ScienceDirect

Journal of Photochemistry and Photobiology B: Biology

Volume 216, March 2021, 112152

# Gut flora-targeted photobiomodulation therapy improves senile dementia in an Aß-induced Alzheimer's disease animal model

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https://doi.org/10.1016/j.jphotobiol.2021.112152 ↗

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## Highlights

- An abdominal irradiation targeting gut flora was designed for Alzheimer's disease.
- Gut flora-targeted photobiomodulation therapy at 630 nm and 730 nm improved AD.
- Increase of Helicobacter and decrease of *Rikenella* in AD were reversed by gf-PBM.

# Abstract

## Background

Emerging evidence suggests that the gut microbiota plays an important role in the pathological progression of Alzheimer's disease (AD). Photobiomodulation (PBM) therapy is believed to have a positive regulatory effect on the imbalance of certain body functions, including inflammation, immunity, wound healing, nerve repair, and pain. Previous studies have found that the intestinal flora of patients with AD is in an unbalanced state. Therefore, we have proposed the use of gut flora-targeted PBM (gf-targeted PBM) as a method to improve AD in an Aß-induced AD mouse model.

## Methods

PBM was performed on the abdomen of the mice at the wavelengths of 630 nm, 730 nm, and 850 nm at 100 J/cm$^2$ for 8 weeks. Morris water maze test, immunofluorescence and proteomic of hippocampus, and intestinal flora detection of fecal were used to evaluate the treatment effects of gf-targeted PBM on AD rats.

## Results

PBM at all three wavelengths (especially 630 nm and 730 nm) significantly improved learning retention as measured by the Morris water maze. In addition, we found reduced amyloidosis and tau phosphorylation in the hippocampus by immunofluorescence in AD mice. By using a quantitative proteomic analysis of the hippocampus, we found that gf-targeted PBM significantly altered the expression levels of 509 proteins (the same differentially expressed proteins in all three wavelengths of PBM), which involved the pathways of hormone synthesis, phagocytosis, and metabolism. The 16 s rRNA gene sequencing of fecal contents showed that PBM significantly altered the diversity and abundance of intestinal flora. Specifically, PBM treatment reversed the typical increase of Helicobacter and uncultured Bacteroidales and the decrease of *Rikenella* seen in AD mice.

## Conclusions

Our data indicate that gf-targeted PBM regulates the diversity of intestinal flora, which may improve damage caused by AD. Gf-targeted PBM has the potential to be a noninvasive microflora regulation method for AD patients.

## Introduction

Alzheimer's disease (AD) is a typical degenerative disease of the central nervous system. It is characterized by cognitive impairment, progressive memory loss, behavioral and social impairment, and dementia [1]. The 2018 World Alzheimer's Report states that AD is both a human problem and a global problem. Every 3 s, there will be a new case of dementia in the world. About 50 million people worldwide had AD in 2018, and that number is expected to rise to 152 million by 2050 [2]. The main pathological feature of AD is senile plaques, which result from amyloid β protein (Aβ) aggregation in the brain. These plaques are tangles formed by tau protein hyperphosphorylation. Plaque formation leads to the dysfunction of neurons and synapses and chronic, long-term inflammation in the brain, which ultimately results in neural degeneration [3]. Although the pathogenesis of AD is still unknown, four hypotheses have been put forward in view of these major neuropathologic features, namely the amyloid-β hypothesis, the tau protein hypothesis, the neurotransmitter disorder hypothesis, and the chronic inflammation hypothesis [4]. Based on these hypotheses, several drugs based on different pathological mechanisms have been developed [5]. Currently, there are five AD drugs approved by the US Food and Drug Administration, including donepezil, rivastigmine, galantamine, huperzine, and memantine [6]. However, these drugs mainly improve symptoms, and there is no drug that will delay disease progression or cure AD.

Recent studies have shown that the intestinal flora is involved in the occurrence and development of AD through a variety of pathways. Therefore, intestinal flora modulation is now being considered as a new target for the treatment of AD [7,8]. The intestinal flora mainly affects the occurrence of AD through the nervous system, the endocrine system, metabolism, and immunity [9,10]. In some animal and human studies, researchers have attempted to regulate the intestinal flora to prevent and treat AD. For example, Woo et al. found that administration of sugar-free *Lactobacillus* plant varieties C29 by gastric perfusion to a cognitively-damaged mice model significantly improved memory dysfunction caused by D-galactose and increased the expression of BDNF (Brain Derived Neurotrophic Factor) in the brain. This reduced the expression of aging marker P16, inflammatory markers p-p65 and p-foxo3a, cyclooxygenase-2, and inducible nitric oxide synthase, and inhibited the expression of TNF-α induced by D-galactose [11]. A randomized, double-blind, controlled clinical trial of patients with AD also confirmed

that there was a significant difference in the degree of improvement in cognitive and metabolic functions in patients who received mixed probiotics (*Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum,* and *Lactobacillus fermentum*) in their milk compared with patients in the sterilized milk intake group [12].

Photobiomodulation (PBM) therapy, also called low-level laser therapy, is a noninvasive light therapy that uses a low power non-thermal light source to irradiate target tissues and regulate body functions. PBM has been effectively applied in many clinical diseases, including chronic shoulder and neck pain, wound healing, jaw joint disorders, oral mucositis, arthritis, muscle injury, bone regeneration, diabetic foot disease, multiple sclerosis, Parkinson's disease, and AD [13,14]. The wavelength of red and infrared irradiation is easily absorbed by tissues and the loss of intensity is minimal, affecting metabolic modifications, DNA activity, ATP formation, and the mitochondrial chain. The effect of PBM is due to the absorption of photons by cytochrome C oxidase in the mitochondrial respiratory chain, which consequently increases cytochrome C oxidase activity and therefore ATP formation. ATP from injured regions or regions of impaired blood perfusion can reactivate injured cells and help treat metabolic disorders [[15], [16], [17]]. PBM is also related to pain relief, inflammation relief, and the prevention of tissue death to avoid neurological degeneration [18,19]. PBM is considered a method of adjusting the imbalance of body functions within a certain range and eventually establishing a new balance. The intestinal flora of patients with AD is in an unbalanced state, with a decrease in beneficial flora and an increase in harmful flora, which leads to the consequential imbalance of inflammation and immunity and eventually induces or aggravates AD. PBM may be useful for regulating the imbalance of intestinal flora in AD.

PBM has a bidirectional regulatory effect on bacteria. This therapy can promote bacterial proliferation or inhibit bacterial growth, depending on the wavelength and dose of PBM and the type of bacteria [20]. Under blue and green light (400–500 nm), bacterial growth was inhibited or inactivated by irradiation with 10–200 J/cm$^2$ light. For example, 95% of *Pseudomonas aeruginosa* could be inactivated by a 405 nm laser at 10 J/cm$^2$, and 90% of *Staphylococcus aureus* could be inactivated by 15 J/cm$^2$ [21]. However, under the irradiation of red and infrared light, the proliferation of bacteria was accelerated at low (1–10 J/cm$^2$) light intensities. Interestingly, 810 nm laser irradiation of 5 J/cm$^2$ could accelerate the proliferation of *Escherichia coli*, while 23% of *Pseudomonas aeruginosa* was inhibited under the same conditions [22]. The bidirectional regulation of PBM on bacteria makes it possible to improve the imbalance of the gut flora in AD patients. In this study,

we proposed the method of gut flora-targeted photobiomodulation therapy (gf-targeted PBM) and explored its improvement of AD in an Aß-induced AD mouse model.



## Section snippets

### Animals

Male C57BL/6 N mice with an average body weight of 24–28 g were used in this study. Mice were obtained from Beijing Vital River Laboratory Animal Technologies Co. Ltd. Mice were fed in cages of 7–8 animals, with free drinking water and food. All experimental protocols involving rats were approved by the animal ethics and welfare committee (approval number: IRM-DWLL-2018125) of the Institute of Radiation Medicine, Chinese Academy of Medical Sciences, Tianjin, China.

The mice were anesthetized by…

### The scheme of gf-targeted PBM treatment for AD mice

The purpose of this study was to explore whether gf-targeted PBM can improve the signs and pathology of AD by regulating the intestinal flora. We produced the AD mouse model by $Aß_{1-42}$ injection and verified the modeling effect by a MWM test in ten mice. The AD mice then received the PBM intervention with different wavelengths for up to two months. After PBM treatment, the cognitive function of AD mice was determined by a MWM test and the changes in Aß amyloid protein, tau protein, microglia…

### Discussion

We applied PBM to the abdomen (referred to as gf-targeted PBM) rather than the brain of AD mice to verify whether PBM could interfere with the AD process by regulating gut flora. Encouragingly, we confirmed that the gf-targeted PBM treated AD by eliminating Aβ plaques and inhibiting neuroinflammation and tau phosphorylation. The diversity and abundance of gut flora changed after long-term PBM irradiation.

The wavelengths of PBM were selected to be 630 nm, 730 nm, and 850 nm in this study.…

## Limitations

First, Aß-induced AD mice is a simple AD model which simulates the main pathological features of AD patients through the deposition of exogenous $Aß_{1-42}$ proteins in the hippocampus. Other causes of AD are not reflected in this model, so we will attempt to verify these results in two or more AD models in future studies. Second, the modeling time was short. The PBM intervention started 2 weeks after modeling, although the intestinal flora of AD mice was significantly altered at the end point…

## Conclusions

In conclusion, gf-targeted PBM with light at 630 nm, 730 nm, and 850 nm reversed the imbalance of intestinal flora and improved learning ability, amyloid plaque deposition, tau phosphorylation, and microglia inflammation of Aß-induced AD mice. A large number of proteins in the hippocampus responded to gf-targeted PBM, with mitochondrial respiratory chain complex enzymes as a possible key intermediate target. In future studies, we will confirm the effect of gf-targeted PBM on the brain-gut axis…

## Funding

This work was supported by the National Key Research and Development Program “Study on optical parameter research, equipment development and demonstration application of LED treatment of skin diseases” [No. 2017YFB0403804].…

## Availability of data and materials

All data generated or analyzed during this study are included in this published article.…

## Author statement

All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.…

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

## Acknowledgments

We thank Korin Albert, PhD, from Liwen Bianji, Edanz Editing China ( www.liwenbianji.cn/ac ↗), for editing the English text of a draft of this manuscript.…

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> …JAT improved hippocampal contextual memory, decreased the Aβ plaques load in the cortex and hippocampus and changed the amount of certain gut microbiota such as the most predominant phyla Firmicutes, Bacteroidetes, and Lactobacillus levels as along with the F/B ratio [208]. Additionally, photobiomodulation (PBM) therapy was suggested as a treatment approach [209]. Normally, PBM uses red or near-infrared light to arouse healing, or relieving pain and inflammation, and induce nerve repair, utilized in diverse range of brain disorders [210]….

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