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The Pantothenic Acid Derivative Dexpanthenol Attenuates Liver Injury Induced by Lung Ischemia-Reperfusion Through Its Anti-Inflammatory Effect

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Abstract

Objective

Pulmonary ischemia-reperfusion (IR) injury can lead to liver damage through inflammation triggered by hypoxic conditions. Dexpanthenol (DEX), known for its anti-inflammatory properties in organs such as the lung, liver, and kidney, may exert hepatoprotective effects. This study investigates the potential of DEX in mitigating hepatic injury following pulmonary IR.

Material and Method

A total of 40 rats were randomly allocated into four experimental groups: control, ischemia-reperfusion (IR), IR treated with dexpanthenol (IR+DEX; 500 mg/kg, intraperitoneally, single dose), and DEX alone. Following left thoracotomy, non-traumatic vascular occlusion was performed for 60 min, followed by a 60-min reperfusion period. Upon sacrification, liver tissues were harvested and fixed in formaldehyde for subsequent histopathological and immunohistochemical evaluation.

Results

Histological evaluation of liver sections from the control and DEX groups revealed normal tissue architecture. In contrast, the IR group exhibited prominent pathological changes, including moderate hyperemia, hepatocellular necrosis, inflammatory cell infiltration, and mild hemorrhage, predominantly around the central veins. Notably, liver sections from the DEX-treated groups demonstrated marked histological improvement compared to the IR group. Immunohistochemical analysis revealed minimal cytoplasmic expression of c-Fos, HIF-1α, and IL-6 in the control group. In contrast, the IR group exhibited a marked increase in the expression of all three markers within liver tissue. DEX treatment notably reduced the expression levels of c-Fos, HIF-1α, and IL-6, suggesting a protective effect against IR-induced hepatic injury. While inflammatory cells and bile duct epithelial cells showed similar expression patterns, hepatocytes were the primary source of these immunoreactive signals. All marker expressions were confined to the cytoplasm. These findings indicate that DEX provides a protective effect against IR-induced liver damage.

Conclusion

In the context of pulmonary IR, damage is likely to occur not only in lung tissue but also in other secondary organs. This is attributed to the dissemination of immunomodulatory cytokines developed within the tissue through the bloodstream to other organs. DEX, a derivative of pantothenic acid recognized in the literature for its tis-sue-protective effects and known anti-inflammatory properties, mitigates inflammation in liver damage resulting from lung IR injury, as evidenced by alterations and changes in immunological markers.

Keywords: Ischemia-reperfusion, Dexpanthenol, Liver, Lung ischemia

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Introduction

Pulmonary ischemia-reperfusion (IR) injury is a serious condition that occurs particularly in cases of pulmonary embolism, cardiopulmonary bypass, circulatory arrest, and lung transplantation (1). The sudden onset of ischemia in the pulmonary artery creates resistance against right ventricular contraction. Since the lungs and liver are interconnected through the circulatory system, any vascular pathology affecting one is expected to impact the other. Another mechanism of damage in liver tissue is the reflection of oxidative stress and inflammation developed in hypoxic tissues to other organs, such as the liver (2).

When oxygenation and blood flow are impaired, hypoxia-related damage begins to develop in the tissue. Liver functions slow down, and the tissue becomes unable to provide the necessary resources to sustain its function. Ischemic damage ultimately results in cell death and the release of damage-associated molecules.

While reestablishing blood flow and oxygenation forms the basis of recovery, it also leads to the formation of another condition known as reperfusion injury. During reperfusion, the oxygen entering the tissues serves as a substrate for the production of reactive oxygen species (ROS) resulting from intracellular metabolic disturbances. On one hand, it provides the tissue with the oxygen it needs, while on the other hand, it increases the formation of ROS, which causes damage to tissues such as the liver. Some studies suggest that reperfusion injury is mediated by inflammatory cell activation in the reperfused liver tissue. Exacerbation of the inflammatory response to ischemic lung injury can lead to dysfunction in other organs, including the liver (3).

During these changes, certain events develop, and pathways are activated at the cellular level in the secondary liver tissue. ROS may come through circulation and primarily occur in liver tissue. Dexpanthenol (DEX), a derivative of vitamin B5, is used in wound healing due to its tissue-protective properties. Recent studies have demonstrated the anti-inflammatory and apoptosis-preventing properties of DEX in various tissues such as nerve, lung, liver, and kidney (4-6). This study aims to investigate the effects of DEX on liver damage resulting from pulmonary IR injury.

Material and Method

Ethics, Animals, and Experimental Model

The experimental design adhered to the guidelines for animal research set forth by the National Institutes of Health and received approval from the Committee on Animal Research at Suleyman Demirel University before commencement of the study (Approval no: 06-538, Date: 12.06.2025).

Rats were kept at 21-22 degrees Celsius, 12 h of light and 12 h of darkness. An ad libitum feeding regimen was applied. 40 rats were randomly divided into four groups, with ten rats in each group. The groups were assigned as follows:

Control group: 0.5-1 ml saline was administered intraperitoneally (i.p.) to the rats. After 30 min, a thoracotomy procedure was performed under anesthesia, but the IR model was not performed, and the hilus was visualized.

IR group: 0.5-1 ml saline was administered i.p. to the rats. After 30 min, a thoracotomy procedure was performed under anesthesia. After left thoracotomy, a non-traumatic vascular clamp was placed on the hilus for 60 min of ischemia, and 60 min of reperfusion were performed (7).

IR+DEX group: 500 mg/kg DEX was administered i.p. to rats. After 30 min, a thoracotomy procedure was performed under anesthesia. After left thoracotomy, a non-traumatic vascular clamp was placed on the hilus for 60 min of ischemia, and 60 min of reperfusion were performed (7).

DEX group: 500 mg/kg DEX was administered i.p. to rats. After 30 min, a thoracotomy procedure was performed under anesthesia, but the IR model was not performed.

Following a 12-hour fasting period, experimental animals were subjected to intraperitoneal anesthesia with Ketamine (90 mg/kg) / Xylazine (8-10 mg/kg). Subsequently, the thoracic region was shaved, and a left thoracotomy was performed under anesthesia. After identification of the left lung hilum and trachea, non-traumatic vascular clamping was applied for 60 min, followed by 60 min of reperfusion. Once reperfusion was confirmed by visualization of blood flow, the animals were euthanized. Surgical exsanguination was carried out via abdominal incision. After sacrification, liver tissues were collected and placed in formaldehyde solution for histopathological and immunohistochemical analyses.

Histopathological Analysis

Liver samples were collected during necropsy and fixed in 10% neutral buffered formalin. The tissues

were subsequently processed using a standard tissue processor, embedded in paraffin, and sectioned at a thickness of 5 µm using a rotary microtome. Sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope to assess histopathological changes, including necrosis, inflammation, and hemorrhage. Lesions were evaluated according to the criteria established by Veteläinen et al. (8), with modifications as presented in Table 1.

Histopathological scoring was performed using a semi-quantitative grading system based on previously published criteria by Veteläinen et al., with minor modifications. The evaluated parameters included hepatocellular necrosis, inflammation, hemorrhage, and hyperemia. Each parameter was scored independently on a scale from 0 to 3 according to severity. Necrosis was graded based on the percentage of affected hepatocytes (0: absent; 1: <10%; 2: 10–50%; 3: >50%). Inflammation was scored according to the extent and distribution of inflammatory cell infiltration (0: none; 1: scattered; 2: focal; 3: diffuse). Hemorrhage and hyperemia were evaluated based on the number and extent of affected areas (0: absent; 1: mild; 2: marked; 3: severe). All scoring criteria are summarized in Table 1.

Immunohistochemical Examination

Three sets of sections were obtained from the paraffin-embedded liver blocks and mounted on poly-L-lysine-coated slides for immunohistochemical analysis. The expression of c-Fos (Anti-c-Fos antibody [N486/32], ab302667), HIF-1α (Anti-HIF-1 alpha antibody – C-terminal, ab228649), and IL-6 (Anti-IL-6 antibody, ab9324) was evaluated using the streptavidin-biotin peroxidase method. All primary antibodies, obtained from Abcam (Cambridge, UK), were diluted 1:100. Following incubation with the primary antibodies for 60 min, the sections were treated with a biotinylated secondary antibody and streptavidin-alkaline phosphatase. Immunodetection was performed using the chromogen 3,3′-Diaminobenzidine (DAB) and the Abcam Mouse and Rabbit Specific HRP/DAB IHC Detection Kit-micro-polymer (ab236466). Negative controls were prepared by substituting the primary antibodies with antigen dilution solution. All analyses were carried out in a blinded manner by a trained pathologist from a different university. For each marker, the percentage of positively stained cells was determined at 40× magnification by examining ten randomly selected fields per slide across all groups. Quantitative analysis was performed using ImageJ software (version 1.48; National Institutes of Health, Bethesda, MD, USA), and representative microphotographs were captured using the Cell Sens Life Science Imaging Software System (Olympus Co., Tokyo, Japan).

This approach was preferred over an H-score–based evaluation to ensure methodological simplicity and consistency, particularly considering the acute nature of the ischemia-reperfusion model and the need for reproducible quantification across experimental groups.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism. The Shapiro-Wilk test was initially applied to assess the normality of the data distribution. As the data exhibited a normal distribution ($P > 0.05$), a one-way analysis of variance (ANOVA) was used to compare the groups. To identify pairwise differences between the groups, the post hoc Tukey test was employed. The results are presented as means ± standard deviations, with a significance level of $P < 0.05$.

Results

Histopathological Examination

Histological assessment of liver tissues revealed preserved hepatic architecture in both the control and DEX groups, with no significant pathological alterations observed. In contrast, liver sections from the IR group demonstrated marked histopathological damage, characterized by hepatocellular necrosis, inflammatory cell infiltration, hyperemia, and focal hemorrhage, predominantly localized around the central veins. Semi-quantitative scoring confirmed significantly higher necrosis, inflammation, hemorrhage, and hyperemia scores in the IR group compared with the control group (Table 1, Figure 1).

Treatment with dexpanthenol markedly attenuated IR-induced histopathological damage. The IR+DEX group exhibited significantly reduced necrosis, inflammation, hemorrhage, and hyperemia scores compared with the IR group, indicating a substantial protective effect of DEX on liver tissue morphology (Table 1, Figure 1).

Immunohistochemical Examination

Immunohistochemical analysis demonstrated minimal cytoplasmic expression of c-Fos, HIF-1α, and IL-6 in liver tissues from the control and DEX groups. In contrast, the IR group showed a pronounced increase in cytoplasmic immunoreactivity for all three markers, predominantly in hepatocytes, with occasional positivity in inflammatory cells and bile duct epithelial cells.

Quantitative analysis revealed a significant upregulation of c-Fos expression in the IR group compared with the

Table 1 Histopathology score of hepatic lesions

Histological criteria	Severity	Description	Score
Hemorrhage	Absent		0
	Mild	< 3 foci	1
	Marked	4-6 foci	2
	Severe	> 7 foci	3
Inflammation	None		0
	Moderate	Scattered	1
	Marked	Foci	2
	Severe	Diffuse	3
Necrosis	Absent	0%	0
	Mild	<10%	1
	Marked	10–50%	2
	Severe	>50%	3

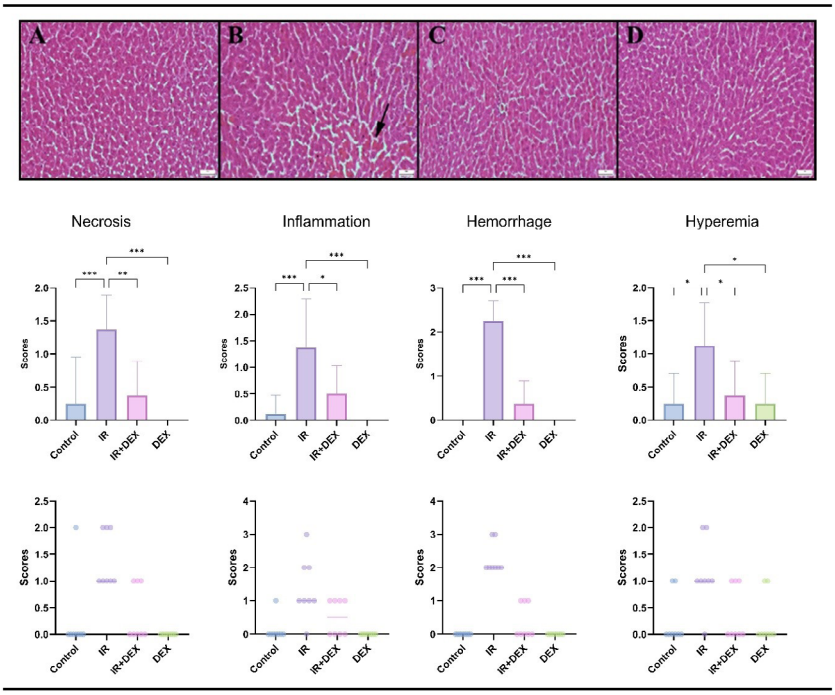


Figure 1

Representative histopathological images of liver tissues from different experimental groups. (A) Control group showing normal liver architecture. (B) IR group displaying necrotic hepatocytes (arrow) along with disrupted tissue structure. (C) IR + DEX group showing reduced pathological alterations. (D) DEX group with preserved tissue morphology and minimal pathological changes. Hematoxylin and eosin staining (H&E); scale bars = 50 µm.

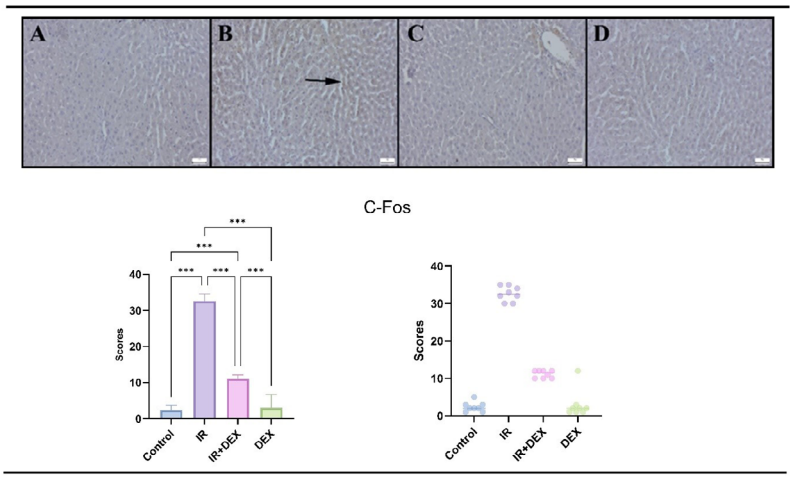


Figure 2

Immunohistochemical expression of c-Fos in liver tissues from different experimental groups. (A) Control group showing negative c-Fos expression. (B) IR group displaying marked c-Fos expression in hepatocytes (arrows). (C) IR + DEX group with reduced c-Fos expression. (D) The DEX group showed no detectable c-Fos expression. Staining was performed using the streptavidin-biotin peroxidase method; scale bars = 50 µm.

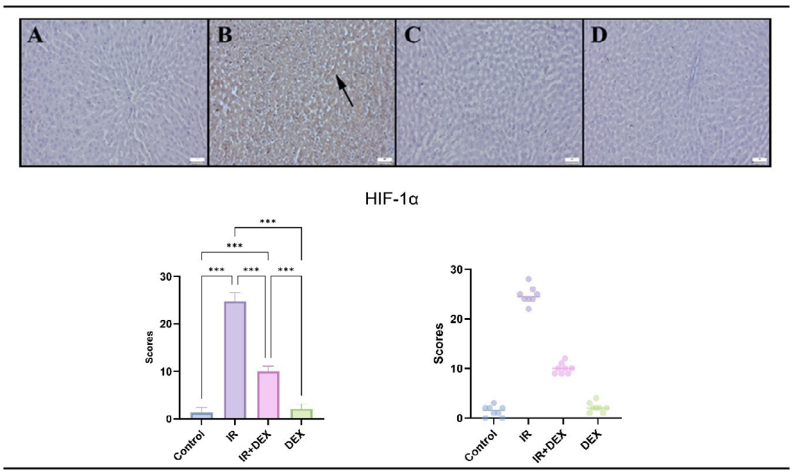


Figure 3

Immunohistochemical expression of HIF-1α in liver tissues from different experimental groups. (A) Control group showing negative HIF-1α expression. (B) IR group displaying marked HIF-1α expression in hepatocytes (arrows). (C) IR + DEX group with reduced HIF-1α expression. (D) The DEX group showed no detectable HIF-1α expression. Staining was performed using the streptavidin-biotin peroxidase method; scale bars = 50 µm.

control group, whereas DEX administration significantly reduced c-Fos immunoreactivity in the IR+DEX group (Figure 2). Similarly, HIF-1α expression was markedly increased following IR and was significantly attenuated by DEX treatment (Figure 3). IL-6 immunoreactivity showed a parallel pattern, with strong cytoplasmic expression in the IR group and a significant reduction in the IR+DEX group (Figure 4).

Overall, these findings indicate that pulmonary ischemia–reperfusion induces robust activation of hypoxia- and inflammation-related signaling pathways in liver tissue, which are effectively suppressed by dexpanthenol treatment.

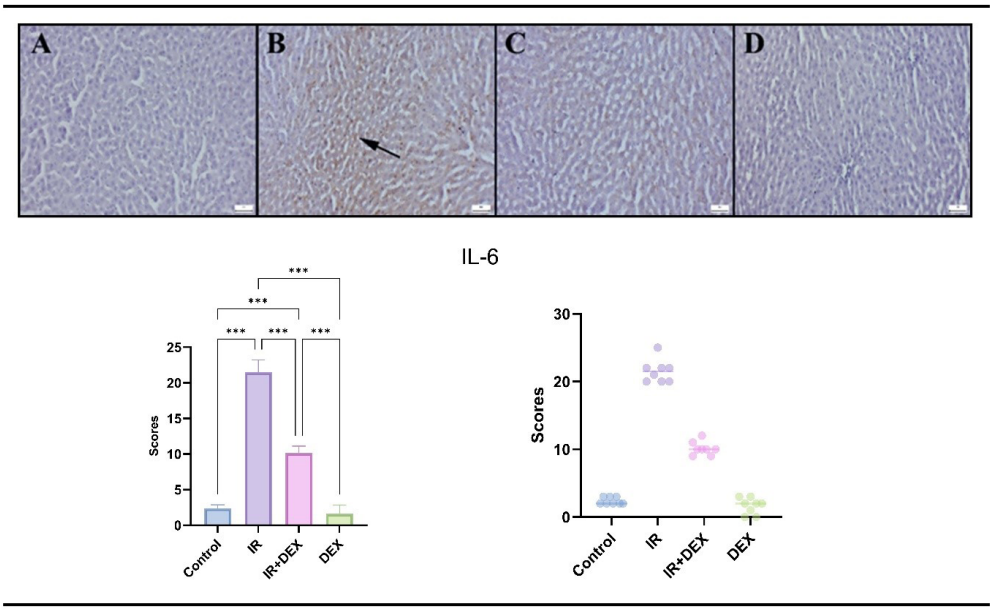


Figure 4

Immunohistochemical expression of IL-6 in liver tissues from different experimental groups. (A) Control group showing negative IL-6 expression. (B) IR group displaying marked IL-6 expression in hepatocytes (arrows). (C) IR + DEX group with reduced IL-6 expression. (D) The DEX group showed no detectable IL-6 expression. Staining was performed using the streptavidin-biotin peroxidase method; scale bars = 50 µm.

Discussion

The present study provides experimental evidence that dexpanthenol (DEX), a pantothenic acid derivative known for its antioxidant and anti-inflammatory properties, exerts a protective effect against liver injury induced by pulmonary ischemia-reperfusion (IR). Pulmonary IR injury, typically occurring during conditions such as pulmonary embolism, lung transplantation, or cardiopulmonary bypass, is recognized for generating a systemic inflammatory response capable of inducing damage not only in the lungs but also in distant organs, including the liver (9, 10).

Histopathological evaluation in the current study clearly demonstrated that liver tissues of rats subjected to pulmonary IR exhibited marked structural damage, characterized by hepatocellular necrosis, inflammatory infiltration, hyperemia, and hemorrhage. These morphological alterations are consistent with previous studies indicating that systemic inflammatory responses can compromise hepatic microcirculation, leading to hepatocyte death and disruption of tissue integrity (11). In contrast, rats treated with DEX before IR exhibited significantly ameliorated histopathological profiles, suggesting that DEX mitigates liver injury by interfering with one or more injury pathways initiated during IR.

Immunohistochemical analysis further confirmed the protective role of DEX at the molecular level. The expression levels of key inflammatory and hypoxia-related markers, interleukin-6 (IL-6), hypoxia-inducible factor-1 alpha (HIF-1α), and c-Fos were markedly elevated in the IR group. IL-6 is a central mediator in the acute-phase response and has been implicated in both hepatocyte apoptosis and liver regeneration. Its upregulation during pulmonary IR reflects a systemic inflammatory response that exacerbates hepatic damage. The administration of DEX significantly downregulated IL-6 expression (7).

HIF-1α is a transcription factor that becomes stabilized under hypoxic conditions and triggers the transcription of numerous genes involved in glycolysis, angiogenesis, and inflammation (12). Its elevated expression in the IR group reflects the hypoxic microenvironment created during the ischemic insult. The reduction of HIF-1α in the DEX-treated group suggests that DEX may either improve oxygen delivery or directly inhibit hypoxia-associated signaling pathways, thereby limiting downstream tissue damage.

Similarly, c-Fos, an immediate early gene and component of the activator protein-1 (AP-1) transcription factor complex, is rapidly upregulated in response to cellular stress and is known to modulate the expression of pro-inflammatory genes. Its increased expression in the IR group and suppression following DEX administration further support the anti-inflammatory and cytoprotective effects of DEX (13).

Taken together, the histological and immunohistochemical findings in this study align with existing literature that highlights DEX's protective effects in models of hepatic, renal, neural, and pulmonary injury (13, 14). Previous research has shown that DEX reduces oxidative stress markers such as malondialdehyde (MDA) and increases antioxidant enzymes like superoxide dismutase (SOD) and catalase. While such biochemical assays were not included in the current study, the observed reductions in IL-6, HIF-1α, and c-Fos expression provide indirect evidence of reduced oxidative and inflammatory stress in the liver.

Despite these encouraging results, several limitations should be acknowledged. First, the duration of reperfusion (60 min) may not fully represent the chronic phase of injury, during which fibrotic changes and more complex immune responses might emerge; however, this time point was deliberately selected to focus on early hypoxic and inflammatory events while maintaining model standardization and minimizing potential animal loss. Second, the lack of serum biochemical markers, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, limits the ability to correlate histopathological changes with functional hepatic impairment, as the primary objective of the study was to evaluate tissue-level histopathological and immunohistochemical alterations rather than systemic functional parameters. Third, although immunohistochemistry provides valuable spatial information about protein expression, it does not offer quantitative or mechanistic insights comparable to molecular techniques such as Western blotting or real-time PCR; these analyses were not included due to technical and logistical constraints. Incorporating these methods in future studies would allow for a more comprehensive understanding of the pathways through which DEX exerts its protective effects.

Furthermore, the dose and timing of DEX administration may influence its efficacy. In this study, a single high-dose intraperitoneal injection (500 mg/kg) was used based on prior preclinical models. However, it remains unclear whether lower or repeated doses would yield similar protective outcomes, or whether alternative routes of administration might be more effective or clinically feasible.

In conclusion, the findings of this study demonstrate that dexpanthenol significantly attenuates liver injury following pulmonary ischemia–reperfusion by suppressing hypoxia- and inflammation-related molecular pathways. The downregulation of IL-6, HIF-1α, and c-Fos expression, together with the preservation of hepatic architecture, suggests that dexpanthenol exerts a notable remote organ-protective effect and holds promise as a systemic therapeutic agent in acute ischemic settings. From a surgical perspective, improved understanding of secondary hepatic injury in pulmonary ischemia-reperfusion models may provide valuable insights into the mechanisms underlying systemic organ damage associated with major surgical procedures, including lung transplantation, pulmonary thromboendarterectomy, and extracorporeal circulation. It should be noted that the dexpanthenol dose used in this experimental model was selected based on previous preclinical studies, and such doses do not directly translate to human clinical dosing; therefore, careful dose-optimization and long-term studies incorporating detailed molecular analyses are warranted to fully elucidate dexpanthenol's mechanism of action and assess its translational relevance.

Conflict of Interest Statement
All the authors have no conflicts of interest to declare in association with this study.

Ethical Approval
The experimental design adhered to the guidelines for animal research set forth by the National Institutes of Health and received approval from the Committee on Animal Research at Suleyman Demirel University before commencement of the study (Approval no: 06-538, Date: 12.06.2025).

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Availability of Data and Materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Artificial Intelligence Statement
The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Authors Contributions

B.T: Conceptualization, Methodology, Formal Analysis, Data Curation, Writing – Original Draft, Visualization,

H.A: Conceptualization, Investigation, Formal analysis, Methodology, Project Administration, Writing – Review & Editing

I.K: Methodology, Investigation, Data Curation

O.O: Resources, Writing – Review & Editing, Supervision, Funding Acquisition

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