International Journal of Design & Nature and Ecodynamics
Vol. 20, No. 12, December, 2025, pp. 2935-2942
Journal homepage: http://iieta.org/journals/ijdne

Photobiomodulation at BL-18 Acupoint Ameliorates Pyrazinamide-Induced Hepatotoxicity in Mice (*Mus musculus*): Optimization of Exposure Duration and Biphasic Dose-Response

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https://doi.org/10.18280/ijdne.201217

Received: 14 November 2025
Revised: 16 December 2025
Accepted: 24 December 2025
Available online: 31 December 2025

Keywords:
laser acupuncture, photobiomodulation, hepatotoxicity, pyrazinamide, tuberculosis

ABSTRACT

Hepatotoxicity induced by anti-tuberculosis drugs (ATDs), particularly pyrazinamide (PZA), continues to be a major barrier to successful tuberculosis (TB) treatment. Non-pharmacological approaches such as laser acupuncture (laser-puncture) have been proposed to provide hepatoprotective effects through photo-biomodulation mechanisms (PBM), yet scientific evidence of their benefits in PZA-induced hepatotoxicity remains scarce. This study aimed to investigate the effects of laser-puncture at the BL-18 acupoint on serum liver enzymes and hepatic histology in mice subjected to PZA-induced liver injury. Mice were assigned to treatment groups based on laser exposure duration (60, 80, 100, and 120 seconds) using a laser with a wavelength of 660 nm, 50 m-Watt, 6 mm spot size, and a control group without intervention. Serum aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) levels were quantified, and liver histology was evaluated using hematoxylin–eosin staining to determine hepatocyte necrosis. Data were analyzed using one-way ANOVA with Duncan's Multiple Range Test for biochemical parameters, and the Kruskal–Wallis test for histological findings. Laser-puncture significantly reduced SGOT and SGPT levels compared with the control group ($p < 0.001$). The 80-second exposure (K2 Group) yielded the most optimal hepatoprotective effects, with SGOT (99.86 U/L) and SGPT (52.43 U/L) restored to normal physiological ranges. Histological evaluation showed the lowest necrosis scores in the 80- and 100-second groups, corroborating the biochemical improvements. The non-linear response pattern observed across exposure durations supports the biphasic dose–response model in photo-biomodulation, indicating the presence of an optimal therapeutic window for maximal biological benefit. Overall, these findings demonstrate that laser-puncture at the BL-18 acupoint has promising potential as an adjunctive intervention to alleviate PZA-induced hepatotoxicity. Improvements at both biochemical and histological levels provide a foundational scientific rationale for further translational research. Future studies incorporating detailed laser parameter characterization, molecular pathway profiling, and validation in higher animal models and clinical populations are recommended to strengthen evidence for its incorporation into TB treatment strategies.

1. INTRODUCTION

Tuberculosis (TB) remains one of the most significant global public health challenges. Between 2020 and 2023, Indonesia consistently ranked among the 30 high TB burden countries according to the World Health Organization (WHO) [1]. Despite the implementation of various national programs, trends in TB incidence and prevalence have not shown meaningful declines, distancing Indonesia from the global TB elimination targets [2, 3]. This situation underscores the need for comprehensive strategies that address not only detection and treatment but also the management of treatment-related adverse effects that may compromise therapeutic success [4]. Over the past decade, attention to adverse drug reactions—particularly hepatotoxicity caused by anti-tuberculosis drugs (ATDs)—has increased substantially. First-line agents such as isoniazid, rifampicin, and especially pyrazinamide (PZA) are known to have a high potential for causing liver injury [5]. This hepatotoxicity has become a major obstacle in TB management, reducing patient adherence and increasing the risk of treatment failure, relapse, and the emergence of drug-resistant TB strains [6].

PZA is a crucial component of standard ATD regimens but is also the drug most frequently associated with drug-induced liver injury (DILI) [7]. Recent studies have shown that PZA may induce liver injury through multiple biological mechanisms, including mitochondrial dysfunction, disturbances in lipid metabolism, and increased oxidative stress within hepatocytes [8]. These effects lead to elevated serum transaminases such as serum aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT), which serve as key indicators of hepatocellular damage [9]. The prevalence of ATD-related DILI ranges from 9% to 16%, a substantial figure that significantly influences the TB treatment landscape. This

hepatotoxicity issue affects not only clinical outcomes but also patient behavior [10]. The adverse effects experienced by patients often lead to dose reduction, premature discontinuation of therapy, or switching healthcare facilities. Such non-adherence can result in the development of drug-resistant TB, further exacerbating the public health burden and increasing treatment costs [11]. Studies in Indonesia have shown that liver function monitoring, early detection of adverse effects, and education on the importance of adherence play critical roles in preventing treatment failure [12].

Serum transaminases, specifically aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT), are routinely used for clinical assessment of hepatic injury. ALT is relatively more specific for hepatocellular damage, whereas AST may also increase in the context of extrahepatic tissue injury, including skeletal muscle damage [13]. However, despite their broad clinical utility, these enzymes have suboptimal sensitivity and specificity for early detection and dynamic monitoring of DILI, which may delay recognition of hepatotoxicity and timely intervention [14]. Accordingly, there is a clear need to investigate adjunctive strategies that can complement biochemical monitoring by attenuating hepatic injury and supporting tissue recovery in individuals exposed to hepatotoxic agents.

Non-pharmacological modalities have been increasingly investigated as supportive interventions to modulate inflammatory responses and enhance cellular resilience. Photo-biomodulation (PBM), including low-level laser therapy (LLLT), as well as acupuncture-derived approaches such as laser acupuncture or laser-puncture, have been reported to influence key pathways implicated in hepatotoxicity, including downregulation of pro-inflammatory mediators, improvement of mitochondrial bioenergetics, and suppression of apoptosis in hepatocytes [15]. Experimental studies further indicate that low-intensity laser exposure can facilitate tissue regeneration and restoration of cellular function, including within hepatic tissue, thereby providing a mechanistic basis for its potential hepatoprotective role [16]. These findings support the premise that PBM may serve not only as a symptomatic adjunct but as a biologically plausible intervention to reduce injury severity and accelerate repair processes.

Laser acupuncture constitutes a targeted PBM application that delivers photonic stimulation at defined acupoints and is proposed to elicit both local and systemic physiological effects. Stimulation of acupoints associated with hepatic function has been associated with improved microcirculation, reduced tissue stasis, and enhanced recovery responses within liver tissue [17]. This approach is particularly pertinent in tuberculosis (TB) treatment, where PZA is a major contributor to ATD-associated hepatotoxicity, which can adversely affect adherence and treatment completion [18]. Nevertheless, a substantive evidence gap persists regarding the specific efficacy of PBM-based laser acupuncture for PZA-induced hepatotoxicity. In particular, limited studies have evaluated laser acupuncture at BL18 for its capacity to attenuate transaminase elevations and concurrently improve hepatic histopathological outcomes in experimental models [19]. Therefore, further investigation is warranted to determine whether acupoint-targeted PBM can be developed as a rational adjunctive strategy to mitigate PZA-associated liver injury and support sustained TB therapy. The study proposes the hypothesis that photobiomodulation stimulation at the BL 18 acupoint can reduce hepatotoxicity severity and enhance liver tissue regeneration. Beyond its scientific contribution, this study is expected to offer a safer alternative therapeutic approach to support long-term TB treatment success.

2. METHODOLOGY

This study employed an experimental design aimed at evaluating the effects of laser acupuncture applied at the BL-18 acupoint on biochemical parameters (SGOT and SGPT) and histological alterations in the liver of mice (*Mus musculus*) experiencing PZA-induced hepatotoxicity. All laboratory procedures and animal handling were conducted in accordance with standard ethical guidelines for the care and use of laboratory animals. The experimental workflow is illustrated in Figure 1.

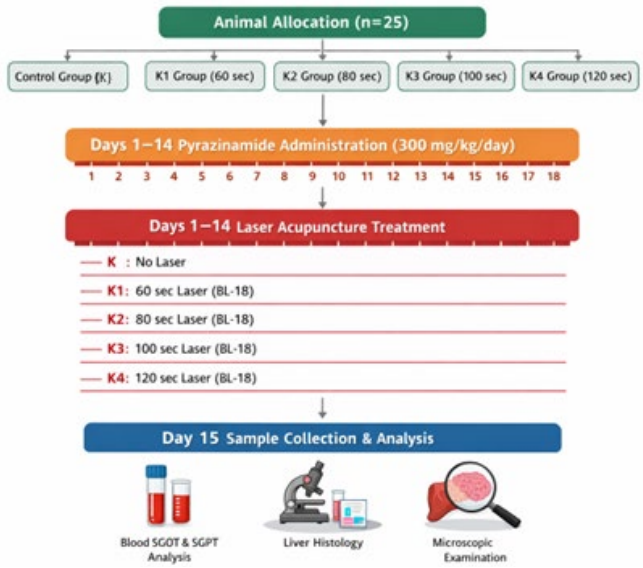


Figure 1. Flowchart of the experimental design, including animal grouping, treatment timeline, and sample analysis

2.1 Experimental design

Adult male *Mus musculus* mice (8 weeks old, 20–30 g) were quarantined and acclimatized for at least one week to minimize variability arising from environmental stress. Animals were housed under a 12-hour light–dark cycle with ad libitum access to food and water. Prior to induction with the antituberculosis agent pyrazinamide (PZA), mice were fasted for 4 hours to standardize pre-administration physiological conditions. Pyrazinamide was administered at a dose of 1.04 mg per animal per day for 14 consecutive days.

The animals were randomly assigned into five experimental groups, each consisting of three animals: K (PZA only), K1 (PZA + 60-second laser acupuncture), K2 (PZA + 80-second laser acupuncture), K3 (PZA + 100-second laser acupuncture), and K4 (PZA + 120-second laser acupuncture). Random allocation was applied to minimize confounding bias and is consistent with standard procedures used in hepatoprotective studies.

In this study, sham-laser and non-acupoint stimulation groups were not included. Accordingly, the experimental design was intended as an exploratory dose–response investigation focusing on optimization of exposure duration at a liver-related acupoint (BL-18) rather than on acupoint specificity. The absence of sham and non-acupoint control

groups is acknowledged as a methodological limitation and is addressed in the Discussion section.

2.2 Induction of hepatotoxicity using pyrazinamide

Hepatotoxicity was induced using PZA administered throughout the treatment period. According to Chirehwa et al. [20], pyrazinamide is given to patients at a daily dose of 20-30 mg/kg, with a maximum dose of 400 mg. With a conversion factor of 0.0026 from adult humans to mice, the calculation of the pyrazinamide dose for mice (20 grams) is as follows: Dosage for mice (20 grams) = 400 mg/day × 0.0026 = 1.04 mg/day. PZA administration may be delivered via oral gavage or intraperitoneal injection, depending on the chosen pharmacokinetic protocol. After the induction period, biochemical and histological parameters were evaluated to determine the extent of liver injury.

2.3 Laser acupuncture protocol (photobiomodulation)

Laser acupuncture was applied at the BL-18 acupoint (Figure 2), traditionally associated with hepatic function. The laser device operated at a wavelength of 660 nm with an output power of 50 mW and a spot diameter of 6 mm. Based on this spot diameter, the laser spot area was calculated to be 0.283 cm^2, resulting in a power density of 176.7 mW/cm^2. Accordingly, the energy densities (fluences) were 10.6, 14.1, 17.7, and 21.2 J/cm^2 for exposure durations of 60, 80, 100, and 120 seconds, respectively. Laser treatment was administered daily during the observation period, with animals gently restrained to ensure consistent exposure. These exposure durations were selected in accordance with the biphasic dose–response phenomenon in photobiomodulation, wherein excessively low or high doses may reduce therapeutic effectiveness.

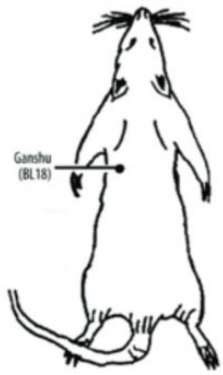


Figure 2. Acupuncture point BL-18 (Gan Shu)

2.4 Blood collection and liver enzyme analysis

Blood samples were collected via cardiac puncture from anesthetized animals following ethical procedures. Approximately 1 mL of blood was collected and allowed to clot for 30 minutes before centrifugation at 3000 rpm for 15 minutes to obtain serum. SGOT and SGPT levels were analyzed using commercial reagents compatible with standard laboratory hematology analyzers, following procedures used in previous studies. Results were converted using appropriate conversion factors and expressed in U/L. Reference ranges for mice (SGOT 99–145 U/L, SGPT 43–60 U/L) served as interpretive baselines, consistent with prior animal studies.

2.5 Liver tissue processing and histological analysis

After euthanasia, liver tissues were excised and fixed in buffered formalin for 24 hours, followed by graded ethanol dehydration, xylene clearing, paraffin embedding, sectioning at 4–5 μm thickness, and hematoxylin–eosin (HE) staining. Histological evaluation focused on hepatocyte necrosis, inflammatory infiltration, and changes in lobular architecture. Observations were performed at 400× magnification across five fields per sample, with necrosis scores used as quantitative parameters for group comparison. Necrosis was assessed semi-quantitatively in a single microscopic field of view using a five-point scoring system: score 0 indicated no observable necrosis in the evaluated area; score 1 corresponded to necrosis affecting 1–20% of the evaluated area; score 2 to 21–50%; score 3 to 51–75% (classified as mild damage); and score 4 to >75% of the evaluated area (classified as severe damage). This method aligns with standard histological procedures reported in hepatoprotective studies [21, 22].

2.6 Statistical analysis

The findings of this study are presented in three main subsections: serum SGOT analysis, serum SGPT analysis, and histological assessment of liver tissue. Quantitative data are expressed as mean ± standard deviation and statistically analyzed to determine differences among treatment groups. All numerical results presented originate from serum measurements and tissue evaluations performed after the treatment period in mice injected with pyrazinamide and exposed to varying durations of laser acupuncture.

3. RESULTS

The findings of this study are presented in three main subsections: serum SGOT analysis, serum SGPT analysis, and histological assessment of liver tissue. Quantitative data are expressed as mean ± standard deviation and statistically analyzed to determine differences among treatment groups. All numerical results presented originate from serum measurements and tissue evaluations performed after the treatment period in mice injected with pyrazinamide and exposed to varying durations of laser acupuncture.

3.1 Effect of laser acupuncture on SGOT levels

The measurement of SGOT levels showed clear differences among groups. The control group exhibited the highest SGOT value at 165.16 U/L, indicating an elevation above the normal physiological range for mice. The group K1 demonstrated a reduction to 152.5 U/L, though it remained above the normal range. The K2 treatment produced the most significant reduction, restoring SGOT to the normal physiological range at 99.86 U/L. K3 also resulted in a value within the normal range (116.56 U/L), while the K4 showed an increase again to 151.11 U/L. This pattern indicates a nonlinear dose–response relationship, with the optimal therapeutic effect occurring at 80 seconds (Figure 3).

One-way ANOVA revealed significant differences among treatment groups (Between Groups Sum of Squares = 9086.766; df = 4; Mean Square = 2271.691; $F = 521.315$; $p < 0.001$) (Table 1). Duncan's multiple range test (DMRT) post

hoc testing indicated that the K2 group received notation a, signifying a significant difference from all other groups. The K3 group was categorized as b, the K1 and K4 groups received notation c, and the control group received notation d (Table 2). These findings confirm that 80 seconds of laser acupuncture produced the most effective SGOT reduction.

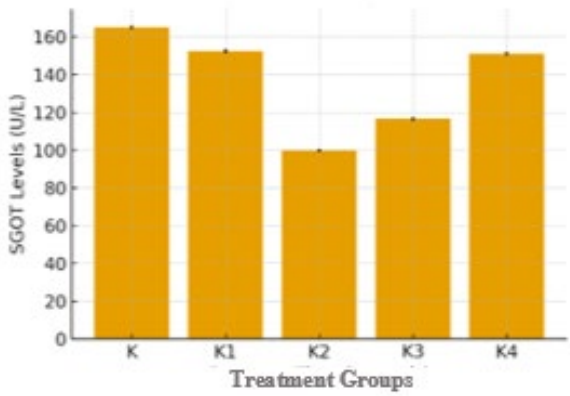


Figure 3. SGOT levels (mean ± SD) across treatment groups

Table 1. One-way ANOVA analysis of SGOT serum levels

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	9086.766	4	2271.691	521.315	0.000
Within Groups	43.576	10	4.358		
Total	9130.342	14			

Table 2. DMRT analysis of SGOT serum levels

Group	Value	Notation
K2	99.86	a
K3	116.56	b
K4	151.11	c
K1	152.5	c
K	165.16	d

3.2 Effect of laser acupuncture on SGPT levels

The pattern observed for SGPT was generally consistent with SGOT findings. The control group showed the highest SGPT value at 91.7 U/L. The K1 reduced SGPT to 77.22 U/L, although still above the normal range. The K2 and K3 treatments produced SGPT values returning to normal limits, at 52.43 U/L and 52.64 U/L, respectively. Conversely, the K4 increased SGPT again to 71.2 U/L. The lowest mean value was recorded in the K2, consistent with SGOT as the most optimal treatment duration (Figure 4).

Table 3. One-way ANOVA analysis of SGPT serum levels

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	3390.377	4	847.594	57.141	0.000
Within Groups	148.333	10	14.833		
Total	3538.710	14			

One-way ANOVA showed significant differences among groups (Between Groups Sum of Squares = 3390.377; df = 4; Mean Square = 847.594; F = 57.141; $p < 0.001$) (Table 3). DMRT analysis grouped the K2 and K3 treatments under notation a, indicating no significant difference between them, but significant differences compared with the other groups. The K1 and K4 groups were categorized as b, while the control group was categorized as c (Table 4).

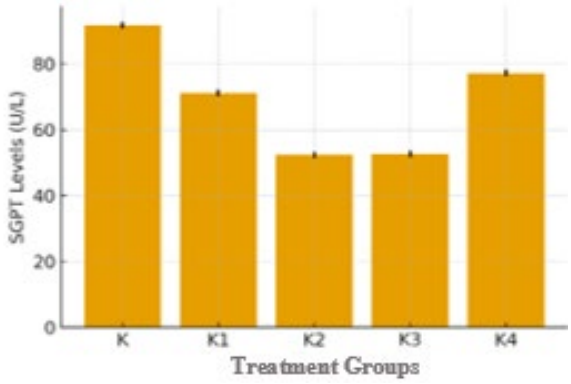


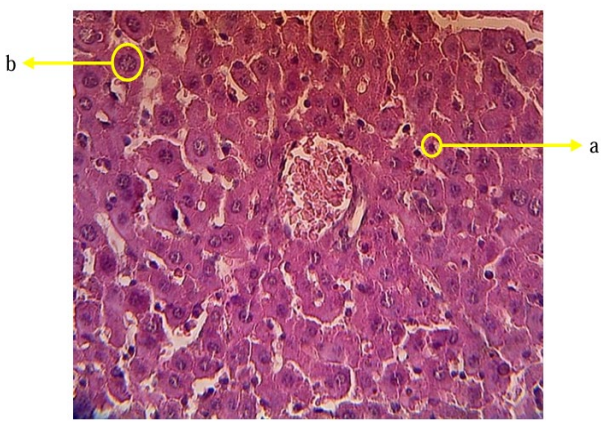
Figure 4. SGPT levels (mean ± SD) across treatment groups

Table 4. DMRT analysis of SGPT serum levels

Group	Value	Notation
K2	52.43	a
K3	52.64	a
K4	71.2	b
K1	77.22	b
K	91.7	c

3.3 Effect of laser acupuncture on liver histology

Histological evaluation was conducted on liver sections stained with hematoxylin–eosin and examined at 400× magnification across five fields per sample (Figure 5). Necrosis scores were used as quantitative indicators of tissue damage. The control group (K) exhibited the most severe histological injury. The K1 group had an average necrosis score of 3, indicating mild to moderate tissue damage. The K2 and K3 groups demonstrated average scores of 2, reflecting improved histological conditions compared to the control. Meanwhile, the K4 group showed an increase in necrosis scores again, mirroring the trend observed in liver enzyme elevations (Figure 6).



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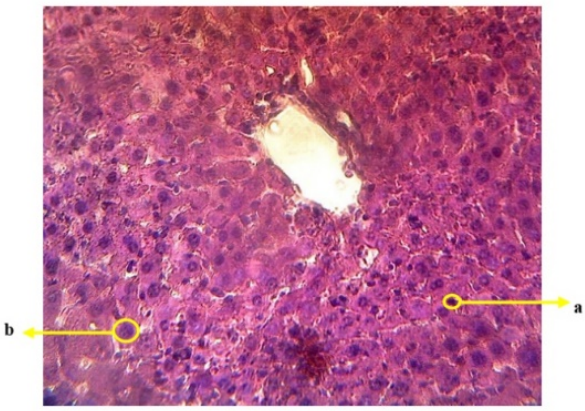

(2)

Figure 5. Histological liver microscopy results of (1) the control group and (2) the 80-second treatment group
(a) necrotic hepatocytes and (b) normal hepatocytes

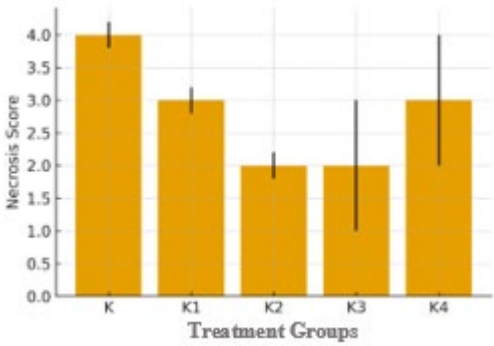

Figure 6. Representative HE micrographs (400×) of liver tissue from each group

Table 5. Kruskal–Wallis analysis

Liver Histology	
Kruskal-Wallis H	11.235
df	4
Asymp. Sig.	0.024

The Kruskal–Wallis test in Table 5 revealed significant differences among groups (H = 11.235; df = 4; p = 0.024). The lowest necrosis scores were observed in the K2 and K3 groups, indicating the greatest histological improvement. Representative micrographs for each group are shown in Figure 4, illustrating differences in hepatocyte morphology and necrosis severity.

4. DISCUSSION

4.1 Interpretation of biochemical and histological findings

The results demonstrated that laser acupuncture exposure produced significant reductions in the hepatic enzymes SGOT and SGPT in the groups treated for 80 (K2) and 100 seconds (K3). The decrease in SGOT from 165.16 U/L in the control group to 99.86 U/L in the K2 group, along with the reduction in SGPT from 91.7 U/L to 52.43 U/L, indicates substantial recovery of hepatocellular function. Histological findings showing the lowest necrosis scores in K2 and K3 groups further support these biochemical outcomes, suggesting that reduced enzyme leakage into the circulation is associated with preserved hepatocyte membrane integrity and decreased necrosis.

The observed response pattern—where the K1 reduced enzymes but remained above normal levels, while the K4 resulted in enzyme elevation—aligns with the biphasic dose-response phenomenon widely reported in photobiomodulation. This concept states that there is an optimal therapeutic dose window in which PBM exerts maximal beneficial effects, whereas exposure that is too low or too high may diminish or even reverse the therapeutic outcomes [23, 24].

4.2 Potential liver-specific mechanisms of BL-18 stimulation

BL-18 (Gan Shu), known as the Liver Shu point, is anatomically located in the paraspinal region corresponding to the T9 spinal segment and has been traditionally associated with hepatic regulation in acupuncture theory. Stimulation of back-shu points has been proposed to influence visceral organ function through somato-autonomic reflex pathways, involving spinal segments that modulate sympathetic and parasympathetic activity. In this context, afferent sensory input from BL-18 stimulation may activate neuro–immune–endocrine signaling pathways that regulate hepatic inflammation, oxidative stress, and metabolic homeostasis [25].

Experimental and clinical acupuncture studies have reported that stimulation of liver-related acupoints can modulate hepatic blood flow, suppress pro-inflammatory cytokine expression, and enhance hepatocyte resilience through central and peripheral neural integration [26]. Such mechanisms may theoretically confer liver-specific protective effects that are superior to non-acupoint or nonspecific photobiomodulation.

However, the present study did not include a non-acupoint or sham control group, and therefore could not directly confirm whether the observed hepatoprotective effects were specific to BL-18 stimulation or reflect generalized photobiomodulation responses. Consequently, the proposed liver-specific neuro–immune–endocrine mechanisms should be interpreted as biologically plausible hypotheses rather than definitive conclusions. Future studies incorporating non-acupoint irradiation and sham controls are essential to delineate acupoint-specific effects and to validate whether BL-18 stimulation produces superior hepatoprotective outcomes through neuro–immune–endocrine regulation.

4.3 Relevant mechanisms of photobiomodulation

The molecular mechanisms underlying PBM's protective effects involve photon absorption by intracellular chromophores, particularly cytochrome c oxidase (CCO) in mitochondria. This interaction enhances ATP production and modulates cellular redox dynamics [27, 28]. Activation of CCO and increased ATP generation may enhance the reparative capacity of hepatocytes, while modulation of reactive oxygen species (ROS) and nitric oxide (NO) contributes to cellular signaling that reduces apoptosis and inflammation [29]. In the context of PZA-induced hepatotoxicity—reported to cause mitochondrial dysfunction and oxidative stress [1, 30]—PBM may restore mitochondrial function, thereby reducing apoptosis rates and enzyme leakage into the serum.

Additionally, PBM may regulate inflammatory responses by reducing the expression of pro-inflammatory mediators and increasing growth factors that support tissue regeneration. These effects are consistent with reports indicating that LLLT accelerates tissue healing and reduces inflammatory infiltration in various disease models [31]. Therefore, the combined mitochondrial and anti-inflammatory effects provide a plausible biological rationale for the improved histological outcomes and decreased SGOT/SGPT levels observed in treatment groups receiving the optimal exposure duration.

4.4 Comparison with previous literature

These findings are consistent with studies reporting hepatoprotective effects of non-pharmacological interventions, including PBM, in various liver toxicity models. Research evaluating other hepatotoxic agents, such as CCl_4 or paracetamol, has shown reductions in transaminases and histological improvements following exposure to LLLT or similar therapeutic combinations [32, 33]. In the case of PZA, hepatotoxic mechanisms involving toxic metabolites and mitochondrial disturbances have been documented [34]. Thus, an intervention that modulates mitochondrial function, such as PBM, has strong mechanistic justification. Nevertheless, literature specifically assessing laser acupuncture at the BL-18 acupoint in PZA-induced hepatotoxicity remains limited, making this study's empirical contribution particularly meaningful. However, the study did not include a sham or non-acupoint control group, limiting the ability to confirm whether the observed benefits are specific to BL-18 stimulation or reflect general photobiomodulation effects. Future studies should include such controls to strengthen the causal attribution to acupoint-specific mechanisms.

4.5 Study limitations and future directions

Despite the promising findings, this study has several limitations that should be acknowledged. First, the relatively small sample size (n = 3 per group) may limit statistical power and reduce the generalizability of the results. Although this sample size is commonly used in exploratory preclinical studies aimed at identifying dose–response trends, larger cohorts are required to strengthen statistical reliability and translational relevance.

Second, the absence of a sham-laser control group and a non-acupoint stimulation group prevents definitive attribution of the observed hepatoprotective effects to BL-18 (Liver Shu point) specificity. Consequently, the beneficial outcomes observed may partially reflect generalized photobiomodulation effects rather than acupoint-specific mechanisms.

Third, this study did not include direct molecular assessments such as oxidative stress biomarkers, apoptosis-related gene expression, or tissue repair mediators. As a result, interpretation of the underlying mechanisms is limited to biologically plausible hypotheses derived from existing photobiomodulation and acupuncture literature.

Future studies should therefore incorporate sham and non-acupoint control groups to validate acupoint specificity, employ larger sample sizes to enhance statistical robustness, and include comprehensive molecular analyses, such as oxidative stress markers (MDA, SOD, GPx), mitochondrial protein expression (e.g., CCO), and apoptosis signaling pathways (Caspase-3, BAX/Bcl-2). In addition, systematic dose–response investigations quantifying fluence (J/cm²), power density (mW/cm²), and laser spot area are essential to precisely define the optimal therapeutic window of photobiomodulation for hepatoprotection.

5. CONCLUSION

This study demonstrates that laser acupuncture exerts significant hepatoprotective effects against pyrazinamide-induced hepatotoxicity in a mouse model. Laser acupuncture applied at the BL-18 acupoint consistently reduced serum SGOT and SGPT levels and improved the histological architecture of hepatic tissue, with the 80-second exposure (K2 group) identified as the most optimal duration within the parameters used. These findings reinforce the concept of a biphasic dose response in photobiomodulation, wherein a specific therapeutic window yields maximal biological benefits. The results provide preliminary scientific support that laser acupuncture may serve as a complementary intervention to reduce the risk of DILI in patients undergoing TB therapy, particularly those receiving pyrazinamide-containing regimens. However, further studies are required to strengthen this evidence, including more comprehensive characterization of photobiomodulation parameters, deeper molecular investigations, larger sample sizes, and validation in higher-order animal models and human populations.

ACKNOWLEDGMENT

This work was supported by the Research and Community Service Institute (LP2M) of Universitas Islam Negeri Maulana Malik Ibrahim Malang.

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