Journal of Lasers in Medical Sciences

J Lasers Med Sci 2020 Autumn;11(Suppl 1):S16-S22

Systematic Review

http://journals.sbmu.ac.ir/jlms

doi 10.34172/jlms.2020.S3

Therapeutic Potential of Photobiomodulation In Alzheimer's Disease: A Systematic Review

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Published online December 30, 2020

Abstract

Introduction: Alzheimer disease (AD) is characterized by the decline of cognitive functions such as learning and memory. Scientific society has proposed some non-pharmacological interventions, among which photobiomodulation has gained prominence for its beneficial effects. Therefore, we investigated, through systematic review, the therapeutic potential of photobiomodulation in AD.

Methods: This systematic review was registered under the number CRD42019128416 in the International Prospective Record of Systematic Reviews (PROSPERO). A systematic search was conducted on the bibliographic databases (PubMed and ScienceDirect) with the keywords based on MeSH terms: "photobiomodulation therapy" or "low-level laser therapy" or "LLLT" or "light emitting diode" and "amyloid" or "Alzheimer". The data search was conducted from 2008 to 2019. We follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The search strategy included experimental *in vivo* and *in vitro* studies in the English language and photobiomodulation as a non-pharmacological intervention. We included 10 studies, being 5 *in vivo* studies, 4 *in vitro* studies and 1 study using *in vivo* and *in vitro*. To evaluate the quality of the studies, we used the Rob tool of the Systematic Review Center for Laboratory Animal Experimentation (SYRLE).

Results: The studies showed that photobiomodulation is able to reduce inflammatory response, oxidative stress and apoptotic effects generated by amyloid beta (Aβ) and restore mitochondrial function and cognitive behavior.

Conclusion: Taken together, these results indicate that photobiomodulation may be a useful tool for treating AD.

Keywords: Photobiomodulation therapy; Low-level laser therapy; LLLT; Light emitting diode; Amyloid; Alzheimer's disease.

Introduction

Worldwide, Alzheimer disease (AD) incidence increases faster than any other age-related dementia.[1] It is estimated that approximately 15 million people around the world suffer from this disease. By the year 2050, it is expected that 13 million people in the United States and 16 million people in Europe will be affected by AD.[2]

AD is a progressive neurodegenerative disease, characterized by gradual loss of memory and motor activities.[3-5] The pathophysiology of AD involves two mechanisms. The formation of senile plaques to which the amyloid peptide (Aβ) is considered the main component.[6] When accumulated in cortical and limbic regions, the senile plaques induce synaptic and dendritic dysfunctions, also the activation of microglia and astrocytes, triggering inflammatory response. These alterations lead to neuronal death due to cellular and biochemical damage, such as the formation of free radicals and reactive oxygen species.[7] Another feature of AD pathophysiology is related to intracellular neurofibrillary tangles, composed of tau protein. Phospho-Tau leads to the development of neurofibrillary tangles, impairing neuronal functioning and structure.[8] These mechanisms are involved in the process of cerebral atrophy, especially in the areas of the temporal lobe, such as the hippocampus and entorhinal cortex, thus determining the impairment of cognitive functions as well as behavioral disorders.[9,10]

Despite the advanced findings in AD, there is still no treatment that can cure the disease. However, some non-pharmacological treatments such as cognitive therapy,[11-12] occupational therapy,[13] and physical exercise [14-15] have provided benefits to cognitive and behavioral impairments. Recently, photobiomodulation has been of interest to the scientific community because it is a noninvasive therapy

Please cite this article as follows: Cardoso, FDS, Lopes-Martins RAB, Gomes da Silva S. Therapeutic potential of photobiomodulation In Alzheimer's disease: a systematic review. *J Lasers Med Sci.* 2020;11(suppl 1):S16-S22. doi:10.34172/jlms.2020.S3.

that provides interesting results for several tissues, such as wound healing, inflammation in various diseases and tendonitis.[16] In addition, promising evidence has emerged about its beneficial effects on the brain.[17-20] However, the results are still not sufficient due to methodological differences. Thus, in this systematic review, we analyzed the effect of photobiomodulation in *in vivo* and *in vitro* studies to provide general information on all available evidence suggesting photobiomodulation as an efficient non-pharmacological tool in AD. In addition, we will present recommendations for possible research on the use of photobiomodulation and methodologies, and finally, we will discuss the mechanisms involved in the improvement of AD symptoms through photobiomodulation.

Materials and Methods

Data Sources and Searches

This systematic review was registered under the number CRD42019128416 in the International Prospective Record of Systematic Reviews (PROSPERO) and can be accessed in https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=128416. We used the PubMed and ScienceDirect databases with the keywords based on MeSH terms: "photobiomodulation therapy" or "low-level laser therapy" or "LLLT" or "light emitting diode" and "amyloid" or "Alzheimer". Data search was conducted from 2008 to 2019. To ensure the clarity and transparency of the articles, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[21]

Selection Criteria

We selected *in vivo* and *in vitro* studies to obtain information related to cellular and molecular effects as well as their impact on cognitive function in AD.[20] The search strategy included experimental *in vivo* and *in vitro* studies and photobiomodulation as a non-pharmacological intervention. In addition, we included literature reviews and experimental studies that addressed our subject without yearly restriction for discussion.

Selection Process

Initially, duplicate articles were excluded. After that, the titles and abstracts of the search results were independently reviewed by two researchers, who applied the inclusion and exclusion criteria (Table 1). The article was considered eligible when the researcher examined the effects of photobiomodulation on brain functions in AD. Studies that included another intervention associated with photobiomodulation were excluded. Next, the results of the selection process were discussed in a consensual way to avoid disagreements regarding the eligibility of the articles. Finally, the articles were read in full to select the final list of articles. At this stage, studies evaluating brain structure (e.g. neurotrophic factors, inflammatory markers, mitochondrial function and neuronal morphology) and cognitive functions (e.g. behavioral analyzes) were included.

Data Extraction and Data Synthesis

The articles included were divided into in vivo and in vitro studies. After that, both of the groups were subdivided according to the type of model used (cell expressing the AD phenotype and animal model of AD) in the studies. In that way, the comparison between the effects provided by the photobiomodulation in different model types became easier to perform. For data extraction, we used an individualized data form,[22] which included information about the reference (author and year), characteristics of the population (sample model), characteristics of the intervention with photobiomodulation (intensity, duration, and frequency), and characteristics of the results (applied analyses and results). The data are presented in the results section as a summary of the study findings. Besides that, a qualitative synthesis of the studies was performed. Due to the variation applied in the intervention, a meta-analysis was not performed.

Quality Appraisal

We used the Rob tool of the Systematic Review Center for Laboratory Animal Experimentation (SYRLE) to evaluate the quality of studies.[23] The Rob was developed to study the methodology of experimental animal studies, based on the Cochrane Rob technique, which evaluated randomized clinical trials. The SYRLE Rob checklist consists of 10 items, which are classified in selection bias (item 1 to 3), performance bias (items 4 and 5), detection bias (items 6 and 7), attrition bias (item 8), selective outcome reporting (item 9) and other sources of bias (item 10). Item 1 is related to the description of the

Table 1. List of Inclusion and Exclusion Criteria

Area	Inclusion Criteria	Exclusion Criteria
Subjects	AD models	Models without AD
Intervention	Transcranial photobiomodulation	Pharmacological intervention and others
Results		
Kind of study	Experimental *in vivo* and *in vitro* studies	Clinical studies, case reports and review
Language	English	Other languages
Year of publication	2008 until 2019	Outside this period

AD: Alzheimer disease

methodology. In order to generate a detailed allocation sequence of the sample, which will allow a comparison among the groups. Item 2 relates to the characteristics of the animals that are compared to evaluate the intervention and groups. Item 3 describes the method for concealing the allocation sequence of the intervention which could have taken place before or during the experiment. Item 4 describes all measures used to shelter the animals in the animal room. Item 5 describes all the measures used to blind the researchers, making it impossible for them to know the intervention that each animal received. Item 6 relates to whether the animals were randomly separated for analysis and how the methods were used for the selection of animals. Item 7 describes all the measures used to blind the evaluators about the intervention that each animal received. Item 8 relates to the integrity of results, attritions, or exclusions. Item 9 relates to how the selective results were examined and what was found. Item 10 describes important concerns about biases not covered by other domains in the tool. The evaluations were made by two evaluators, who classified the information as positive (yes) which indicates a low risk of bias, negative (no) which indicates a high risk of bias, and inaccurate (unclear) which indicates an unclear risk of bias. Disagreements were resolved by consensus.

Results

Study Selection

The search in PubMed and ScienceDirect databases resulted in 306 studies. After exclusion by duplicity (49) and screening (242), 15 studies were left for reading in full. After reading, 5 studies were excluded, with 10 studies remaining in the systematic review, 5 *in vivo* studies, 4 *in vitro* and 1 study using both *in vivo* and *in vitro*. The process of selection of the articles is illustrated in Figure 1.

Study Characteristics

Characteristics of In Vivo Studies

The total number of studies using rats and mice was 5 articles. The studies used Wistar rats,[24] a K369I tau transgenic model,[25] an APPswe/PSEN1dE9 transgenic model,[18,25] 5XFAD mice[26] and Sprague Dawley rats.[27] The age of the animals varied from 3 to 12 months. Only in the works of Da Luz Eltchechem et al[24] and Lu et al,[27] the animals were free of disease at the start of the study. It is noteworthy that in all studies, the animals received transcranial photobiomodulation treatment. Most of the studies aimed to analyze the effects of photobiomodulation on damages caused by high levels of Aβ, inflammatory response and oxidative stress; mitochondrial function, signaling pathways and cognitive function were also a target of interest for the authors. The summary of the findings is given in Table 2.

Characteristics of In Vitro Studies

The total number of studies using cells expressing AD was 4 articles. The studies used PC12 cells[28-30] and primary rat astrocytes.[31] Following the idea of *in vivo* studies, in the *in vitro* studies, the aim was to verify the effects of photobiomodulation on Aβ levels. In addition, the authors gave attention to signaling pathways related to cell survival and death as well as the inflammatory process. The summary of the study findings is given in Table 3.

Characteristics of the Use of Both In Vivo and In Vitro Model of AD

Only the study of Meng et al[17] did both cells (human neuroblastoma cell line SHSY5Y) and AD model animals

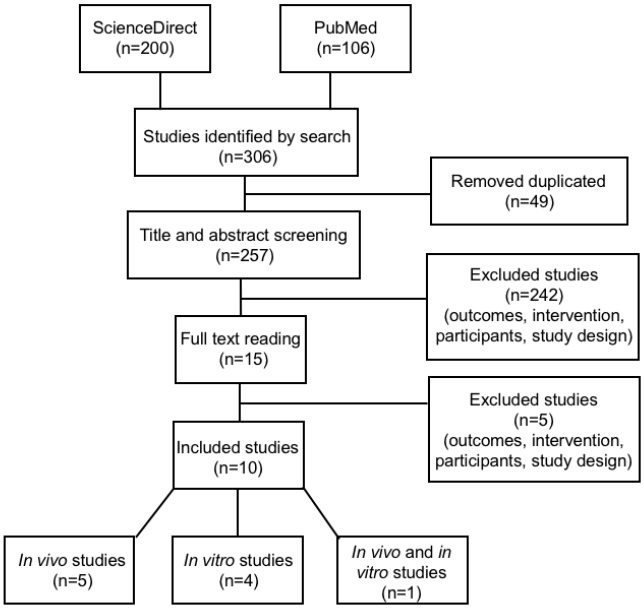

Figure 1. Article Search and Selection Process.

Table 2. Results of *In Vivo* Studies

Autor	Subjects	Intervention	Main Results	Level of Evidence
De Taboada et al[18]	APPswe/PSEN1dE9 transgenic model	**Parameters:** wavelength: 808nm; fluence: 1,2 J/cm², 6 J/cm², 12 J/cm². **Frequency:** 3 times/week for 6 months.	- Reduction in amyloid load; - Mitigation of the cognitive effects; - Reduction in the expression of inflammatory markers; - Increase in ATP levels and mitochondrial function.	50%
Purushothuman et al[25]	APPswe/PSEN1dE9 and K369I tau transgenic model	**Parameters:** wavelength: 670 nm; fluence: 9,6 J/cm². **Frequency:** 5 times/week for 4 weeks.	- Reduction in hyperphosphorylated tau and neurofibrillary tangles - Reduction in oxidative stress markers levels; - Restoration of expression of the function mitochondrial; - Reduction in the size and number of amyloid-β plaques.	40%
Lu et al[27]	Sprague-Dawley rats	**Parameters:** wavelength: 808 nm; fluence: 15 J/cm². **Frequency:** 5 consecutive days	- Attenuation of the toxic effects of Aβ; - Preservation of mitochondrial activity and integrity; - Suppression of oxidative stress; - Inhibition of inflammatory response; - Memory restoration (spatial and recognition memory).	40%
Da Luz Eltchechem et al[24]	Wistar rats	**Parameters:** wavelength: 627 nm; fluence: 7 J/cm². **Frequency:** 7, 14 and 21 consecutive days	- Reduction in the presence of Aβ plaques; - Increase in spatial memory and behavioral and motor skills.	50%
Cho et al[26]	5XFAD mice	**Parameters:** wavelength: 610 nm; fluence: 2 J/cm². **Frequency:** 3 times/week for 14 weeks.	- Reduction in amyloid accumulation, neuronal loss, and microgliosis; - Mitigation of spatial memory and aversive memory.	40%

Table 3. Results of *In Vitro* Studies

Autor	Subjects	Intervention	Main Results	Level of Evidence
Zhang et al,[29] 2008	PC12 cells	**Parameters:** wavelength: 632.8 nm; fluences: 0.156 J/cm² and 1248 J/cm²	- Inhibition of cell apoptosis via PKC-mediated regulation of bax/bcl-xl mRNA ratio.	40%
Yang et al,[31] 2010	primary rat astrocytes	**Parameters:** wavelength: 632,8nm; fluence: 16.2 J/cm²	- Suppression of cellular pathways of oxidative stress; - Reduction in inflammatory response.	30%
Liang et al,[28] 2012	PC12 cells	**Parameters:** wavelength: 632.8 nm; fluence: 2 J/cm²	- Promotion of prosurvival effects through the Akt/GSK3b/b-catenin pathway.	40%
Zhang et al,[30] 2012	PC12 cells	**Parameters:** wavelength: 632.8 nm; fluence: 2 J/cm²	- Promotion of prosurvival effects through the Akt/YAP/p73 signaling pathway.	40%

(APPswe/PSEN1dE9 transgenic model), with 50% of the evidence level.

In the study by Meng et al,[17] the cells were irradiated by a red laser, with a wavelength of 632.8 nm, using 4 fluences (0.5 J/cm², 1 J/cm², 2 J/cm² and 4 J/cm²). They noted the inhibition of Aβ-generated toxicity as well as the restoration of dendritic atrophy by the activation of ERK/CREB/BDNF signaling pathway.

Quality Evaluation

In Vivo Studies

According to the SYRCLE tool, no study reached the maximum score. The classified items maintained a prevalence of 44% for ''yes", 44% for "no" and 8% for "unclear". Items 1 (selection bias) and 9 (reporting bias) had the best ranking, with all studies writing them correctly. In contrast, item 5 (performance bias) was the lowest-ranked item, with all studies writing it incorrectly. The studies with the best evaluation were those by De Taboada et al[18] and Da Luz Eltchechem,[24] with 5 items classified as "yes". The other studies had 4 items classified as "yes".

In Vitro Studies

According to the SYRCLE tool, no study reached the maximum score. The classified items maintained a prevalence of 37.5% for "yes", 52.5% for "no" and 10% for "unclear". Items 1, 2 (selection bias) and 9 (reporting bias) had the best ranking, with all studies spelling them correctly. However, items 3 (selection bias), 6, 7 (detection bias) and 8 (attrition bias) had the lowest rating. The studies with the best evaluation were those by Zhang et al,[29] Liang et al[28] and Zhang et al,[30] with 4 items classified as "yes". The study with the worst evaluation was conducted by Liang et al,[28] with 3 items classified as "yes".

Studies Using Both In Vivo and *In Vitro Model of AD*

Despite using tact cells as animals, we evaluated them, mainly considering the conditions related to *in vitro* studies. According to the SYRCLE tool, the study conducted by Meng et al[18] had 4 items classified as ''yes".

Discussion

The objective of this systematic review was to analyze the therapeutic potential of photobiomodulation in AD.

In vivo and in vitro studies have provided promising findings on the effects of photobiomodulation in AD.

Amyloid Beta

It was observed that photobiomodulation reduced the accumulation, size and quantity of Aβ in AD model animals.[18.24,25,26] Only in the study by Lu et al. (2017), this effect was not observed. Probably, this divergence should be in the protocol used, in which the animals received the highest fluency (15J/cm^2) with the shortest treatment period (five consecutive days) between the studies. Nevertheless, the protocol used by the authors inhibited Aβ-induced toxic effects.[27] Possibly, this reduction in Aβ levels promoted by photobiomodulation may be related to changes in the activity of BACE1 and cathepsin B, enzymes that cleave amyloid precursor protein (APP), which in turn produces Aβ.[32,33]

Inflammatory response and oxidative stress

We noted that photobiomodulation reduced inflammatory response and oxidative stress in the *in vivo* [18,25,27] and *in vitro* studies.[31] For example, it has been observed that AD model animals exposed to photobiomodulation decreased the levels of TNFa, IL-1b e IL-6 inflammatory markers and oxidative stress as NADPH.[27] These processes are closely related to AD. Inflammatory and neurotoxic mediators are known to contribute to neuronal degeneration.[34,35,36] In addition, it has been noted that these processes occur in senile plaques due to the presence of microglia and astrocytes activated by Aβ in or near these plaques.[37,38,39] Given this, photobiomodulation may be a potent non-pharmacological therapy, as it reduces inflammatory response and oxidative stress by reducing Aβ levels.

Mitochondrial function

The studies by De Taboada et al. (2011), Purushothuman et al. (2014) and Lu et al. (2017) revealed beneficial effects on mitochondrial function of AD model animals exposed to photobiomodulation. For example, De Taboada et al. (2011) noted that ATP concentration and oxygen consumption of AD model animals were restored with photobiomodulation treatment three times a week for six months. Lu et al[27] observed that 5 consecutive days of photobiomodulation treatment is capable of suppressing fission protein expression and preserving mitochondrial fusion. These effects are promising since patients with AD exhibit impaired ATP levels and synthesis, such as, oxidative phosphorylation.[40-42] These effects are possibly related to the ability of photobiomodulation to increase the enzyme cytochrome c oxidase (CCO), which represents the fourth unit of the mitochondrial respiratory chain. The CCO has the function of reducing oxygen and water, facilitating electrons transference in the mitochondrial membrane, and promoting changes in molecular levels due to increased cellular metabolism.[43,44] In this sense, these data suggest that photobiomodulation may restore mitochondrial damage observed in AD by increasing CCO levels.

Signaling Pathways

In vitro studies have highlighted the effects of photobiomodulation on signaling pathways.[17,28,29,30,31] For example, Zhang et al[29] observed that photobiomodulation could promote anti-apoptotic effects by high regulation of *bcl-x* and low regulation of *bax* mediated by PKC signaling on PC12 cells. Liang et al[28] also observed that photobiomodulation attenuated the pro-apoptotic effects of Aβ through the Akt/GSK3b/b-catenin on PC12 cells. The photobiomodulation inhibits GSK3b, abolishing its effects of b-catenin mediated neuronal degeneration. Zhang et al[30] showed that photobiomodulation inhibited the anti-apoptotic effects generated by Aβ via Akt/YAP/p73/Bax signaling activation. They observed that Akt promoted a cytoplasmic distribution of YAP, which interacted with p73, targeted by Bax, thereby inhibiting the apoptotic effects caused by Aβ. In fact, most studies pay attention to the effects of photobiomodulation on signaling pathways related to cell survival, proposing targets for the inhibition of apoptotic effects of Aβ. In the study conducted by Meng et al,[18] it was observed that photobiomodulation treatment restored Aβ-induced dendritic atrophy. They identified that the cellular mechanism involved in this phenomenon was in the activation of the ERK/CREB/BDNF signaling.

Cognitive Function

Regarding cognitive function, several studies have shown that photobiomodulation is able to improve the cognitive function of AD model animals.[18,24,26,27] For instance, Lu et al[27] observed that photobiomodulation was able to restore cognitive impairment of AD model animals in the Barnes maze test and recognition of objects and hippocampal-dependent tasks.[45,46] These data are interesting since the cognitive deficit observed in AD is due to an impairment in the CA1 region (Important memory-related hippocampal sub-region), compromising a series of molecular reactions, which trigger synaptic failures.[47] Therefore, it is possible to assume that photobiomodulation can improve memory by maintaining hippocampal integrity.[24,27]

Conclusion

Taken together, these results indicate that photobiomodulation may be a useful tool for treating AD due to its ability to reduce inflammatory response, oxidative stress, and apoptotic effects generated by Aβ and to restore mitochondrial function and cognitive function.

Ethical Considerations

Not applicable.

Conflict of interests

The authors declare that they have no conflicts of interest.

Acknowledgements

This study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo ao Ensino e Pesquisa (FAEP) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; #2017/16443-0). Sérgio Gomes da Silva is a researcher (level 2) of CNPq (PQ #306442/2016-7).

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