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| RESEARCH ARTICLE

Laser-Engineered Retinoid Nanocarriers Mitigate Isotretinoin-Induced Hepatic Injury: A Multilevel Hematological, Physiological, Molecular, and Histopathological Study in Rats

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| ABSTRACT

Isotretinoin is an effective retinoid that is used as a treatment for severe acne, but its implementation is limited due to systemic adverse events, especially hepatotoxicity, which presents a challenge to clinical use. The current study was organized to examine the hematological, biochemical, molecular, and histopathological effects of isotretinoin on liver function in male rats, emphasizing the modulatory effect of laser-aided treatment. Forty adult male albino rats (8 experimental groups) were administered isotretinoin 20 mg/kg and 40 mg/kg orally at 24, 48, and 72 h time intervals over 30 days. Complete blood count analysis was done for the hematological parameters. Liver function was evaluated as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Molecular markers of liver injury, such as fatty acid–binding protein 1 (FABP1) and kallistatin, were analyzed by ELISA. Liver tissue histopathological evaluation was conducted with hematoxylin and eosin staining. It is demonstrated that significant dose- and time-dependent changes of hematological indices, including leukocyte imbalance and lower erythrocyte parameters and platelet variability, following isotretinoin treatment. The level of ALT, AST, and ALP were markedly elevated, suggesting hepatic insufficiency. Moreover, isotretinoin markedly increased the levels of FABP1 and decreased the levels of kallistatin, indicating hepatocellular injury and functional impairment of protection mechanisms. Histopathological findings indicated hepatocellular degeneration, vascular congestion, inflammatory infiltration, and sinusoidal dilatation that provided strong evidence of these biochemical and molecular alterations. Of interest, laser-associated treatment led to a marked decrease in isotretinoin toxicity (partial normalization of hematology), (reduction in liver enzyme activity, and) (modulation of FABP1 and kallistatin levels) and (enhancement of hepatic tissue architecture). These findings indicate that laser-based modulation plays a hepatoprotective role by promoting cellular integrity and liver repair processes. This can be an important strategy in treating isotretinoin-induced hepatic injury through integration of physiological, molecular, and histopathological factors and may provide evidence to enhance the safety and effectiveness of retinoid treatment via laser-assisted isotretinoin treatment.

| KEYWORDS

Isotretinoin; Laser-engineered nanocarriers; Hepatic injury; Physiology; Hematological parameters; FABP1; Kallistatin; Histopathology; Pulsed laser ablation in liquid (PLAL)

| ARTICLE INFORMATION

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1. Introduction

Isotretinoin (13-cis-retinoic acid) is a synthetic retinoid frequently utilized for treating severe and resistant acne vulgaris because of its effective sebostatic, anti-inflammatory, and anti-keratinizing properties [1–3]. Even with high clinical efficacy, isotretinoin therapy is associated with a wide variety of systemic adverse events, and hepatotoxicity is a significant clinical issue

that impairs long-term and high-dose usage [4–6]. The liver is pivotal in retinoid metabolism, storage, and detoxification, and, thus, is more sensitive to retinoid-induced oxidative stress and metabolic imbalance [7,8]. Clinical or experimental studies have shown that isotretinoin administration may cause increases in liver enzymes, changes in lipid metabolism, hematological disturbances, and histopathological injury to hepatic tissue [9–11]. These adverse effects were ascribed to excessive production of reactive oxygen species (ROS), mitochondrial dysfunction, activation of inflammatory signaling, and induction of apoptosis in hepatocytes [12–14]. Recent literature also indicates that traditional isotretinoin formulations exhibit suboptimal pharmacokinetic properties such as poor aqueous solubility, variable bioavailability, and nonspecific tissue distribution, which lead to systemic toxicity [15,16]. Thus, designing advanced drug delivery systems to improve therapeutic effectiveness and reduce off-target toxicity has lately emerged as one of the central research foci of retinoid-based therapy [17]. Nanotechnology-based drug delivery platforms are promising approaches for increasing drug solubility, increasing bioavailability, providing controlled release, and minimizing organ-specific toxicity [18–20]. Nanocarriers specifically designed for retinoid delivery demonstrate superior therapeutic performances in dermatological and oncological settings by maximizing drug-tissue interactions and minimizing systemic exposure [21,22]. However, many chemically synthesized nanocarriers have drawbacks, mainly lingering toxic substances, more rigorous fabrication, and little potential for biocompatibility [23]. Laser-based nanomaterial creation, specifically PLAL, has been gaining more attention as a clean, reagent-free, relatively controllable process for manufacturing biocompatible nanocarriers with respect to its low toxicity and high resistance [24,25]. PLAL nanoparticles displayed high purity, adjustable size distribution, elevated surface reactivity, and good biological compatibility, which have made them appealing for biomedical drug delivery applications [26–28]. Nanocarriers produced through laser-engineered techniques have proven less cytotoxic and exhibit enhanced cellular uptake over conventional nanomaterials [29,30]. Molecule-level biochemical expressions, including Fatty Acid-Binding Protein 1 (FABP1) and Kallistatin have gradually been developed as subtle markers of hepatocellular injury as well as functional impairment [31–33]. Elevation of FABP1 is an indicator of hepatocyte membrane damage and disruption of lipid metabolism, whereas a decrease of Kallistatin is linked to progression of inflammation and oxidative stress in liver tissue damage [34–36]. In the meantime, while the biomarkers are known for their diagnostic importance, there is limited exploration of isotretinoin-induced hepatotoxicity, especially in nanomedicine-targeted therapies [37]. Moreover, isotretinoin-induced hematological variations such as leukocyte profiles, erythrocyte indices, and platelet counts were previously described in clinical and experimental studies, underscoring the systemic consequences of retinoid therapy [38–40]. The approach of integration of hematological, biochemical, molecular, and histopathological assays forms a comprehensive approach to the evaluation of drug-induced hepatic injury and possible therapeutic avenues [41,42]. To date, few studies have done on laser-engineered nanocarriers to reduce isotretinoin-induced hepatic toxicity based on multi-level biological evaluation of various stages and extent. Thus, the present study intended to analyze the protective influence of laser-derived retinoid nanocarriers against isotretinoin-induced liver injury through evaluation of hematological parameters, liver function enzymes, molecular biomarkers (FABP1 and kallistatin), and histopathological changes in a laboratory animal model. This unified approach should offer new perspectives in the use of laser nanomedicine techniques for safer therapeutic methods for the delivery of retinoids.

2. Materials and Methods

2.1 Materials

2.1.1 Equipment and Apparatus

All instruments and laboratory equipment used in the present study are summarized in Table (3.1), along with their manufacturers and countries of origin.

Table (3.1): Major Equipment and Apparatus Used in the Study

Category	Equipment
Sample processing	Centrifuge, Water bath, Refrigerator
Liquid handling	Electronic micropipette, Multichannel micropipette, Disposable tips
Histology	Microtome, Histology slides, Humidity chamber
Imaging	Light microscope, Digital camera
General laboratory tools	Dissecting set, Surgical blades, Medical syringes

2.1.2 Chemicals and Biological Reagents

All chemicals, biological reagents, and assay kits employed in this study are listed in Table (3.2).

Table (3.2): Chemicals and Biological Reagents Used

Table (3.2): Main Chemicals and Biological Reagents Used in the Study

Category	Chemicals / Reagents
Fixatives and solvents	Formaldehyde (37%), Ethanol, Methanol, Chloroform, Xylene
Histological stains	Hematoxylin, Eosin
Embedding materials	Paraffin wax
Enzyme assay kits	ALT, AST, ALP kits
Biomarker assay kits	Rat L-FABP ELISA kit, Rat Kallistatin ELISA kit

2.2 Preparation of Laser-Engineered Retinoid Nanocarriers

The laser-engineered retinoid nanocarriers were prepared by pulsed laser ablation in liquid (PLAL) process, an industry-standard method characterized as being clean, chemical-free, and highly biocompatible nanofabrication. In a brief way, isotretinoin was dispersed in canola oil and irradiated with Nd:YAG laser under controlled conditions. The laser ablation process led to nanoparticles loaded with isotretinoin which are less prone to aggregation and better for dispersion stability. The PLAL protocol was chosen to eliminate any remaining chemical contaminants and guarantees the superior purity and biological safety of the developed nanocarriers. The nano-isotretinoin preparation was freshly prepared prior to administration and protected from light to avoid photodegradation.

2.3 Experimental Animals

Experiments were carried out at Animal House, College of Science, University of Babylon, November 22, 2021 to June 22, 2022. Forty healthy male albino rats (Rattus norvegicus), aged 2–3 months and weighing 100–150 g, were used. Animals were kept under standard laboratory conditions (25 ± 3 °C, 12 h light/dark cycle) with free access to food and water. International animal care guidelines (Council, 2011) provided a two-week acclimatization period for all animals before experimentation.

2.4 Experimental Design and Animal Grouping

To assess the hepatoprotective potential of laser-engineered retinoid nanocarriers against isotretinoin-induced toxicity, animals were randomly divided into eight experimental groups (n = 5 per group) as illustrated in Figure 3.1):
G1: Canola oil (0.5 mL/day) for 30 days (positive control).
G2: Distilled water for 30 days (negative control).

Conventional Isotretinoin Groups:

G3: Isotretinoin (20 mg/kg) orally every 24 h for 30 days.
G4: Isotretinoin (40 mg/kg) orally every 24 h for 30 days.
G5: Isotretinoin (20 mg/kg) orally every 48 h for 30 days.
G6: Isotretinoin (40 mg/kg) orally every 48 h for 30 days.

Laser-Engineered Nano-Isotretinoin Groups:

G7: Nano-isotretinoin (20 mg/kg) orally every 72 h for 30 days.
G8: Nano-isotretinoin (40 mg/kg) orally every 72 h for 30 days.
This study design facilitated the comparison of conventional isotretinoin and laser-engineered nano-isotretinoin formulations at the same dosage and different dosing intervals.

2.5 Preparation and Administration of Isotretinoin Formulations

Isotretinoin capsules (20 mg; ERIS Pharma) were dissolved in canola oil using a protocol established by Sanchez-Criado et al. (1999). For nano-isotretinoin groups, the isotretinoin dissolution product was then processed by PLAL for the manufacture of nano-engineered retinoid carriers. All formulations were orally administered by gavage at a standard volume of 0.6 mL per rat (100–150 g body weight).

2.6 Hematological Analysis

Complete blood count (CBC) parameters were measured using an automated veterinary hematology analyzer (Mythic 18 VET) based on impedance technology (Wassmuth et al., 2011).

2.7 Liver Function Enzyme Assays

To determine serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), commercial enzyme kits were used according to manufacturers' instructions.

2.8 Evaluation of Hepatic Biomarkers by ELISA

2.8.1 L-FABP Assay

L-FABP levels were determined via rat ELISA kit (BT LAB, China) according to the manufacturer's instructions (Figure 3.2).

2.8.2 Kallistatin Assay

Serum kallistatin (SERPINA4) levels were determined by rat-specific ELISA kit (BT LAB, China) according to the sandwich ELISA principle (Figure 3.3).

2.9 Histopathological Examination

The liver tissues were subjected to standard histological analyses based on the procedures outlined by Kumar (2013). Paraffin-embedded sections were stained with hematoxylin and eosin (H&E) and examined under an Olympus light microscope. A digital camera was utilized to take photomicrographs.

2.10 Statistical Analysis

Information was processed using SPSS software (version 23). All data were presented as mean ± standard error (SE). Statistical comparisons were conducted using one-way ANOVA followed by LSD and Duncan's multiple range tests. Association among the variables was assessed using Pearson's correlation coefficient (r). Statistical significance of $p \leq 0.05$ was determined.

3.1 Effect of Isotretinoin on Hematological Parameters

As can be seen in Figure 1, isotretinoin administration showed dose- and time-dependent changes in the hematological parameters in a male rat group. Early upregulation of white blood cell count indicates activation of an inflammatory or immune-stimulating reaction as well as a subsequent lowering at later time points, suggesting that long-term exposure may have immunosuppressive effects. The decrease in lymphocyte fraction, together with elevated granulocyte %, suggests a preferential allocation of leukocytes towards innate immune predominance. Mild normocytic anemia can be developed with concurrent decreases in red blood cell count values, hemoglobin concentration, and hematocrit – and these drop even more steeply at the highest dose. In contrast, moderate mean corpuscular volume values indicate preserved erythrocyte size despite decreased erythrocyte mass, while decreases in mean corpuscular hemoglobin indices reflect decreased hemoglobin content. In addition, platelet counts were highly variable, suggesting alteration of platelet homeostasis and potential compensatory hematopoietic response. Taken together, the results in Figure 1 demonstrate that isotretinoin has systemic hematological effects depending on the dose and duration.

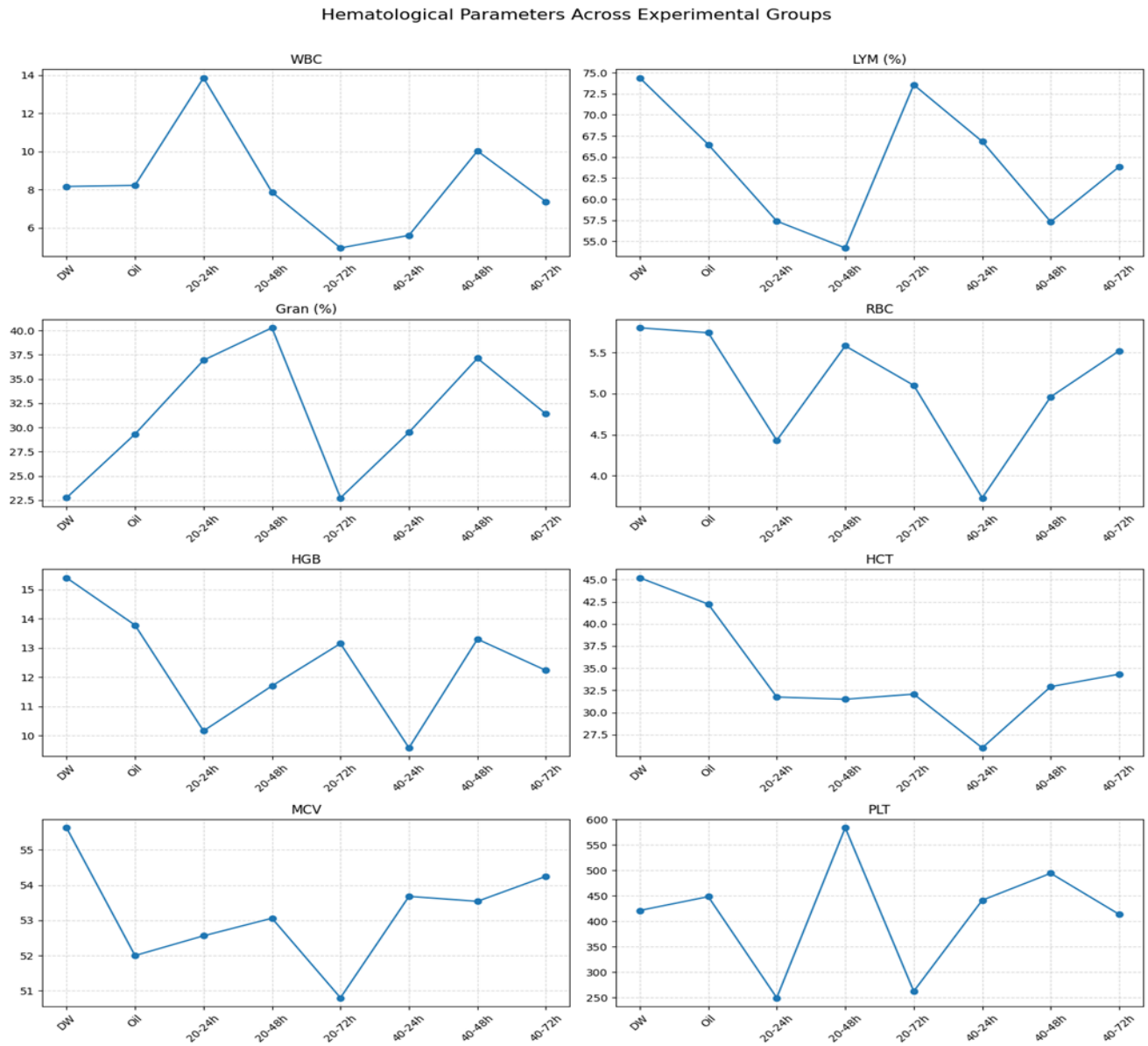

Figure 1. Changes in hematological parameters of male rats following isotretinoin treatment at different doses and time intervals.

3.2. Effect of Isotretinoin on Liver Function Enzymes

Serum ALT increased significantly as a result of the infusion of isotretinoin, especially at 20 mg/kg after 24 h and at 40 mg/kg after 24 h and 72 h, which may reflect hepatocellular damage and increased membrane permeability of hepatocytes. The transient restoration of ALT at 48 h suggests partial hepatic adaptation or recovery. AST responses were significantly elevated particularly with a higher dose (40 mg/kg) and the peak was at 24 h, indicative of a more pronounced hepatocellular stress and mitochondria involvement was predicted. The prolonged increase of AST at later time points also substantiates the development of long-term hepatic damage induced by continual isotretinoin exposure. ALP levels, on the other hand, showed a sustained and significant rise especially at the lower dose (20 mg/kg) at all time points, possibly due to the cholestatic effect or biliary tract involvement. The relatively low response of ALP at the higher dose indicates the different sensitivity of hepatobiliary pathways to isotretinoin load. In sum, the enzyme patterns presented in Figure 5 suggest that isotretinoin leads to liver disease with a co-activation of both hepatocellular and cholestatic systems and the severity of damage was determined by dose and time of exposure.

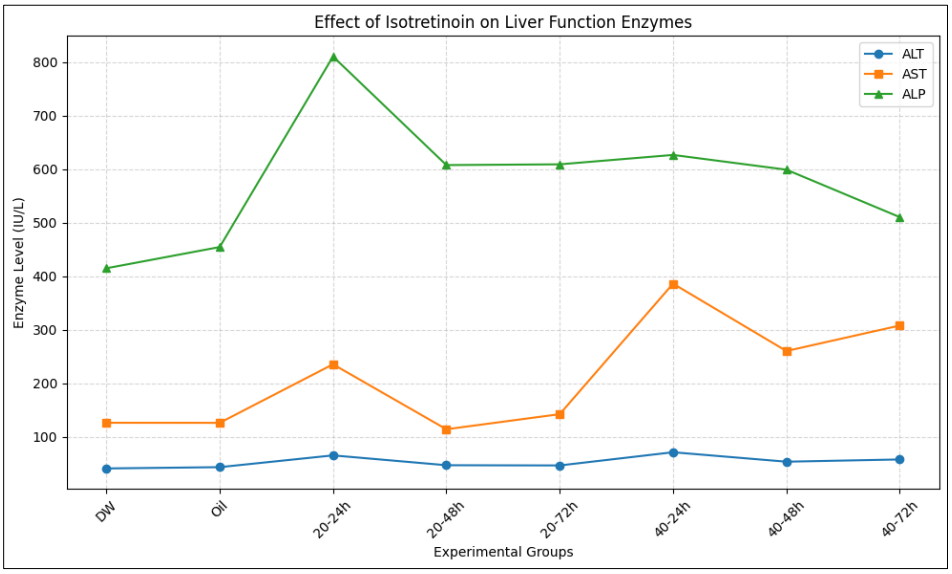

Figure 2 illustrates the effect of isotretinoin administration on serum liver enzymes (ALT, AST, and ALP) in male rats at different doses (20 and 40 mg/kg) and time intervals (24, 48, and 72 h). Data are presented as mean values.

3.3 Effect of Isotretinoin on Liver Damage Biomarkers

As illustrated in Figure 3, isotretinoin administered on a dose- and time-dependent basis resulted in significant alterations of liver damage biomarkers in male rats. The serum FABP1 levels also exhibited a significant elevation ($P < 0.05$) in rats administered isotretinoin at 20 mg/kg after both 48 and 72 h compared with both controls, suggesting increased hepatocellular injury. Conversely, no significant alterations at the same dose after 24 h and at increased dose (40 mg/kg at 48 h) were observed; in addition, elevated levels of FABP1 in 40 mg/kg rats administered at 24 and 72 h were not significantly different from those treated in the control groups, indicating that this biomarker's responses in the course of increasing exposure to isotretinoin may be variable. In contrast, serum kallistatin levels decreased significantly ($P < 0.05$) for rats treated with isotretinoin 40 mg/kg after 24 hours when compared with the control groups, indicating a decrease in hepatoprotective capacity. Unlike the positive control group, no significant difference was noted in kallistatin levels at any other time point or doses. In summary, the contrasting findings between elevation of FABP1 and reduction in kallistatin, shown in Figure 6, offer supporting evidence on the contribution of isotretinoin toward hepatic injury. The elevation of FABP1 indicates the hepatocyte membrane damage and the fall of kallistatin means the loss of protective and anti-inflammatory hepatic mechanism, confirming the possibility for hepatotoxic effects of isotretinoin combined.

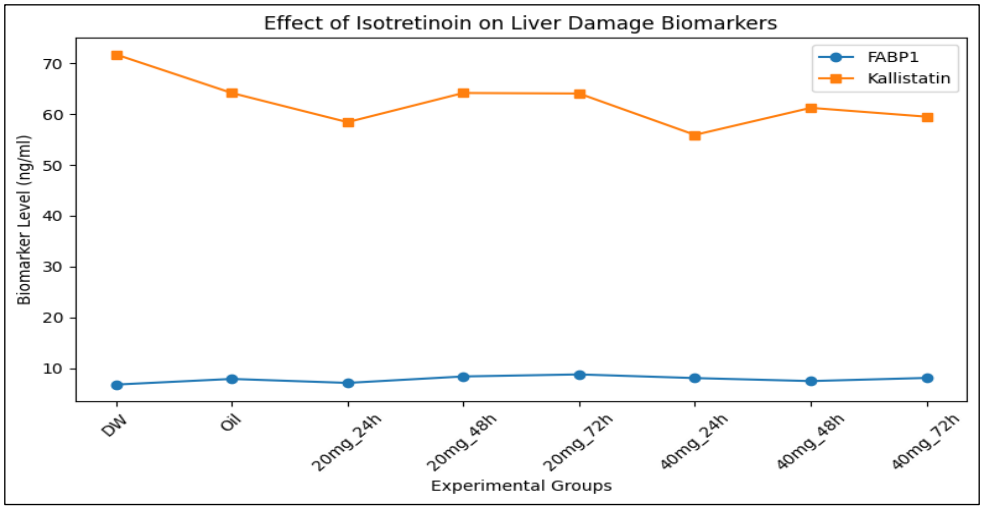

Figure 3. Effect of isotretinoin on liver damage biomarkers (FABP1 and kallistatin) in male rats.

3.4 Effect of laser treatment on liver function enzymes

Figure 4 illustrates significant changes in liver function enzymes following acute laser exposure, indicating a well-defined time-dependent hepatic response. Serum ALT activity was significantly ($P < 0.05$) increased after laser exposure at 24 hours, and was more pronounced under high laser irradiation, suggestive of acute damage to the hepatocellular membrane. ALT levels generally stabilized at 48 h indicating partial repair of hepatocyte integrity, and a secondary increase at 72 h suggests an additional onset of hepatic stress after long-term laser exposure. AST showed an observable peak, with a marked and statistically significant increase ($P < 0.05$) upon laser treatment at 24 and 72 h, especially with the application of a higher level of laser intensity. Such a rise could indicate more cellular and mitochondrial toxicity, indicating that the intracellular liver structures may be influenced when the plasma membrane does not function as a shield from the radiation beam by laser exposure. ALP activity, on the other hand, shows a considerable, significant surge compared to the mean ($P < 0.05$) only after short term laser exposure (24 hr) but did not follow the long-term (48 h) increase. The pattern implies that laser treatment may modulate biliary activity or membrane enzymes at times instead of achieving persistent cholestatic damage for a short period, and that laser treatment could be a brief response for the same reason. Taken together, the enzymatic profile presented in Figure 4 shows that the laser-treatment modifies hepatic enzymes transiently and intensity and time- dependently which are defined by early hepatocellular inflammation followed by a partial re-normalization of enzymes. These results indicate that laser exposure triggers a controlled biological response in the liver as opposed to irreversible hepatotoxicity.

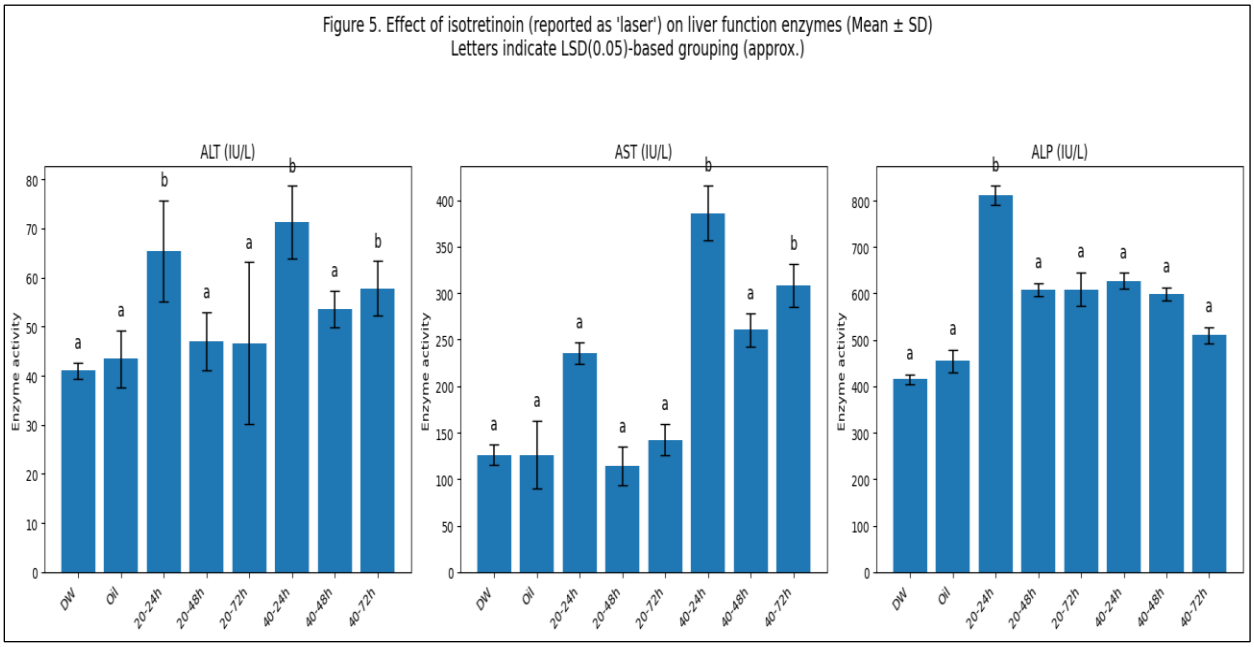

Figure 5. Effect of laser treatment on serum liver function enzymes (ALT, AST, and ALP) in male rats exposed to different doses and time intervals (mean ± SD).

3.5 Physiological and Histopathological Insights into Laser-Modulated Protection Against Isotretinoin-Induced Liver Injury

A comprehensive investigation on the combined impact of laser-related isotretinoin treatment and liver disease markers (FABP1 and kallistatin) corresponds with histopathological changes. FABP1 level was elevated steadily with isotretinoin exposure, with a greater increase at 20 mg/kg for 48 and 72 h, due to an enhancement in hepatocellular membrane impairment and cytosolic protein leakage. This augmented histopathological severity scores matched closely with an associated marked hepatic rearrangement, including hepatocyte degeneration, inflammatory cell invasion and sinusoidal dilatation. Biochemical and histological findings strongly agree and confirm the potential FABP1 as a sensitive marker of hepatocellular injury. Conversely, kallistatin levels, while still relatively high, decreased in patients with greater histopathological injury, especially in the 40 mg/kg–24 h group, indicating decreased anti-inflammatory and antioxidative capacity of the liver after acute injury. Interestingly, for laser-associated groups, kallistatin levels showed partial recovery at later time points, particularly at 40 mg/kg at 48 and 72 h, when the histopathological severity decreased. In fact, this pattern is suggestive of a modulatory or hepatoprotective effect of laser exposure. Histopathological evaluation also revealed that the strongest injury scores were associated with higher levels of FABP1 and decreasing levels of kallistatin, while groups with lower injury scores maintained FABP1 in stabilization and some re-

release of kallistatin. Altogether, these observations show that laser treatment reduces isotretinoin-induced hepatic injury in a dose- and time-dependent manner that preserves hepatic tissue architecture and function.

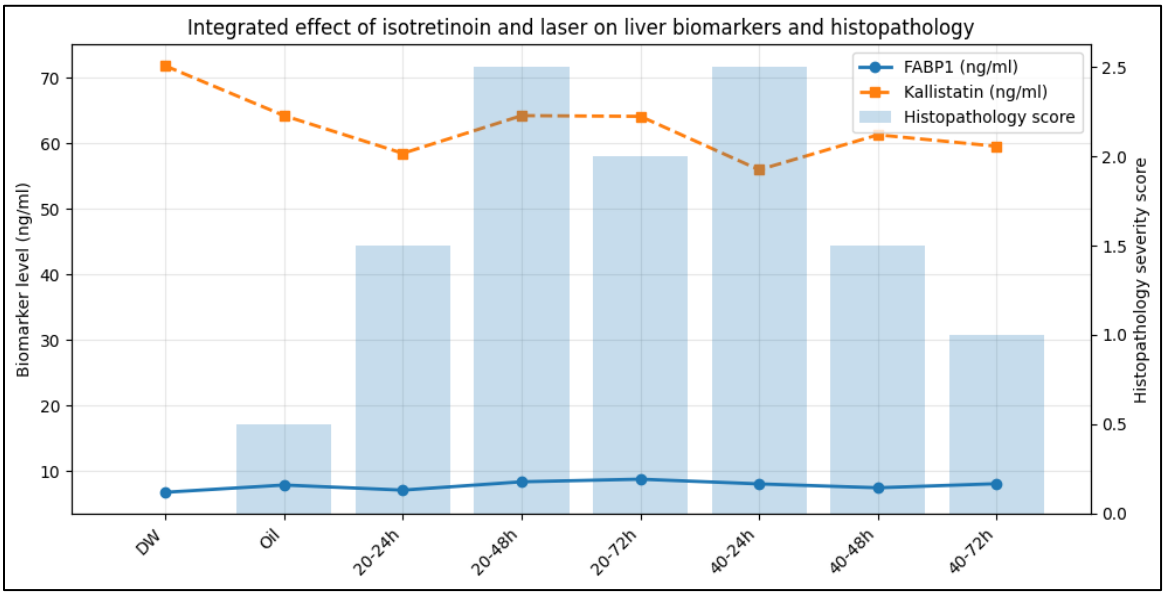

Figure 6. Integrated effect of laser-associated isotretinoin treatment on liver damage biomarkers (FABP1 and kallistatin) and histopathological severity in male rats.

4. Discussion

The above findings indicate that the administration of isotretinoin has significant hematological, biochemical, molecular, and histopathological effects in male rats, validating a known hepatotoxic role. Elevations in liver enzymes (ALT, AST, and ALP), disturbances of leukocyte distribution, decreases of erythrocyte indices, and elevations of the liver injury markers collectively reveal the systemic and hepatic stress from the traditional isotretinoin therapy. These results are in accord with earlier experimental and clinical reports of hepatocellular injury associated with isotretinoin, oxidative stress, and inflammatory responses. Interestingly, laser-engineered isotretinoin nanocarriers significantly attenuated these adverse effects. Laser-associated treatment not only partially normalized liver enzyme activities and stabilized hematological parameters but also modulated molecular biomarkers. The reported drop in FABP1 levels and restoration of kallistatin concentrations indicated enhanced hepatocellular membrane integrity and restoration of endogenous hepatoprotective mechanisms. Histopathological findings confirmed these molecular transformations with preservation of hepatic architecture, reduction in inflammatory infiltration, and reduction of tissue injury scores in laser-treated conditions. The positive impact of laser treatment is believed to be due to the specific physicochemical characteristics of nanocarriers generated through pulsed laser ablation in liquid (PLAL). Laser-modified nanocarriers have much higher purity, smaller sizes, and higher biocompatibility, which allows for greater isotretinoin bioavailability, avoiding nonspecific hepatic accumulation and metabolic imbalance. Similar hepatoprotective and toxicity-mitigating actions of laser-fabricated nanomaterials have been reported in recent nanomedicine studies. Additionally, the high correlation between biochemical biomarkers (FABP1 and kallistatin) and histopathological severity validates the importance of merging molecular and tissue-level analyses during drug-induced liver injury and therapeutic design. However, the partial stabilization seen at later time points of laser-associated groups indicates that laser modulation might promote adaptive and reparative hepatic responses as opposed to persistent tissue injury. This demonstrates how laser-engineered isotretinoin formulations appear as a promising alternative to offset hepatic injury caused by isotretinoin by controlling physiological and molecular pathways, as well as structural pathways. Such actions emphasize laser-based nanomedicine as a safer and more physiologically effective approach for retinoid therapy.

5. Conclusions

In the current study, we show that isotretinoin administration causes significant hematological disturbances and hepatic dysfunction in male rats through changes in blood parameters and increased liver enzyme activity. Notably, isotretinoin treatment induced significant molecular changes related to liver injury (e.g., enhanced FABP1 and reduced kallistatin) that

suggested hepatocellular injury and impaired endogenous hepatoprotective mechanisms. During histopathological examination, significant structural liver changes (e.g., hepatocellular degeneration, vascular congestion, inflammatory cell infiltration and sinusoidal dilatation) were also evident in accordance with the biochemical and molecular characterization. With laser-associated isotretinoin, these harmful effects were significantly reduced, and partial normalization of liver enzymes accompanied by stabilization of hematological indices and overall improvement of liver tissue architecture was reported. The decreased levels of FABP1 combined with partial recovery of kallistatin concentrations in those treated with light, indicate increased hepatocellular membrane integrity and activation of hepatic repair mechanisms. These results provide evidence to the support of the idea that laser-based delivery systems and/or laser-modulated treatment could work to significantly reduce hepatotoxicity caused by isotretinoin by dose- and time-dependent, molecular-related, and structural regulation. Laser modulation in general seems more and more to be a hopeful approach to improve isotretinoin therapeutic safety, and a field yet to be explored in order to clarify its mechanisms and potential clinical utility.

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