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EXPERIMENTAL STUDY OF THE PHOTOBIOMODULATION EFFECT ON WOUND HEALING: THE ROLE OF CYTOKINES AND GROWTH FACTORS

Actuality. *Chronic wounds are characterized by impaired intercellular and cell-matrix interactions, as well as altered dynamics of regulatory cytokines. One innovative strategy for wound healing is the use of photobiomodulation therapy. Photobiomodulation therapy can be a tool for optimizing the reparative process by correcting it with intercellular mediators.*

The aim – to study the role of intercellular mediators (interleukin-1β, interleukin-6, interleukin-4, tumor necrosis factor-α, interleukin-10, interferon-γ, and granulocyte macrophage colony-stimulating factor) influencing the development of reparative processes of chronic wounds using photobiomodulation therapy.

Material and methods. *The study was conducted on 18 rats randomized into intact, control, and experimental groups. Rats of the control and experimental groups were modeled with trophic wounds. Wound defects of animals of the experimental group were exposed to photobiomodulation therapy once a day for 5 days (wavelength 660 nm, power 50 mW, energy density 5 J/cm^2). On the 7th day after surgery, animals of all groups were euthanized. Studies of intercellular mediators in blood serum were performed using commercial ELISA kits. Histological analysis of wound samples was performed.*

Research results. *On day 7 of the experiment, animals with wound defects subjected to photobiomodulation therapy exhibited a decrease in serum levels of interferon-γ and interleukin-6 compared to the control group. Under the influence of photobiomodulation therapy, the concentrations of interleukin-4 and tumor necrosis factor-α in the blood serum of animals in the experimental group increased compared with those of rats with wounds without photobiomodulation therapy. Semi-quantitative analysis revealed a significantly higher number of newly formed collagen fibers in the granulation tissue of experimental group animals' wounds, which may reflect an increase in the synthetic function of fibroblasts.*

Conclusion. *The use of photobiomodulation therapy allows for the correction of disorders of the reparative processes of wounds.*

Key words: *photobiomodulation therapy, reparative processes, chronic wounds, cytokines, growth factors.*

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ЕКСПЕРИМЕНТАЛЬНЕ ДОСЛІДЖЕННЯ ВПЛИВУ ФОТОБІОМОДУЛЯЦІЇ НА ЗАГОЄННЯ РАН: РОЛЬ ЦИТОКІНІВ ТА ФАКТОРІВ РОСТУ

Актуальність. *Хронічні рани характеризуються порушеннями міжклітинних і клітинно-матриксних взаємодій, а також змінами динаміки регуляторних цитокінів. Однією з інноваційних стратегій загоєння ран є застосування фотобіомодуляційної терапії. Фотобіомодуляційна терапія може бути інструментом оптимізації репаративного процесу, шляхом його корекції міжклітинними медіаторами.*

Мета дослідження *– вивчення ролі міжклітинних медіаторів (інтерлейкіна-1β, інтерлейкіна-6, інтерлейкіна-4, фактору некрозу пухлин-α, інтерлейкіна-10, інтерферону-γ та гранулоцитарно-макрофагального колонієстимулювального фактору), які впливають на розвиток репаративних процесів хронічних ран, у використанні фотобіомодуляційної терапії.*

Матеріал і методи. *Експериментальне дослідження було проведено на 18 щурах, рандомізованих на інтактну, контрольну й експериментальну групи. Щурам контрольної та експериментальної груп моделювали трофічні рани. Ранові дефекти тварин експериментальної групи піддавали впливу фотобіомодуляційної терапії раз на добу протягом 5 днів (довжина хвилі 660 нм, потужність 50 мВт, щільність енергії 5 Дж/см^2). На 7-му добу після операції тварин усіх груп піддавали евтаназії. Дослідження міжклітинних медіаторів у сироватці крові проводили за допомогою комерційних наборів методом ІФА. Виконали гістологічний аналіз зразків ран.*

Результати дослідження. *У тварин, ранові дефекти яких піддавалися фотобіомодуляційній терапії, на 7-му добу експерименту спостерігали зменшення сироваткових рівнів інтерферону-γ та інтерлейкіна-6 порівняно з аналогічними показниками тварин контрольної групи. Під впливом фотобіомодуляційної терапії концентрації інтерлейкіна-4 та фактору некрозу пухлин-α у сироватці крові тварин експериментальної групи збільшилися порівняно з показниками щурів з ранами без фотобіомодуляційної терапії. Напівкількісний аналіз виявив достовірно більшу кількість новоутворених колагенових волокон у грануляційній тканині ран тварин експериментальної групи, що може відображати підвищення синтетичної функції фібробластів.*

Висновок. *Використання фотобіомодуляційної терапії дає змогу коригувати порушення репаративних процесів ран.*

Ключові слова: *фотобіомодуляційна терапія, репаративні процеси, хронічні рани, цитокіни, фактори росту.*

Introduction. Actuality. Chronic wounds are a problem both clinically, economically, and socially. Chronic wound care costs between 2 and 5% of total health care expenditure in Europe and Australia (Graves et al., 2022). Diabetic ulcers are the main cause of amputation in 47,6% of cases (Wolny et al., 2024). The most significant factors affecting healing outcomes are infections, hormonal and dietary disorders, hyperglycemia, stress, and others (Litvinova et al., 2025; Seliukova et al., 2025). Chronic wounds are characterized by failure of inflammation resolution (Wang et al., 2022). Intercellular and cell-matrix interactions, as well as the dynamics of regulatory cytokines, are disrupted. Cytokines are promising therapeutic targets because they regulate all stages of wound healing. Interleukins such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) promote leukocyte recruitment and removal of dead cells at the initial stage of inflammation, while transforming growth factor-β (TGF-β), interleukin-4 (IL-4), and interleukin-13 (IL-13) suppress inflammation and stimulate fibroblast proliferation by triggering extracellular matrix deposition (Wong et al., 2025). Understanding the interactions of cytokines and their diverse cellular targets, as well as unlocking the potential of cytokine therapy, may significantly improve the quality of care for patients with chronic wounds.

Methods of influence on reparative processes are being improved. Along with the use of herbal medicines (Pinyazhko et al., 2025), nanotechnology, stem cells, physical methods, etc., are used in the treatment of wounds (Babenko et al., 2023). However, there are complexities and limitations in using these methods. For example, the low effectiveness of pharmacological stimulation of reparative regeneration, especially in wound treatment. This is because the cellular and molecular mechanisms underlying tissue repair are poorly understood. There are problems with drug delivery to the wound and with the limitations and reproducibility of existing preclinical models. With the increasing levels of antimicrobial resistance, there are fewer treatments available, so the search for new approaches to address this problem continues. One innovative strategy for wound healing is the use of photobiomodulation (PBM) therapy. PBM is the process of exposing tissues to low-intensity light to induce physiological responses (Frankowski et al., 2025). PBM therapy is non-invasive and cost-effective. Exposure to PBM of appropriate wavelength and certain parameters reduces inflammation, accelerates cell proliferation and extracellular matrix deposition, and improves tissue repair (Mgwenya et al., 2025). Various molecular targets and signaling pathways have been identified in investigating the mechanisms of action of PBM on biological tissues: intracellular mitochondria (cytochrome C oxidase), cell membrane (photosensitive transporters and receptors like TRPV1, opsin 2–4), and extracellular milieu (latent TGF-β1 activation) (Varsani et al., 2024).

A picture of the wound can be obtained by assessing both proinflammatory and anti-inflammatory cytokines (Kim et al., 2024). PBM therapy can be a tool for optimizing the reparative process by correcting it with intercellular mediators (Pavlov et al., 2022). A complete understanding of the pathophysiologic mechanisms at the cellular and molecular levels is needed. Also, it is necessary to reach a consensus on the applied parameters of PBM therapy, taking into account the "dose-effect" of laser radiation.

The aim of the study – to study the role of intercellular mediators (interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-4 (IL-4), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), interferon-γ (IFN-γ), and granulocyte macrophage colony-stimulating factor (GM-CSF)) influencing the development of reparative processes of chronic wounds using PBM therapy.

Materials and research methods. *Animals.* In this study, 18 rats weighing 200–220 g, 8–9 months of age, from the Vivarium of Kharkiv National Medical University, were used. The study was planned and conducted consistently: "European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes" of 18.03.1986, as amended on 02.12.2005; "Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes" of 22.09.2010; "General Ethical Principles for Animal Experiments" adopted by the Fifth National Congress on Bioethics (Kyiv, 2013). The experiment was approved by the Bioethics Committee of Kharkiv National Medical University, Ukraine (Protocol № 17, dated March 6, 2024). All animals used in this study were kept in individual cages under standard vivarium conditions (temperature of 22 ± 2 °C and light/dark cycle of 12 h) and had free access to food and water. Rats were randomized into three groups (six rats in each). The first group (Int) represented intact animals. The rats of the control (Con) and experimental (Exp) groups were modeled with chronic wounds. For surgery, rats were given an anesthetic injection dose of zoletil solution (tiletamine hydrochloride and zolazepam hydrochloride, Virbac, France) at a rate of 10 mg/kg body weight. The back skin of the animals was depilated. Chronic wounds with the reproduction of hypoxic conditions and microcirculation disturbance were formed as a result of the surgical removal of skin layers in the animal (fig. 1). The wound was a 2-cm-diameter circle (Pavlov et al., 2024).

Fig. 1. The induced wound

PBM therapy. Wound defects of the experimental group animals were exposed to PBM therapy once a day for 5 days. The first application was performed the next day after wound modeling. The laser device Lika-therapist M (Cherkasy, Ukraine) was used with a 660 nm wavelength, 50 mW energy power, and 5 J/cm^2 energy density. The laser tip was held perpendicular to the irradiated surface to illuminate the entire wound area. The wounds of the animals in the control group were treated with a sham. Blood samples were collected from the heart on day 7 after surgery and centrifuged to obtain serum. Intercellular mediators were assayed using commercial ELISA kits according to the manufacturer's instructions. GM-CSF concentration was determined using an ELISA kit (eBioscience, USA; Catalog № BMS283INSTCE). The levels of IL-1β, IL-6, IL-4, IL-10, IFN-γ, and TNF-α were determined using the ELISA kits (Vector-Best, Ukraine): IL-1β (Catalog № A-8766), IL-6 (Catalog № A-8768), IL-4 (Catalog № A-8754), IL-10 (Catalog № A-8774), IFN-γ (Catalog № A-8752), and TNF-α (Catalog № A-8756).

Histological Analysis. A biopsy was taken for histopathologic analysis covering the entire wound, including the margins. Standard methods were used to prepare histological specimens, stained with hematoxylin-eosin and van Gieson's picrofuchsin. A Primo Star light microscope (Zeiss, Germany) and a Microocular digital camera were used for the study. Histological parameters and structures, including the degree of re-epithelialization, the number of polymorphonuclear leukocytes (PMNLs), fibroblasts, newly formed vessels, and collagen fibers, were evaluated using a semi-quantitative method, with a scale of 0, 1, 2, 3, and 4 (Gal et al., 2008).

Statistical Analysis. Statistical analysis was performed using Statistica 12.0 software (StatSoft, USA). After checking normality and homoscedasticity of data using Shapiro-Wilk's and Levene's tests, the effect of PBM on selected parameters was analyzed using one-factor analysis of variance (ANOVA) or nonparametric Kruskal – Wallis analysis. Accordingly, significant differences between the groups were assessed using the Tukey test or the Mann – Whitney test. The data are presented as mean ± standard error (SE) or median and interquartile range (Me; Q25 – Q75). The significance level for all tests was set at $p < 0{,}05$. Histograms were created in the GraphPad Prism 9 program (GraphPad Software, USA).

Research results and their discussion. The results of our study showed that on day 7 of the experiment under the influence of PBM therapy, the levels of IFN-γ and IL-6 in animal serum of the experimental group decreased by 1,46 times ($p = 0{,}000605$) and 1,26 times ($p = 0{,}000179$), respectively, compared with those of rats with wounds without PBM therapy (table 1). At the same time, the levels of these cytokines in the control group were elevated compared to intact animals by 1,22-fold ($p = 0{,}030611$) and 1,34-fold ($p = 0{,}000178$), respectively. The concentrations of IL-4 and TNF-α in the blood serum of animals whose wound defects were subjected to PBM therapy increased by 1,87 times ($p = 0{,}000299$) and 1,77 times ($p = 0{,}001781$), respectively, compared to the same indicators of the control group. At the same time, there was an increase in serum levels of IL-4 and TNF-α in the experimental group rats compared to intact animals by 2,74 times ($p = 0{,}000179$) and 2,09 times ($p = 0{,}000451$), respectively (table).

Microscopic examination of wound samples showed signs of the beginning of the re-epithelialization process in all animals. The epidermis at the wound edges was thickened due to the proliferation of cells in the basal layer. A layer of poorly differentiated, flattened keratinocytes was located at the wound edges, sprouting between the surface of the granulation tissue and the scab. The wound cavities in rats of both groups were filled with young granulation tissue with a large number of fibroblasts and newly formed capillaries. A significant amount of PMNL indicated the continuation of the inflammatory phase. Semi-quantitative analysis showed a significantly higher number of newly formed collagen fibers in the granulation tissue of wounds of animals of the experimental group ($p < 0{,}05$), which may reflect an increase in the synthetic function of fibroblasts (fig. 2).

PBM has an immunomodulatory effect (Al Balah et al., 2025). PBM therapy is also known to alter enzyme activation and cell cycle progression, thereby affecting redox-sensitive cellular transcription factors (Karkada et al., 2022). Under the influence of PBM, morphological, molecular, and biochemical changes occur within the cell. This has a reparative effect and regulates proteins associated with cell death, thereby modulating apoptosis pathways (Faria et al., 2020).

Table

Changing the levels of the studied indicators in animal serum

Group	Indicators						
	IL-1b, pg/ml	IFN-γ, pg/ml	IL-6, pg/ml	GM-CSF, pg/ml	IL-10, pg/ml	IL-4, pg/ml	TNF-α, pg/ml
Int	2,515 ± 0,079	127,292 ± 5,257	4,920 ± 0,102	1,826 ± 0,062	217,607 ± 24,743	2,030 ± 0,401	1,911 ± 0,144
Con	3,405 ± 0,554	155,208 ± 9,574*	6,600 ± 0,172*	0,788 ± 0,286*	204,986 ± 15,795	2,982 ± 0,397	2,257 ± 0,465
Exp	3,103 ± 0,070	106,667 ± 4,910#	5,254 ± 0,069#	1,370 ± 0,018	260,567 ± 5,128	5,571 ± 0,065# *	3,987 ± 0,063# *

Differences are significant in comparison with the intact group (*) and with the control group (#), ($p < 0,05$); Int – intact group, Con – control group, Exp – experimental group; ($n = 6$).

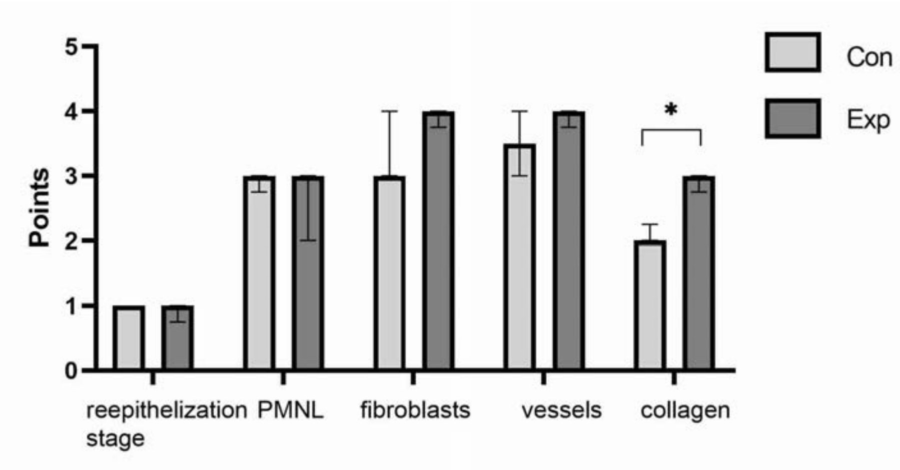

Fig. 2. Results of semi-quantitative histologic analysis; Con – control group, Exp – experimental group; differences are significant relative to the control group (*), (p < 0,05); bars and error bars represent median values and interquartile range for each indicator (n = 6)

It is well established that in pro-inflammatory conditions, PBM can lead to a decrease in the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 (Al Balah et al., 2025). In our study, exposure to PBM therapy resulted in decreased IFN-γ levels, confirming the creation of an immune environment that is prone to the development of non-polarizing M2 macrophages (Peña et al., 2025). IFN-γ in the proliferation phase has also been shown to contribute significantly to wound strength and suppression of inflammation (Kanno et al., 2019).

IL-6 levels were decreased in the experimental group under the influence of PBM. It is well established that IL-6 plays a dual role, both as a promoter of the initial inflammatory response and as a mediator of the subsequent healing process (Jiang et al., 2022). IL-6 promotes angiogenesis, re-epithelialization, and granulation tissue formation (Mahmoud et al., 2024). According to the literature, PBM treatment was accompanied by a decrease in IL-6 levels in the blood of animals with skin flaps (Pinto et al., 2025).

In our study, TNF-α levels were increased in the serum of rats with wounds exposed to PBM therapy. TNF-α is known to enhance the proliferation and migration of keratinocytes and fibroblasts and is essential for re-epithelialization. But excessive levels of TNF-α can lead to persistent inflammation (Mahmoud et al., 2024). The histologic analysis performed in our study showed no effect of PBM on the number of PMNL. The balance of indicators seems to play a more important role in inflammation than changes in these indicator levels. In our previous work on the effects of PBM therapy at a lower energy density (1 J/cm²), TNF-α serum levels were reduced; however, IL-1β levels, similar to those in this study, did not change (Pavlov et al., 2020).

In our study, exposure to PBM did not affect the GM-CSF levels in the animals' serum in the experimental group compared to those of animals in the control group. GM-CSF can stimulate inflammatory responses by activating macrophages during wound healing (Kinali et al., 2024). GM-CSF acts in an autocrine manner by enhancing epidermal proliferation. GM-CSF deficiency leads to impaired production of vascular collagen matrix (Vaidyanathan, 2021).

Anti-inflammatory cytokines counteract the activity of pro-inflammatory cytokines because they inhibit the recruitment of inflammatory mediators to reduce inflammation. Thus, IL-10 is often considered the dominant anti-inflammatory and anti-fibrotic player in active inflammation and wound healing (Steen et al., 2020). In our work, the concentration of this cytokine tended to increase in the experimental group animals' serum.

IL-4 and IL-13 suppress inflammation and stimulate fibroblast proliferation to initiate extracellular matrix deposition (Wong et al., 2025). But overactive expression of IL-4 and IL-13 contributes to the onset and persistence of fibrotic skin disease (Nguyen et al., 2020). In our study, IL-4 levels were elevated in the experimental group. Histologic evaluation showed an increase in collagen in the wound samples of animals whose wound defects were exposed to PBM therapy. According to the literature, exposure to PBM therapy did not alter IL-4 levels during skin graft integration in rats (Castro et al., 2020).

According to the literature, PBM therapy increased wound strength on day 7 of wound healing. Exposure to PBM enhanced granulation tissue formation and angiogenesis during the inflammatory and proliferative phases of wound healing (Bagheri et al., 2020).

However, the variation in the applied parameters of PBM therapy reported in the literature limits the generalizability, repeatability, and clinical interpretation of the results.

Conclusions

1. The role of expression of intercellular mediators IL-1β, IL-6, IL-4, TNF-α, IL-10, IFN-γ, and GM-CSF in the development of chronic wound repair processes using PBM therapy was shown in a model of chronic wound at the inflammation to the proliferation transition stage.

2. It has been shown that the use of PBM therapy can correct wound reparative disorders. Thus, there is a decrease in IFN-γ and IL-6 levels and an increase in TNF-α and IL-4 levels compared to similar indicators of control group animals at the parameters of PBM therapy: wavelength 660 nm, energy density 5 J/cm^2, power 50 mW.

3. Histological analysis confirms more intense fibrillogenic in wound samples from the group of animals treated with PBM therapy compared to wound samples from the control group.

4. It is necessary to continue researching the effect of PBM therapy on the wound process, paying attention to both cellular and molecular mechanisms of wound healing and optimization of laser radiation parameters.

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