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Photobiomodulation with Low-Level Laser Therapy to Treat Rheumatoid Arthritis: Experimental and Clinical Evidence

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that primarily affects the joints and can cause severe deformities, progressive destruction of joint structures, and significant functional impact. Although several mechanisms are known, the etiology is multifactorial and three times more women than men are affected. In addition to the joints, the disease can affect other systems, causing manifestations such as fatigue, fever, cardiovascular and nephrological changes, which together reduce patients' quality of life. Despite therapeutic advances with immunomodulatory and biological drugs, there are still many limitations, such as adverse effects and insufficient control of disease progression. In this scenario, photobiomodulation (PBM) using low-intensity lasers or LEDs has emerged as a promising complementary therapeutic approach due to its ability to modulate inflammatory processes, relieve pain, and stimulate tissue repair, all in a safe and non-invasive manner. This study aims to evaluate the effects of PBM in the treatment of RA based on a systematic review of the literature, examining the physical aspects of the technique, the pathophysiological mechanisms of RA in humans and in experimental models, and the clinical and experimental evidence related to the efficacy of PBM. The results indicate that PBM works by reducing oxidative stress and promoting tissue regeneration, with significant benefits in controlling inflammation and pain. Recent technological advances in the field of PBM, including more precise and adaptable devices, strengthen its potential as an effective complementary therapy, but challenges remain in terms of standardization of application parameters and clinical validation.

Keywords: photobiomodulation, arthritis, low-level laser therapy

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a chronic inflammatory process that primarily affects the joints, leading to progressive degradation of cartilage and bone tissue [1]. The inflammatory process results in clinical symptoms such as pain, edema, limited range of motion, fatigue, increased local temperature, and anemia, significantly affecting the quality of life of patients [2, 3].

This condition affects approximately 1% of the world's population and is one of the most common rheumatologic diseases. Its incidence is significantly higher in women, especially between the ages of 30 and 50, suggesting a possible hormonal influence on its etiology. Although the exact causes of the disease are not fully understood, it is known that genetic and environmental factors play an important role in the development of RA [2].

In Brazil, data of RA are still limited and not very detailed. The estimated prevalence of the disease in the country varies between 0.2% and 1%. Based on data from the 2022 census, which indicates a total population of 203,080,756 inhabitants, it is estimated that approximately two million Brazilians are affected by RA [4]. A 2018 study on the cost of RA treatment in the Unified Health System (SUS) in Minas Gerais highlighted that costs are associated with factors such as gender, age, and sociodemographic conditions [5].

Conventional treatment of RA involves the use of non-steroidal anti-inflammatory drugs and corticosteroids. However, these treatments can have significant side effects such as erosions, peptic ulcers, hypertension, diabetes mellitus, nephropathy, and cataracts. In addition, immune dysfunction increases susceptibility to opportunistic infections [6].

Therapies for the treatment of RA include disease-modifying drugs, steroidal anti-inflammatory drugs, among others, but they can be harmful in the long term, while photobiomodulation (PBM) with low-level laser therapy (LLLT) uses intense low-power light with its own characteristics such as monochromaticity, coherence and collimation, in the infrared spectral range, stimulating biological processes like upregulation of gene and protein expression and consequently improvement of joint tissues [7, 8].

Preclinical and clinical studies indicate that PBM can control the inflammatory process reducing cell migration, reduce pain, stimulate tissue regeneration, and improve joint function, making it a non-invasive and safe approach for the treatment of chronic inflammatory diseases [7, 9].

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The aim of this paper is to review the experimental and clinical evidence on the application of PBM with LLLT in the treatment of RA. This review aims to highlight the effects of PBM on inflammation control and joint repair, as well as to explore the challenges and future prospects of this therapeutic approach.

2. Methods

This study was performed through a systematic literature search of scientific articles published in journals between 1977 and 2024. The databases consulted included PubMed, LILACS, and Scielo. DeCS descriptors such as PBM, RA, laser treatment, and clinical trials were used to select articles. These terms were searched in isolation or in combination using Boolean operators (AND and OR) in the MeSH terms. The selected articles were analyzed with the aim of understanding the impact of PBM in the treatment of RA based on experimental and clinical evidence. The analysis included studies using animal models, case series, and clinical trials evaluating parameters such as control of the inflammatory process, morphological, molecular and protein changes, symptom relief and functional recovery in different experimental and clinical conditions.

3. Literature Review

3.1. Human RA and experimental models

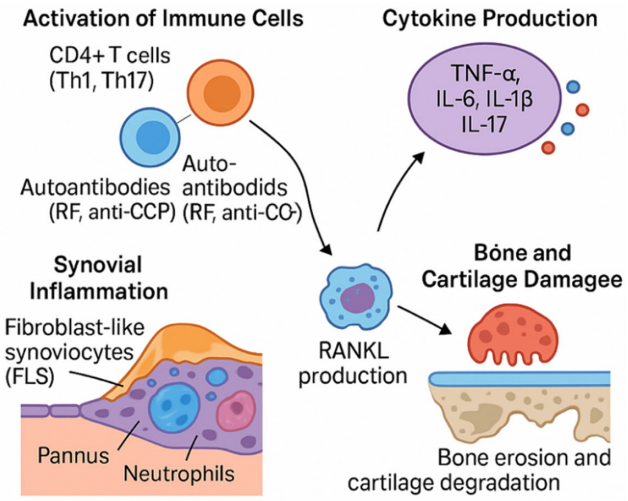
RA is a chronic inflammatory, autoimmune, and systemic disease characterized by persistent inflammation of the joints, which over time can lead to deformity, joint destruction, and significant functional disability. The disease is multifactorial, resulting from a complex interaction between genetic predisposition and environmental and immunologic factors. The primary targets of inflammation are the synovial joints, where abnormal proliferation of the synovial membrane occurs, accompanied by infiltration of inflammatory cells and progressive degradation of the underlying cartilage and bone. Clinically, RA manifests as pain, prolonged morning stiffness, swelling, and heat in the affected joints, usually symmetrically, with the small joints of the hands and feet being the first to be affected [6].

In addition to joint symptoms, the disease can have extra-articular manifestations, including rheumatoid nodules, pulmonary involvement, vasculitis, ocular changes (such as episcleritis and scleritis), and a high risk of cardiovascular disease, which is a major cause of mortality in patients with RA. The psychological and social impact of the disease is significant, as chronic pain and functional limitations adversely affect quality of life and interpersonal relationships. Studies indicate that patients with RA have a higher prevalence of depressive and anxiety disorders, often related to the difficulty of coping with disease progression and disability. The progressive nature of RA, if not treated effectively, can lead to permanent disability and increased dependence on caregivers. Therefore, early diagnosis and prompt intervention are essential to slow disease progression and prevent irreversible damage to joints and organ systems [10, 11].

In humans, the pathogenesis of RA involves the exaggerated activation of T and B lymphocytes, the production of autoantibodies such as rheumatoid factor, and the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are the main factors in sustaining the inflammatory response within this pathology [12, 13].

Histopathologic studies show that the inflammatory trigger of the disease leads to synovitis, resulting in an inflammatory tissue that invades and destroys the underlying cartilage and bone. This process is mediated by activated synovial fibroblasts and osteoclasts that promote bone erosion [14]. These pathogenic mechanisms are related to cellular activation and the inflammatory cascade involved in the progression of RA (Figure 1).

Figure 1
Immunopathogenesis of rheumatoid arthritis



Experimental models of RA have been widely used to study pathogenic mechanisms and to test potential treatments. Induced arthritis in mice or rats is one of the most commonly used models, mimicking several clinical and immunologic features of RA in humans. Another commonly used model is arthritis induced by zymosan (Zy), a substance derived from the cell wall of yeast. Zy arthritis is characterized by an acute inflammatory response mediated mainly by macrophages, allowing the study of early inflammatory mechanisms and the impact of therapeutic interventions in the acute phase of the disease [15, 16].

The use of intra-articular injections of Zy in rats to study the pathogenesis of RA was pioneered by Keystone et al. [17] in 1977. Zy is a glycan derived from the cell wall of the yeast Saccharomyces cerevisiae and is capable of inducing arthritis-like effects such as proliferative inflammation. Induction by Zy leads to synovitis, which is the formation of purulent exudate in the synovial space and an infiltrate of polymorphonuclear neutrophils, as well as clinical signs such as edema and loss of joint function [17].

Diagnostic approaches have identified novel pathways and potential therapeutic targets. Human clinical trials also continue to advance, such as TNF-α inhibitors, which are revolutionizing disease management and providing significant relief to many patients [14, 18].

Another important aspect is the reduction in the quality of life of patients affected by the disease. Chronic pain and functional limitations often lead to anxiety and depression, increasing the psychological and emotional impact on patients [13].

3.2. PBM in RA

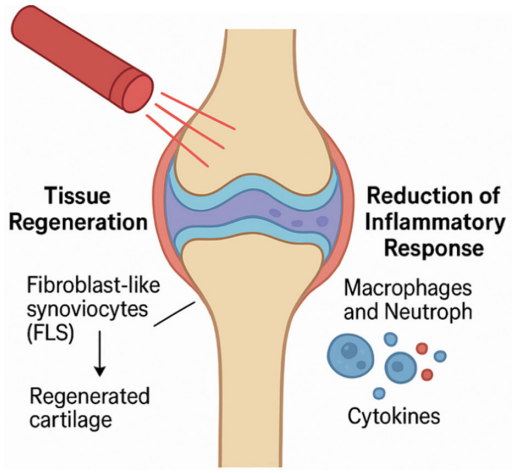
The use of PBM in RA has emerged as a promising therapeutic approach, with positive results in both experimental models and clinical trials. RA is a chronic inflammatory disease characterized by progressive joint destruction, severe pain, morning stiffness, and fatigue. It affects millions of people worldwide and, in its advanced stages, can lead to severe loss of mobility and joint function. Low-intensity laser PBM is a therapy that aims to modify the course of the disease by reducing inflammation, modulating the immune response, and promoting tissue regeneration [3, 19, 20].

Experimental studies in animal models of RA, such as rats and mice, have demonstrated the beneficial effects of PBM in alleviating symptoms and modulating the immune response. Hossein-Khannazer et al. [21] conducted experiments using a low-intensity laser and observed a significant reduction in pro-inflammatory cytokines such as TNF-α and IL-6, which are often associated with the inflammatory process in RA. Laser treatment not only reduced inflammation but also improved joint function, resulting in increased mobility in the treated animals. These effects can be explained by the action of PBM on intracellular signaling pathways involving the activation of protein kinases and transcription factors, directly influencing inflammatory processes [21, 22].

The results in humans are also very encouraging. Patients with RA who received low-intensity laser treatments showed a significant reduction in pain, morning stiffness, and joint swelling, as well as an increase in joint functionality. The effectiveness of PBM may be attributed to its ability to improve local microcirculation and reduce inflammation, factors that contribute to recovery and symptom relief [23, 24]. In addition, a study by Diógenes Alves Uchôa Lins et al. [23] reported that low-intensity laser therapy can act to reduce oxidative stress, which helps prevent further cell damage in joints affected by RA. These positive therapeutic effects were observed after a relatively small number of treatment sessions, demonstrating the rapid response of the therapy [23, 24]. This interaction between the laser and the biological tissue is represented by the mechanisms of absorption and cellular response to the treatment (Figure 2).

Another important aspect of PBM in RA is its regenerative potential. Laser therapy has been shown to be effective in stimulating collagen synthesis and proliferation of chondrocytes, the cells responsible for maintaining articular cartilage. Repairing damaged cartilage is one of the major challenges in the treatment of RA, and PBM may play a critical role in this process once studies showed lower cartilage injury and higher preserved cartilage morphology. In addition, reducing oxidative stress in the joints can limit progressive damage, thereby slowing the degenerative process of RA [16, 25]. This is particularly important because the preservation of articular cartilage can prevent the disease from worsening and improve the quality of life of patients in the long term [16, 26].

Figure 2
Effect of photobiomodulation with LLLT on rheumatoid arthritis: Tissue regeneration and reduction of the inflammatory response



Personalization of PBM treatment is a key factor in maximizing the effectiveness of this therapy. According to Joniová et al. [27], adapting therapeutic parameters to the stage of disease and individual patient characteristics has shown more satisfactory results in the treatment of RA. Adjustment of laser parameters such as dose, frequency, and application time may be critical to optimizing outcomes.

Studies such as that of Silva Gomes et al. [15] have shown that the use of personalized protocols that include not only PBM but also its combination with other treatments has resulted in significant improvements in the reduction of inflamed areas in experimental models of RA. This suggests that PBM may be more effective when combined with other therapeutic approaches, such as physiotherapy and medication, to create a more comprehensive and effective treatment [7, 27].

The multidisciplinary approach, including PBM, has shown satisfactory results in controlling the symptoms of RA. For example, the reduction of chronic pain has a significant impact on patients' quality of life, allowing them to resume their daily activities. In addition, psychological support also plays an important role in improving patients' well-being, as shown in studies by Silva Gomes et al. [15]. When combined with complementary therapies such as physiotherapy, PBM not only contributes to physical improvement but also has beneficial psychological effects that improve patients' mental and emotional health. Combining these therapeutic approaches has the potential to reduce the need for more invasive interventions such as surgery, providing a more conservative and effective solution for RA patients [15, 21].

The application of LLLT in RA involves a variety of relevant parameters that can pose challenges in clinical practice. The choice of the best laser setting depends not only on the device used but also on the parameters offered by the device and the guidelines found in the literature that support the use of different parameters for the treatment of RA. These parameters are often discussed in studies such as that of Fangel et al. [28]. They highlight how the variation of laser parameters can influence the effectiveness of the treatment and suggest that the choice of the appropriate protocol should be personalized according to the patient and the stage of the disease. A detailed analysis of these parameters is presented in Table 1, which summarizes the different settings used in RA studies. It provides a comprehensive overview of the different low-intensity laser treatment protocols and is a valuable guide for clinical practice [28, 29].

In addition, the combination of LLLT with other therapeutic modalities has been shown to be an effective approach in the treatment of RA. Integrating PBM with physical therapy, anti-inflammatory medications, and psychological support may provide a more effective approach to treating RA. The literature also suggests that the best results may be achieved by using a combination of therapies, tailored to the patient's needs. In a study conducted by Mazulo-Neto and Souza [16], patients who received combined treatment showed significant improvements in pain levels, stiffness, and joint functionality compared to those treated with medication alone. This suggests that PBM, when combined with other treatments, can not only reduce physical symptoms but also improve patients' mental and emotional health [15, 16].

3.3. PBM: Therapeutic advances in the treatment of RA

PBM is an innovative therapeutic approach that uses low-intensity light (LIL), primarily in the red and infrared bands, to interact with biological processes in the body. This technique is based on the absorption of photons by intracellular chromophores

Table 1
Evidence of different LLLT parameter effects on experimental and clinical rheumatoid arthritis

Authors	Study	Frequency of the treatment	Diode	Wavelength (λ)	Energy density	Power (output)	Outcomes
Meireles et al. [30]	Human, sex and age not specified	Twice a week, 16 sessions	GaAlAs	785 nm	0.6 J/cm^2	70 mW	Pain reduction and morning stiffness
Ferreira de Meneses et al. [31]	Human, sex not specified 50–75 years old	Three sessions per week for 3 weeks	GaAs	904 nm	1 J/cm^2	30 mW	Pain reduction and increased mobility
Yavas et al. [10]	Human, sex and age not specified	Five sessions per week for 3 weeks	GaAlAs	830 nm	3 J/cm^2	50 mW	Reduction in morning stiffness
Mazulo-Neto and Souza [16]	Rat RA animal model	Data not informed	GaAs	904 nm	27 J/cm^2	50 mW	Pain reduction and protection of joint morphology
Hossein-Khannazer et al. [21]	Rat RA animal model	Single dose after the induction	GaAs	635 nm	3 J/cm^2	50 mW	Decrease in cellular inflammation and expression of IL-1β and IL-6
Lourinho et al. [32]	Human, sex not specified 49–79 years old	Three sessions per week for 8 weeks	HeNe	632,8 nm	8 J/cm^2	7, 3 mW	Decreased morning stiffness, swelling, tenderness, and pain
Silva Gomes et al. [15]	Rat RA animal model	Single dose 24 h after the induction	GaAs	808 nm	20 J/cm^2	25 mW	Changes in IL-6 and C3 gene and protein expression
do Bomfim et al. [7]	Rat RA animal model	Single dose 24 h after the induction	GaAs	808 nm	20 J/cm^2	25 mW	Reduction of inflammation in the synovial membrane and regulation of iNOS expression

such as cytochrome c oxidase, an essential component of the mitochondrial respiratory chain. This process promotes an increase in the production of adenosine triphosphate (ATP), which plays a central role in cell regeneration, collagen synthesis, and mitigation of oxidative stress. Parameters such as energy density, power, and application time are critical to the success of the treatment, as inappropriate settings can compromise the therapeutic response and exacerbate inflammatory processes [33–36].

The devices used in PBM can be classified into high- and low-intensity lasers. While high-intensity lasers are widely used in surgical procedures, low-intensity lasers have gained prominence in biological stimulation of tissues by promoting beneficial photoelectric effects. The efficacy of PBM in inflammatory diseases such as RA has been widely documented, with benefits observed in pain reduction, inflammation control, and restoration of joint function [16, 37, 38].

Studies show that PBM reduces the infiltration of inflammatory cells into the synovial membrane and regulates the release of pro-inflammatory cytokines such as TNF-α and IL-6, two critical markers of sustained inflammation in this pathology. These effects help maintain joint integrity and protect against structural and functional joint damage. Clinical studies support these findings, pointing to significant improvements in patients treated with PBM, such as reduced morning stiffness and increased range of motion, especially when combined with conventional pharmacological treatments [7, 15].

Another aspect is its ability to modulate oxidative stress in affected joints. By stimulating mitochondria, LIL promotes increased ATP production, thereby improving cellular functionality. In experimental models, PBM has been shown to restore the balance of nitric oxide and reactive oxygen species, critical elements in the control of inflammation. This regulation is essential not only to reduce inflammation but also to promote repair of damaged tissue, providing a comprehensive approach to RA management [7, 15, 35].

In addition to alleviating pain and reducing the inflammatory process, PBM promotes benefits in various phases of tissue regeneration, including angiogenesis and cell remodeling. These mechanisms are fundamental to the functional and structural recovery of diseased joints. However, the efficacy of the treatment depends on precise application, adjusted according to the specific parameters of each case, such as wavelength, dose, and exposure time [13, 36, 39].

Recent advances in the development of portable and affordable devices have greatly expanded the use of PBM in the treatment of inflammatory diseases such as RA. Technological innovations, including lasers with automatic wavelength adjustment and high-power LEDs, allow for personalized treatments according to the specific needs of each patient. These technologies not only increase therapeutic efficacy but also promote treatment adherence, making supervised home use feasible. Early studies suggest that wearable devices that incorporate artificial intelligence to automatically adjust therapeutic parameters have shown promising results in reducing chronic pain and preserving joint functionality [40–42].

At the same time, other studies have identified novel molecular mechanisms that explain the therapeutic benefits of PBM. In addition to stimulating ATP production and regulating inflammatory cytokine levels, LIL has been shown to activate specific cell signaling pathways such as AMPK (AMP-activated protein kinase) and SIRT1 (sirtuin 1). These pathways are fundamental in regulating

cell metabolism and the response to oxidative stress. These findings suggest a broad role for PBM in protecting articular cells from apoptosis and promoting mitochondrial repair mechanisms. These advances point to new avenues for therapeutic intervention in autoimmune diseases [39, 43, 44].

With the growing body of scientific evidence and publications, PBM is proving to be a valuable therapeutic tool in the treatment of RA. Its beneficial effects in reducing pain, modulating inflammation, and promoting cell regeneration offer new possibilities in the management of this debilitating disease, providing patients with a more promising and safer alternative for recovery [28, 29, 42, 45].

Another important point to discuss is related to the sessions applied to treat RA, it can be observed in literature (Table 1) different protocols to treat RA which become a difficult to standard RA management.

Laser therapy has been increasingly explored as treatment modality in RA, with various protocols differing in wavelength, dosage, duration, and number of applications. PBM with LLLT is the most commonly studied form, typically using wavelengths between 600–1000 nm to induce anti-inflammatory and analgesic effects. Studies have reported significant variability in application frequency, ranging from daily sessions to two or three sessions per week, over periods spanning from two weeks to several months. For example, one protocol may involve 15 sessions of LLLT over five weeks, applying a 780 nm wavelength at an energy density of 4 J/cm^2 per joint, whereas another might utilize a 904 nm pulsed laser for 10 sessions over two weeks with 1 J/cm² energy density. These discrepancies reflect the lack of standardized treatment protocols, complicating the comparison and replication of clinical outcomes across studies [46, 47].

Furthermore, the selection of parameters such as power output, energy per point, and mode of delivery (continuous vs. pulsed) also varies significantly among clinical trials. For instance, continuous-wave lasers with power outputs of 50–100 mW have been employed for smaller joints, while higher power settings are sometimes used for larger affected areas. The number of treatment points per joint and the cumulative energy delivered per session are also key variables influencing therapeutic efficacy. In some studies, up to 12 points per joint are treated with 2–8 J per point, aiming for a total energy dose of 24–96 J per joint per session. The heterogeneity in these laser parameters and the treatment schedules underscores the need for further randomized controlled trials to establish optimal dosimetry and frequency that maximize clinical benefits for RA patients while minimizing risks and inconsistencies in treatment outcomes [48, 49].

4. Conclusion

The studies in this review show that PBM is effective in the treatment of RA because it reduces morning stiffness, the inflammatory process, and pain, which leads to the promotion of joint regeneration. Its use provides a safe, non-invasive therapy that can be combined with conventional treatments to optimize clinical outcomes. The combination of PBM with multidisciplinary therapies could represent an important advance in the treatment of RA, in addition to a thorough understanding of the light-tissue interaction based on the parameters used, since there are a wide variety of parameters described in the literature that can lead to photo-stimulation or photo-inhibition.

Recommendations

The use of PBM as a therapy in the management of RA is suggested, in conjunction or not with conventional treatments such as medication and physiotherapy, with the aim of optimizing inflammation control, pain relief, and tissue regeneration. In order to achieve the most effective results, it is crucial to adjust the application parameters, such as intensity, duration, and frequency, according to the individual characteristics of each patient and the stage of the disease. Long-term clinical studies should be conducted to assess the cumulative effects of PBM and its efficacy in different patient profiles, while experimental research can deepen the understanding of its cellular and molecular mechanisms of action. The standardization of evidence-based protocols, together with the training of professionals, is essential to ensure the safe and effective application of this therapy, as well as to promote its inclusion in public policies and its economic viability, thus expanding access to the population.

Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contribution Statement

Sabrina Zanchetta Lanza: Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Gaspar de Jesus Lopes Filho:** Methodology, Writing – review & editing, Supervision, Project administration. **Fernando Russo Costa do Bomfim:** Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

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