Transcranial Low-Level Laser: A Novel Approach for Depression Treatment (Postprint)

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Abstract

Depression, as the second leading medical disorder worldwide, remains unclear in its etiology and pathogenesis. Current treatments for depression primarily involve pharmacological and psychological therapies; however, these approaches face bottlenecks due to the significant side effects and high relapse rates of antidepressant medications, the professional expertise required of psychotherapy practitioners, and the sophisticated equipment required for electroconvulsive therapy. Transcranial low-level laser therapy for depression has demonstrated efficacy in both in vivo research experiments and clinical treatment of patients with depression. Although the molecular and cellular mechanisms of this therapeutic approach are not yet fully established, it penetrates the skull in a non-invasive manner, does not cause reversible damage to the organism, exhibits photobiomodulatory effects, and provides neuroprotective effects on neurons, thus serving as an innovative non-pharmacological therapy that can guide clinical depression treatment.

Full Text

Preamble

Transcranial Low-Level Laser: A Novel Treatment for Depression

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Abstract: Depression, as the second most prevalent medical disorder worldwide, has unclear etiology and pathogenesis. Current treatments primarily involve pharmacotherapy and psychotherapy, but these approaches face significant limitations due to substantial side effects of antidepressants, high recurrence rates, and the need for highly specialized practitioners and sophisticated equipment for psychotherapy and electroconvulsive therapy. Transcranial low-level laser therapy has demonstrated efficacy in both animal research and clinical treatment of patients with depression. Although its molecular and cellular mechanisms remain to be fully elucidated, this non-invasive approach penetrates the skull without causing reversible damage to living organisms, exerts photobiomodulatory effects, and provides neuroprotective effects on neurons. It represents an innovative non-pharmacological therapy that can guide clinical depression treatment.

Keywords: Low-level laser; Depression; Mitochondria; Neurotransmitter; Neuroplasticity; Neuroinflammation

Introduction

The global spread of COVID-19 has triggered a sharp increase in secondary mental health consequences, including depression, anxiety, insomnia, and acute stress reactions [1]. Depression, a type of mood disorder affecting higher brain functions such as emotion, reward, and cognition, affects approximately 300 million people globally with a prevalence rate of 12.8%, making it the second leading cause of medical disability. In China, the incidence of mental and psychological disorders reaches about 17% [1]. While stress-induced hippocampal damage represents a primary pathogenic factor in depression, the detailed mechanisms remain incompletely understood [2]. Depression poses a persistent challenge in psychiatric medicine due to its multiple etiological factors, complex pathogenesis (including biological, psychological, and social environmental factors), and characteristics of high prevalence, recurrence, disability, and suicide risk, severely impacting quality of life and social stability [3].

Current standard treatments for depression include pharmacotherapy, psychotherapy, electroconvulsive therapy, transcranial magnetic stimulation, and transcranial direct current stimulation. Pharmacotherapy remains the first-line approach, with clinicians primarily relying on the "monoamine neurotransmitter deficiency hypothesis" to target synaptic monoamine levels (5-HT, NE, DA) using monoamine oxidase inhibitors, tricyclic and tetracyclic antidepressants, and selective serotonin and norepinephrine reuptake inhibitors [4]. Representative drugs such as fluoxetine, paroxetine, sertraline, fluvoxamine,

and citalopram—known as the "five golden flowers" of antidepressants—demonstrate an overall response rate of approximately 41% [5]. However, these medications suffer from significant side effects, slow onset (typically 2–4 weeks), and addictive potential, while some patients show response rates below 30% and experience relapse upon discontinuation [6]. Psychotherapy serves as an adjunctive treatment effective for mild, chronic, and remitted depression, but major depressive disorder (MDD) requires combination therapy ("antidepressants plus" psychotherapy, electroconvulsive therapy, repetitive transcranial magnetic stimulation, or transcranial direct current stimulation), demanding highly specialized clinical expertise and sophisticated equipment. Consequently, with rising social pressures driving increased depression prevalence and unclear pathogenic mechanisms, there is urgent practical significance for developing targeted antidepressant drugs or treatments.

This review examined literature from PubMed, Web of Science, and CNKI (China National Knowledge Infrastructure) databases, primarily from 2017–2022, using Chinese keywords including "low-level laser,""depression,""mitochondria,""neurotransmitter,""neuroplasticity,"and "neuroinflammation,"and English terms including "Low-level laser," "Depression," "Mitochondria," "Neurotransmitter," "Neuroplasticity," and "Neuroinflammation." Studies addressing depression risk factors, pathogenesis, treatment, and meta-analyses were included, yielding 60 final articles, while irrelevant or low-quality papers were excluded. Based on this literature, we review animal experimental and preclinical studies on low-level laser therapy for depression.

1. Overview of Low-Level Laser (LLL)

Since Theodore Maiman' s invention in 1960, lasers have been widely applied in clinical medicine due to their high monochromaticity, directionality, coherence, and energy properties, as well as their photobiological effects [7]. Laser biological effects primarily include thermal, pressure, photochemical, and electromagnetic field effects, plus photobiomodulation (PBM)—a unique property of LLL that encompasses both biostimulatory and bioinhibitory actions [8].

LLL, a common light source for PBM, refers to red light (wavelength 600–1600 nm, output power 1–500 mW) or near-infrared (NIR) light (wavelength 760–1440 nm, output power 50–500 mW). Primary sources include He-Ne lasers, ruby lasers, and LEDs, with He-Ne lasers being commonly used.

Research confirms that LLL, as a non-pharmacological, non-invasive physical treatment and innovative therapy, has attracted considerable attention in experimental and preclinical studies for years. Initially applied to rabbit models of acute embolic stroke, LLL can penetrate skin and deep tissues, is non-carcinogenic, non-invasive, safe, economical, and free of side effects, without causing reversible damage to organisms [9]. In rodents, the differential light absorption rates of 810 nm laser across species primarily correlate with variations in water and protein content within skull bone [10], with 808 nm NIR

demonstrating superior penetration of human brain tissue compared to 940 nm NIR and 660 nm red light. LLL wavelengths of 1064–1072 nm more readily penetrate surrounding tissues due to light scattering effects [11]. PBM influences endogenous photoreceptors—specifically cytochrome c (CytC) oxidase activity —triggering cellular signal transduction and metabolic changes in tissue cells [12]. LLL photons at specific wavelengths (810 nm) interact with tissue photoreceptors to initiate biological responses, including improved bioenergetics, increased regional blood flow, stimulation of growth factors, reduced apoptosis, oxidative stress, and tissue inflammation. Clinically, LLL is widely used for anti-inflammatory effects, wound healing promotion, tissue repair and regeneration, and alleviation of neuropathic pain [13–15]. Transcranial LLL shows potential therapeutic value for neuropsychiatric disorders including traumatic brain injury, stroke, neurodegenerative diseases (PD, AD), schizophrenia, and mood disorders [9,16–18].

2.1 Low-Level Laser Improves Depressive Symptoms

Behavioral changes in animal models serve as both indicators of successful depression model establishment and standards for evaluating antidepressant efficacy. Primary assessment measures include the open field test (OFT, evaluating "locomotor activity and exploratory behavior"), tail suspension test (TST) or forced swimming test (FST, assessing "behavioral despair"), sucrose consumption test (FCT, measuring "anhedonia"), and body weight measurement (BWM).

Preclinical studies demonstrate that transcranial LLL improves depressive-like behaviors and regulates biological processes in chronic unpredictable mild stress (CUMS) depression model rats [19]. Transcranial LLL (810 nm, 10 Hz, 1.2 J/cm^2) significantly reduces immobility time in the forced swimming test in CUMS rats, with efficacy comparable to citalopram and superior to red laser [20]. Combined transcranial LLL (810 nm, 10 Hz, 33.3 J/cm^2) and coenzyme Q10 reduces depressive-like behaviors in CUMS mice [21]. Transcranial LLL (804 nm, 80 mW, 0.64 W/cm^2) significantly decreases immobility time and increases swimming and climbing time in both FST-induced and reserpine-induced depression model rats, whereas high-dose LLL (804 nm, 400 mW, 3.18 W/cm^2) produces opposite effects [22]. Four weeks of transcranial LLL (808 nm, 30 mW, 23 mW/cm^2) significantly reduces immobility time in TST and FST in space-restricted mice and Ahi1 knockout mice, improving depressive-like behaviors [23]. Transcranial LLL (810 nm, 10 Hz, 8 J/cm^2) significantly improves both depressive and anxiety behaviors in CUMS mice, with superior efficacy compared to both 4 J/cm^2 and 16 J/cm^2 doses [24].

Clinical studies confirm that transcranial LLL (780 nm, 70 mW, 105 J/cm^2) alleviates anxiety and depressive symptoms in elderly patients with temporomandibular joint disorders while improving sustained attention, short-term memory, and executive function [25]. Transcranial LLL (1064 nm, 250 mW/cm^2, 60 J/cm^2) significantly improves rule-based learning in the prefrontal cortex

of student subjects, though striatal information-integration learning showed no significant difference, suggesting potential for cognitive enhancement [26]. Transcranial LLL (810 nm, 10 Hz, 4.75 W/cm^2) increases frontal cortical hemodynamics and reduces depression scores in patients with anxiety and depression [27]. Both transcranial near-infrared irradiation (808 nm, 700 mW, 84 J/cm^2) and transcranial LLL (810 nm, 250 mW/cm^2, 60 J/cm^2) reduce depressive states in MDD patients [28]. In postmenopausal obese women, laser biostimulation combined with low-calorie diet significantly reduces body mass index, inflammatory markers, and depressive symptoms compared to diet alone [29]. Transcranial LED (945 nm, 9.35 J/cm^2) PBM improves brain activity and reduces anxiety and depression in university students [30]. Transcranial PBM (850 nm) enhances cognitive function, electrophysiological characteristics, and attention in both healthy adolescents and patient subjects [31].

2.2 Neurobiological Mechanisms of LLL in Improving Depressive Symptoms

Research confirms that depression results from interactions among biological factors (genetics, neurochemistry, neuroendocrinology, neuroplasticity), psychological factors, and social environmental factors. Current research hotspots regarding biological factors include: brain energy metabolism consumption theory, monoamine neurotransmitter and receptor theory, neuroendocrine dysfunction theory, immune system abnormalities theory, and hippocampal neuroplasticity impairment theory. The neurobiological mechanisms through which LLL improves depression primarily include the following aspects:

2.2.1 Enhancement of Brain Energy Metabolism

Neuronal functional activity correlates directly with energy consumption. Brain tissue is rich in mitochondria, whose functional activities are closely related to energy metabolism, signal transduction, neurogenesis, and neuronal plasticity. High energy metabolism may contribute to emotional disturbances in depression. Mitochondrial dysfunction in the prefrontal cortex, hippocampus, and other regions correlates with mood disorders including depression and anxiety [31]. Mitochondria serve as the primary initiators of PBM in the brain and represent the main organelle for ATP generation, with ATP content being a crucial factor affecting depression development. Mitochondrial dysfunction reduces ATP biosynthesis, disrupts calcium homeostasis, and increases free radicals [32]. Cytochromes a and b in the mitochondrial respiratory chain selectively absorb red and NIR light, enhancing electron transport chain coupling, accelerating electron transfer, promoting ATP synthesis, strengthening cell membrane ion pump activity, increasing intracellular cAMP concentration, and triggering biological effects [32]. Mitochondrial complex IV (mitochondrial complex IV), or CytC oxidase, serves as the terminal enzyme of the respiratory chain and the primary intracellular photoreceptor, transferring electrons from respiratory substrates to molecular oxygen. Therefore, CytC oxidase plays a crucial role in

neuronal biological effects, acting as a node between energy metabolism and cell signaling pathways and as an endogenous metabolic marker of neural activity. It strongly absorbs wavelengths from red to near-infrared lasers (812–846 nm) and promotes mitochondrial energy metabolism [33]. LLL can non-invasively deliver energy to CytC oxidase, activating the mitochondrial electron respiratory transport chain, accelerating ATP synthesis, and regulating oxidative stress [34].

Preclinical studies show that depression model mice exhibit low ATP content in the hippocampus and prefrontal cortex, with ATP treatment improving depressive-like behaviors [35]. Transcranial LLL (810 nm, 10 Hz, 8 J/cm^2) activates CytC oxidase, regulates mitochondrial function, and increases ATP generation, improving mitochondrial function and cognitive impairment in D-galactose-induced aging mice [36]. Metformin alleviates depressive-like behaviors in elderly apoE4 mice by improving glucose metabolism and mitochondrial function, while also reducing metabolic disturbances and depressive-like behaviors in corticosterone-induced rats via glucose metabolism pathways [37–38]. Transcranial LLL (808 nm, 23 mW/cm^2, 30 min daily for 28 days) effectively increases mitochondrial respiratory chain coenzyme IV expression and ATP biosynthesis in the prefrontal cortex of chronic restraint stress (CRS) depression model mice and Ahil knockout mice, thereby improving depressive-like behaviors, though without affecting the hippocampus or hypothalamus [23]. Clinical studies confirm that transcranial LLL (1064 nm, 162 mW/cm^2, 107 J/cm^2) significantly upregulates CytC and blood oxygen supply in the human brain, improving hemodynamic changes and enhancing cerebral oxygenation and energy metabolism [39]. Patients with depression show abnormal glucose metabolism in the anterior cingulate cortex, hippocampus, and prefrontal cortex, which improves after antidepressant treatment [40]. LLL (808 nm, 250 mW/cm^2, 60 J/cm^2) delivered to the cerebral cortex increases frontal cortical blood flow and improves depressive and anxiety symptoms in MDD and anxiety patients [41]. These studies collectively suggest that transcranial LLL may improve depressive symptoms in patients and depressive-like behaviors in animal models by enhancing mitochondrial function and brain energy metabolism [42].

2.2.2 Increased Monoamine Neurotransmitter Content

The monoamine neurotransmitter deficiency hypothesis in central nervous system synapses represents a milestone in elucidating depression pathogenesis. Monoamine transmitters include catecholamines such as norepinephrine (NE) and dopamine (DA), and indoleamines such as serotonin (5-HT). These neurotransmitters regulate neuroplasticity through receptor expression modulation and affect mood. Studies confirm that transcranial LLL (808 nm, 23 mW/cm^2, 42 J/cm^2) significantly increases 5-HT and DA content in hippocampal tissue of CRS depression model mice and Ahil knockout mice [43]. Transcranial LLL (810 nm, 200 mW, 8 J/cm^2) more effectively improves depressive and anxiety behaviors in CRS mice compared to 4 J/cm^2 and 16 J/cm^2 doses, with

mechanisms related to reducing 5-HT and DA content while increasing NO levels in the prefrontal cortex and hippocampus [24]. Combined transcranial electrical stimulation and 5-HT laser phoresis alleviates depressive symptoms in athletes, possibly by modulating 5-HT and DA systems [44]. Transcranial LLL (830 nm, 127.4 mW/cm^2, 15.28 J/cm^2) improves depressive-like behaviors in reserpine-induced depression model rats by increasing 5-HT, NE, and DA content in hippocampal and prefrontal cortical tissues while reducing oxidative stress damage [9].

2.2.3 Improvement of Hypothalamic-Pituitary-Adrenal Axis (HPAA) Function

The neuroendocrine theory of depression posits that dysfunction involves hypothalamic-pituitary-thyroid axis (HPTA) and hypothalamic-pituitary-gonadal axis (HPOA) hypofunction combined with HPAA hyperfunction. The HPAA represents the primary neuroendocrine system mediating stress responses: stress → cerebral cortex → HPAA activation [hypothalamus releases corticotropin-releasing hormone (CRH) → anterior pituitary releases adrenocorticotropic hormone (ACTH) → increased serum/plasma glucocorticoids (GC) and corticosterone → attacks hippocampus (rich in GC receptors) → hippocampal neuronal damage and apoptosis → triggers negative emotions including depression, anxiety, and post-traumatic stress]. Patients with hypothyroidism show significantly higher MDD incidence than the general population, with decreased plasma T3 and T4 predisposing to depression. Sex hormone replacement therapy improves depressive mood in elderly AD patients, and depression onset shows gender differences and age clustering. Transcranial near-infrared laser (810 nm, 10 Hz, 1.2 J/cm^2) significantly reduces serum cortisol levels in CUMS depression model rats, with superior efficacy compared to red laser (630 nm, 10 Hz, 1.2 J/cm^2) [45]. Transcranial near-infrared light (810 nm, 10 Hz, 1.2 J/cm^2) combined with coenzyme Q10 alleviates depressive-like behaviors in CRS mice by reducing serum corticosterone and glucocorticoid levels [46].

2.2.4 Regulation of Hippocampal Neuroplasticity

Depression is closely associated with hippocampal neuroplasticity dysregulation, which primarily includes neurogenesis and synaptic plasticity modulation. Hippocampal neurogenesis mainly occurs in the subgranular zone (SGZ) of the dentate gyrus and subventricular zone (SVZ). Postmortem studies of suicide patients with depression reveal reduced hippocampal volume, and MDD patients show significant hippocampal atrophy. Structural and functional brain damage in depression model animals correlates morphologically with hippocampal neuronal atrophy, loss, apoptosis, reduced regeneration, decreased dendritic number, and altered length. Antidepressants inhibit hippocampal neuronal damage and apoptosis while stimulating neurogenesis to regulate neuroplasticity. The cAMP response element-binding protein (CREB)-brain-derived neurotrophic

factor (BDNF)/tyrosine kinase B (TrkB) signaling pathway critically influences neurogenesis, synaptic plasticity, and long-term memory. This pathway is essential for understanding depression neuroplasticity mechanisms, antidepressant efficacy, neurodegenerative diseases (PD, AD), and drug addiction formation. BDNF, a primary CREB target gene, promotes differentiation, proliferation, nutrition, and maturation of various neuron types, particularly regulating plasticity of dopaminergic, cholinergic, and serotonergic neurons. CREB, a nuclear third messenger and convergence point for various signal transduction proteins, regulates neuronal apoptosis through multiple genes. The Bcl-2 protein family controls apoptosis programs, comprising pro-apoptotic genes (e.g., Bax, Bid, Bak) and anti-apoptotic genes (e.g., Bcl-2, Bcl-xl, Mcl-1). Bcl-2 and Bax regulate apoptosis through protein binding and dissociation, with mitochondrial membrane permeability and potential changes representing a crucial apoptosis step that triggers cytochrome c release and activates the caspase cascade.

Studies confirm that transcranial LLL exerts antidepressant effects by regulating hippocampal neuroplasticity. Preclinical research shows PBM stimulates neurogenesis and protects cells from death. Near-infrared light (670 nm) protects against oxidative stress damage and cyanide-induced neuronal injury [28]. Transcranial LLL (810 nm) improves neuronal regeneration and synaptogenesis in traumatic brain injury mice, upregulates macrophage secretion of neurotrophic factors via the AC-cAMP-PKA-CREB pathway, promotes neuronal differentiation and axonal regeneration, and reduces oxidative stress damage in primary cultured neurons [47–48]. Transcranial LLL (810 nm, 25 mW/cm^2, 18 J/cm^2) improves memory and learning in traumatic brain injury mice by increasing BDNF expression, enhancing neural progenitor cell proliferation and synaptogenesis [49]. Transcranial LLL upregulates BDNF expression via the ERK/CREB pathway, improving neuronal loss and dendritic atrophy in AD mice [50]. Low-level He-Ne laser (632.8 nm, 10 mW or 12.74 mW/cm^2, 0.5–3.8 J/cm^2) activates IP3 receptor signaling, increases intracellular Ca^{2+}, activates the Ca^{2+}-ERK-CREB pathway, and elevates BDNF, phosphorylated CREB protein, and mRNA expression in cultured spinal dorsal root ganglion neurons, effectively regulating BDNF protein expression in the nervous system. However, blocking this pathway with the ERK inhibitor PD98059 reduces BDNF, phosphorylated CREB protein, and mRNA expression [51]. Additionally, transcranial LLL improves neuroplasticity by reducing neuronal apoptosis, enhancing Bcl-2 expression, and decreasing Bax and Caspase-3 protein expression [52–53]. Transcranial LLL (670 nm, 50 mW/cm^2, 15 J/cm^2) improves behavioral changes and Bcl-2/Bax expression in traumatic brain injury SD rats [49]. In cultured PC12 cells injured by A$ 25–35, $LLL(640nm, 0.09mW/cm^{\{2\}}, 60min) reduces apoptosis and DNA fragmentation [53]. In cultured SH-SY5Y, PC12, an
catenin signaling pathway [54].

2.2.5 Regulation of Anti-Inflammatory Responses

The cytokine theory of depression, proposed in 1991, has been continuously validated and refined. This theory suggests depression may relate to immune system abnormalities, specifically excessive cytokine secretion. Cytokines, bioactive proteins secreted by activated immune cells, are classified as pro-inflammatory (e.g., IL-1α, IL-1β, IL-6, IFNα, IFNγ, TNFα) or anti-inflammatory (e.g., IL-4, IL-10). Stress activates the immune system and releases pro-inflammatory cytokines, with immune activation and stress producing similar behavioral effects. Immune-inflammatory responses may represent one mechanism through which stress regulates depression progression, as peripheral or central inflammation can affect immune function and cause depression. Postmortem studies of suicide patients with depression show increased pro-inflammatory factors and apoptosis in the prefrontal cortex. Antidepressant treatment subjects show elevated IL-1α, IL-1β, IL-6, and IL-8. MDD patients exhibit significantly higher IL-6 in cerebrospinal fluid than in serum and higher than healthy controls. Red/NIR light significantly reduces IL-6, IL-1β, and IL-8 levels in rheumatoid arthritis model rats [28]. Antidepressants inhibit microglial activation and pro-inflammatory cytokine production, while activated microglia in inflammatory and stressful environments suppress neurogenesis and damage hippocampal neuroplasticity. Anti-inflammatory drugs exhibit antidepressant characteristics, and many depression patients show elevated inflammatory markers even without clear inflammatory etiology. Studies confirm that transcranial infrared laser improves cognitive dysfunction in traumatic brain injury mice by reducing neuroinflammation [28]. Transcranial LLL (810 nm, 33.3 J/cm^2) combined with coenzyme Q10 (CoQ10) improves depressive-like behaviors in CRS stress mice [21]. PBM alleviates anxious-depressive-like behavior in TgF344 rats by reducing neuronal damage, degeneration, apoptosis, and inhibiting neuroinflammation and oxidative stress [55]. Therefore, LLL represents a potential therapy for depression triggered by neuroinflammation.

3. Conclusion and Outlook

In summary, transcranial LLL' s photobiomodulatory effects enhance neuronal metabolic capacity and stimulate anti-inflammatory, anti-apoptotic, antioxidant stress responses, as well as neurogenesis and synaptogenesis [28]. At the cellular level, PBM reduces apoptosis and excitotoxicity, increases antioxidant superoxide dismutase, neurotrophic factors, and stimulates neural progenitor cell generation. At the tissue level, PBM increases blood flow and angiogenesis, reduces inflammation, and facilitates new neuronal connections. Transcranial LLL has demonstrated efficacy in treating anxiety, depression, and cognitive dysfunction, though optimal dosing parameters and mechanisms remain incompletely defined [56–57]. With its safety and durability, LLL may serve as a potential alternative therapy for treatment-resistant depression, anxiety, and other neuropsychiatric disorders [9,58]. However, some studies show transcranial laser therapy fails to improve cognition or PTSD-related behavioral traits in rats exposed to repeti-

tive low-level blast injury [59]. Treatment efficacy for neuropsychiatric disorders is influenced by multiple factors including light source, wavelength, fluence or total dose, output power, repetition frequency, irradiation area, duration, operation mode (continuous or pulsed), and tissue light penetration attenuation [60]. Future research must explore optimal intracranial or intranasal laser therapy doses for specific conditions to achieve optimal stimulation intensity, requiring extensive randomized controlled animal experiments and clinical trials to establish safety and efficacy. Further preclinical work is needed to elucidate the neurobiological mechanisms underlying LLL' s antidepressant effects and provide theoretical foundations for physical therapy of traumatic brain injury, depression, anxiety, and other neuropsychiatric disorders.

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Note: Figure translations are in progress. See original paper for figures.