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Photobiomodulation and Alzheimer's Disease

Review

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Abstract – Alzheimer's disease (AD) is one of the basic neurodegenerative diseases and the most extreme common state of dementia. Described through the loss of learning, memory, critical thinking, language, and different abilities to address, AD applies an adverse consequence on every patients' and families' style of life. Despite the fact that there were enormous advances in data , the basic pathogenesis and progression of AD, there's no solution for AD. The disappointment of several molecular focused pharmacologic clinical preliminaries closes in a rising research shift towards non-invasive medicines. We, first and foremost, assessed the pathological changes of AD and the requesting circumstances for AD research. We then, at that point, added those non-invasive medicines and referenced the components which can affect the results of those therapies. Furthermore, we assessed the results of those therapies and the suitable components underlying those outcomes. At long last, we summed up the requesting circumstances of the Photobiomodulation cure in future AD studies and clinical applications. We presumed that it would be essential to perceive the exact fundamental components and find the optimal cure parameters to upgrade the translational value of the Photobiomodulation treatment.

Keywords – Alzheimer's Disease, Photobiomodulation.

I. INTRODUCTION

First described in 1906 through Dr. Alois Alzheimer, Alzheimer's disease (AD) has been distinguished for more than 100 years [1]. As the most common state of dementia, AD reasons progressive memory weakness and is described through amyloid plaques and neurofibrillary tangles [2]. There are as of now expected to be over 55 million people living with Alzheimer's disease or various dementias wherever on the planet, and more than 6.2 million Americans are living with Alzheimer's disease [3]. In spite of the fact that researchers have made improvement in higher understanding the molecular mechanisms underlying amyloid-β and tau pathology in the past years, a presice systems of AD stay beneath hot discussion, and there aren't effective pharmacologic disease altering treatments for AD [4].

The failure of molecular focused pharmacologic medicines has provoked developing studies to move towards non-invasive medicines [5]. Non-invasive brain cure portrays solutions for brain diseases that don't need a cut into the brain or tissue removal [6]. In the past many years, non-invasive medicines, including PBM treatment (furthermore alluded to as low-level laser treatment, light treatment), transcranial magnetic stimulation (TMS), transcranial direct current stimulation(tDCS), and exercise treatment, have acquired duplicated interest as potential solutions for many brain disorders [7-11]. Albeit large advances were completed in investigating the effectiveness and underlying components of those non-invasive medicines, the present day downplaying of the exact fundamental system in AD is restricted. This review sums up the pathological changes of Alzheimer's

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disease, gives an escalated assessment of the greatest comprehensively concentrated on photobiomodulation approach, and examines the main challenges of this strategy in AD clinical applications.

1. Neurotic changes in Alzheimer's disease

1.1 Amyloid plaques

Amyloid plaque is one of the signs of AD [12]. It is formed through the accumulation of extracellular Aβ, a 40-42 amino acid peptide got from the amyloid precursor protein (APP) [13]. The amyloid hypothesis has been the standard purpose for AD's etiology and pathogenesis since 1991 [12,14]. APP, a transmembrane protein, is divided through 3 catalysts: α, β, and γ-secretase [15]. In the normal physiological state, most of the APP (90% or more) are divided through α-secretase and γ-secretase, which produces sAPPα and C terminal pieces (p3, CTF 83, and AICD50). The remaining APP is separated through β-and γ-secretase and creates Aβ, that is removed or degraded [12]. Be that as it may, under pathological circumstances, most of the APP goes through the amyloidogenic APP handling pathway, in which Aβ generation is considerably increased and prompts the arrangement of Aβ amyloid fibrils [16]. The gathering of Aβ actuates neurotoxicity, which in this way leads to neuronal death and neurodegeneration [16].

1.2 Neurofibrillary tangles

Neurofibrillary tangles (NFTs) are some other hallmark concerning the pathogenesis of AD [17]. NFTs are made from abnormally hyperphosphorylated tau, a microtubule-binding protein that keeps the microtubule structure [18]. Microtubules are α tubulin and β tubulin subunits-formed hollow cylinder structures [19]. Under ordinary circumstances, tau ties to the microtubules promoting microtubule adjustment [20]. As a major component of the cytoskeleton, microtubules play a fundamental role in axonal transport, cell motility, and the maintenance of cell shape [19]. What's more, the tau-related regulation of microtubules is concerned in the dynamic control of protein kinases and phosphatases [21]. In AD, the abnormally phosphorylated tau separates from the microtubules, and the phosphorylated tau proteins shape neurofibrillary tangles [2], which results in the interference of axonal transports and cell signal communication [18].

1.3 Mitochondrial Dysfunction

The mitochondria are significant organelles in eukaryotic cells that play out multiple significant capabilities, including of the generation of adenosine triphosphate (ATP), intracellular signaling, biosynthesis of neuronal iron-sulphur centers and heme, regulation of cell endurance, and apoptosis under various stresses [22-24]. Until now, a major casing of studies has demonstrated that mitochondrial dysfunction and impared energy metabolism because of deleterious fragmentation is an early and causal event in AD [22]. Distorted mitochondrial fragmentation, because of the imbalance of the fusion-fission process, plays out an imperative position in the induction of mitochondrial dysfunction and adds to the pathogenesis and pathology of AD [22, 23].

In the living cell, mitochondrial morphologies are quite far from static [25] and go through exact mitochondrial dynamics concerning coordinated patterns of mitochondrial fission and fusion [26]. Mitochondrial fission is significant for creating new mitochondria and mitochondrial quality control (pushing off broken mitochondria and mitochondrial apoptosis eventually of highly cellular stresses levels) [25]. Mitochondrial fission is mediated through Drp1, Mff, and Fis1. Drp 1 is set in the cytosol, and Fis1 and Mff are at the outer mitochondrial membrane [27]. Mitochondrial fission happens while the Fis1 and MFF recruit cytosolic Drp1 to the external mitochondrial membrane [25]. Conversely, mitochondrial fusion is a process that consolidates mitochondria, that is significant in protective mitochondrial integrity [25]. Likewise, mitochondria can offer to set things right for various mitochondria's imperfections eventually of mitochondrial combination through sharing added substances to save their integrity [25].

Mitochondrial fission and fusion cooperate to protect mitochondrial wellbeing and function [25,28].Mitochondrial fission isolates the most seriously harmed mitochondria and eliminates them through quality control, while mitochondrial fusion remedies low levels of damage by sharing parts [25, 29]. In the AD brain, the harmony between mitochondrial fission and fusion is upset by altogether expanded fission protein expression and diminished fission protein expression, which prompts excessive mitochondrial fragmentation in vulnerable neurons [7, 30, 31].

Notwithstanding abnormal mitochondrial dynamics, the role of mitochondrial bioenergetic defecits in AD has been well established [32, 33]. The high energy interest of neuronal cells proposes that mitochondrial bioenergetic deficits add to neuronal

death in AD [34]. There are five multiprotein protein enzymes in the mitochondrial internal membrane associated with ATP creation: complex I (NADH-ubiquinone oxidoreductase), complex II (succinate-ubiquinone oxidoreductase), complex III (cytochrome bc1 complex), complex IV (cytochrome c oxidase), and complex V (ATP synthase) [22]. These five enzyme complexes' diminished expression and activity have been tracked down in the brain of AD patients and animals, recommending mitochondrial bioenergetic deficit goes before Alzheimer's pathology [32, 35, 36].

1.4 Oxidative stress

Unquestionable proof has shown the significantly expanded oxidative stress in AD brains [37]. The imbalance between free radical creation and antioxidative prevention in AD prompts excessive oxidative stress in the AD brains [37]. As the "powerhouses of the cell," mitochondria are likewise the essential intracellular source of oxygen radicals under both physiological and neurotic circumstances[22,23].Under physiological circumstances, few electrons spill out of the electron transport chain (ETC) and are moved to oxygen to deliver reactive oxygen species (ROS) [38]. The ROS produced fills in as second messengers in mediating several critical intracellular pathways [39,40]. In pathological circumstances, mitochondrial dysfunction and the impeded mitochondrial complex action prompt essentially expanded ROS creation. This prompts deleterious impacts and an endless loop causing mitochondrial damage, energy exhaustion, neuronal damage, and cell death [41,42]. Several studies exhibit the expansion in oxidative damage to DNA, proteins (protein carbonyl), and lipids (lipid peroxidation), which add to the commencement and progression of AD [43-45].

2. Neuroinflammation, polarization of glial cells, and microglial phagocytosis

Neuroinflammation triggered by pathological particles including Aβ, tau, and damage -associated molecules patterns (DAMPs) in AD has been very much exhibited [44, 46]. In the early phases of AD, the deposition of Aβ intensely starts the actuation of microglia to remove Aβ through phagocytosis [47]. During this stage, the initiation of microglia works as a defensive reaction against AD [48]. In any case, microglial phagocytosis neglects to eliminate amyloid plaques, and the expanding microglial activation delivers an array of proinflammatory of mediators that add to AD's progression [49]. the activated microglia can be partitioned into proinflammatory subtype M1 and M2 anti-inflammatory phenotype [50]. The M1 phenotype creates proinflammatory cytokines (i.e., IL-1β, TNF-α, IL-6, and IL-12), exacerbating AD progression. Be that as it may, the M2 phenotype delivery anti-inflammatory cytokines (i.e., IL-4, IL-10, IL-13, and TGF-β), giving neuroprotective impacts in AD [51,52]. Moreover, the M1 phenotype display poor phagocytosis of Aβ, and the M2 phenotype shows raised phagocytosis [53,54]. Taken together, in the beginning phase of AD, the quiescent microglia are energized into the M2 phenotype to give a neuroprotective impact by delivering anti-inflammatory and neurotrophic factors.

The microglia are polarized into the M1 phenotype, actuating neuronal loss and exacerbating AD progression by delivering anti-inflammatory cytokines and ROS [51]. As of late, a review utilizing single-cell RNA-seq in the AD animal models distinguished a novel microglia type called disease associated microglia (DAM), which address a distinctive microglia states recognized in AD however not in the wild type brains. The DAM exists together with the homeostatic microglia and infiltrating monocytes. Likewise, the change between the homeostatic microglia to the DAM subtype is predictable with the direction of AD progression [55, 56].

Like microglia, the actuation of astrocyte, another sub-type of glial cells in the central nervous system, is additionally found close to the sites of amyloid plaques [57]. In after death tissues from both AD patients and animal models, astrogliosis is noticed and corresponded with cognitive decline in AD [58-60]. As indicated by ongoing investigations, astrocytes are grouped into A1 neurotoxic phenotype and A2 neurotrophic/neuroprotective phenotype [61,62]. A1 phenotype can be activated by factors and fragmented mitochondria set free from microglia to trigger and exacerbate neuroinflammation in AD [63, 64]. Conversely, the A2 phenotype is proposed to be a therapeutic and neuroprotective astrocyte phenotype in the brain [65]. As per past studies, the phenotypical change from the A1 phenotype to the A2 phenotype improves AD pathology [66, 67].

A past study demonstrated the way that young microglia could re-establish the capacity of amyloid plaque clearance of aged microglia [68], and approaches that trigger the recruitment of microglia around amyloid plaques show an expected impact on weakening AD pathology [69, 70]. As of late, the crosstalk among astrocytes and microglia gives a novel system to the microglial recruitment around amyloid plaques [71]. In both the human and mice, the astrocytic interleukin-3 (IL-3) can focus on the microglial IL-3 receptor (IL-3R) to prompt the recruitment of microglia and improve the capacity to clear Aβ and tau,

recommending the astrocytic IL-3 is a significant mediator of microglial recruitment and a likely objective for the regulation of microglial phagocytosis [71].

3. Parameters of PBM therapy

PBM therapy, otherwise called low-level laser (light) therapy, is a non-invasive photoceutical approach including the use of generally low levels of visible (frequency somewhere in the range of 400 and 720) or near infrared light (frequency somewhere in the range of ~700 and 100 nm) on biological tissues to work on healing, ease inflammation and pain, and save tissue function [22,72]. As a non-invasive treatment strategy, PBM treatment portrays the utilization of the low-level laser (light) straightforwardly to a particular district of interest on the body to balance different biological processes [6]. It was first found by Endre Mester, a Hungarian doctor working with wound mending and hair regrowth in 1967 [73,74]. He found speedier hair development and twisted recuperating in the rodents with low-level laser treatment [81, 82], which was the principal concentrate on that found the useful utilization of low-level laser light on biological cycles [75]. From that point forward, a rising paper has depicted this treatment as "laser bio stimulation," "low-level laser (light) treatment (LLLT)," and presently "PBM treatment" [76-78]. Despite the fact that PBM treatment was at first applied to advance hair regrowth and wound mending [73, 74], the helpful impacts of PBM on easing pain and inflammation and advancing muscle recuperation have been generally considered [79-82]. In the previous many years, the possible role of PBM treatment in the treatment of brain problems has collected expanding consideration [7, 8, 83, 84]. Ongoing studies give impressive proof of PBM's promising remedial potential in AD treatment [7, 69, 70].

Various parameters at the same time influence the effectiveness of PBM treatment, including frequencies, powers, duration, target region, and operation mode. As of now, the most broadly utilized frequency is red (~600-700 nm) and close infrared frequencies (~780-1100 nm) [85]. For the PBM treatment with frequency inside 600-1100, the essential objective is the cytochrome c oxidase (CCO), the unite IV of the mitochondrial respiratory chain [22]. Furthermore, proof supports that blue and green light with more limited frequencies inside 450-570 nm can likewise present PBM impacts . The impacts might depend on intracellular calcium and light-gated ion channels. Notwithstanding, the low transmission tissue restricts the utilization of blue or green light within 450-570 nm [86].One more basic parameter of PBM is the dose of the light source. The therapy dosages of PBM rely upon the intensities, duration, and PBM targeted region [85, 87, 88]. Right now, there is no agreement about treatment doses of PBM therapy. Aside from the proficiency of the PBM treatment, the essential concern for the treatment dose of PBM is the thermal impacts [89]. The forces that produce the inadmissible thermal effect of the tissue are ~300 mW/cm2 at 600 to 700 nm, around 750 mW/cm2 at 800 to 900 nm, and 100 mW/cm2 at 400-500 nm [88]. Besides, the exposure length is additionally basic for the effectiveness of PBM treatment [88, 90]. Studies demonstrated the way that even a few moments of PBM treatment could cause biological changes [91,92]. Notwithstanding, the best exposure span likewise depends on different parameters utilized in the PBM application [88].Beside these parameters, the method of operation of PBM can either be a pulsed wave or a continuous wave [93]. Both pulsed and continuous wave PBM show useful impacts in AD [7, 69, 70, 94]. The pulsed wave PBM alludes to the PBM effect prompted by the light source in pulses of some duration at some repetition rate [95]. The most generally concentrated on frequency is 10 Hz or 40 Hz in AD [69, 70]. Albeit different activity method of PBM makes comparative impacts, the fundamental system varies.

4. PBM treatment for AD

Intriguingly, expanding human and animal studies recommend that PBM treatment is a promising possible treatment in AD [69,70, 96-99]. Progressive memory weakness is one of the essential indications of AD and is generally the first and common complaint for the patient to look for diagnosis [7,100,101]. As a sign of AD, memory impedance/loss is one of the most widely recognized clinically pertinent markers to evaluate the impact of a potential treatment [102]. In a past report, the learning and memory deficiencies were fundamentally improved by PBM at 40 Hz (light-discharging diode) in the AD mouse model [70]. The non-invasive 40-Hz light additionally diminished the degrees of Aβ1-40 and Aβ1-42, managed microglia's morphological change, and worked on both the phagocytosis and migration/cell adhesion related genes in the hippocampus, and cortex which helped the improvement of cognitive function [70]. In a new report, PBM with 1070-nm pulsed wave light at 10 Hz could likewise further develop learning and memory impairments after PBM treatment in AD mice [69]. Also, the AD animals with PBM treatment showed diminished Aβ burden and further developed Aβ clearance by controlling microglia and angiogenesis [69]. Another study discovered that PBM could advance the permeability of BBB, which results in expanded Aβ spillage followed by additional enactment of the lymphatic clearance of Aβ [103]. The PBM has been applied to the frontal cortex, temporal regions , base of the

skull, wrist, nose cavity, abdomen, and forehead bilaterally or produced gamma entrainment involving sensory stimuli through the eyes in human clinical preliminaries. As of now, most PBM-related clinical preliminaries are continuous or ended due to the Covid. Thusly, whether PBM can decrease the amyloid plaques in the entire cerebrum is unclear. Notwithstanding, as per past animal studies, the PBM treatment can ease basically amyloid plaques in the cortex and hippocampus [70,104]. These discoveries added more proof to the restorative impact of pulsed- mode PBM.

Notwithstanding PBM with beat pulsed light, several studies recognized the valuable role of PBM with continuous wave light [7,102]. In an Aβ-actuated AD rodent model, PBM treatment with the continuous wave laser diode at 808 nm for 5 days safeguarded against Aβ-prompted cell toxicity and long term spatial and object recognition memory [94]. Moreover, the 5-day PBM treatment eased the hyperphosphorylated tau (PHF1) protein expression and neuronal apoptosis [94]. These discoveries were predictable with one more study that found that PBM treatment with the continuous wave laser at 632.8 nm stifled neuronal loss and dendritic decay in the APP/PS1 twofold transgenic AD mouse model [105]. Besides, anxious-depressive like conduct has been identified and perceived as an early sign of AD pathogenesis [7]. Developing proof inferred that early treatment of anxious-depressive like way of behaving could bring down the risk of growing AD [7,106]. The useful impact of PBM treatment in mitigating anxious-depressive like ways of behaving has been generally detailed [92,107-109]. Intriguingly, PBM treatment with a continuous wave laser could weaken anxious-depressive like way of behaving and safeguard against neuronal harm and apoptosis in the AD rodent animal model, supporting the expected role of PBM treatment in preventing or slowing down the progression of AD [7].

Besides, the gainful impact of PBM on AD has likewise been recognized by various clinical preliminaries [96-99]. Utilizing an 810-nm, 10-Hz pulsed LED light source PBM treatment, AD patients with moderate-to-extreme mental impairment were assigned to get 12-week PBM treatment. Results showed that 12 weeks of dynamic PBM treatment essentially worked on AD patients' cognitive function and decreased anxiety [99]. One more clinical preliminary with continuous wave near infrared PBM treatment presumed that in PBM treatment patients showed better cerebral perfusion and resting-state functional connectivity and an essentially cognitive and behavioural capability [97]. Besides, a case report additionally upheld these past perceptions [11]. For this situation report, patients determined to have both cognitive decline and olfactory dysfunction got a combination of continuous wave mode red (635 nm), near infrared light (NIR) LEDs (810 nm), and 10-Hz pulsed wave mode NIR (810 nm) PBM treatment. After PBM treatment, critical enhancements were recognized in the Montreal Mental Evaluation and Working Memory Poll [110].

A rising number of clinical preliminaries are trying non-invasive treatment in AD. Among these clinical preliminaries, a clinical preliminary including gamma entrainment treatments (otherwise called gamma entrainment utilizing sensory stimuli , or GENUS). Past studies found that gamma entrainment treatments mitigate cognitive deficits and work on the clearance of amyloid plaques by recruiting neuronal and glial responses, moving neurons to a less degenerative state, delivering neuroprotective elements, upgrading synaptic capability, lightening neuroinflammation, and diminishing DNA harm related cytotoxicity in neurons [70,94]. In these studies, 40-Hz pulsed light or 40-Hz blue light with 40-Hz auditory stimulation was utilized to create GENUS and displayed neuroprotective outcomes in the AD mouse model, recommending a substitute mode of PBM in treating neurodegenerative diseases. In general, these discoveries support the possible therapeutic use of PBM treatment in improving cognitive impairment and diminishing anxious-depressive like ways of behaving of AD.

4.1 Preserving mitochondrial capability

As referenced beforehand, mitochondrial dysfunction and aberrant mitochondrial fragmentations are engaged with the event and development of AD and are perceived as common highlights of neurodegenerative disease [22]. It is broadly acknowledged that mitochondrial cytochrome c oxidase (CCO, complex IV of the respiratory chain) is the essential activity site of PBM treatment [8,22]. Large body of proof recommends that the gainful impact of PBM treatment on AD is primarily because of the regulation of mitochondrial capability and mitochondria-related processes [8,22]. The essential component basic PBM's regulation of mitochondria is engaged with the modulation of CCO action [111-114]. Nitric oxide (NO), a molecule that binds non-covalently to the heme iron and copper centers of CCO to inhibit the action, is the main medium in this cycle [111-114]. PBM treatment stimulates CCO activity by photo dissociating NO from CCO, in this way reversing the hindrance of the electron transport chain because of extreme NO binding [115,116]. The impact of PBM on CCO demonstrates that PBM treatment is a likely mediation for promoting mitochondrial capability in AD [115].Other than the immediate impact on mitochondrial CCO, PBM treatment manages mitochondrial dynamic and fragmentation [117,118]. The equilibrium of mitochondria fission and fusion is urgent for

the typical capability of mitochondria and the support of mitochondrial morphology [22,119]. Abnormal or expanded mitochondrial fission in AD prompts expanded mitochondrial fragmentation and neuronal death [120]. Intriguingly, a few past studies have exhibited that PBM treatment saved the dynamic equilibrium between mitochondrial fission and fusion in different brain sicknesses like worldwide cerebral ischemia, neonatal hypoxic ischemia, AD, and Parkinson's illness [8,117,121,]. In an Aβ1-42-induced AD rodent model, PBM treatment with continuous wave low-level diode laser fundamentally mitigated unnecessary mitochondrial fission prompted mitochondrial fragmentation by advancing mitochondrial fusion related proteins (OPA1 and MFN1) and restraining mitochondrial fission related protein (Drp1, Fis1, Mff, and Mief) [94]. Comparable regulation of these proteins was additionally seen in other brain disease models [8,22, 111]. Taken together, PBM, a mitochondria-targeted treatment, exhibited its restorative potential in AD treatment by managing the mitochondrial structure and mitochondrial capability. Arising proof from past studies showed the advantageous role of PBM treatment in controlling glial cells and neuroinflammation [8,69,70,113,123]. In a past study, 40-Hz light flicker PBM treatment selected microglia around amyloid plaques and improved microglial phagocytosis and migration/cell adhesion related genes in numerous mouse models [70]. The adjustment of microglia after PBM treatment triggers microglia to expand Aβ take-up [70], showing the possible role of PBM treatment in improving microglial phagocytosis. As of late, results from another study further comprehension we might interpret PBM treatment on the guideline of glial cells [69]. As announced in their work, PBM treatment with 1070-nm pulsed wave light at 10 Hz can likewise diminish cerebral Aβ burden by advancing the activity of microglia (e.g. expanded cell body, decreased number and length of branches) and microglial phagocytosis [69]. Remarkably, they found a diminished proinflammatoryM1 phenotype and the expanded M2 anti-inflammatory phenotype after PBM treatment [69]. These discoveries show the way that PBM can repress neuroinflammation by advancing the change of microglia from a neurotoxic to a neuroprotective phenotype in AD [69]. Anti-inflammatory impacts were likewise found in PBM treatment utilizing continuous wave lasers [94]. In the Aβ1-42-actuated AD rodent model, Aβ infusion into the hippocampus of rodents prompted the expanded arrival of pro-inflammatory of cytokines (i.e., IL-1β, IL-5, and TNF-α), mitochondrial dysfunction, demyelination, and axonal damage of neurons [94,124,125]. Curiously, PBM treatment with continuous wave low-level diode laser essentially suppressed Aβ-initiated neuroinflammation and safeguarded against Aβ-actuated neuronal injury and neurodegeneration [94]. Notwithstanding, in this AD rodent model, PBM treatment with continuous wave lasers altogether suppressed Aβ-actuated reactive gliosis [94],which is unique in relation to the pulsed wave PBM's advancing the enactment of glial cells [94]. One of the clarifications for the distinction might be because of the animal model. Aβ-incited AD like rodent model is an intense AD rodent model, wherein Aβ prompts receptive gliosis quickly. Nonetheless, in the transgenic mouse model, glial cells are enacted dynamically. PBM represses glial cells' intense enactment to safeguard against inflammatory reaction prompted neuronal damage in the intense AD animal models however advances the actuation and polarization of glial cells to a neuroprotective phenotype in the dynamically grown AD models [51,94].

4.2 Hinders oxidative stress and oxidative damage

The anti-oxidative impact of PBM has been generally concentrated on in the skeletal muscle after physical activity [126-128]. Oxidative pressure is likewise embroiled in AD's pathogenesis and progression [37,129]. The fundamentally raised levels of 4-hydroxyhexenal (4HHE), a lipid peroxidation marker, have been found in animal models and invitro cell societies [44,130]. Besides , the degree of 8-hydroxydeoxyguanosine (8-OHdG), a broadly utilized DNA oxidative marker, was a triple expansion in the post-mortem brain tissue of AD patients contrasted with age-matched controls [131]. Comparable outcomes were found in AD like animal models [44,132]. Besides, the oxidative damage of protein prompted by over the excessive free radicals was distinguished in sporadic AD rodent and transgenic AD models [7,44, 133]. Also, a several enzymes basic to neuron and glial capabilities are inclined to oxidative damage and decline in AD [37]. For instance, the enzymes susceptible to oxidative stress, the glutamine synthetase and creatine kinase, are fundamentally diminished in AD brains, actuating diminished glutamate synthetase and excitotoxicity enhancement [37,133]. Also, oxidative stress impeded creatine kinase action and caused diminished energy metabolism in AD [37,133]. Curiously, PBM with various light sources and parameters shows its critical anti-oxidative impact in neuronal cell culture and AD brains. PBM treatment with 660-nm continuous wave LED at 20 mW/cm2 safeguards against neuronal cell death by diminishing H2O2-actuated oxidative stress in vitro study [134], wherein the better anti-oxidant enzyme agent and redox homeostasis are considered as the key component basic this protection [134]. Additional proof from two transgenic mouse models (APP/PS1 and K369I tau transgenic model) upholds the anti- oxidative impact of 670-nm near infrared light [135].After getting 90-s PBM treatment for 5 days of the week, the AD animal showed a critical decrease in neurofibrillary tangles, hyperphosphorylated tau, and oxidative stress markers (4-HNE and 8-OHdG) in the cortex and hippocampus [135].

The anti-oxidative impact of PBM is firmly connected with the safeguarding of mitochondrial function [22]. As referenced over, the essential activity sit of PBM treatment is CCO [8, 22]. A short burst of ROS is created when NO is photo dissociated from CCO after PBM treatment [8,22]. The transitory and moderately modest increment of ROS creation prompts the actuation of the NF-κB and PI3K/Akt pathway [117,138,139]. The actuation of NF-κB will prompt the activation from the cytoplasm to the nucleus. It incites in excess of 150 gene expression, incorporating genes related with anti-oxidant activity action and mitochondrial dynamics [22,138]. Accordingly, oxidative stress is altogether reduced in the cells exposed to stress with PBM treatment [147]. This proof makes sense of how PBM treatment diminishes clinical oxidative pressure and safeguarded neurons from death in different lesions and AD [139].

5. Difficulties of PBM treatment in AD

Albeit the gainful impacts of PBM treatment have been found in various tissues and generally concentrated on in brain disease, challenges stay in the clinical utilization of PBM on AD patients [75]. In the first place, there is no settlement on the parameters and protocols of PBM treatment in the clinical use of AD [88]. As referenced beforehand, a several light source parameter are engaged with the impacts of PBM treatment. The predominant utilization of a wide variety of light sources, the brightening parameters (e.g., frequency, power density, pulse structure, fluence), and treatment protocols (a single use of light or multiple doses) prompt critical varieties in the review plan [75, 90]. The conflict on light/laser parameters and the varieties in study on plans prompted many adverse outcomes in clinical preliminaries and represented a many controversy in PBM's review and application [83]. Second, despite the fact that CCO has been broadly acknowledged as the essential objective of PBM, there is as yet conflicting information questioning whether it is the primary acceptor [140,141]. For instance, a study discovered that PBM could promote ATP creation and increment cell multiplication in CCO knockout cells, proposing that CCO may not be the essential or just objective of PBM treatment [141]. Hence, more studies are as yet required for the precise mechanisms of PBM treatment in AD. Albeit expanding proof upheld the helpful impact of pulsed wave PBM treatment, the specific components of pulsed wave PBM treatment in AD stay subtle [69,70].

II. Conclusion

Non-invasive treatments have the potential and promise to accomplish therapeutic objectives of slowing down or preventing AD, the improvements in cognitive function and other behavioral changes after PMB treatments depend on various cell changes and adaptive reactions. No agreement on the optimal treatment parametrs in clinical application and finding the exact or explicit targets are the primary challenges for future studies. If future studies are effective in non-invasive approaches, they will reveal insight into AD treatment and prevention.

III. Conflict of Interest

All authors declare no conflicts of interest.

IV. Author Contribution

Authors have equally participated and shared every item of the work.

V. ABBREVIATIONS

AD	**Alzheimer's disease**
PBM	**Photobiomodulation**
TMS	**Transcranial magnetic stimulation**
tDCS	**Transcranial direct current stimulation**
APP	**Amyloid precursor protein**
NFTs	**Neurofibrillary tangles**
ATP	**Adenosine triphosphate**
ROS	**Reactive oxygen species**
DAMPs	**Damage-associated molecular patterns**
IL-3	**Interleukin-3**
PS1	**Presenilin-1**
LLLT	**Low-level laser (light) therapy**
CCO	**Cytochrome C oxidase**
PHF1	**Hyperphosphorylated tau**
NIR	**Near-infrared light**
NO	**Nitric oxide**
4HNE	**4-Hydroxyhexenal**
8-OHDG	**8-Hydroxydeoxyguanosine**
rTMS	**Repetitive transcranial magnetic stimulation**
MDD	**Major depressive disorder**
FDA	**Food and Drug Administration**
TBS	**Theta-burst stimulation**
MCI	**Mild cognitive impairment**
LTP	**Long-term potentiation**
LTD	**Long-term depression**
BDNF	**Brain-derived neurotrophic factor**
TrkB	**Tropomyosin-related kinase B**
5-HT	**Serotonin**

DLPFC	**Dorsolateral prefrontal cortex**
GABA	**Gamma-aminobutyric acid**
OGD	**Oxygen-glucose deprivation**
ChAT	**Choline acetyltransferase**
Ach	**Acetylcholine**
PD	**Parkinson's disease**
CBF	**Cerebral blood flow**
SOD2	**Superoxide dismutase 2**
TRX2	**Thioredoxin 2 (TRX2)**
HO-1	**Heme oxygenase 1 (HO-1)**
NQO1	**NAD(P) H dehydrogenase [quinone]**
Nrf2	**Nuclear erythroid 2-related factor 2**
ARE	**Antioxidant response element**
CNS	**Central nervous system**
AQP4	**Aquaporin 4**
ETC	**Electron transport chain**
PGC-1α	**Proliferator-activated receptor gamma coactivator 1-alpha**
BBB	**Blood-brain barrier**

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