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Chapter

Therapeutic Approaches for Alzheimer's Disease: New Perspectives

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Abstract

Alzheimer's disease (AD) was defined as a neurodegenerative disorder, being more affected in the elderly. It is estimated that every 3.2 seconds a person in the world is affected by the high disease that rate in 2050 to 1 second. Therefore, research has been carried out on new therapeutic approaches, such as Transcranial Photobiomodulation and treatment based on antioxidants, such as Resveratrol. Therefore, the objective is to conduct a literature review on these two approaches and their effects on the treatment of AD. It was carried out according to the PRISMA recommendation and the articles were selected according to the years of publication (between 2015 and 2020) and extracted from the following databases: Science Direct, PubMed PMC, Scopus, PubMed NCBI, SciELO, LILACS, MEDLINE and PEDro. In several studies it has been reported that both therapies provide improvements at the molecular and behavioral level, recovering brain functions, acting in a neuroprotective way, improving quality of life, with few adverse effects and in a less invasive way. Thus, both treatments have numerous benefits that can be useful in the treatment of AD. However, there is a need for further research that includes interventions with greater specificity and control, so that they are defined as ideal doses and treatment protocols.

Keywords: Alzheimer's disease, dementia, photobiomodulation, LED, resveratrol, β-amyloid

1. Introduction

Over the past few years Alzheimer's disease (AD) has been studied as a designation of neurodegenerative dysfunction, leading to the most causal dementia in the elderly population [1]. According to the International Alzheimer's Association

(2015), it is estimated that there are approximately 46.8 million people with dementia in the world, and it is believed that this number will double every 20 years, reaching 74.7 million in 2030 and to 131.5 million in 2050. Therefore, it is calculated that every 3.2 seconds, a new case of dementia is detected in the world and a prediction for 2050 is a new case every second [2].

Alzheimer's disease (AD) is characterized by several factors, such as the loss of cholinergic neurons, the formation of intracellular fibrillar tangles of the hyperphosphorylated tau proteins, and due to the abnormal processing of amyloid precursor proteins that causes extracellular deposition of βA proteins [3, 4]. Therefore, it is known as a progressive neurodegenerative disorder that is related to the individual's age and causes gradual physical and mental decline resulting in death [5, 6].

Memory impairment is not always the main symptom presented in patients with Alzheimer's disease [7]. Some patients may experience significant disturbances in the visuospatial or language functions [8].

2. Amyloid cascade hypothesis

This hypothesis suggests that the characteristic neurodegeneration of AD occurs due to the accumulation of beta-amyloid (βA) protein in several brain areas, triggering the formation of senile plaques and a series of neuron injuries related processes, and formation of neurofibrillary clusters of the tau protein, which lead to neuronal dysfunction and cell death (**Figure 1**) [10–12].

The deposition of senile plaques is a result of an abnormal processing of amyloid β protein, induced by errors in the proteolytic cleavage of amyloid precursor protein by β and γ secretases. This process results in the production of different fragments, which are: the β amyloid protein 1–42, highly neurotoxic and prone to aggregation, found in the brains of patients with AD; β amyloid 1–40, a soluble and less neurotoxic protein that contributes to local plasticity and is found in healthy brains; and the β amyloid protein 1–43, presenting high amyloidogenic and neurotoxic potential, capable of depositing before the other fragments. In AD patients, the proportion of neurotoxic forms is significantly higher than β 1–40 amyloid [10–12]

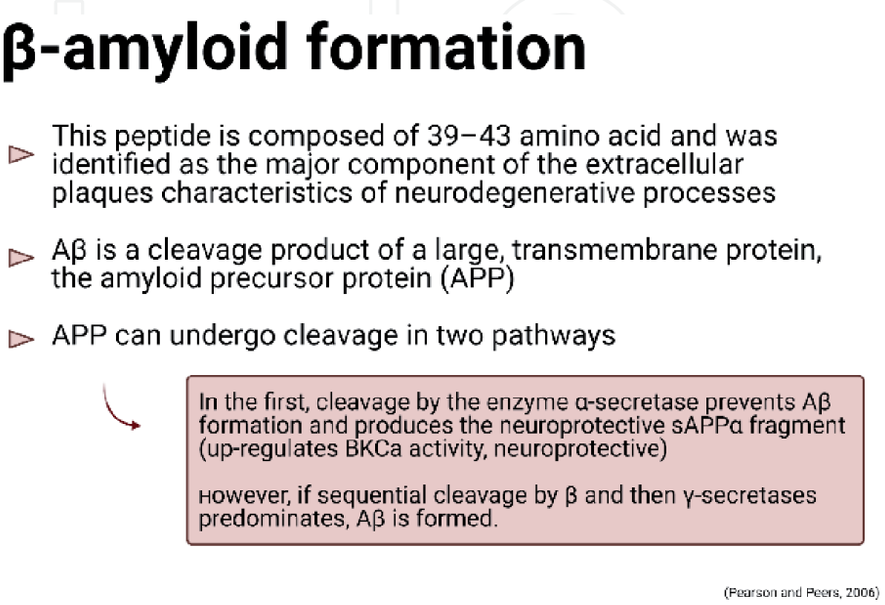

Figure 1.
β-amyloid (βA) formation [9]. Source: personal file.

Thus, the excess of βA- protein formed in the brain can trigger the formation of senile plaques, lead to inflammation, oxidative stress, hyperphosphorylation of the tau protein and, consequently, cause dementia (**Figure 2**) [10–12].

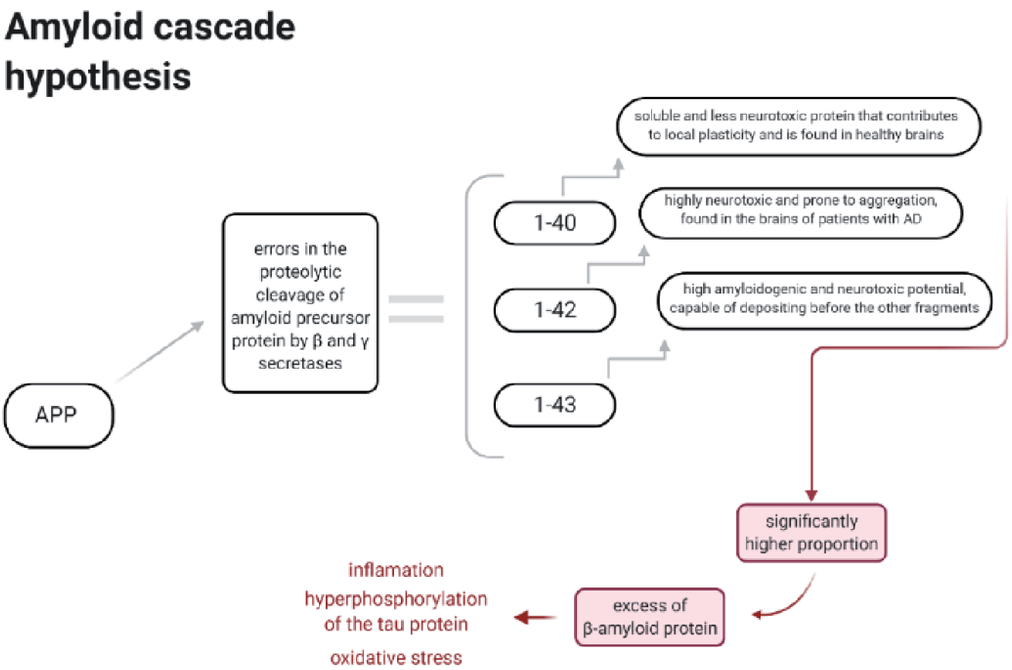

Figure 2.
Simplified schematic of the amyloid cascade. Source: Personal file.

3. Tau protein

The Tau protein is strongly associated to the responsibility of stabilizing and connecting the microtubes of the axions and dendrites. Conformational modifications in these structures and the accumulation of amyloid fragments appear to be responsible for the hyperphosphorylation of the tau protein (**Figure 3**) [14].

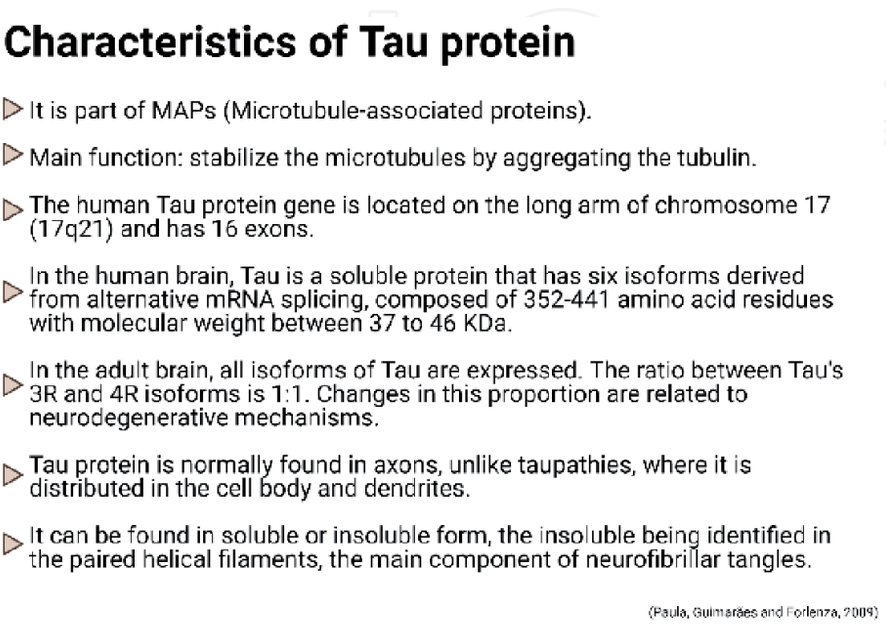

Figure 3.
Characteristics of tau protein [13]. Source: Personal file.

The hyperphosphorylation of tau in AD begins primarily in the intracellular process with the sequestration of regular tau and other proteins associated to the microtubes, causing a structural failure and thus compromising the neuronal and synaptic function [15].

The hyperphosphorylation hypothesis is due to the fact that, after the phosphorylation, an insoluble filamentous product is generated, which possibly causes the deregulation of the cytoplasmic cascade of phosphorylation and dephosphorylations. There is also a relation that the aggregations of β-amyloid may be the activating event of the protein hyperphosphorylation (**Figure 4**).

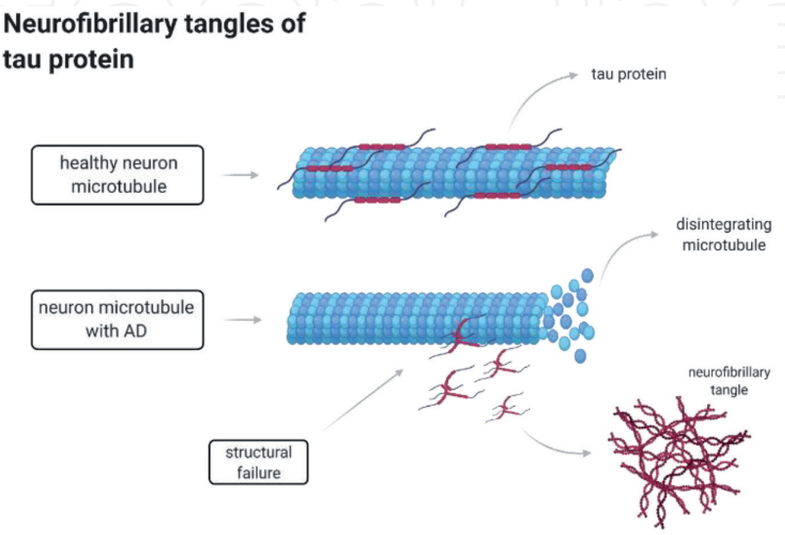

Figure 4.
Representation of the structural failure of neuronal microtubules and formation of tau protein tangles. Source: Personal file.

4. Metal hypothesis

The metal hypothesis is based on the precipitation of β-amyloid by zinc and copper radicalization, ionic zinc and copper are capable of accelerating the aggregation of Aβ, the main component of the deposition of β-amyloid [16, 17]. This hypothesis is related to the disturbance of endogenous metals in the brain, the ionic zinc and copper probably act on the cortical glutamatergic synapse, modulating the response of the inotropic receptor activated by the glutamic acid (NMDA), which can explain the vulnerability of β-amyloid to the abnormal interaction with the metallic ions on the synaptic region, leading to the aggregation and causing toxicity

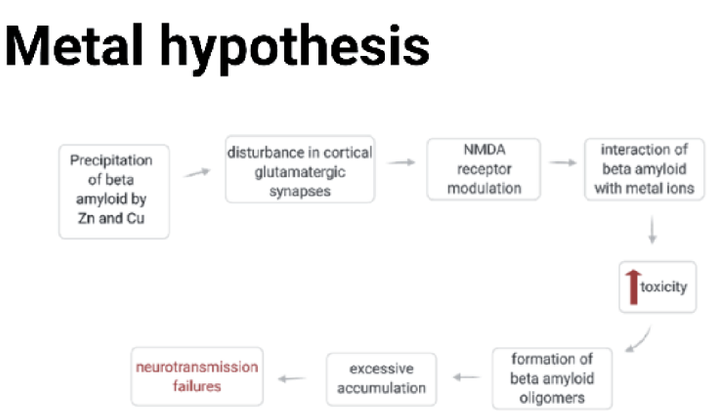

Figure 5.
Simplified scheme of the metal hypothesis. Source: Personal file.

[16]. The metals in the synapses can also lead to the formation of Aβ oligomers that have the role of modulating the long-term potentiation, which controls synaptic levels of the NMDA receptor, and this excessive accumulation of Aβ oligomers on the synaptic cleft affect the synaptic neurotransmission (**Figure 5**) [17].

5. Oligomeric hypothesis

The βA is one of the main mechanisms associated to Alzheimer's disease, and it has two main alloforms, Aβ 1–40 and Aβ 1–42, the last with more toxic oligomers [18, 19]. Studies show that the soluble oligomers, unlike the plaques, are the main cause of the synaptic disfunction and neurodegeneration. Oligomeric soluble Aβ interacts with several proteins, such as NMDA glutamatergic receptors and some proteins responsible for the maintenance of glutamate homeostasis, such as absorption and liberation [18].

It was discovered that βA oligomers were seen as intermediates in the path of disease-causing fibrils instead of impelling fully developed conditions. After that, oligomers were reported as a possible cause of Alzheimer's disease and neuronal death [20].

In the 2000s it was possible to understand that the βA fibrils are weakly toxic, but induce the neuroinflammation and, when agglomerating, they become dense and tend to detach and turn into oligomers. It is believed that currently βA oligomers exert their harmful effects connecting directly to the neuron membranes or to other specific receptors such as the insulin and glutamate (NMDA) ones, which are necessary for the neuronal signaling (**Figure 6**) [20].

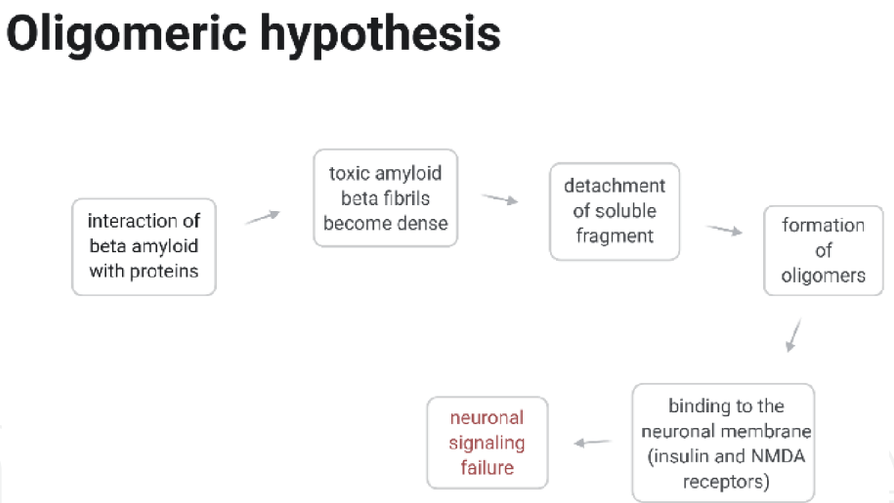

Figure 6.
Simplified scheme of the oligomeric hypothesis. Source: Personal file.

6. Glutamatergic dysfunction

The glutamatergic hypothesis refers to the biggest excitatory system of the central nervous system, the glutamatergic system. In AD, as well as in other acute and chronic neurodegenerative diseases, the loss of neurons may be due to an excessive synaptic excitation mediated by the glutamate amino acid, which explains the other denomination of the hypothesis as excito-toxic [11].

The glutamatergic system includes ionotropic and metabotropic receptors, both activated by glutamate, but in this hypothesis the ionotropic receptors stand out, such as NMDA, α-amino-3-hidroxi-5-metil-4-isoxazolepropionic acid (AMPA) and kainate, which contain ionic channels related to the neuronal polarization and depolarization processes [11, 21].

The NMDA receptors are responsible for the control of ion conductance, and when activated they determine mainly the entrance of Ca^{+2}, which increases the intensity and duration of the depolarization of the post-synaptic neuron, characterizing the long-term potentiation (LTP), which strengthens and shapes synapses, influencing phenomena such as learning and memory [11].

The activation of these receptors is essential, but in excess it can create pathogenic mechanisms related to neurodegenerative processes due to the calcium homeostasis, for when it is in high amounts in the intercellular medium, it can operate in the process of neuron degeneration and death (**Figure 7**) [21].

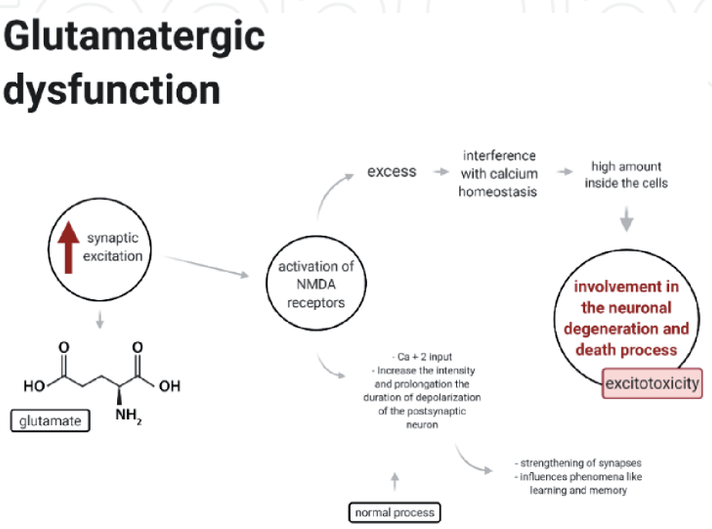

Figure 7.
Simplified scheme of the hypothesis of glutamatergic dysfunction. Source: Personal file.

7. Cholinergic hypothesis

The importance of acetylcholine (ACh) in the learning process and memory is known since the 70's, when studies showed a reduction of choline acetyltransferase (enzyme that synthesizes ACh) in the cortex and hippocampus, and less cholinergic neurons on Meynert's basal nucleus in subjects with AD [11, 22].

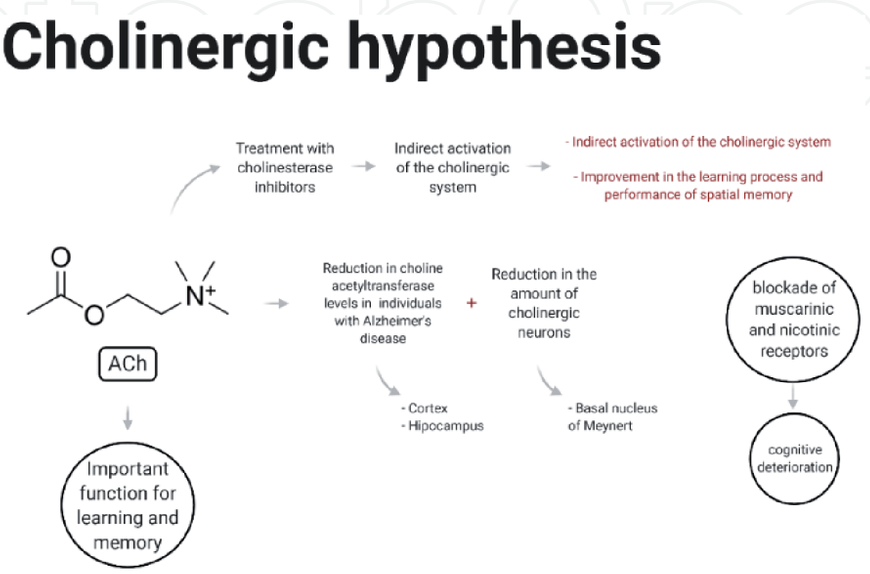

Figure 8.
Simplified scheme of the cholinergic hypothesis. Source: Personal file.

It was demonstrated that substances that inhibit acetylcholinesterase (enzyme that degrades ACh) cause positive effects on the learning and spatial learning performance, due to an indirect activation of the cholinergic system [22].

In addition to that, it is been reported that the blocking of muscarinic and nicotinic receptors leads to cognitive deterioration, indicating the importance of two kinds of receptors in the mechanism of memory and learning (**Figure 8**) [23].

8. Type 3 diabetes hypothesis

Metabolically, the brain is one of the most active organs of the human body because it processes big amounts of carbohydrates to generate energy as ATP. The brain does not count with the possibility of turning different substrates into energy, therefore, there is a higher use of glucose, and in the event that this supply or the ability of metabolization are compromised, this organ tends to become unprotected, and synapses failures are likely to happen, resulting in cognitive alterations [24].

Insulin has an important role in memory processing, it is capable of crossing the hematoencephalic barrier and is also produced in the brain tissue. Patients with AD show reduced insulin concentration and a smaller number of its receptors. When this is corrected with pharmacological intervention, there is an improvement in the processes related to cognition [25].

Also, studies show that toxic effects of βA might cause resistance to insulin, and this process may lead to an accumulation of βA, which constitutes in a positive feedback associated to the progressive neurodegeneration process characteristic of AD (**Figure 9**) [25, 26].

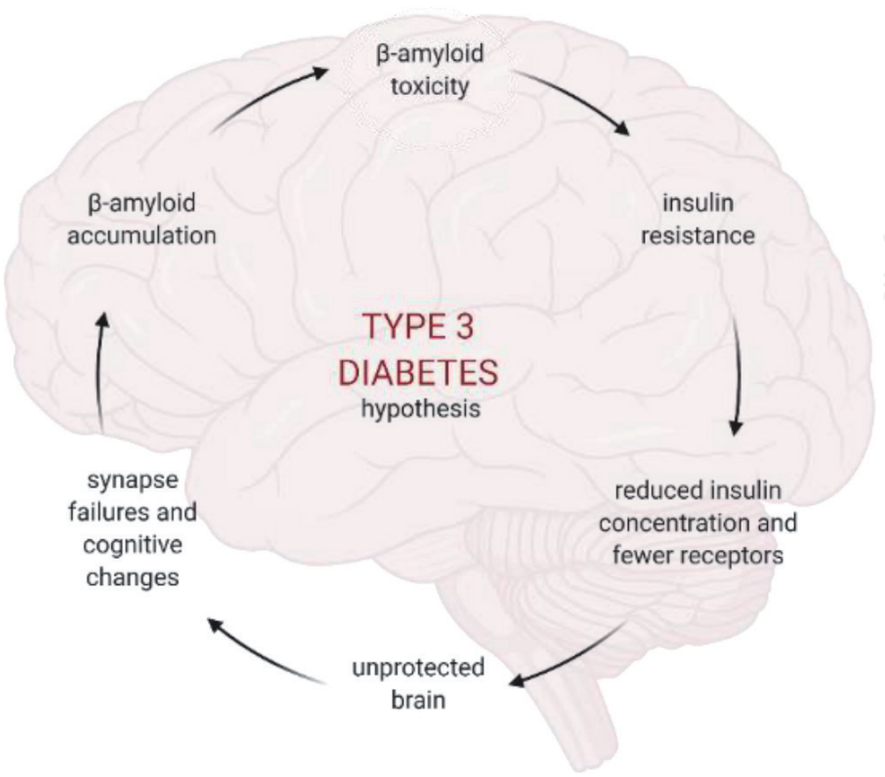

Figure 9.
Simplified scheme of the type 3 diabetes hypothesis. Source: Personal file.

9. New therapeutic approaches

Because there are only two classes of compounds commercially available for the AD treatment, and due to the failure of other approaches, several studies have been carried out in search of new therapies that are equally effective, safe, or better for treating the disease [10]. In this chapter, two forms of therapies that have been widely studied are discussed, namely: transcranial photobiomodulation (with LED) and treatment with antioxidants (Resveratrol).

9.1 Research method and inclusion of articles

The evaluation of clinical trials carried out on models of Alzheimer's and/or dementia that were treated by Photobiomodulation using light emitting diodes (LEDs) and Resveratrol was performed.

It was carried out in accordance with the PRISMA recommendation, which consists of a checklist with 27 items and a flowchart in four stages that assist in the eligibility of the selected questionnaires and work development.

For the Transcranial Photobiomodulation approach, academic articles published between 2015 and 2020 will be selected in the following databases: Science Direct, PubMed PMC, Scopus, PubMed NCBI, SciELO, LILACS, MEDLINE e PEDro. The descriptors will be in the English language only: Alzheimer's disease, light-emitting diode.

For treatments with Resveratrol, articles published between 2015 and 2020 will be selected and found in the following databases: Science Direct, PubMed PMC, Scopus, PubMed NCBI, SciELO, LILACS e MEDLINE. The descriptors will be in English: Resveratrol, Alzheimer's, neuroprotection.

Eight and six articles were selected to Transcranial Photobiomodulation and Resveratrol, respectively, to elaborate the discussion of this work.

9.2 Description of articles

9.2.1 Transcranial photobiomodulation (using LED)

In a report of a series of cases on subjects with AD or mild to moderately severe dementia, Saltmarche et al. [27] investigated the effects of photobiomodulation by 810 nm LED. The sample was composed of 5 patients with moderate to severe AD. The therapeutic adopted was infrared photo-biomodulation by pulsed LED (810 nm, 10 Hz), the device placed transcranial and intranasally for 12 weeks. Were used Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS- cog) and statistical analysis, being investigated the effect of photo-biomodulation on clinical dementia. The results suggested that significant improvement in dementia while presenting functional increase, improvement of sleep, and less outbreaks of anxiety as well as rage, and that this device can be used safely and that there were no adverse effects.

Chao [28] used 8 participants (mean age: 79.8 ± 5.8 years old) diagnosed with dementia. The patients were treated with intranasally photobiomodulation with the Vielight Neuro Gamma device three times a week for 12 weeks and analyzed by Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog); Neuropsychiatric Inventory (NPI); Magnetic resonance. The results were based on cognitive and behavioral function, cerebral perfusion, and functional connectivity at rest. It was found that the therapy provided improvements in ADAS-cog and PNI, increased cerebral perfusion and the enhancement of the connectivity between the posterior cingulate cortex and the lateral parietal nodes in the network in a standard

way. Furthermore, the therapy was well tolerated and not associated with any adverse effects, indicating potential use as a viable home treatment for patients with dementia and AD.

Purushothuman et al. [29] used 2 models of mice with AD, a tau model K369I (K3), containing 15 animals and the other βA model APPs/PSEN1dE9 (APP-PS1) containing 18 animals. The therapeutic adopted was light from the LED device (670 nm), cycles of 90s (4 J/cm^2), 5 days a week, for 4 weeks, exposed 1 to 2 cm above the head. In relation the methods of analysis, they used histology by the Bielschowsky silver staining method, morphological analysis, histochemical analysis, and statistical analysis. Evaluating the effects on the cerebellar region, was observed that the positive effects of LED extend to the other brain regions; provoking a reduction of the neurodegenerative effects caused by AD in the cerebellum, such as the deposition of βA, neurofibrillary tangle formation and oxidative stress damage. So, in the findings of Purushothuman, LED was shown as an effective and safe alternative for treatment of neurodegenerative effects, being able to minimize and delay the pathological changes caused by dementia in different regions of the brain such as the hippocampus, neocortex and cerebellum.

Han et al. [30] used animal model APP/PSEN1, 30 female mice divided into 3 groups with 10 animals each: treatment group, positive control group, and negative control group. The therapeutic adopted was LED emitting infrared light for 6 minutes for a period of 40 days, and the animals were analyzed by the method of Morris Aquatic Labyrinth and the results by statistical analysis. The measured parameters were spatial memory and cognitive performance after treatment with LED. The results suggested that infrared therapy emitted by LED can improve the performance in spatial learning and memory capacity.

Han et al. [31] used animal model C57BL/6 J, being females divided into 3 groups: rats without irradiation (n = 10), rats with irradiation (n = 10), and normal rats without irradiation (n = 12). The therapeutic adopted was LED with wavelengths between 1040 nm and 1090 nm, power of 15 mW/cm2; 6 minutes a day, for 40 days, suspended for 28 days, and then starting the treatment again for another 15 days. The measured parameters were spatial memory and the presence of senile plaques after the LED treatment period. They found that LED is able of improving performance in spatial learning and moderately reduces senile plaques.

Eltchechem et al. [32] used 60 rats, 30 treated (GT group) and 30 in a control group (GC group). The treatment was with LED (627 nm 7 W/cm^2, 70 mV) in the frontal region, one time every day for 100 s for 21 days. The methods of analysis were Morris Aquatic Labyrinth, Open field, histological analysis, immuno-histochemical analysis, and statistical analysis. The measured parameters were the βA deposits in the GT in relation to the GC with 7, 14 and 21 days after LED irradiation. The results found were better movement, exploration, and spatial memory of the GT in relation to the CG.

Yue et al. [33] used APP/PS1 AD model mice treated, APP/PS1 control mice and healthy C57BL/6 mice as a negative control. The treatment was with photobiomodulation by LED 630 nm with application of 40 minutes and light intensity of 0.55 mW/cm2 in the skull and abdomen 5 days a week for 2 months. The methods of analysis were Morris Aquatic Labyrinth, fluorescent microscopy; magnetic resonance; biochemical analysis and statistical analysis. It was observed destruction of βA plaques group and activation of the formaldehyde dehydrogenase enzyme, that degrades formaldehyde, which acts by accelerating the deposition of βA in the extracellular space and, consequently, attenuation of βA aggregation facilitated by formaldehyde. In addition, the light reduced βA deposition in the extracellular space, positively influenced the flow of interstitial fluids and recovered cognitive functions in AD mice.

Cho et al. [34] evaluated the effect of photobiomodulation using 610 nm LED on amyloid plaques, gliosis, and neuronal loss to prevent and/or recover cognitive functions and the ideal time to start therapy. 5XFAD AD model rats were used, divided into a group that started therapy at 2 months old, and another at 6 months old. The treatment consisted of the simultaneous application of light in two places (midpoint of the parietal bone and midline of the seventh cervical vertebra) for 20 minutes, 3 times a week, for 14 weeks. From behavioral tests, immunohistochemical analysis and Western blot, it was found in the initial stages the reduction of the accumulation of amyloid plaques, neuronal loss and microgliosis, and the relief of cognitive dysfunction.

9.2.2 Resveratrol: Neuroprotective action

Yin et al. [35] investigated if resveratrol could mitigate the early loss induced by βA in the neuron excitability in the hippocampus and the mechanism involved on it. The excitability and the potassium currents dependent on the pyramidal neuron CA1 voltage of rats were analyzed using the whole-cell patch-clamp technique. The authors discovered that resveratrol reverted the increase of βA peptide and the increase induced in the frequency of the repetitive shots, mitigated the decrease induced by βA in the transitory potassium channels, and rectified the delay on neuron potassium channels. Besides, it was shown that resveratrol decreased the levels of kinase A (PKA) and inhibited the activation of the signaling path PI3K/Akt.

Sarroca et al. [36] assessed the beginning and progression of the pathology of Alzheimer's disease through a diet rich in fat (HFD) and the influence of resveratrol in this situation. Many evidences suggest that HFD increases the risk of Alzheimer's disease (AD), but the molecular mechanisms through which the HFD causes its negative effects on the brain and the pathophysiology of AD are still widely unknown. The authors used wild mice (WT) and AD 5XFAD transgenic (5XFAD mice represent an aggressive model of AD due to the exposure to intraneuronal β-amyloid-42 in 1,5 months, extracellular amyloid plaques in 2 months, gliosis in 2 months, memory deficits in 4 months and neuronal loss in 9 months) treated with a control diet of HFD (60% kcal of fat) or HFD supplemented with 0,1% of resveratrol for 16 weeks. From the analysis of behavioral tests, glucose intolerance tests, preparation of tissue samples, coloring with Thioflavin-S, Western Blotting, and proteasome activity test, it was possible to observe that the results showed the resveratrol reduced the amyloid load aggravated by HFD in 5XFAD model (model of Alzheimer's disease with a pathology of low tau protein), the analysis by Western Blotting showed thar the cortex tissue did not show modification in the levels of tau protein. However, HFD was responsible for inducing a significant increase in the levels of pTau in both WT and 5XFAD mice, and resveratrol indicated the ability to normalize the levels of pTau in both groups fed with HFD. Resveratrol also inhibited the amyloidogenic processing enhanced by HFD.

Ma et al. [37] reported that AD and diabetes mellitus (DM) usually coexist in patients because one increases the incidence of the other. In this context, the authors studied the neuroprotection induced by resveratrol in mice with DM and AD caused by the injection of streptozocin (intraperitoneal) and β-amyloid 1–40 (hippocampus). Through biochemical and immunological analysis it was demonstrated that resveratrol increased SIRT1 expression, inhibited memory damage, increased the levels of acetylcholinesterase (responsible for the hydrolysis of acetylcholine in cholinergic synapses), malondialdehyde (marker of oxidative stress), interleukin-1β and interleukin 6 (interleukin-1β acts in the hypothalamus stimulating the release of corticotrophin by the posterior pituitary gland and the corticotrophin acts on the anterior pituitary gland, releasing adrenocorticotrophic hormone, and interleukin 6 is responsible for the influence on the immunological

responses, mediating the acute stage of the inflammation), and showed decreased levels of choline acetyltransferase (mediator of the synthesis of acetylcholine), superoxide dismutase (responsible for catalyzing the dismutation of the superoxide in oxygen and hydrogen peroxide, an important antioxidant defense), and glutathione (causes several antioxidants, neutralizes free radicals).

Corpas et al. [38] evaluated the neuroprotection effects of resveratrol in two groups of mice: non-transgenic control (NoTg) and AD transgenic model (3xTg-AD). Both groups were fed with a supplemented diet of 100 mg/kg from 2 months of age for 10 months. Using Western Blotting, behavior and cognitive tests and proteasome activity test, it was possible to analyze how resveratrol induced complete protection against memory loss and brain pathology in 3xTg-AD mice and induced a cognitive increase in healthy NoTg mice. It also reduced anxiety in both strains, reducing the presence of hippocampal βA and tau protein in 3xTg-AD. As for the proteostases analysis, an increase of the levels of the enzyme neprisilin was observed, being responsible for the degradation of β-amyloid, reduction of amyloidogenic secretase BACE1, increase of the levels of proteasome protein in both mice groups, vital role in the increasing of the adenosine kinase activated by monophosphate (AMPK) and the positive regulation of the SITR1 path.

Chen et al. [39] evaluated the levels of resveratrol in Tg6799 mice (transgenic model with five family mutations on Alzheimer's disease). The mice were divided in a group treated with resveratrol (solution 0.5%, 60 mg/kg) and a control group (treated with saline solution). The treatment was administered orally, daily, for 60 days. To interpret the results, the tests performed were the open field test, Y maze test, Morris aquatic labyrinth test, coloring with Thioflavin-S, ELISA Aβ40 and Aβ42 and finally Western Blotting, demonstrating that resveratrol reduced the disposition of the amyloid plaques, β-amyloid levels of −42 and β-secretase levels. Resveratrol also reduced the expression of the amyloid precursor protein and its cleavage products. Besides, there was a behavioral improvement related to the spatial working memory, according to the Y maze test, and improvement on the spatial memory deficits, evaluated by the Morris aquatic labyrinth test. However, resveratrol did not influence the motor function.

Wang et al. [40] used AD model rats (by hippocampal injection of β-amyloid 1–42) to investigate the possible effects of resveratrol on the behavior of spatial learning, memory and synaptic plasticity, as well as changes on the expression and phosphorylation of SIRT1 of the protein connecting to the response element of cyclic AMP (CREB). In addition to the already accepted analysis, protein extraction and Western Blotting were also done, and it was shown that resveratrol reverted the spatial learning memory damage evaluated by the Morris aquatic labyrinth, and to investigate the underlying mechanisms of the neuroprotector effects of resveratrol on the memory and learning, the long-term potentiation (LTP) was registered in the CA1 area of the hippocampus. So, it was demonstrated that the Aβ1–42 hippocampal injection did not affect significatively the basal excitatory post-synaptic potential (fEPSP), while Aβ1–42 suppressed the induction of hippocampal LTP. In addition to that, resveratrol avoided reductions on the expression of SIRT1 and phosphorylation of the cyclic AMP response element connecting protein (CREB).

10. Discussion

10.1 Transcranial photobiomodulation

LED is a radiation of varying wavelength, not coherent and which is standing out in the field of medical treatment and phototherapy for being an alternative

to the high cost of laser therapy [41]. The use of light with Low-intensity Laser Therapy or by Light-emitting Diode is called photobiomodulation [42] and among its functions, it is the stimulation of neural activity, that occurs through interaction with cytochrome c oxidase (unit IV of the mitochondrial electrons transport chain), which through a series of reactions, stimulates the ATP synthase enzyme to produce more ATP, improving brain function [27]. LED, however, emerged as an innovation in the field because it does not give off heat, is portable, is easy to apply, and is more durable when compared to other methods such as laser therapy (**Figure 10**) [27].

Recent advances in optogenetics and the development of microscale LED platforms have elevated the viability of phototherapy for use on target brain cells [43]. The method in the treatment of neurodegenerative diseases is under development, and studies show that this therapy can act on amyloid aggregates [44, 45].

Although biological effects of the light emitted by the LED have been reported for a wide spectrum of wavelengths, the research related to the effects on the Alzheimer disease has focused on the wavelengths in the region of the nearby infrared. This approach involves the tissue irradiation with a low intensity light and promotes protective effects on the central nervous system [46].

In this approach, the primary photoreceptors are the mitochondria, and there is evidence that the action is responsible for preserving and restoring the function of the neurons by their action on the mitochondrial cytochrome *c* oxidase enzyme, which, due to a series of biochemical reactions, results in a greater production of ATP by the stimulation of the ATP synthase enzyme. Moreover, the effect is also related to the signaled pathways activated by reactive oxygen species, release of nitric oxide and increased cyclic adenosine monophosphate. Thus, these factors work together to produce effects in the regions in which the function was compromised by ischemia, traumatic injuries, and neurodegeneration [47].

Thus, both in animal models and in human patient trials, the treatment promotes satisfactory results. As for the studies described in the results and referring to those that used animal models, the photobiomodulation, with the different protocols tested, brought together some results. Results described in *in vivo* studies using animal models showed reduction of hyper phosphorylation of the tau protein, attenuation of neurofibrillary tangles, decreased oxidative stress markers, reduced deposition, number, and size of β-amyloid plaques, reduced neuronal loss, formaldehyde dehydrogenase activation, positive influence on the flow of interstitial fluids, and capacity to recover and improve cognitive functions, such as learning and spatial memory capacity [30–34].

Regarding the application places and treatment time in animal models, most of the studies focused on the transcranial application, except for the research by Yue et al. [33] who performed transcranial and abdominal application.

About treatment time, in general, irradiation protocols between 21 and 40 days were used, except in the study by Cho et al. [34] in which the treatment (both early and late) was carried out for 14 weeks, and represented a longer irradiation protocol, which differs from those established by other authors.

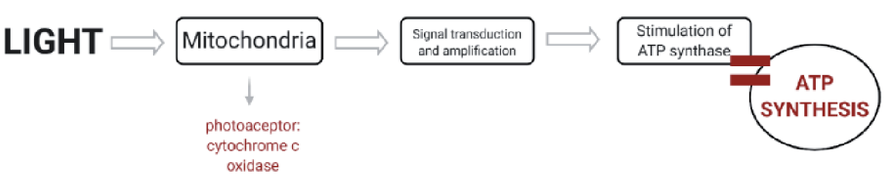

Figure 10.
Simplified scheme of the action mechanism of photobiomodulation. Source: Personal file.

In relation to human patients, the effects were mostly focused and described on mental and cognitive performance states. It was observed that the therapy provided a significant improvement in dementia, and presented cognitive functional increase, sleep improvement and fewer anxiety and anger outbreaks [27, 28]. It has also provided an increase in cerebral perfusion between the posterior cingulate cortex and the lateral parietal nodules in the network in a standard way [28].

The locations of application and time of treatment in clinical research were similar. Both studies that involved human models reported the use of transcranial and intranasal photobiomodulation. The treatment time did not differ either. A twelve-week protocol was adopted, which the only difference was in the post-treatment follow-up, with a period of four weeks without treatment being observed in the research by Saltmarche [27].

As for safety in the human model, the treatment was described as well tolerated and did not induce any adverse effects. These results support the therapeutic potential for viable treatment (including home treatment) of patients with dementias. However, larger, and more controlled studies are still necessary. It is indispensable, for consolidating the therapy, to clarify the ideal irradiation parameters such as application time, active treatment, and follow-up, as well as the general efficacy and safety profile [27, 28].

Regarding considerations for future research, they should be carried out by following longer and not discontinued treatment protocols. As according to Saltmarche [27] a period of four weeks without treatment, after initiation, resulted in deterioration of the positive effects achieved with twelve weeks of active treatment, and it caused difficulties for patients and caregivers. Furthermore, the author describes that the movement of patients to the clinic for LED applications caused stress. Therefore, for future work, home treatment is expected, which is possible considering the facility and viability of the application if it is properly oriented and performed.

Finally, it is interesting to use standardized cognitive assessments that consider different aspects, such as quality sleep, communication and social interaction, reduction of anxiety, depression, and disturbing behaviors to cover most of the effects induced by photobiomodulation.

10.2 Resveratrol

The importance of oxidative stress in AD has been increasingly recognized. Several studies have shown evidence that oxidative stress may contribute to the pathogenesis of AD through the formation of oxygen free radicals. Thus, the therapeutic focus has also been directed towards the use of antioxidants in the treatment of AD [10, 48].

Although antioxidants do not provide objective improvement in cognition, they can delay the natural evolution of the disease due to their supposed neuroprotective effect [48]. Polyphenols from food consumption plants have already been confirmed as neuroprotective compounds, including by a reduction on the aggregation of β-amyloid protein, such is the case of the trans-3,5,4′-trihydroxystylbene, Resveratrol [12].

Resveratrol is widely found in grapes used to produce red wine and in cereals and has been tested in different models of the disease (*in vitro* and *in vivo*), presenting neuroprotective effect and inhibiting the aggregation of βA [12].

Among its different proven forms of action, the following stand out: (a) competition with coenzyme Q to reduce the oxidative complex, the site of production of reactive oxygen species (ROS); (b) neutralization of oxygen free radicals formed; and (c) inhibition of lipid peroxidation induced by Fenton reaction products, in the mitochondria (**Figure 11**) [49].

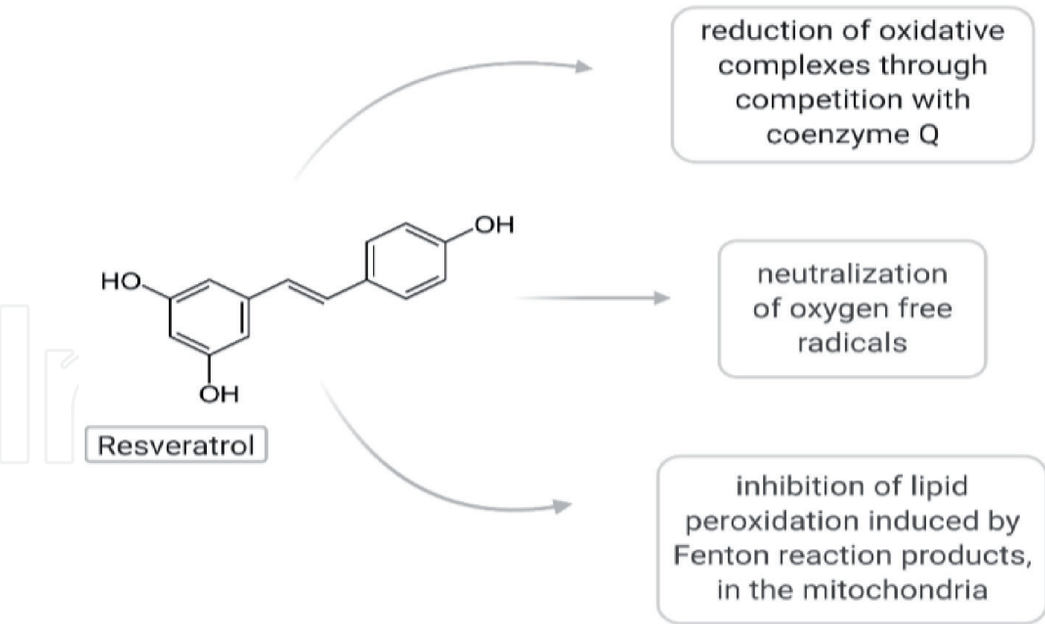

Figure 11.
Effects of resveratrol already proven. Source: Personal file.

In vitro studies have shown that Resveratrol has neuroprotective and preventive effects related to oxidative damage induced by β-amyloid and memory loss by reducing the accumulation of lipid peroxides, positive regulation of the endogenous antioxidants action and increased expression of memory associated proteins [50]. Although the effects of Resveratrol are mostly attributed to its antioxidant activity, studies suggest that its biological activity may be associated with different pathways. Yin et al. [35] demonstrated that Resveratrol act on the nervous system by inhibiting the electrical activity, relieving β-amyloid induced dysfunction in hippocampal CA1 pyramidal neurons, associating this effect with the ability to recover potassium currents.

In view of its ability to modulate potassium channels, Resveratrol plays a promising activity to attenuate neural impairments induced by β-amyloid. However, as the antioxidant has shown a variety of neuroprotective actions, it is also possible that other signals are involved, such as other ion channels, e.g., calcium and sodium channels, which can be exploited in the future to elucidate the effects achieved by Resveratrol due to the relationship with certain central nervous systems disorders [35].

Regarding the in vivo studies, the effects of resveratrol were already expressed and described in different ways, and among them the ones of note are reduction of amyloid load and inhibition of the amyloidogenic processing [37–39], neuroprotection of memory loss, cognitive improvement and acetylcholinesterase inhibition [38, 39], anxiety reduction, increase on the AMPK levels [36, 39], positive regulation of the SIRT1 path [37–40] and reversion of the damage on spatial memory [39, 41].

As a future perspective, based on the neuroprotectant activities observed in vitro and in vivo, it is expected that clinical trials are done with long term treatments and low formulations with improved pharmacokinetic properties (due to the low availability shown) to sustain the possibility of a therapeutic alternative for the treatment of AD, as well as the clarification of its mechanisms of action, safety and efficiency.

11. Conclusion

Thus, it is concluded that both the treatment with Transcranial Photobiomodulation using LEDs as light sources, and the treatment with

Resveratrol have numerous benefits that can be useful in the treatment of AD. However, there is a need for new research that covers interventions with greater specificity and control, so that the ideal doses and treatment protocols are defined.

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