicates that the burden of mitochondrial cholesterol can influence mitochondrial function regardless of its conversion to pregnenolone or oxysterols, emerging as a key factor in the pathology of several neurological diseases associated with mitochondrial dysfunction, as in the case of AD. In this way, neurons are strictly dependent on the presence of healthy mitochondria, especially in the synapses where these organelles produce ATP and concentration of Ca2 + ions, fundamental

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processes for the implementation of neurotransmission and generation of membrane potential along the axon. Controlling ROS, as well as reducing the inflammatory cascade in neurons can be a good strategy in controlling the disease. The reduction of cholesterol in the external mitochondrial membrane may be another interesting path for the reentry of glutathione in the control of ROS, which occurs due to the imbalance in the metabolism of the mitochondrial respiratory chain seen in AD. In this review, we discuss the role of mitochondria in AD as well as alternative therapies for controlling this disease with specific herbal and nutraceuticals.

Keywords: Alzheimer disease; Mitochondria; Inflammation; Beta amyloid plaques; Cholesterol; Reactive oxygen species

Introduction

The epidemiology of Alzheimer's disease (AD) is notable. North America and Western Europe have the most expressive rates (6.4% and 5.4% at age 60), followed by Latin America (4.9%) and finally, China (4%) [1]. It should also be noted that the prevalence is lower for Africans in their homelands, as opposed to the higher rates in the diaspora in American and Western Europe [2]. The most important fact is that head trauma increases the deposition of amyloid βeta (Aβ) and the expression of neuronal tau, and diabetes, obesity and trans fats also increase the risk of AD [3, 4, 5, 6, 7, 8]. The modality of treatment of agitation and other behavioral symptoms in patients with dementia has been a challenge. In 2015, the global economic and social cost of dementia was estimated at $ 818 billion, and that number is expected to exceed one trillion dollars by the next decade [9, 10]. However, virtually no current pharmacotherapy is approved for agitation / excitation caused by AD, only for the purpose of maintaining the memory of those affected by this disease (Table 1). When considering these facts, understanding the relationship between the functioning of mitochondria linked to AD has been a challenge for science in the search for new evidence that can be observed in the changes between fusion / fission of these organelles, as well as their genetic code [11].

Table 1

S.no.	Drugs	Neurological Function	Side effects
1	Aricept® (donepezil)	Cholinesterase inhibitor - Prevents the breakdown of acetylcholine in the brain	Nausea, vomiting, diarrhea, muscle cramps, fatigue, weight loss
2	Exelon® (rivastigmine)	Cholinesterase inhibitor - Prevents the breakdown of acetylcholine and butyrylcholine (a brain chemical similar to acetylcholine) in the brain	Nausea, vomiting, diarrhea, weight loss, indigestion, muscle weakness
3	Razadyne® (galantamine)	Cholinesterase inhibitor - Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain	Nausea, vomiting, diarrhea, decreased appetite, dizziness, headache
4	Namenda® (memantine)	N-methyl D-aspartate (NMDA) antagonist - Blocks the toxic effects associated with excess glutamate and regulates glutamate activation	Dizziness, headache, diarrhea, constipation, confusion
5	Namzaric® (memantine and donepezil)	NMDA antagonist and cholinesterase inhibitor - Blocks the toxic effects associated with excess glutamate and prevents the breakdown of acetylcholine in the brain	Headache, nausea, vomiting, diarrhea, dizziness, anorexia

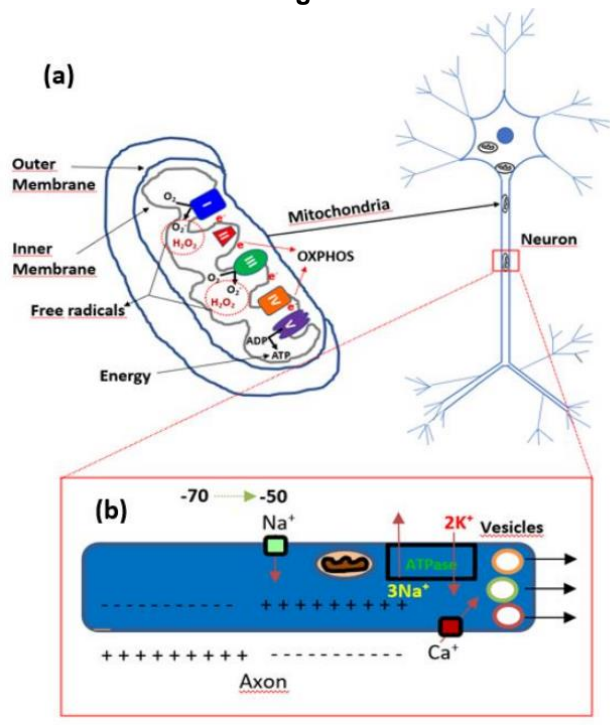
The relationship between Alzheimer's disease and mitochondria

There is substantial evidence that some dysfunctions in mitochondria are involved in AD [11,

[12, 13, 14]. The brain receives 15% of the cardiac output and is responsible for 20% of the body's total oxygen consumption [15]. This need for energy substrate is largely driven by the neuronal demand for energy to maintain ion gradients across the plasma membrane that is critical for generating action potentials [16]. Mitochondria are essential for neuronal function because the limited glycolytic metabolism of these cells makes them highly dependent on aerobic oxidative phosphorylation (OXPHOS) for their energy needs. However, OXPHOS is the main source of endogenous free radicals, also known as reactive oxygen species (ROS), including hydrogen peroxide (H2O2), hydroxyl radicals (HO radical dot) and superoxide (O2-radical dot) from normal cell respiration (Fig. 1) [17].

In 2010, the study by Swerdlow et al proposed the mitochondrial cascade hypothesis in AD [18]. In summary, the study pointed out that an individual's genetics determines the underlying mitochondrial function, and how mitochondria changes as the person ages and is exposed to various environmental assaults [18]. In effect, decreased mitochondrial function results in a specific pathology for AD [19]. In addition, morphological changes were observed in the mitochondria, such as abnormal sizes and shapes, as well as the fact that the electron transport chain enzymes encoded in the mitochondrial genome are altered and the expression modified [20, 21]. According to studies on mitochondria and aging, efficient mitochondrial proteostasis helps to compensate for the effects of Aβ aggregation, which can alter the speed of the disease [22, 23]. A recent study on mitochondria and AD raised a discussion about bioenergetic changes linked to this pathology. In this study, some evidence was presented pointing to a defective mitochondria function in AD. This had been elucidated in prior therapeutic development [24]. In the same way that the classic neuropathological characteristics of the disease (Aβ and Tau [τ]) and the sporadic risk genes of Alzheimer's (APOE) can trigger mitochondrial disorders, mitochondrial dysfunction can also incite the pathology [24]. Although this study also demonstrated that pre-clinical and clinical efforts were predominantly concentrated on the amyloid pathway, clinical trials have not yet clearly revealed its benefits.

Figure 1



(a) : Normal production of free radicals in cellular respiration. (b): Need for adenosine triphosphate (ATP) in activating the ATPase enzyme to trigger the Na+/K+ pump by neurons.

Therapies in AD aimed at mitochondrial dysfunction are few and focus on reversing oxidative stress and cell death pathways [25]. Even though the validity of the mitochondrial cascade hypothesis has not yet been demonstrated in different models of AD in human patients, the following mitochondrial functions have been severely impaired in the context of the disease as reported by several studies, including the mitochondrial morphology and number [26], oxidative phosphorylation [26,27], Ca2+ buffer [11], ROS production [27], mitochondrial DNA (mtDNA) oxidation and mutation [28], mitochondrial biogenesis [11, 29], mitochondrial transport along the neuronal axon and mitophagy [30], were some of the changes presented in these studies to date. In a neuronal context, any of these dysfunctional processes can lead to synaptic deficits and critical consequences, not only for single neurons, but mainly for a more complex structure like the brain [31].

Table 2

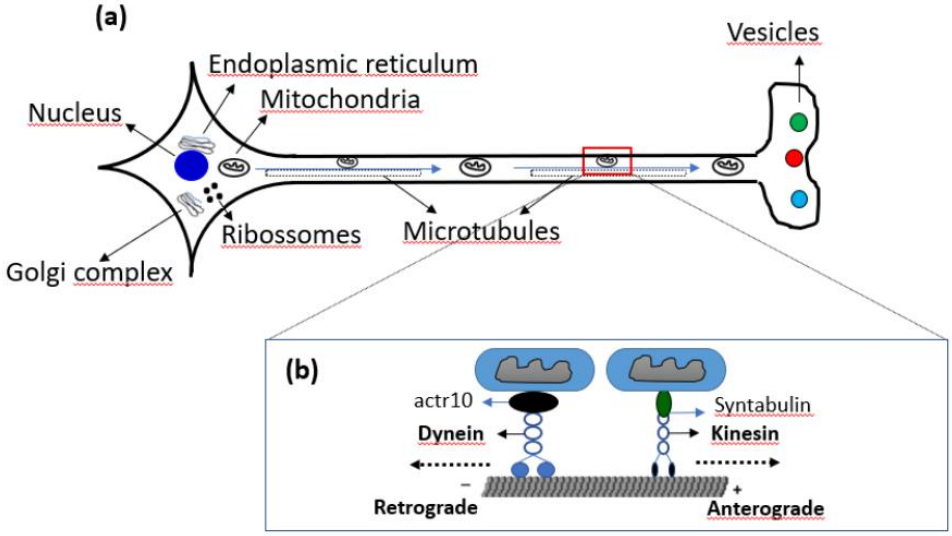
S.no.	Mitochondrial alteration	Reference
1	*Beta* Amyloid (Aβ) aggregation	Ortiz & Swerdlow (2019)
2	Morphology and number	Khan et al (2015)
3	Oxidative phosphorylation	Missiroli et al (2020)
4	Ca^{2+} buffer	Cenini & Voos (2019)
5	Reactive oxygen species (ROS) production	Missiroli et al (2020)
6	Mitochondrial DNA (mtDNA) oxidation and mutation	Taylor (2005)
7	Mitochondrial biogenesis	Wang (2020)
8	Mitochondrial transport along the neuronal axon and mitophagy	Mattson (2008)

Reactive Oxygen Species in Neurodegenerative Diseases

Neurons are totally dependent on the presence of mitochondria, especially in the synapses where these organelles produce adenosine triphosphate (ATP) and Ca2+ ion concentration, which are fundamental processes for the function of neurotransmission and generation of membrane potential, mainly along the axon (Fig. 1) [32]. This justifies the high number of mitochondria in the synaptic area, superior to any other part of neurons. Linked to this a correct and efficient transport of neuronal mitochondria in the synaptic terminals is essential for their correct functioning [11, 33]. Mitochondria are usually synthesized in the neuronal sum and then transported to the other area of neurons where they are needed [34]. The transport of mitochondria in the axons is doing through microtubules and requires motor proteins such as kinesin, dynein and the mitochondrial outer membrane protein Rho GTPase (Fig. 2) [35]. This axonal transport of mitochondria is also influenced by metabolic demand and the status of Ca2+ at the synaptic level [35,36]. Thus, the enzymatic activity of the mitochondrial respiratory chain complex essentially results in two parameters. First, the generation of the inner membrane potential along the membrane is also essential for the execution of mitochondrial import of encoded nuclear proteins, and, in general, it is considered a parameter that reflects the health of mitochondria and cells [37]. The second parameter would be the verification of an electron leak from the respiratory chain complex, which contributes significantly to the formation of ROS (Fig. 3). Increased concentrations of ROS are known to result in molecular damage to the site where they are produced, triggering what science calls oxidative stress [17, 38]. According to

Di Meo (2016), ROS targets comprise essentially all cellular macromolecules, from proteins, lipids and carbohydrates to nucleic acids [38, 39]. The hippocampus region, the cortex, and, in general, the brain, are particularly vulnerable to oxidative stress due to high oxygen consumption and dependence on mitochondrial energy production [40]. This susceptibility is increased when low levels of antioxidant defenses are found in the cells, along with high levels of polyunsaturated fats, which are extremely vulnerable to oxidative changes [41,42].

Figure 2



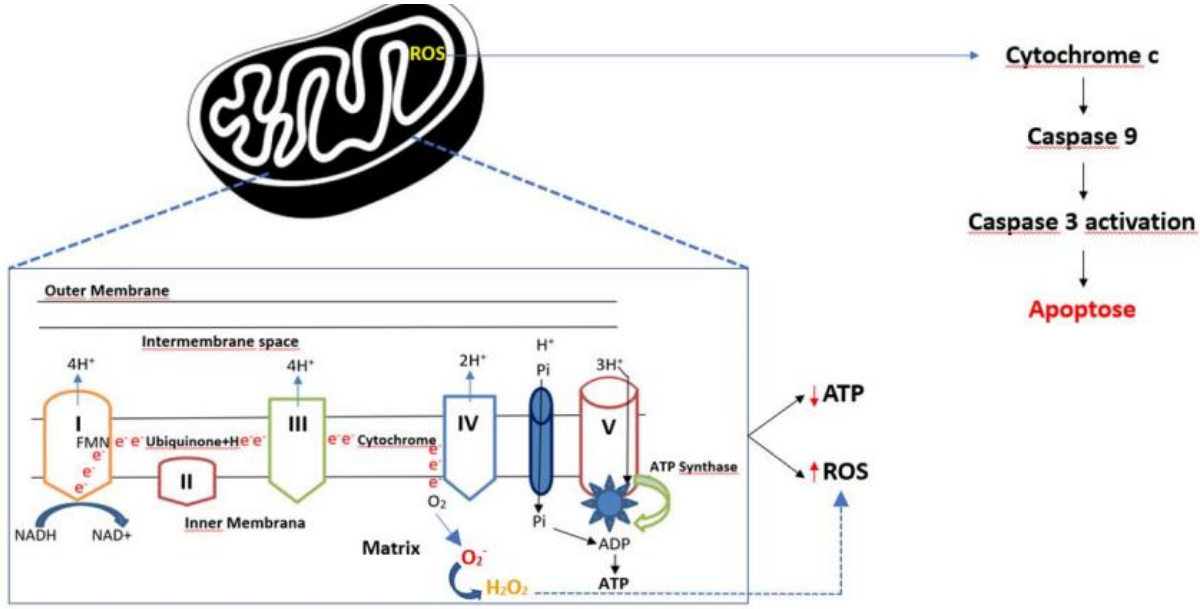
An example on transport of mitochondria along the axons through microtubules and motor proteins such as kinesin, dynein. Kinesin follows the anterograde path, that is, from the cell body to the axon terminal, while the dynein follows the retrograde path.

In a study on energy pathways in neurodegenerative diseases, it was reported that in the brain with AD alteration of energy pathways linked to reduced glucose consumption is considered a well-established characteristic of the disease [43]. Normally, glucose uptake in the brain is measured with the 18-fluorodeoxyglucose (fDG) positron emission tomography (PET) marker [44]. Through this marker, Mosconi (2013) reported a considerably low rate of glucose metabolism in individuals with AD (between 20% and 30% less than healthy individuals) in the brain regions involved in memory processing, such as the hippocampus, the posterior cingulate, and the temporal and parietal lobes [45]. Although the real cause is still unclear, it is a fact that the defective metabolism that characterizes Alzheimer's disease can be easily linked to high ROS in mitochondrial dysfunction [11].

In the study by Du et al (2010) with transgenic mice that overexpress the human amyloid precursor protein (APP) (Tg mAPP mice), an early and progressive accumulation of Aβ peptide in synaptic mitochondria led to mitochondrial synaptic dysfunction, such as impaired mitochondrial respiratory activity, increased ROS and impaired mitochondrial axonal transport [46]. The results from this study demonstrated that the bioenergetics of compromised mitochondria, together with high levels of ROS are early phenomena that appear even before the development of observable Aβ plaques. This can be corroborated with the studies by Cenini et al (2019), where the authors reported the similar results: the bioenergetics of compromised mitochondria together with high levels of oxidative stress are early phenomena that appear even before the development of observable Aβ plaques [11]. Evidence for mitochondrial dysfunction as a key factor in age-associated neurodegenerative diseases, such as AD and Parkinson's disease (PD), continues to increase [47]. Disorders in mitochondrial function have

long been observed in samples derived from patients with AD and clinically confirmed, including altered mitochondrial morphology, enzyme complexes compromised in the Krebs cycle and reduced COX activity [48].

Figure 3



Electron leak from the respiratory chain complex, which contributes significantly to the formation of ROS. NAD -Nitotinamide adenine dinucleotide; NADH - Reduced nitotinamide adenine dinucleotide; ADP - Adenosine diphosphate; ATP - Adenosine triphosphate; ROS - Reactive oxygen species.

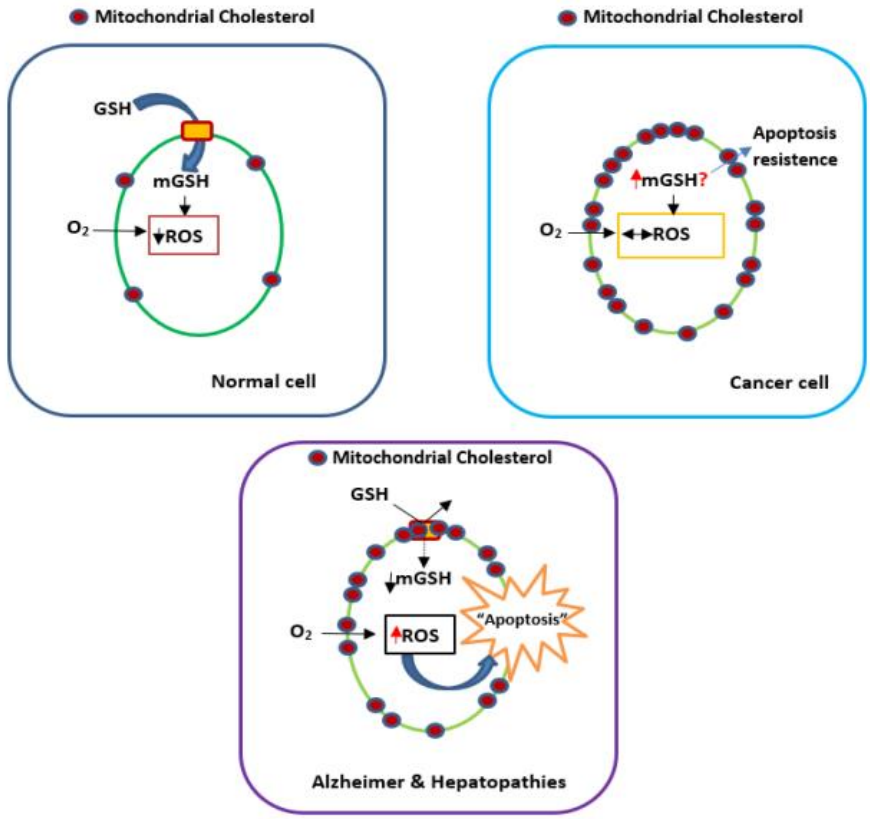
Inflammation and Cholesterol in Mitochondria Membranes: Its association with Alzheimer's Disease

Cholesterol is an essential component of the cell membrane bilayers. It determines the physico-chemical and functional properties for the perfect functioning of the membrane [49]. Cholesterol is present in the brain, where it regulates essential biological functions such as signal transduction pathways, myelin formation and synaptogenesis [50]. In the central nervous system (CNS), cholesterol is synthesized through its precursor mevalonate in a biochemical cascade that begins with acetyl-CoA producing Hydroxymethylglutaryl-CoA (HMG-CoA) in the endoplasmic reticulum (ER) [51].

Although the physiological levels of cholesterol in the mitochondrial membranes are low compared to the plasma membrane, mitochondrial cholesterol is essential for maintaining the physiological properties of the mitochondrial membrane and synthesis of neurosteroids [52]. The main regulatory enzymes responsible for the synthesis of steroids in the CNS include the cleavage of the cytochrome P450 side chain (P450scc) and the acute steroidogenic regulatory protein (StARD1), the member of a lipid transport family [53]. The trafficking of cholesterol to mitochondria has been well elucidated in the context of steroidogenesis, but the relevance of mitochondrial cholesterol in neurodegeneration has not yet been recognized. New evidence indicates that the burden of mitochondrial cholesterol can influence mitochondrial function regardless of its conversion to pregnenolone or oxysterols, emerging as a key factor in the pathology of several neurological diseases associated with mitochondrial dysfunction, as in the case of AD [54]. Cholesterol can lead to mitochondrial dysfunction and can be a fundamental step in the progression of AD [55]. This dysfunction includes reduced fluidity of the mitochondrial membranes, reduced generation of ATP and decreased import of mitochondrial glutathione (mGSH) into the mitochondrial matrix, which can be a fundamental factor in disease progression (Fig 4) [56]. In addition, there is a direct link between altered membrane lipids and mitochondrial function, which is detrimental to

brain bioenergetics [57]. Cholesterol renewal in the brain is modulated by cytochrome P450 46A1 (CYP46A1), which initiates the main route of its elimination [58]. In an amyloid precursor protein (APP23) in a mouse model with AD, Aβ peptides have been shown to accumulate after inhibition of CYP46A1 expression resulting in generalized neuronal death when compared to normal mice [59]. Therefore, decreasing the expression of the CYP46A1 gene in the neurons of the hippocampus of normal mice, increases the concentration of cholesterol in neurons with subsequent cognitive deficits and atrophy of the hippocampus due to apoptotic neuronal death [59, 60].

Figure 4



Cholesterol in the outer mitochondrial membrane induces mitochondrial dysfunction and can be a fundamental step in the progression of AD. This dysfunction includes reduced fluidity of the mitochondrial membranes, reduced generation of ATP and decreased import of mitochondrial GSH into the mitochondrial matrix. GSH - Reduced glutathione; mGSH - mitochondrial glutathione; ROS - reactive oxygen species.

Nutraceuticals and phytotherapies in Alzheimer's disease

As the critical processes in Alzheimer's disease is oxidative stress formed in neurons, the levels of glutathione (GSH) are decisive for the control of ROS in these tissues [56]. Normally, GSH levels are decreased in pathologies with high oxidative stress, and there is significant evidence of using glutathione precursors as a preventive therapy to control AD [61]. Some studies have stated that redox-sensitive proteins can be protected from oxidative stress by GSH, such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH), α-enolase and p53 [62]. These enzymes have been identified as GSH, with GAPDH and α-enolase also having reduced activity in the brain with AD and have previously been reported as oxidatively modified [63]. Unlike cancer, where it is intended to lower GSH levels to assist apoptosis-inducing therapies, in neurodegenerative diseases, as in the case of AD, the process is completely reversed [64]. When there are significant amounts of GSH in neurons, there is greater protection in relation to oxidative stress, and consequently a decrease in relation to the process of apoptosis [61]. One

of the ways to increase GSH is by using its direct precursors: N-Acetyl cysteine (NAC) or γ-glutamylcyesteine ethyl ester (GCEE) [65, 66]. NAC proved to be an effective precursor of GSH production due to the ease of crossing the blood-brain barrier [67]. Balatori et al (2009) have reported that intraperitoneal (ip) injection of NAC in rodents increased GSH in the brain and synaptosomes, offering protection against peroxynitrite, hydroxyl radicals, acrolein and oxidative stress induced by 3-nitropropionic acid [61]. A change in the redox status due to NAC, altered the signaling pathways involved in the apoptosis signaling cascade, demonstrating that the protection of NAC against Aβ involves several signaling pathways, among them the activation of the Mitogen-activated protein kinase (MAPK) pathway [68]. NAC also acted as a transcription factor, activating the Ras-ERK pathway, rescuing neurons from apoptotic cell death [68]. What we can observe from these studies is that in addition to the antioxidant properties and the increase in GSH levels, NAC protects against Aβ toxicity through the activation of anti-apoptotic signaling pathways [69].

Another precursor to GSH that has been drawing the attention of the scientific community is gamma-glutamylcysteine (GGC) [70]. Studies have reported that the administration of GGEE increased cellular levels of GSH, bypassing the regulation of GSH biosynthesis by providing the limiting substrate [71]. In addition to being the direct precursor to GSH synthesis, GGEE is an essential cofactor for the enzyme glutathione peroxidase (GPx) a very important metal chelator [70]. The study also reported that although the administration of oligomeric Aβ40 decreases the activity of the antioxidant enzymes superoxide dismutase (SOD) and GPx compared to untreated cells, as well as the reduction in GSH levels and the total antioxidant capacity in brain cell homogenates and increased ratio oxidate/reduced glutathione (GSSG / GSH), concomitant administration with GGEE completely reversed the process significantly increasing SOD and GPx activity [70]. Likewise, GGEE increased the GSH levels and the total antioxidant capacity of the cell, and significantly reduced the GSSG / GSH ratio, demonstrating to attenuate the Aβ40-mediated oligomeric interruption of endogenous antioxidant enzymes and replenish the GSH levels in the cells of the human brain [72]. In a study treating human brain cells with oligomeric Aβ40, there was a significant decrease in the levels of anti-inflammatory cytokineinterleukin 10 (IL-10) and increased levels of pro-inflammatory cytokines, tumor necrosis factor alfa (TNF-α), interleukin 6 (IL-6) and interleukin 1β (IL-1β), compared to treated cells [73]. On the other hand, GGEE effectively modulated the oligomeric changes induced by Aβ40 observed in the levels of inflammatory cytokines in vitro [72]. At this point, significant positive regulation of IL-10 levels and significant negative regulation of TNF-α, IL-6 and IL-1β was observed in cells treated with GGEE, suggestive of the beneficial effects of GGEE against the neuroinflammatory response induced by Oligomeric Aβ40 [72]. Likewise, the effects of GGEE on human astrocytes are relevant to neuroprotection in AD, as well as in other neurodegenerative diseases, since astrocytes represent support cells in the brain and protect neurons against oxidative stress, increasing neuronal survival during cytotoxic conditions [74]. Furthermore, studies with astrocytes have shown that astrocytes depleted of GSH have lost their neuroprotective roles leading to neuronal toxicity and a consequent reduction in cell viability [75]. These cells are responsible for removing debris in the extracellular space and are necessary to maintain the stability of the blood-brain barrier [76]. The loss of astrocyte function can compromise the function and structure of neurons, culminating in neurodegeneration and general brain dysfunction [77]. Thus, the maintenance of ideal GSH levels is necessary for neuroprotection against oxidative stress and neuroinflammation in astrocytes, maintaining a healthy environment in the CNS [70, 77]. Kulas et al (2019) also reported that changes in the levels of GSH or GSSG can affect the function of the insulin-degrading enzyme (IDE), which is involved in mediating in-

sulin degradation [78]. IDE is a major regulator of Aβ peptides and reduced IDE activity can reduce Aβ plaque degradation by more than 50% [79]. Nevertheless, additional studies are needed to confirm whether GGEE can increase IDE activity due to increased levels of GSH and may even represent an additional mechanism to explain the potential neuroprotective effects of GGEE in AD.

An interesting fact in scientific research in the last decade was the cannabidiol (CBD) agonist activity in non-cannabinoid receptors, demonstrating that CBD is not restricted to cannabinoid CB1 and CB2 receptors [80]. On the contrary, studies have indicated that CBD influences the expression of several genes, mainly in the activation of peroxisome proliferatoractivated receptor gamma (PPAR-γ) [81, 82]. CBD's ability to activate PPAR-γ has promising therapeutic implications, particularly on AD, PD and in metabolic disorders [83]. Various in vitro and in vivo evidence supported CBD's role in degenerative inflammatory diseases. This is because CBD has a strong ability to inhibit the production of inflammatory cytokines, including IL-1β, IL-6 and interferon-β (IFN-β) in murine microglial cells stimulated by liposaccharides [84, 85]. In fact, microglia act as primary cells in response to infections and pathogen lesions, but prolonged or excessive activation can result in pathological forms of inflammation that contribute to the progression of neurodegenerative diseases (PD and AD, multiple sclerosis and dementia associated with HIV), as well as neoplastic diseases [86]. In addition, the effects of CBD in inflammation are not mediated by CB1 and CB2 receptors, nor receptors sensitive to abn-CBD, as studies have shown that its ability to decrease inflammatory activity is associated with the control of NF-kB signaling and the signal transducer and transcription activator 1 (stat1), key participants in inflammatory processes [87]. Thus, it was found in vitro that CBD produced neuroprotection in ischemic stroke, through a mechanism mediated by PPAR-γ and 5-HT1A receptors [88]. Another neuroprotection mechanism exerted by CBD is mediated by the positive regulation of the mRNA levels of copper-zinc superoxide dismutase (Cu-Zn SOD), an important enzyme in endogenous defenses against oxidative stress, characterizing the mechanisms by which CBD regulates Ca2 + homeostasis and mediates the neuroprotection in neuronal preparations, stating that CBD can be beneficial in preventing apoptotic signaling by restoring Ca2 + homeostasis [89, 90, 91]. Neurons have a particularly high energy demand and correspondingly high metabolic activity in addition to large Ca2 + fluctuations. Mitochondria play a particularly important role in these types of cells [92].

In the same way that CBD acts as a PPARγ agonist to control inflammation, another receptor has attracted the attention of the scientific community in the control of neuroinflammation, the retinoic X receptor (RXR) [93]. This receptor has retinoic acid, in the form of cis retinoic acid as its agonist. When the receptors, PPARs and RXR are activated at the same time by their respective agonists, this heterodimer interact simultaneously in the DNA-binding domain activating the peroxisome proliferator response element (PPRE) to control inflammation [94, 95].

Naturally occurring retinoids, such as all-trans-retinoic acid and 9-cis retinoic acid regulate a wide variety of physiological functions through two subfamilies of nuclear receptors called retinoic acid receptors (RARs) and RXRs [96]. Each of these subfamilies has three subtypes (α, β and γ), which are encoded by a single gene. Retinoic acid in cis form is the main RXR receptor agonist [97]. In a study on the action of retinoic acid in rats, it was shown that retinoic acid regulates the expression of genes related to AD and attenuates amyloid pathology in a transgenic mouse model [98]. The 9-cis retinoic acid inhibits γ-secretase (enzyme complex to generate betaamyloids) through both nuclear receptors, retinoic acid-α (RARα) and retinoid X receptor-α (RXRα) [99]. These findings provide a new mechanistic explanation for the neuroprotective role of retinoic acid in the pathology of AD.

Neuroinflammation is characterized by the ac-

tivation of glial cells [100]. This is closely associated with the pathogenesis of several neurodegenerative diseases, including AD, PD and amyotrophic lateral sclerosis (ALS) [101, 102, 103]. Nevertheless, microglia have become an important target for research in scientific works [104]. These immune cells become activated and induce significant and highly damaging neurotoxic effects by excessively producing a wide variety of cytotoxic and pro-inflammatory mediators, including inflammatory enzymes nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [105]; proinflammatory cytokines, such as IL-1β and TNF-α [73, 106]; chemokines, such as monocyte chemo-attracting protein (MCP-1) [107]; and, transcription factors, such as the NF-κβ [108]. Therefore, anti-inflammatory treatment via inhibition of microglial activation is a promising strategy for the prevention of neurodegenerative diseases and one of the molecules which drew the attention of the scientific community to this is pyrroquinoline quinone (PQQ) [109].

PQQ is a naturally occurring redox cofactor that acts as an essential nutrient as well as a potent antioxidant [110]. PQQ also has potent immunosuppressive effects and works to eliminate free radicals [111]. In studies carried out with PQQ, the authors reported significant antineuroinflammatory actions of PQQ in microglial cells, which regulate the NF-κB and p38 MAPK signaling pathways in vitro [111]. In addition, the in vivo efficacy of PQQ was also demonstrated, in an animal model with systemic treatment of polypiposaccharides (LPS) [109]. Since microglial activation and the consequent release of various inflammatory components contribute to neurodegeneration, PQQ can potentially protect against microglia-mediated neurodegenerative diseases [112].

Another metabolism intermediary that has attracted the attention of the scientific community is the mononucleotide nicotinamide (NMN). NMN is an intermediate precursor to the biosynthesis of nicotinamide dinucleotide (NAD+) [113]. This molecule has demonstrated several beneficial pharmacological activities in preclinical studies, which suggests its potential therapeutic use [114]. Mediated primarily by their involvement in NAD+ biosynthesis, the pharmacological activities of NMN include its role in cellular biochemical functions, cardioprotection, diabetes, AD and complications associated with obesity [115]. In the recent past, this molecule was known only for its activity as an intermediary in the biosynthesis of NAD+. During this NAD+ biosynthetic process, NMN acts as an important substrate for enzymes such as nicotinamide mononucleotide adenylyltransferase 1 or NMNAT 1 of nuclear origin and NMNAT 3 of mitochondrial origin, which helps in enzymatic conversion to NAD+ in humans [115, 116]. Regarding the treatment of AD, NMN showed promising activity. Studies have reported that NMN can treat underlying causes of the disease, such as morphological abnormalities of mitochondria, decreased oxygen consumption rates and content of the NAD+ itself [116]. In a study with NMN, Hong et al (2020) have also suggested that as the pharmacological interventions currently available aim only to provide symptomatic treatment and these drugs cause several side effects, the choice of NMN may be a promising option as it directly affects the etiology of this disease [117, 118]. NAD+ is recognized for its catalytic activity in aerobic respiration, where oxygen is consumed by mitochondria [119]. Due to aging and the pathophysiology of AD, the availability of NAD+ decreases, which leads to a decline in oxygen consumption by the mitochondria of the brain and muscle cells [114]. Therefore, the mitochondrial dynamics depends entirely on the fission and fusion of the mitochondria [120]. Consequently, in neurodegenerative diseases, mitochondria tend to suffer more fragmentation, that is, increase in fission and decrease in fusion leading to the morphology and abnormal function of mitochondria [121]. On the other hand, NMN demonstrated the ability to decrease plaque formations by 140% when these were induced bylong-term potentiation dependent on the NMDA receptor, in chemical synapses in the brain compared to the values basal [122]. NMN restored the levels

of NAD + and ATP, eliminating the accumulation of ROS in the hippocampus slices treated with Aβ oligomers [122]. In the study by Qin et al (2009) the authors reported that NMN activated a protein also know sirtuin 1 (SIRT1) via NAD+ biosynthesis via rescue which in turn, stimulated the de-acetylation of the target protein PGC-1α, responsible for mitochondrial biogenesis [123]. This demonstrates that NMN has anti-aging properties, as it activates both proteins linked to aging, mitochondrial biogenesis and ROS control.

Table 3

S.no.	Herbs/Nutraceuticals	Mitochondrial interaction	Reference
1	N-acetyl cysteine	Increase in GSH levels and protects against Aβ toxicity through the activation of anti-apoptotic signaling pathways	Tardiolo et al (2002)
2	γ-Glutamylcysteine	Increase in GSH levels, and significant positive regulation of IL-10 levels and significant negative regulation of TNF-α, IL-6 and IL-1β	Zarka & Bridge (2017)
3	CBD	↑PPAR-γ and ↓NF-kβ	Burstein (2005)
4	PQQ	Regulate the NF-κB and p38 MAPK signaling pathways	Cenini & Voos (2019)
5	NMN	Improve morphological abnormalities of mitochondria, oxygen consumption rates and content of the NAD+ itself	Long et al (2015)

Discussion

In brain studies of postmortem patients, the excessive amounts of Aβ plaques formed in the brain of these individuals were remarkable, being considered one of the main characteristics of AD [124]. Also characteristic of the disease is the loss of connection between nerve cells in the brain [31]. While most mitochondrial proteins are nuclear encoded causing the mitochondria to malfunction, the mitochondrial genome encodes several important proteins for the electron transport chain, which if damaged, can lead to mitochondrial changes seen in AD. In 2010, the study by Swerdlow et al proposed the mitochondrial cascade hypothesis in AD [18]. The study pointed out that an individual's genetics determines the underlying mitochondrial function and how mitochondria changes as the person ages and is exposed to various environmental assaults. In effect, the decrease in mitochondrial function results in a specific pathology for AD. This hypothesis was supported by several lines of evidence that suggest an important role for mitochondrial dysfunction in AD.

Because new research efforts aim to increase mitochondrial function and bioenergetics by offering an alternative treatment strategy for the disease, the improvement of these treatments in preclinical models can produce favorable effects to benefit people with AD [24]. As we know, neurons are strictly dependent on the presence of mitochondria, especially in the synapses where these organelles produce ATP and concentration of Ca2 + ions, fundamental processes for the implementation of neurotransmission and generation of membrane potential along the axon [11]. Therefore, controlling ROS, as well as reducing the inflammatory cascade in neurons can be a good strategy in controlling the disease [39]. The reduction of cholesterol in the external mitochondrial membrane may be another path for the reentry of glutathione in the control of ROS, which occurred due to the imbalance in the metabolism of the mitochondrial respiratory chain seen in AD [125]. Apparently, using GSH precursors [70, 71] with phytotherapics and nutraceuticals that control inflammation,

especially those that inhibit NF-kβ can become an interesting way for the alternative treatment of this pathology.

Another not less important factor would be to use the agonists of the PPARs α and γ. PPAR-α acts as one of the most important signalers in mitochondrial biogenesis, being the main regulator modulating energy and lipid homeostasis through transcriptional regulation of fatty acid metabolic enzymes [126]. Increasing the activity of this receptor by specific agonists may be an alternative therapy. The same process occurs with PPAR-γ. Studies have shown that the micro RNA128 (miR-128) that form the Aβ plaques are antagonistic to the activity of the PPAR-γ [127]. Once the activity of this receptor is increased by specific agonists, Aβ formations can be mitigated by inhibiting miR-128 expression [126]. In the same way, John et al (2008) also suggests that PPAR-γ agonist inhibit NF-kβ activity controlling the neuroinflammatory cascade [128]. It may be important to control inflammatory cascade and to restore the oxidative state of the mitochondrial tricarboxylic acid (TCA) in respiratory chain to control neurological diseases. This, together with an improvement in glucose metabolism by neurons, could, in theory, bring numerous benefits to patients with AD.

Several studies have already shown that the insulin-degrading enzyme (IDE) has low activity in AD. [129]. According to Vekrellis et al (2000), IDE degrades and clears Aβ in the brain [130]. IDE is also seen as a potential target for upregulation in the treatment of AD. In the studies by Leal et al (2013), the authors evaluated post-mortem brains of patients with Alzheimer's disease and suggested that the oxidative damage induced by the accumulation of mitochondrial β amyloid (mitAβ) is associated with mitochondrial dysfunction [131]. Although the regulation of mitAβ metabolism is still unknown, isoform IDE (IDE-Met1) was detected in these brains, demonstrating that its expression is regulated by the mitochondrial biogenesis pathway through peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) and nuclear respiratory factor 1 (NRF-1). A strong positive correlation between PGC-1α or NRF-1 and long IDE isoform transcripts was found in brains without dementia. This correlation was weaker in AD. In the same study, in vitro inhibition of IDE increased mitAβ and impaired mitochondrial respiration. These results suggest that IDE-Met1links the mitochondrial biogenesis pathway with mitAβ levels and mitochondria's functionality [131].

Conclusion

Therapies focused both on controlling mitochondrial biogenesis as well as reducing the ROS produced by these organelles have been a promising path for alternative treatments in AD. This demonstrates how closely mitochondria are correlated with AD. There are numerous protocols for alternative treatments that could serve to help combat AD. Cannabinoid treatments is one of the most promising at the moment. However, future clinical trials are crucial to report the pharmacodynamic of the plant, as well as the possible adjuvants to cannabinoids in controlling not only neuroinflammation, but also mitochondrial health. Various nutraceuticals and medicinal plants can potentiate the effects of cannabinoids in the control of the disease, especially when thinking about PPAR agonists. Administering agonists of both PPAR-α and PPAR- γ has become a target for neuroinflammatory therapies to control not only AD, but several other
neurodegenerative diseases.

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