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The effectiveness of photobiomodulation therapy in modulation the gut microbiome dysbiosis related diseases

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ABSTRACT

Maintaining a healthy balance between commensal, and pathogenic bacteria within the gut microbiota is crucial for ensuring the overall health, and well-being of the host. In fact, by affecting innate, and adaptive immune responses, the gut microbiome plays a key role in maintaining intestinal homeostasis and barrier integrity. Dysbiosis is the loss of beneficial microorganisms and the growth of potentially hazardous microorganisms in a microbial community, which has been linked to numerous diseases. As the primary inducer of circadian rhythm, light can influence the human intestinal microbiome. Photobiomodulation therapy (PBMT), which is the use of red (630-700 nm), and near-infrared light (700 and 1200 nm), can stimulate healing, relieve pain, and reduce inflammation, and affect the circadian rhythm and gut microbiome beneficially. Our focus in this paper is on the effects of PBMT on gut microbiota, to provide an overview of how it can help control gut microbiota dysbiosis-related disorders.

Keywords: Gut microbiota, Photobiomodulation, Inflammation, Dysbiosis.

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Introduction

The human gut microbiome is commonly regarded as an organ within the body, and there are 10 times more bacterial cells (10^{14} in total) than the body's cells in adulthood (1). Gut microbiome homeostasis is essential to maintain the health of the host and a multifaceted communication exists between the human body and its microbiome. The gut microbiota (GM) and its metabolites, like short-chain fatty acids (SCFAs), and Gram-negative bacterial lipopolysaccharides (LPS), exert anti- or pro-inflammatory effects by acting on macrophages and regulate host metabolism (2-5). Dysbiosis, characterized by an aberrant and perturbed bacterial composition and distribution, has been associated with a range of pathological conditions including inflammatory bowel disease (IBD), colitis, colorectal cancer, liver disease, cardiovascular and neurodegenerative disorders, asthma, and metabolic disorders, such as type 2 diabetes (1). Dysbiosis can arise from various factors, such as anxiety behaviors, clinical depression, high-fat diets, and antibiotic usage, among others. (2). Moreover, it was shown that the host circadian rhythm can affect the gut microbiota community (3). Light, as a main inducer of circadian rhythm, can affect the human gut microbiota and its metabolic products (4, 5).

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Numerous treatment options are available for gut dysbiosis, including dietary modulation, the administration of food supplements, probiotics, prebiotics, and fecal microbiota transplant (FMT). FMT involves transferring beneficial bacteria to the patient's gastrointestinal tract, which aids in repairing their gastrointestinal function (2, 6). Recently, it was reported that Photobiomodulation therapy (PBMT), known as low-level laser therapy (LLLT) or light therapy, can affect the gut microbiome in a beneficial way (7-9). In fact, PBM therapy is using red and near-infrared light to stimulate healing, relieve pain, and reduce inflammation, which can affect the circadian rhythm and microbiota composition (10). This study intends to gather current evidence on the therapeutic benefits of photobiomodulation therapy (PBMT) as an adjuvant treatment for periodontal treatment in the management of different illnesses. Specifically, it focuses on the potential of PBMT to address gut microbiome dysbiosis and its related disorders.

Gut microbiota components and inflammation

Recently characterizing the human gut microbiome becomes the core objective of several health related projects, such as a Human Microbiome Project (HMP), and the European Metagenomics of the Human Intestinal Tract (MetaHIT) (11). The gut microbiota is comprised of a diverse array of both commensal and pathogenic microorganisms (12). Dysbiosis refers to the shift in microbial community composition characterized by a reduction in helpful bacteria and an increase in potentially dangerous microorganisms (12). Based on the findings, the dominants intestine bacterial phyla are *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Fusobacteria*, *Actinobact*,eria and *Verrucomicrobia* (2). Approximate 90% of gut microbiota composition belong to *Firmicutes* (64%) and *Bacteroidetes* (23%) (13, 14). The gut microbiota produces various metabolites that are crucial for human health when it is in a healthy state. However, if there is an imbalance in the gut microbiota, known as dysbiosis, the production of these metabolites can be disrupted, resulting in the onset of several diseases. In fact, the microbiota has a multifaceted role to modulate anti and pro-inflammatory responses (15). Certain components of gut bacteria, such polyamines (putrescine and spermine) and short-chain fatty acids (SCFAs), have immunomodulatory and anti-inflammatory properties. The gut uses short-chain fatty acids (such as acetate, propionate, and butyrate) as an energy source. These fatty acids are principal byproducts of gut commensal bacteria, which are created by the fermentation of carbohydrates under anaerobic circumstances. They regulate the proliferation, and differentiation of intestinal epithelial cells and affect host metabolism, transcription, epigenetics, and reduce inflammation (16-18). SCFAs by inducing metabolic and transcriptional changes in macrophages increase their antimicrobial activity (19). These components can improve gut health, maintain intestinal integrity, and suppress inflammation by modulating the production of inflammatory mediators (20, 21).

On the other hand, Gram-negative bacterial lipopolysaccharides (LPS), as a component of their outer membrane, exert pro-inflammatory effects, and consequently, induce inflammatory cytokines (like interleukin (IL)-6, macrophage inflammatory protein (MIP)-3α and tumor necrosis factor (TNF)-α) production (22). This pro-inflammatory feature reduces tight junction protein levels, mucus construction, and antimicrobial peptides (like lysozyme and RegIII) production (23). The result is gut barrier disruption and an increase in intestinal bacterial translocation associated with intestinal inflammation, which causes further dysbiosis.

Moreover, microbiota-derived metabolites regulate the differentiation and function of different immune cell types, the most important of which are macrophages (MQs). The gut microbiota can alter pro- and anti-inflammatory effects of Monocyte-derived MQs, which are critical regulators of inflammatory responses in the body (25). The gut microbiome has an important role to preserve the intestinal homeostasis and barrier integrity by influencing both innate and adaptive immune responses. Any disruption in this balance can lead to the development of numerous inflammatory disorders (24).

Gut microbiome and human diseases

Studies showed that gut dysbiosis is associated with the onset of a wide range of diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), celiac diseases (CeD), neurological diseases, obesity, type 2 diabetes mellitus

(T2DM), etc. Interestingly, in most disorders, the reduction of some bacteria with potent anti-inflammatory effects (such as *Bifidobacterium* and *Faecalibacterium prausnitzii*) has been reported (25, 26). The most important question about the potential association between gut dysbiosis and the occurrence of diseases is whether gut microbiota alterations cause the onset of diseases or does the occurrence of diseases makes an alternation in the gut microbiome?

In the following, the role of dysbiosis in the occurrence of some of these diseases was discussed.

Dysbiosis and inflammatory bowel disease

Dysbiosis has a proven role in the progress of intestinal inflammation which is reported to be associated with both forms of IBD, including Crohn's disease (CD) and ulcerative colitis (CD) (30, 31). There are reports suggesting that the patients with IBD display alterations in the diversity and composition of their intestinal microbiota. Previous studies in IBD patients showed that intestinal macrophage activation, increased Th2/Th1 ratio, stimulate IL-22 production and consequently intestinal inflammation occurs as a result of dysbiosis and changes in the gut microbial metabolites (32).

Dysbiosis and irritable bowel syndrome

IBS is a common functional gastrointestinal disorder with multifactorial pathogenesis (27). Evidence suggests that dysbiosis causes the activation of gut's innate immune responses and increased expression of toll-like receptors (e.g., TLR4) by MQs and enhances the expression of the pro-inflammatory cytokines (like IL-1β, IL-6, IL-8, TNF-α, etc.) (28). Furthermore, the adaptive immune response showed an imbalance in Th1/Th2 regulation and an increase of proinflammatory cytokine in IBS patients (29). The changes in gut microbiota such as an increase in Lactobacillus, *Veillonella*, and *Enterobacteriaceae*, and a decrease in *Bifidobacterium* and *Clostridium* were reported in IBS patients in comparison to the healthy controls.

Dysbiosis and celiac diseases

CeD is a common autoimmune enteropathy, stimulated by aberrant innate, and adaptive immune responses to undigested gliadin peptides in the lamina propria of susceptible individuals (30). Dysbiosis plays a role in the pathophysiology of CeD by rupturing the intestinal barrier's integrity and allowing partially digested gliadin peptides to enter the lamina propria. This in turn sets off the activation of the immunological response (31). Gram-negative bacteria like *Bacteroidetes*, *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria* produce LPS, which activates TLR4-related inflammatory responses, damage intestinal barrier integrity and increase its permeability (32). On the other hand, Gram-positive bacteria, including *Lactobacilli* and *Bifidobacterium* families, which are considered probiotics, by enhancing the expression of cell-binding protein try to control inflammation (33). Based on the reports, Lactobacilli and *Bifidobacterium* spp. show a decrease in CeD patients relative to the control groups (34).

Dysbiosis and neurological diseases

There are several hypotheses about the effect of gut microbiota on brain function (35). Some gut microbiota metabolomes, such as SCFA, gamma-aminobutyric acid, noradrenaline, acetylcholine, dopamine, and serotonin exhibit neuroactive properties. Furthermore, GM interacts with the central nervous system (CNS) via the brain-gut-microbiome axis (36). The microbiome in the mouth, and gastrointestinal tract produces LPS, which may act as a trigger for neuroinflammation. This inflammation can contribute to the development of various neurological disorders (37). Research showed that the patients with severe autism, amyotrophic lateral sclerosis, and Alzheimer's disease have higher levels of this endotoxin in their serum compared to the levels observed in healthy individuals (38, 39).

Previous studies showed that dysbiosis may lead to the overstimulation of innate immune responses through toll-like receptor 4, as well as oxidative stress activation. This can eventually trigger the development of Parkinson's disease by activating enteric neurons and enteric glial cells (40).

Photobiomodulation therapy and its anti-inflammatory effects

Photobiomodulation therapy was found by Endre Mester in 1967 (41). PBMT, which is the use of red (630-700 nm) and near-infrared light (700 and 1200 nm), was shown to have the potential to be used as a supportive treatment option for reducing inflammation and accelerating pain and wound healing (42). In PBMT, photons interpenetrate to the tissue and are

absorbed by cytochrome c oxidase in mitochondria and calcium ion channels, which leads to an increase in enzyme activity, oxygen consumption, and ATP production (43). Additionally, photons have the ability to separate nitric oxide (NO) into an active form from the heme and Cu centers of cytochrome c oxidase (44). Vasodilation and increased blood flow are two of the most significant physiologic processes in which NO is involved (45). Furthermore, under normal conditions, photons of PBMT increase reactive oxygen species (ROS) production leading to the activation of several transcription factors, increased gene expression, enhanced protein synthesis, etc. (7, 44). But, under oxidative stress and pathological conditions, PBMT reduces ROS, NO, and NF-kB production, and induces anti-inflammatory effects (12). PMBT can decrease the production of prostaglandin E2 (PGE2) and pro-inflammatory cytokines, such as IL-1ß, IL-6, IL-8, IL-12 and TNFα (32). Sousa et al. in 2017 showed that 660 nm PMB could significantly diminish the TNFα, CCL,3 and CXCL2 mRNA expression by activating M1 macrophages 4 hours after irradiation (46). In another recent study, it was shown that PBM can modulate the ratio of M1 and M2 macrophage phenotypes, suppress a range of macrophage-associated pro-inflammatory cytokines and chemokines, and increase anti-inflammatory cytokines in a time-dependent and wavelength-dependent manner (47).

Moreover, PBMT, in terms of its anti-inflammatory properties, was introduced as an alternative therapeutic option for various clinical conditions.

Photobiomodulation therapy in different clinical conditions

The positive effect of PBMT to improve several disorders, such as arthritis, traumatic brain injury, spinal cord injury, wound healing, inflammatory pain, lung inflammation, multiple sclerosis (MS), type 2 diabetes, autoimmune thyroiditis, psoriasis and acrodermatitis continua (two chronic autoimmune skin diseases), cardiovascular disease, endothelial dysfunction, and IBD has been reported so far (48-51). Additionally, Nagy et al. demonstrated that PBM may provide a novel, non-invasive treatment option for obesity and non-alcoholic fatty liver disease (54). According to recent research, PBM may improve neurological conditions including Parkinson's, Alzheimer's, and traumatic brain injuries while also enhancing nerve function (41, 49, 52). Considering its anti-inflammatory properties, PBMT is a promising candidate for further exploration of its potential effects on various diseases, particularly autoimmune disorders.

PBMT therapeutic potentials in GM-related disorders

As mentioned earlier, dysbiosis is associated with the onset of several diseases, and PBMT is effective in improving many of them. At first Liebert in 2019 used the ‘‘photobiomics’’ term to show the light (PBM) effect on the microbiome, metabolomics, and the communication between them (7). Recently, several animal studies showed that PBM significantly altered the diversity and abundance of gut microbiome (8, 53). Although the precise processes by which light treatment impacts the gut microbiota remain unclear, many potential avenues are suggested here. Research suggests that PBMT may have a beneficial effect on gut microbiota by modulating the composition of the microbial communities. For example, PBMT was shown to increase the abundance of certain beneficial bacteria, such as *Akkermansia*, *Faecalibacterium*, and *Roseburia* and decrease the number of potentially pathogenic genera (54). Furthermore, PBMT was shown to reduce inflammation in the gut, which may contribute to its positive effects on gut microbiota. This reduction in inflammation may be due to the ability of PBMT to reduce oxidative stress and increase antioxidant capacity (55, 56). PBMT was found to increase the level of Vitamin D, which can affect the composition of the gut microbiota (57, 58). It was shown that diurnal oscillations and light stress could influence the composition and activities of mouse microbiome (59-61). Bicknell et al. used the PBM (NIR light; 808 nm) to the abdomen three times a week for 12 weeks for altering microbiome diversity in healthy mice and showed an increase in the number of *Allobaculum* (10,000-fold), which is a bacterium related to the healthy microbiome (8). Continuous dark or light exposure in mice was also shown by Kim et al. to change the makeup of the microbiota; continuous light exposure resulted in an increase in *Bacteroidales* S24-7 (26), whereas continuous dark exposure was accompanied with a rise in *Bacteroidales* and *Rikenellaceae*. Thus, studies investigated the effect of

light stress on the number and species of epithelial-associated commensal bacteria in murine, and showed ten-fold abundance in the dark phase (5). Furthermore, seasonal variations in microbiome composition due to the alteration in sunlight/UVB light have also been reported (60). The protective effect of UVB against inflammatory diseases, such as IBD, to which changes in gut microbiota are associated, was proven (61).

Bosman indicated that decreased exposure to Narrow-band ultraviolet B and deficiency in vitamin D production is promoter for gut microbiome modulation resulting in dysbiosis (61). Bosman has introduced a novel theory called the skin-gut axis, which demonstrates a strong bidirectional connection between gut bacteria and skin health. Therefore, sunlight exposure is considered to be one of the potencies modulating the gut microbiome, which doubles the importance of PBMT (62).

PBMT can be used for improving gut microbiome-related neurological disorders, such as, Alzheimer and Parkinson diseases. Based on Chen and colleagues, in animal models of Alzheimer's disease (AD), PBMT at wavelengths 630 nm and 730 nm decreased the amount of *Helicobacter pylori* and uncultured *Bacteroidales* while increasing the presence of *Rikenella* in the gut microbiome. These results suggest that *Rikenella* may have therapeutic potential as a target for treating AD (53). PBM630 and PBM850 were also discovered to alter the metabolome composition of the intestinal flora, resulting in a treatment that brought lipopolysaccharide production, bacterial toxins, and pyrimidine metabolism closer to normal (53). Liebert Ann and Bicknell and their co-workers showed that the PBM therapy (delivered to the head, nose, neck and abdomen) can diminish a range of clinical symptoms of Parkinson's disease and affect the gut microbiome composition. Their research showed positive changes in the *Firmicutes* to *Bacteroidetes* (F: B) ratio in these patients (52). To better understand this concept, the results of mentioned studies were summarized in Table 1.

Numerous studies were conducted to investigate the potential of PBMT as a treatment modality for various diseases. For instance, Liebert et al. conducted a study to assess how effective remote PBM is in reducing clinical signs of Parkinson's disease. During the 12-week study, seven participants received PBM treatment on their abdomen and neck three times per week resulting in improvements in mobility, cognition, dynamic balance, spiral test, and sense of smell. Although COVID-19 lockdowns resulted in some lost improvements, the overall conclusion was that remote PBM treatment was effective to reduce the clinical signs of Parkinson's disease. The study shows the potential of remote PBM as a treatment option for Parkinson's disease (63).

De Menezes et al. studied the effectiveness of LLLT in preventing oral mucositis in patients with solid tumors undergoing chemotherapy. They discovered that applying LLLT at a frequency of 630nm and a dose of 2J/cm2 is an effective method of reducing the development, and the severity of oral mucositis (up to grade I/II) in the patients receiving chemotherapy for non-hematological tumors. The study noted that the application of LLLT protocol prevented a reduction in superoxide dismutase (SOD) activity in patients, which is typically associated with leukopenia and oral mucositis. In general, the study's recommended prophylactic laser therapy protocol

Table 1. A summary of photobiomodulation therapy effects on gut microbiome composition

PBMT Application	Results
NIR light (808 nm) on abdomen	Increase in *Allobaculum* (10,000-fold)
Continuous dark or light exposure in mice	Dark exposure: increase in *Bacteroidales* and *Rikenellaceae*; Light exposure: increase in *Bacteroidales* S24-7
Light stress	Ten-fold abundance of epithelial-associated commensal bacteria in dark phase
Seasonal variation in sunlight/UVB light	Alteration in microbiome composition
Decreased Narrow-band ultraviolet B exposure and vitamin D deficiency	Promotes gut dysbiosis
PBMT at wavelengths 630 nm and 730 nm	Decrease in *Helicobacter pylori* and *uncultured Bacteroidales*; Increase in *Rikenella*
Photobiomodulation on head and abdomen of a mouse model	Improvement in Alzheimer's symptoms
PBM therapy on head, nose, neck, and abdomen	Positive changes in *Firmicutes* to *Bacteroidetes* ratio and clinical symptoms of Parkinson's disease

shows promise in reducing the prevalence of oral mucositis in the patients receiving chemotherapy for solid tumors (64).

Hsieh et al. conducted a study using a prospective cohort design to investigate the effects of PBMT on 17 patients with gastrointestinal cancer. The study included pre- and post-intervention assessments. The results of the study showed that after receiving twelve sessions of PBMT, the neurotoxicity symptoms of the patients significantly reduced, and their cold and mechanical allodynia disappeared (65).

Conclusion

Considering PBMT can impact the composition of gut microbiota and has shown beneficial effects in treating diseases related to the gut microbiota, it can be suggested as a non-invasive supportive therapy for various clinical conditions. The few adverse side effects and high level of tolerability of this uncomplicated treatment method among elderly patients underscore the importance of giving it due consideration. Nevertheless, it is essential to evaluate the effect of PBMT on different GM-related disorders that have not yet been studied and identify the most effective doses, as well as the ideal frequency and duration for each specific condition.

Conflict of interests

There is no conflict of interest for authors of this article.

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