EXPERIMENTAL INVESTIGATIONS

Ukrainian Journal of Clinical Surgery. 2026. September/October; 93(5):73-79
DOI: 10.26779/2786-832X.2026.5.73

Modulation of soft tissue inflammation in cases of soft tissue defects using photobiomodulation therapy

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Abstract

Objective. To assess the potential of photobiomodulation therapy for modulating soft tissue inflammation in cases of soft tissue defects by analysing its effect on the levels of interleukin-8, platelet-derived growth factor and the amino-terminal propeptide of type III procollagen, including their correlation with histological findings.

Materials and methods. An experimental study was conducted on 24 rats, which were randomly divided into four groups: a group of intact animals, a control group, and the first and second experimental groups. Soft tissue defects were simulated in the rats of the control group and both experimental groups. Animals in the control group underwent simulated wound irradiation, whilst those in the experimental groups received photobiomodulation therapy at a wavelength of 660 nm, a power of 10 mW, an energy density of 1 J/cm^2 (first experimental group) or 2 J/cm^2 (second experimental group); the spot area was 3.14 cm^2; the duration of a single session was 314 or 628 s; and the power density was 3.18 mW/cm^2. Three days later, levels of interleukin-8, platelet-derived growth factor and the N-terminal propeptide of type III procollagen in blood serum were assessed using an enzyme-linked immunosorbent assay (ELISA), and wound healing parameters were evaluated histologically.

Results. After 3 days, thanks to photobiomodulation therapy, interleukin-8 levels increased 2.08-fold in the first experimental group and 2.5-fold ($p < 0.05$) in the second experimental group. The level of platelet-derived growth factor increased by a factor of 1.71 ($p < 0.05$) in the second experimental group. Levels of the amino-terminal propeptide of type III procollagen were elevated in both the control group and the second experimental group compared with intact animals. Histologically, in wounds treated with photobiomodulation, there was enhanced granulation tissue formation, as evidenced by an increase in the number of fibroblasts, neovascularisation and collagen deposition. Semi-quantitative analysis revealed a lower number of polymorphonuclear leukocytes in the first experimental group and an increase in the number of fibroblasts in both experimental groups compared with the control group ($p < 0.05$).

Conclusions. Photobiomodulation therapy exerts a parameter-dependent and non-linear effect on inflammatory and early reparative processes in soft tissues. The data obtained support the need to standardise the parameters of laser treatment for chronic wounds in order to improve the effectiveness of their treatment.

Keywords: photobiomodulation; chronic wounds; inflammatory response; fibroblast proliferation; collagen; tissue regeneration.

Chronic wounds represent a global medical problem, with approximately 14 million people diagnosed with them each year [1]. Over a five-year period, from 2014 to 2019, the prevalence of chronic wounds among participants in the Medicare health insurance scheme in the USA rose from 14.5% to 16.4% [2]. There are no precise data on the prevalence of chronic wounds among the population in Ukraine.

The development of chronic wounds is influenced by comorbidities, age, smoking, obesity, stress and other factors [3, 4]. The problem of multi-drug resistance in microorganisms causing wound infections also remains a pressing issue [5].

The healing of any wound involves four interrelated stages: haemostasis, inflammation, proliferation and remodelling. The wound healing process is regulated by cytokines, growth factors and other bioactive molecules. Disruption of the healing process can lead to chronic wounds or the formation of hypertrophic scars. Signs of chronic wounding include prolonged inflammation, characterised by increased recruitment of neutrophils and macrophages. In the wound environment, leukocytes release pro-inflammatory cytokines, reactive oxygen species, matrix metalloproteinases and other proteases. Consequently, in wounds, obstacles are created to the action of growth factors, the migration and proliferation of fibroblasts, keratinocytes and endothelial cells, and the accumulation of extracellular matrix components. All these disturbances have a negative impact on the subsequent stages

of repair and may lead to delayed epithelialisation, excessive scarring, pathological wound angiogenesis, and so on [6]. Reducing the duration of inflammation and ensuring its timely resolution (elimination) may limit these pathological consequences [7]. It is therefore important to study the wound healing process at this stage.

Photobiomodulation helps to prevent prolonged inflammation—one of the problems associated with wound healing—by regulating key cellular processes [8]. The use of photobiomodulation therapy enables the correction of disturbances in wound repair processes [9]. The mechanisms of action of photobiomodulation include the stimulation of mitochondria and the modulation of the inflammatory signalling pathways NF–κB (Nuclear Factor kappa B) and MAPK (Mitogen–Activated Protein Kinase) [10]. Exposure to red light enhances the release of nitric oxide and reduces fibrosis [11]. However, the cellular and molecular mechanisms underlying the regenerative effect of photobiomodulation on wound healing remain largely unexplored. Furthermore, no standardised dosimetric guidelines have been established. Therefore, an important aspect of the research is the optimisation of the parameters of the photobiomodulation therapy used, taking into account the biphasic dose response of low-intensity laser radiation.

Aim of the study: to assess the potential of photobiomodulation therapy for modulating soft-tissue inflammation in the context of soft-tissue defects by analysing its effect on the levels of interleukin–8 (IL–8), platelet-derived growth factor (PDGF) and the N-terminal propeptide of type III procollagen (PIIINP), including their correlation with histological findings.

Materials and methods

An experimental study was conducted on 24 rats weighing 230 g and aged 9 months. The animals were housed under standard vivarium conditions. Following a two-week quarantine period, the rats were randomly assigned to four groups of six in each. Healthy rats that underwent no procedures constituted the intact group. In the control group and the two experimental groups, a circular skin defect 2 cm in diameter was created, followed by the application of perpendicular loop-like fascio-cutaneous sutures along its edges [12]. Prior to surgical intervention, the animals were anaesthetised by intramuscular injection of a Zoletil solution – telethamine hydrochloride and zolazepam hydrochloride (Virbac, France) at a dose of 10 mg/kg body weight, after which the skin in the area of the planned procedure was depilated. To further disrupt microcirculation and induce trophic changes in the defect area, mutually perpendicular incisions were made in the superficial fascia at the base of the defect, creating 5 × 5 mm areas, which were then secured with U-shaped sutures. This technique was used to create conditions of local hypoxia, ischaemia and trophic disturbances, simulating the key pathophysiological features of chronic wounds by restricting blood supply and altering the structural integrity of the skin and subcutaneous tissues. The parameters under investigation were assessed 3 days after the creation of the skin defect, which corresponds to the early inflammatory phase of the wound healing process. Consequently, the model obtained reflects the initial stages of ischaemic wound development with a predisposition to chronicity, rather than a fully formed chronic wound.

The choice of 3 days as the final observation time point was determined by the aim of assessing the early stages of the wound healing process, in particular the initial inflammatory and early proliferative responses, which directly shape the subsequent course of repair. This time point allows the detection of primary changes in the cytokine profile and cellular infiltration under the influence of photobiomodulation therapy prior to the development of fully formed granulation tissue.

All procedures were carried out in accordance with the guidelines for the use of animals in biomedical research (Strasbourg, 1986), as amended in 1998, the General Ethical Principles for the Conduct of Animal Experiments (Kyiv, 2001), which comply with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes. The experimental design was approved at a meeting of the Bioethics Committee of Kharkiv National Medical University (Minutes No. 8 of 17 October 2025).

The wound defects in animals from both experimental groups were treated with photobiomodulation therapy. For this purpose, the 'Lika–Therapist M' (Ukraine) therapeutic laser device was used in continuous mode. Taking into account the divergence of the diode laser beam (0.5 rad ± 20 per cent) and the diameter of the extension handle aperture of the laser device (0.2 cm), the wound was irradiated from a fixed distance of 3.53 cm from its surface, which corresponded to the device's technical specifications and ensured the formation of a light spot with an area of 3.14 cm², which completely covered the wound defect. Photobiomodulation therapy was

Table 1. **Parameters of photobiomodulation therapy in the experimental animal groups**

Experimental group	Photobiomodulation parameters						
	wavelength, nm	Mode	Power, mW	Energy density, J/cm²	Spot area, cm²	Exposure time, s	Power density, mW/cm²
1st	660	Continuous	10	1.0	3.14	314	3.18
2nd	660	Continuous	10	2.0	3.14	628	3.18

carried out the day after wound modelling and 48 hours later.

The irradiation parameters were calculated in accordance with the device's technical specifications, taking into account the area of the light spot (*Table 1*). It should be noted that if the distance from which the wound is irradiated changes, variations in power density may occur due to beam divergence; however, a fixed irradiation geometry was used in this study, which ensured the reproducibility of the experimental conditions. The actual power directly at the wound surface was not calibrated, which should be taken into account when interpreting the results.

Animals in the control group underwent simulated wound irradiation. On day 3, the animals were euthanised. Blood was collected via open cardiac puncture. Subsequently, the concentrations of IL-8, PDGF and PIIINP in serum were determined using eBioscience (USA) kits for enzyme-linked immunosorbent assay (ELISA). Wound samples were taken from animals in the control and both experimental groups for histological examination, which was carried out using standard methods. Histological sections were examined using a 'Primo Star' light microscope (Zeiss, Germany) and a 'Microocular' digital camera. The degree of re-epithelialisation, the number of polymorphonuclear leukocytes (PMNLs), fibroblasts, newly formed blood vessels and collagen were assessed using a semi-quantitative method based on a scale of 0, 1, 2, 3, 4 [13].

The normality of the data distribution for each variable was assessed using the Shapiro–Wilk test, as well as through visual analysis of histograms and Q–Q plots. Homogeneity of variances was tested using Levene's test. If the assumptions of normality of distribution and equality of variances were met, the effect of photobiomodulation therapy on the parameters under investigation was analysed using one-way analysis of variance (ANOVA). Where statistically significant differences were detected, post hoc comparisons were performed using Tukey's test. If the aforementioned assumptions were not met, the non-parametric Kruskal–Wallis test was applied, followed by pairwise comparisons using Dunn's test. The results are presented as mean values (M) with standard deviation (SD) – M ± SD, or as medians (Me) and interquartile range (Q25–Q75) – Me (Q25–Q75), if the data distribution was non-normal. The relationship between the variables under study was assessed separately in each group using Spearman's rank correlation coefficient (r_s) – a non-parametric measure suitable for ordinal data and data with a non-normal distribution. Statistica 12 (StatSoft, USA) was used for statistical analysis with a significance level of $\alpha = 0.05$. Histograms were plotted using GraphPad Prism 9 (GraphPad Software, USA).

Results

After 3 days of the experiment, differences were observed between the study groups across all analysed parameters (*Table 2*).

Under the influence of photobiomodulation therapy, the serum IL-8 level in animals in the first experimental group increased 2.08-fold ($p = 0.00315$), and in the second experimental group by a factor of 2.50 ($p = 0.00025$) compared with the corresponding values in rats with wounds that had not received photobiomodulation therapy. Furthermore, the level of this cytokine in the serum of animals in the second experimental group increased 1.60-fold ($p = 0.01057$) compared with the corresponding value in intact animals. At the same time, no statistically significant difference in IL-8 concentrations was found between the animals in the first experimental group and the intact animals.

The PIIINP level in animals in the control group was 1.72 times higher, and in animals in the second experimental group – 2.03 times higher, than in intact animals ($p = 0.00315$ and $p = 0.00023$, respectively). However, the differences in this parameter between the second experimental and control groups, as well as between the first experimental and control groups, remained statistically insignificant.

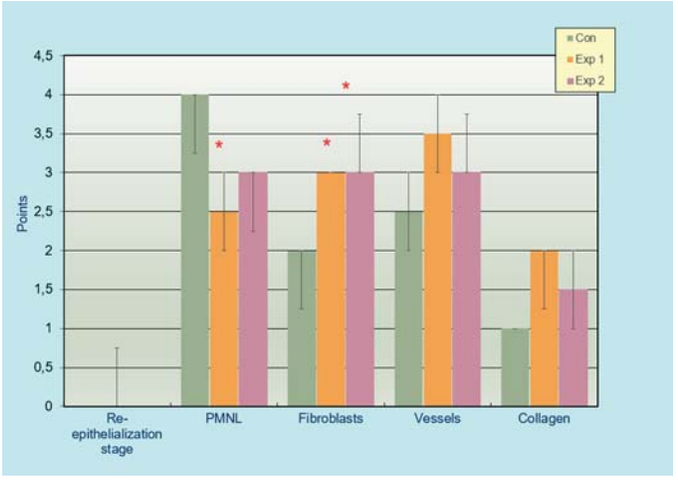
The concentration of PDGF in the second experimental group was 1.71 times higher than in the control group ($p = 0.00150$) and 1.87 times higher than in intact animals ($p = 0.00055$). No statistically significant differences in this parameter were found between the other groups.

Histological analysis showed that the wounds were healing under a scab. After 3 days, microscopic examination of histological sections in animals from all groups revealed signs of proliferation of basal layer keratinocytes and ingrowth of the epithelial layer beneath the scab along the wound margins. The wound cavities in animals of the control group were filled with fibrin fibres. The cellular component consisted of neutrophils, macrophages and isolated fibroblasts. Wound defects in animals from the experimental groups predominantly contained young granulation tissue with significant num-

Table 2. **Levels of the parameters studied in the animals' blood serum after 3 days**

Group of animals (n=6)	Parameter		
	IL-8, pg/ml	PIIINP, pg/ml	PDGF, pg/ml
Intact	1.302 ± 0.192	13.054 ± 0.932	25.843 ± 5.226
Control	0.833 ± 0.123	22.410 ± 2.912*	28.246 ± 2.466
1st experimental	1.736 ± 0.173#	16.684 ± 0.634	31,853 ± 1,564
2nd experimental	2.083 ± 0.126*,#	26.462 ± 0.886*	48.214 ± 2.206*,#

Note. Differences are statistically significant ($p < 0.05$): * – compared with intact animals; # – compared with the control group.



Results of a semi-quantitative histological analysis of samples from rat wounds after 3 days: Con – control group (n=6), Exp 1 – 1st experimental group (n=6), Exp 2 – 2nd experimental group (n=6); * – statistically significant differences ($p < 0.05$) compared to the control group; the bars and error bars represent the median values and interquartile range for each parameter.

bers of fibroblasts, newly formed capillaries and fine, chaotic bundles of collagen fibres, along with a moderate number of inflammatory cells.

A semi-quantitative histological analysis (*see figure*) revealed a lower number of PMNLs in animals from the first experimental group and a higher number of fibroblasts in the of animals from the first and second experimental groups compared with those in the control group ($p < 0.05$).

Correlation analysis, carried out separately in each group, revealed heterogeneous relationships between the variables under study. Although significant correlations were found in some groups, they differed in strength and direction depending on the experimental conditions. Thus, in the control group, IL-8 levels correlated with the number of PNMLs ($r_s = –0.83$, $p < 0.05$), whilst PDGF levels correlated with the number of blood vessels ($r_s = –0.88$, $p < 0.05$). In the first experimental group, IL-8 and PIIINP concentrations correlated ($r_s = 0.94$, $p < 0.05$). In the second experimental group, the IL-8 level correlated with the PDGF level ($r_s = 0.83$, $p < 0.05$), whilst the number of blood vessels correlated with the number of PNMLs and the number of fibroblasts ($r_s = –0.89$ and $r_s = 0.89$ respectively, $p < 0.05$).

Discussion

An experimental study was conducted on rats. Rodent models enable the investigation of the wound-healing process, in particular cellular responses, molecular signalling and the dynamics of extracellular matrix remodelling [14]. The parameters for photobiomodulation therapy were selected on the basis of data from the literature and our previous studies. The effect of photobiomodulation is usually limited to the 'optical window' of 600–1100 nm [15]. The application of photobiomodulation therapy at a wavelength of 661 nm and an energy density of 2.4 J/cm² significantly improved wound healing [16]. In our previous experimental study, we demonstrated a reduction in inflammation and accelerated wound healing when using photobiomodulation at a wavelength of 660 nm, a power of 50 mW and an energy density of 1 J/cm² [17].

The study was conducted during the inflammatory phase. As is well known, the initial stage of wound healing involves inflammation as a necessary process. However, if inflammation does not subside in a timely manner—for example, due to ischaemia and other factors—it may subsequently become chronic [3].

In this study, levels of the pro-inflammatory cytokine IL–8 were statistically significantly elevated following photobiomodulation therapy in both experimental groups. It is known that IL–8 stimulates neutrophil degranulation and the formation of reactive oxygen species, as well as increasing the expression of adhesion molecules [18]. According to the literature, laser therapy at an intensity of 0.84–1.4 J/cm² enhanced the secretion of IL–6 and IL–8, whilst an intensity of 1.97 J/cm² inhibited the secretion of these cytokines in cells stimulated by lipopolysaccharide [19]. In other words, low doses of light have a stimulatory effect, whilst high doses have an inhibitory effect.

IL-8 levels reflect the intensity of the chemokine signalling pathway in the inflammatory response, whilst the accumulation of neutrophils in the tissue is determined by a series of sequential processes, including endothelial adhesion, transendothelial migration and the characteristics of the local tissue microenvironment [20]. The reduction in IL–8 levels in the control group compared with intact animals likely indicates a transition of the inflammation from the acute phase to the resolution phase. At this stage, chemokine production may decrease as a result of down-regulatory mechanisms, whilst neutrophils that had previously infiltrated the tissue remain at the site of injury. This temporary discrepancy between the level of chemokine signalling and cellular infiltration may explain the observed negative correlation between IL-8 levels and the number of PMNLs in the control group.

In animals from the experimental groups receiving phytobiomodulatory therapy, the increase in IL-8 levels may indicate modulation of the inflammatory response, in particular the activation of signalling pathways that regulate the production of pro-inflammatory mediators. However, despite the increase in IL-8 levels—a key chemokine involved in neutrophil recruitment—PMNL infiltration was reduced in these groups. This suggests that phytobiomodulation likely influences not only the level of chemokine signalling but also the stages of cell migration, which may lead to a reduction in PMNL infiltration whilst IL–8 levels remain unchanged or are elevated. The observed discrepancy between the increase in systemic IL-8 levels and the reduction in neutrophil infiltration may also be explained by a change in the local distribution or retention of IL-8 in wound tissue, which may contribute to its

increased release into the systemic circulation. Furthermore, the influence of phytobiomodulatory therapy on the interaction of IL–8 with the CXCR1 and CXCR2 receptors on neutrophils, or on the cells' sensitivity to chemokine signals—which could potentially reduce the efficiency of cell migration to the site of injury—cannot be ruled out. It is known that IL–8 transmits signals via the CXCR1 and CXCR2 receptors and regulates neutrophil migration and inflammatory responses, forming a key signalling axis that coordinates the recruitment, activation and effector functions of neutrophils in the site of inflammation [18]. Disruption or functional modification of this axis under the influence of external factors, in particular phytobiomodulation, may lead to a disconnect between the level of chemokine signalling and the actual cellular response in the tissue.

It is important to note that correlation analysis revealed a significant association between IL–8 levels and PMNL counts only in animals in the control group, whilst no such association was observed in the experimental groups, which may indicate an altered coordination between chemokine signalling and the cellular response. Thus, the data obtained suggest that phytobiomodulatory therapy may lead to a functional dissociation between the production of pro-inflammatory mediators and cellular infiltration, reflecting a change in the regulation of the inflammatory process rather than its enhancement or suppression.

The identified characteristics of the relationship between IL-8 levels and PMNL infiltration, as well as the results of the correlation analysis—which demonstrate a loss of stable association between these parameters in the experimental groups—support the concept of a reorganisation of chemokine signalling under the influence of photobiomodulation therapy. This suggests that the observed changes reflect functional, rather than quantitative, shifts in the regulation of the inflammatory response. However, further studies assessing the local expression of IL–8 and its receptors in wound tissue are required to elucidate these mechanisms.

IL–8 stimulates the synthesis of type III collagen in fibroblasts [21]. Since type III collagen, which forms fine fibres, is generally considered to be the juvenile collagen of the early phase of wound healing [22], PIIINP levels were assessed in this study. It is known that PIIINP levels are used as a biomarker of increased type III collagen synthesis [23]. Contradictory, though statistically insignificant, changes in PIIINP levels were observed in the experimental groups following photobiomodulation therapy. PIIINP levels, as a marker of type III collagen synthesis, reflect fibroblast activity during the formation of the extracellular matrix. In the first experimental group, a tendency towards a decrease in PIIINP levels was observed compared with the control group, which may indicate less pronounced activation of collagen formation at this stage. This may be due to the fact that, given the parameters used, photobiomodulation therapy in the first experimental group predominantly affected the early inflammatory phase—as confirmed by the increase in IL-8 levels—but did not sufficiently stimulate the transition to the phase of active matrix synthesis. At the same time, a strong positive correlation was found in the first experimental group between IL-8 and PIIINP levels, indicating a close relationship between the intensity of the inflammatory response and the initial activation of fibroblasts. This may suggest that inflammatory mechanisms act as a trigger for fibroblast activation; however, under the parameters of photobiomodulation therapy used, this process does not reach a statistically significant level.

In the second experimental group, a trend towards an increase in PIIINP levels was observed, although this did not reach statistical significance. However, when combined with a statistically significant increase in PDGF levels, this may be regarded as an indication of a potential trend towards the activation of matrix synthesis, as this growth factor plays a key role in stimulating fibroblast proliferation and the formation of extracellular matrix components [24]. It should be noted that serum PDGF levels reflect a systemic reparative response and are not a purely specific marker of local processes within the wound. At the same time, they can be regarded as a comprehensive indicator of the activation of growth factors associated with tissue healing. There is little data in the literature regarding the effect of photobiomodulation on PDGF levels. An increase in PDGF–BB (platelet-derived growth factor BB) levels has been demonstrated following the application of photobiomodulation at a wavelength of 660 nm to optimise periodontal tissue healing [25]. In this study, following photobiomodulation therapy, varying results were obtained depending on the parameters used. In the first experimental group (1 J/cm²), no differences were observed compared with the control group. As the energy density increased to 2 J/cm², PDGF levels rose in the second experimental group. PDGF is one of the key growth factors regulating the transition from the inflammatory to the proliferative phase of wound healing [26]. It stimulates the migration and proliferation of fibroblasts, as well as angiogenesis. A statistically non-significant increase in PDGF levels in the first experimental group compared with the control group, despite a tendency towards an increase, may indicate insufficient intensity of stimulation of reparative processes under these parameters of photobiomodulation therapy. It is likely that, under this regime, photobiomodulation predominantly activates early inflammatory mechanisms, as noted above, but does not fully induce the growth factors responsible for proliferation.

In contrast, in the second experimental group, PDGF levels increased significantly, indicating full activation of the proliferative phase of healing. This is confirmed by the observed positive correlation between IL-8 and PDGF levels, reflecting the functional link between the inflammatory response and the activation of reparative processes. Furthermore, it was found that the number of blood

vessels correlates negatively with the number of PMNLs and positively with the number of fibroblasts, indicating a reduction in inflammatory infiltration as angiogenesis develops and the formation of granulation tissue is coordinately activated.

Thus, according to the results obtained, photobiomodulation therapy exerts a parameter-dependent modulatory effect on key stages of the wound healing process. The increase in IL-8 levels in both experimental groups compared with the control group indicates the activation of an early inflammatory response, which is necessary for the initiation of repair, whilst the increase in PDGF levels and the trend towards an increase in PIIINP levels in the second experimental group indicate the involvement of growth factors and the early activation of fibroblasts, associated with the initial stages of extracellular matrix formation.

These findings are corroborated by the results of the histological examination. In the first experimental group (1 J/cm²), a statistically significant reduction in the number of PMNLs was observed, indicating a reduction in inflammatory infiltration, whilst in the second experimental group (energy density 2 J/cm²), the number of PMNLs did not differ from that in the control group. At the same time, in both experimental groups, the number of fibroblasts increased, indicating the activation of reparative processes. Histological analysis also revealed an increase in the number of newly formed blood vessels and collagen in the animals of the experimental groups; however, these changes were predominantly descriptive in nature and did not reach the level of statistical significance between the groups. The morphological features identified may point to a potential mechanism for the activation of reparative processes; however, they require further confirmation in studies with a longer observation period.

Taken together, the data obtained indicate that the effect of photobiomodulation therapy is parameter-dependent and that there are consistent changes in the indicators of the inflammatory and early reparative responses depending on the treatment regimens. The most pronounced changes, observed in the second experimental group, may indicate a more favourable course of early reparative processes than under other experimental conditions, which is significant for optimising the healing of soft-tissue defects.

Thus, photobiomodulation contributes not so much to the intensification as to the physiological activation and regulation of the inflammatory response necessary to initiate reparative processes. This is particularly important in the context of treating chronic wounds, which are characterised by a state of impaired or 'stagnant' inflammatory response. In other words, photobiomodulation can be regarded as a factor that helps to shift the wound healing process from a state of relative functional inertia into a phase of activated inflammatory response, which is necessary for the subsequent initiation of regenerative mechanisms.

At the same time, given that the study is limited to the early stages of observation, the data obtained reflect predominantly the initial stages of healing and require further investigation to assess the impact of photobiomodulation therapy on subsequent phases, including remodelling.

Conclusions

1. Photobiomodulation therapy modulates reparative processes during the inflammatory phase by altering the levels of biologically active molecules.

2. It has been established that the effect of photobiomodulation therapy on the healing of soft-tissue defects is parameter-dependent. Under the modes used, optimal parameters may contribute to a more coordinated dynamics of the inflammatory and early reparative responses, manifested by signs of fibroblast activation and the initiation of processes involved in the formation of extracellular matrix components.

3. Given the observed dose-dependent and non-linear nature of the tissue response to photobiomodulation therapy, standardisation of laser radiation parameters is necessary to improve the efficacy of treatment for chronic wounds.

Declarations

Funding. This work was supported by the Ministry of Health of Ukraine and carried out using funds from the state budget. The study was conducted as part of a research project at Kharkiv National Medical University on the topic 'Implementation of the concept of surgical and orthopaedic Damage Control in military and civilian populations during martial law' (state registration number 0126U002120).

Contributions of the authors. Pavlov S. B. – study concept and design, supervision of the study; Makeyeva N. I. – study concept and design, editing and finalising the article; Babenko N. M. – study methodology, conducting experiments, data collection and analysis, drafting the first version of the manuscript; Kumechko M. V. – conducting experiments, data collection and analysis, writing the first draft of the manuscript; Litvinova O. B. – conducting experiments, data collection and analysis, editing and finalising the article.

Availability of data and materials. Data are available on request.

Statements

Ethical approval and consent to participate. The study was reviewed and approved by the Bioethics Committee of Kharkiv National Medical University (Minutes No. 3 of 8 March 2026). All patients provided written informed consent to participate in this study.

Human rights or animal welfare. All procedures in the study were carried out in accordance with the 1964 Declaration of Helsinki.

Statement on the use of generative artificial intelligence in scientific works. The authors did not use artificial intelligence whilst writing this paper.

Statement on the use of generative artificial intelligence in scientific papers. The authors did not use artificial intelligence whilst writing this paper.

Use of artificial intelligence. During the preparation of the manuscript, artificial intelligence tools were used exclusively for linguistic and stylistic editing of the text, without affecting the interpretation of the research results.

Consent to publication. All authors have approved the final version of the manuscript for publication and are responsible for the accuracy and reliability of the data presented.

Conflict of interest. The authors declare that they have no conflicts of interest or financial obligations.

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Received April 16, 2026
Reviewed June 26, 2026
Accepted for publication August 28, 2026
Published online October 23, 2026