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Dual Role of Cannabidiol in Mitigating Apoptosis and Inflammation in Cardiovascular Complications of Lung Ischemia-Reperfusion

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Abstract

Objective

Lung ischemia-reperfusion (I/R) injury is a critical complication in thoracic surgeries and lung transplantation, leading to oxidative stress, inflammation, and apoptosis. Secondary cardiac damage often occurs due to the systemic inflammatory response, highlighting the need for protective interventions. Cannabidiol (CBD), known for its anti-inflammatory, antioxidant, and anti-apoptotic properties, may mitigate this damage through modulation of apoptotic (B-cell lymphoma 2 [Bcl-2], Bcl2-associated X protein [Bax] and inflammatory (interleukin 10 [IL-10]) markers.

Material and Method

This study involved forty male Wistar albino rats divided into four groups: Control, Lung I/R induced cardiac injury (LICI), LICI treated with CBD (LICI+CBD), and CBD-only. Lung I/R was induced by clamping the left lung hilus for 60 minutes, followed by 60 minutes of reperfusion. The cardiac and aortic tissues were collected post-intervention, and histopathological as well as immunohistochemical analyses were conducted to assess the expression levels of Bax, Bcl-2, and IL-10.

Results

Histopathological findings revealed significant tissue damage in the LICI group, including increased hyperemia, hemorrhage, mononuclear cell infiltration, and necrosis compared to the control. CBD treatment markedly reduced these pathological markers. Immunohistochemical analysis showed a significant increase in pro-apoptotic Bax and a decrease in anti-apoptotic Bcl-2 and IL-10 in the LICI group. Conversely, the LICI+CBD group demonstrated reduced Bax levels and elevated Bcl-2 and IL-10 expression, indicating CBD's role in reducing apoptosis and inflammation.

Conclusion

CBD exhibits cardioprotective effects in lung I/R-induced cardiac injury by decreasing Bax-driven apoptosis, maintaining Bcl-2 levels, and upregulating IL-10 expression. These findings suggest CBD as a promising therapeutic agent for reducing secondary cardiac injury in lung I/R scenarios, though further studies are warranted to confirm its efficacy in clinical settings.

Keywords: Cannabidiol, lung ischemia-reperfusion injury, cardioprotection, apoptosis, inflammation.

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Introduction

Lung ischemia-reperfusion (I/R) injury is a serious complication observed during various clinical procedures, such as lung transplantation, cardiopulmonary bypass, and certain thoracic surgeries. It involves a period of restricted blood flow (ischemia), followed by the restoration of blood flow (reperfusion). Although reperfusion is essential for tissue survival, it paradoxically exacerbates cellular damage through oxidative stress, inflammation, and apoptosis. The heart is one of the key organs affected by lung I/R injury, suffering secondary damage from systemic inflammation and oxidative stress (1,2). This phenomenon, known as remote organ injury, underscores the importance of understanding and mitigating the cardiovascular effects associated with lung I/R injury.

Apoptosis, or programmed cell death, is a significant factor in the progression of I/R-related myocardial damage. The balance between pro-apoptotic and anti-apoptotic proteins determines the extent of cell survival or death following I/R. Bcl2-associated X protein (Bax), a well-known pro-apoptotic protein, promotes mitochondrial membrane permeabilization, leading to cell death, while B-cell lymphoma gene 2 (Bcl-2) is an anti-apoptotic protein that counters these effects by inhibiting Bax activity and stabilizing the mitochondrial membrane. The Bax/Bcl-2 ratio is a critical indicator of apoptosis, with higher ratios favoring cell death and lower ratios supporting cell survival (3,4). Therefore, targeting the regulation of these proteins is a promising strategy to mitigate myocardial injury secondary to lung I/R.

In addition to the apoptotic pathway, inflammation plays a central role in lung I/R-induced cardiac injury. Anti-inflammatory cytokines, such as interleukin-10 (IL-10), help suppress pro-inflammatory cytokine production and reduce tissue damage during reperfusion. IL-10's protective effects have been demonstrated in various models of I/R injury, where it limits the extent of myocardial and pulmonary damage by reducing oxidative stress and neutrophil infiltration (5). Therefore, increasing IL-10 expression represents a potential therapeutic strategy to counteract the inflammatory damage associated with lung I/R.

Cannabidiol (CBD), a non-psychoactive compound derived from Cannabis sativa, has attracted attention for its broad-spectrum therapeutic properties, particularly its anti-inflammatory, antioxidant, and anti-apoptotic effects. Recent studies have demonstrated the ability of CBD to reduce oxidative stress, modulate apoptotic pathways, and enhance anti-inflammatory cytokine production in various models of tissue injury, including myocardial and pulmonary damage (6). However, its protective effects against cardiac injury secondary to lung I/R have not been fully elucidated. This study aims to investigate the cardioprotective effects of CBD by examining its impact on key molecular markers such as Bax, Bcl-2, and IL-10, which are crucial in modulating apoptosis and inflammation during lung I/R-induced cardiac damage (7).

By focusing on the balance between apoptotic and anti-apoptotic pathways (Bax/Bcl-2) and the regulation of anti-inflammatory responses (IL-10), this research seeks to explore how CBD may offer a protective effect against secondary cardiac injury following lung I/R. Understanding these mechanisms could provide valuable insights into the development of novel therapeutic strategies for managing lung I/R injury and its associated cardiovascular complications.

Material and Method

Reagents

CBD was obtained from the Natural Products Application and Research Centre of a university. The source of the CBD was the extract of Cannabis sativa L. (Cannabaceae). CBD content was >99.9, and the tetrahydrocannabinol content was < 0.01. Limits of residual alcohol and heavy metals comply with the USP and EU pharmacopeias. Ketamine (Keta-Control, Doğa İlaç, Turkey) and Xylazine (Xylazinbio 2%, Bioveta, Czech Republic) were used to induce sedation and anesthesia applications.

Experimental Design

In the experiment, forty adults male Wistar albino rats weighing 350–400 g were kept at 21–22 °C and 60% ± 5% humidity. They were fed commercial feed ad libitum and had a 12-hour light 12-hour dark cycle and were divided into 4 groups (each containing ten rats) after they were obtained. Groups as:

Control Group: Rats received 0.5-1 ml saline intraperitoneally (i.p). After 30 minutes, a thoracotomy was performed, but lung ischemia was not created. The hilus was visualized.

LICI Group: Rats were administered 0.5-1 ml saline i.p. After 30 minutes, a non-traumatic vascular clamp was placed on the hilus following the left thoracotomy, and 60 minutes of ischemia and 60 minutes of reperfusion were applied (8).

LICI+CBD Group: Rats received 5 mg/kg CBD i.p. (9). Following the left thoracotomy, a non-traumatic vascular clamp was placed on the hilus, and 60 minutes of ischemia and 60 minutes of reperfusion were applied.

CBD Group: Rats received 5 mg/kg CBD i.p. After 30 minutes, a thoracotomy was performed, but the lung ischemia model was not created.

Surgical Procedure

After 12 hours of fasting, the thorax area was shaved, and the left thoracotomy was performed under i.p. Ketamine (90 mg/kg) / Xylazine (8-10 mg/kg) anesthesia. After the left lung hilus was identified by visualizing the trachea, it was clamped with a nontraumatic vascular clamp (in LICI and LICI+CBD groups) for 60 min, and reperfusion was performed for 60 min. Animals were sacrificed after collecting blood from the inferior vena cava through an abdominal incision for surgical exsanguination. Then the heart and aorta tissues were removed, fixed in formaldehyde for subsequent histopathological and immunohistochemical analysis.

Histopathological Analysis

During the necropsy, samples of the heart and aorta were taken, and they were preserved in a 10% buffered formalin solution. Before the tissues were embedded in paraffin wax, a standard tissue processing method was carried out using a fully automated tissue processing apparatus (Leica ASP300S, Wetzlar, Germany). Sections of the paraffin blocks were prepared at a thickness of 5µm using a fully automatic rotary microtome (Leica RM2155 Leica Microsystems, Wetzlar, Germany). Hematoxylin-eosin (HE) and coverslips were used to stain the sections, which were then seen under a light microscope.

The evaluated parameters (hyperemia, hemorrhage, mononuclear cell infiltration, and necrosis) were pre-determined based on established ischemia-reperfusion injury scoring systems. Each parameter was semi-quantitatively graded on a scale of 0–3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) by a blinded pathologist, modified by Asci et al. 2022 (Table 1).

Immunohistochemical Examination

For immunohistochemical analysis, three sections were cut from the paraffin blocks and placed on slides covered in poly-L-lysine. Sections were then stained immunohistochemically using the streptavidin-biotin procedure, as directed by the manufacturer, to assess the expression of Bax, Bcl-2, and IL-10. Primary antibodies for Bax (Anti-Bax antibody [E63] (ab32503)), Bcl-2 (Anti-Bcl-2 antibody (ab194583)), and IL-10 (Anti-IL-10 antibody [JES5-2A5] (ab189392)) (Abcam, Cambridge, UK) were used for this aim. Primary antibodies were used at a 1/100 dilution and were bought from Abcam in Cambridge, UK. Streptavidin-alkaline phosphatase conjugate and a biotinylated secondary antibody were used for immunohistochemistry on the sections after they had been incubated with the primary antibodies for 60 minutes. The rabbit-specific HRP/DAB Detection IHC Kit (ab64261) from Abcam in Cambridge, UK was used as a secondary antibody. Diaminobenzidine (DAB) was used as the chromogen. Instead of using primary antibodies, an antigen dilution solution was used for the negative controls. On blinded samples, a trained pathologist from a different university performed each evaluation.

For each antibody, slices were examined independently for immunohistochemical examination. Using a grading score that ranged from 0 to 3, semiquantitative analysis was carried out to assess the strength of the immunohistochemical reactivity of cells with markers. In this case, (0-) denotes negativity; (1) focal weak staining; (2) diffuse weak staining; and (3) diffuse marked staining. In each part, ten distinct locations were inspected under 40X objective magnification for evaluation. Utilizing the Database Manual Cell Sens Life Science Imaging Software System (Olympus

Table 1 Stages used in histopathological and immunohistochemical evaluation.

HEART		AORTA	
0	No change	0	No change
1	Mild (only one area)	1	1–2 desquamated cells
2	Moderate (2-3 area)	2	3–4 desquamated cells
3	Severe (more than 4 areas)	3	5 or more desquamated

At 40x magnification

Co., Tokyo, Japan), morphometric analysis and microphotography were carried out. After being saved, the outcomes were statistically examined. The immunohistochemical expression of Bax, Bcl-2, and IL-10 was predominantly cytoplasmic.

Statistical Analysis

For the statistical analysis of histopathological scores and the number of immunohistochemically positive cells, the GraphPad Prism 10.1 software was utilized. Initially, the Shapiro-Wilk method was employed to assess the normality of the data distribution. One-way ANOVA was employed as a means of comparing the groups since the data showed a normal distribution ($p>0.05$). The pairwise differences between the groups were obtained using the post hoc Tukey test. The significance threshold was set at $p<0.05$, and the findings are shown as means ± standard deviation.

Results

Histopathological Examination

The control and CBD groups showed normal tissue histology at the histological analysis of the heart and aorta sections. When comparing the control group to the LICI group, the LICI group exhibited significantly elevated levels of hyperemia ($p\leq0.001$), hemorrhage ($p\leq0.001$), mononuclear cell infiltration (MNCI) ($p\leq0.05$), and necrosis ($p\leq0.01$). In the LICI+CBD group, CBD treatment reduced the pathological results; compared to the LICI group, hyperemia ($p\leq0.01$) and hemorrhage ($p\leq0.001$) levels significantly decreased. There wasn't a significant difference between these groups' MNCI and necrosis levels. In the CBD group, hyperemia ($p\leq0.001$), hemorrhage ($p\leq0.001$), and necrosis ($p\leq0.01$) levels were found to be significantly lower compared to the damage group, while MNCI levels weren't significant. The results of this investigation showed hyperemia, hemorrhage, MNCI, and necrosis were seen in the LICI group. These pathological findings were significantly reduced in LICI+CBD and CBD treatment groups (Figs. 1 and 2).

Immunohistochemically Examination

Bax, Bcl-2, and IL-10 expressions were examined by immunohistochemistry, and the results indicated that the control and CBD groups had significant Bcl-2 and IL-10 expressions but very little or no Bax expression. The LICI group exhibited significantly elevated levels of Bax (Heart: $p\leq0.001$, Aorta: $p\leq0.01$), and significantly decreased levels of Bcl-2 (Heart: $p\leq0.05$, Aorta: $p\leq0.01$) and IL-10 (Heart: $p\leq0.001$, Aorta: $p\leq0.05$) expressions in the aortic endothelium and myocardium. In the LICI+CBD groups, compared to the LICI groups, Bax levels significantly decreased (Heart: $p\leq0.001$, Aorta: $p\leq0.01$), while IL-10 levels were observed to increase significantly (Heart: $p\leq0.01$, Aorta: $p\leq0.05$). There was no significant difference between the Bcl-2 levels of these groups. In the CBD group, Bax levels were found to be significantly lower compared to the damage group ($p\leq0.001$ for both tissues), while Bcl-2 (Heart: $p\leq0.05$, Aorta: $p\leq0.01$) and IL-10 (Heart: $p\leq0.001$, Aorta: $p\leq0.01$) levels were significantly higher. These findings demonstrate that CBD can reduce heart and aortic damage caused by LICI (Figs. 3-6). Immunohistochemical expression of Bax, Bcl-2, and IL-10 was predominantly cytoplasmic.

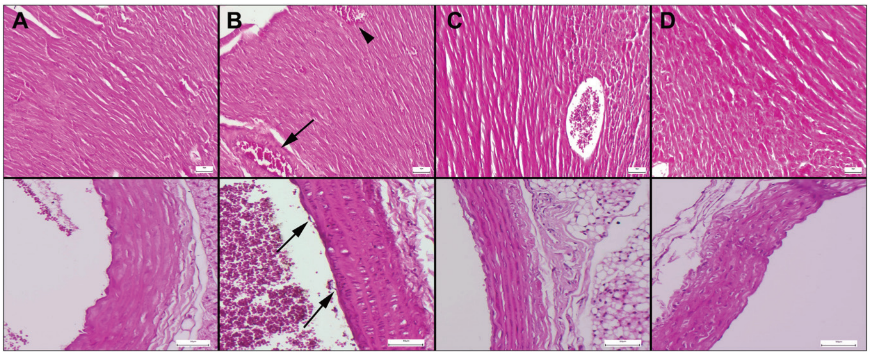

Figure 1

Representative histopathological figures of hearts (upper row) and aorta (below row) sections between the groups. (A) Normal tissue architecture in the control group. (B) Marked hyperemia (arrow) and hemorrhage (arrowhead) in the myocardium and endothelial sloughing in the aortas (arrows) in the LICI group. (C) Decreased pathological findings in the LICI+CBD group (D). Normal in the myocardium and aortic histology in the CBD group, HE, scale bars=50µm.

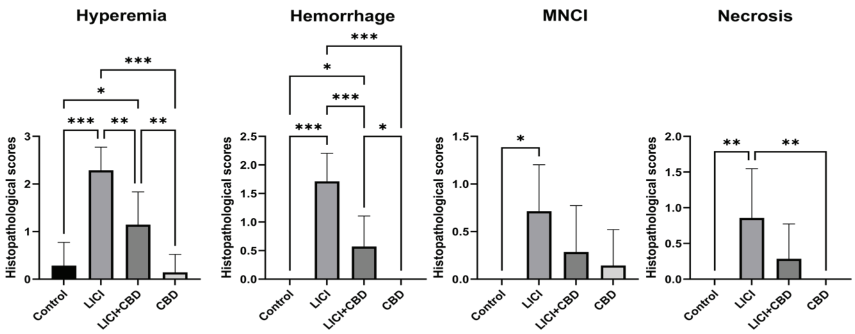

Figure 2

Histopathological appearance of the heart and aorta among the groups.

Values are presented as the mean ± SD. Group comparisons of histopathological scores were conducted using a one-way ANOVA, followed by Tukey's test. MNCI: Mononuclear cell infiltration, LICI: Lung ischemia-reperfusion induced cardiac injury, CBD: Cannabidiol. *p≤0.05, **p≤0.01, ***p≤0.001

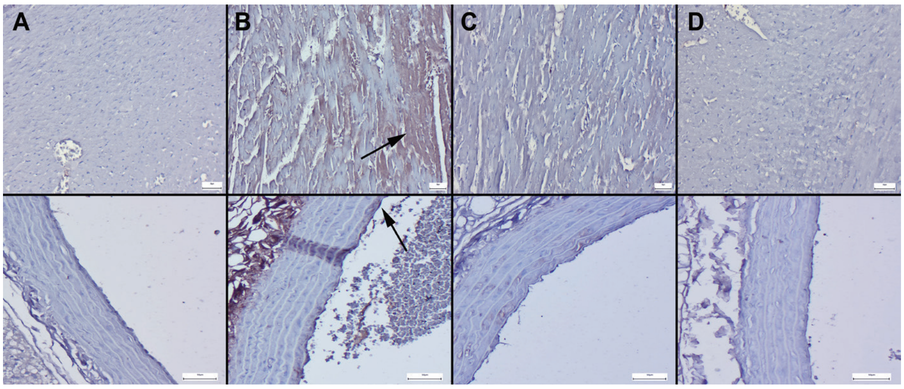

Figure 3

Bax immunohistochemistry findings of hearts (upper row) and aortas (lower row) between the groups. (A) Negative expression in the control group. (B) The marked increase in expression in myocardial and endothelial cells (arrows) in the LICI group. (C) Decreased expression in the LICI+CBD group. (D) Negative expression in both myocardial cells and endothelial cells in the CBD group, Streptavidin biotin peroxidase method, scale bars=50µm.

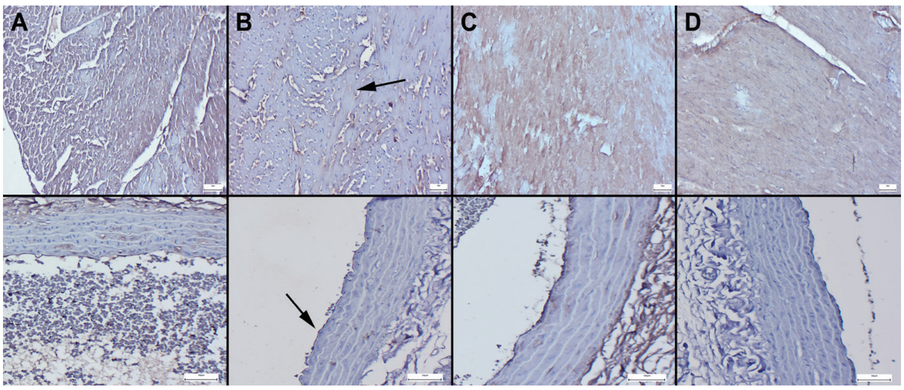

Figure 4

Bcl-2 expression of hearts (upper row) and aortas (lower row) between the groups. (A) Significant expression in the control group. (B) The marked decrease in expressions in both myocardium and endothelial cells (arrows) of the aortas in the LICI group. (C) Increased expressions in the LICI+CBD group. (D) Marked expression in myocardial and endothelial cells in the CBD group, Streptavidin biotin peroxidase method, scale bars=50µm.

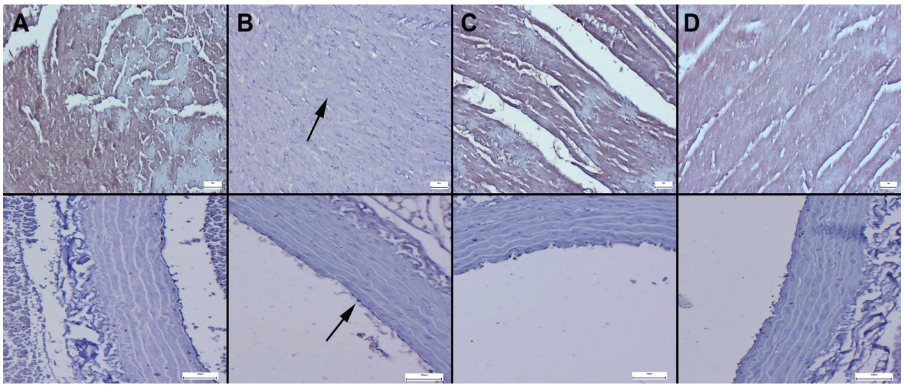

Figure 5

IL-10 immunoexpression of the heart (upper row) and aortas (lower row) between the groups.
(A) Marked expression in the control group. (B) Negative expression in both myocardium and endothelial cells (arrows) in the LICI group. (C) Increased expression in the LICI+CBD group. (D) Marked expression in myocardial and endothelial cells in the CBD group, Streptavidin biotin peroxidase method, scale bars=50µm.

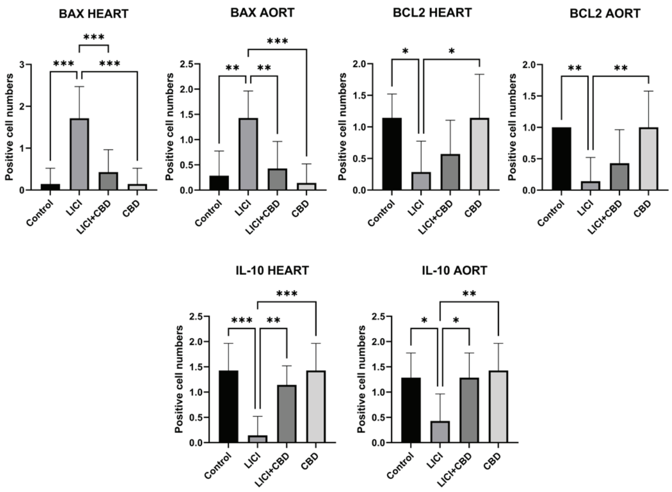

Figure 6

Graphs showing the immunohistochemical appearance of Bax,
Bcl-2, and IL-10 expressions between the groups
Values are presented as the mean ± SD. Group comparisons of immunohistochemical analyses were conducted using a one-way ANOVA, followed by Tukey's test. LICI: Lung ischemia-reperfusion induced cardiac injury, CBD: Cannabidiol, Bax: Bcl-2 associated X protein, Bcl-2: B-cell lymphoma 2, IL-10: Interleukin-10. *p≤0.05, **p≤0.01, ***p≤0.001)

Discussion

This study investigates the molecular mechanisms by which CBD may reduce cardiac injury secondary to lung I/R, specifically through its effects on key apoptotic and inflammatory markers: Bax, Bcl-2, and IL-10. Each of these markers plays a distinct but interconnected role in the cellular response to ischemic injury, where oxidative stress and inflammation often lead to significant tissue damage (11).

Bax and Bcl-2 belong to the Bcl-2 protein family, which tightly regulates the mitochondrial pathway of apoptosis. Bax is a pro-apoptotic protein that, when activated, translocates to the mitochondria, promoting the release of cytochrome c, triggering caspase activation and subsequent cell death. In contrast, Bcl-2 functions as an anti-apoptotic protein, preserving mitochondrial membrane integrity and preventing cytochrome c release (12). The balance between these two proteins, often quantified as the Bax/Bcl-2 ratio, is critical for determining cell fate in response to stressors like I/R injury (13,14).

In this study, lung I/R significantly increased Bax expression in cardiac and aortic tissues while decreasing Bcl-2 expression in the LICI group. This shift, resulting in a higher Bax/Bcl-2 ratio, indicates heightened susceptibility to apoptosis, with myocardial and aortic cells more prone to programmed cell death (15). However, in groups treated with CBD (LICI+CBD and CBD-only), Bax expression decreased significantly while Bcl-2 levels were preserved or elevated. This shift towards a lower Bax/Bcl-2 ratio suggests that CBD's cardioprotective effect may be partly due to its ability to reduce mitochondrial-mediated apoptosis (16,17). By lowering the Bax/Bcl-2 ratio, CBD likely stabilizes mitochondrial membranes, thus reducing cytochrome c release and subsequent activation of caspases that execute cell death.

IL-10 is a potent anti-inflammatory cytokine known for its ability to suppress the expression of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), which are heavily implicated in I/R-related tissue damage. IL-10 achieves this by inhibiting nuclear factor-kappa B signaling, a critical pathway that mediates inflammatory responses following I/R injury (18). Cao et al. have shown that increased IL-10 expression is associated with reduced neutrophil infiltration, lower levels of reactive oxygen species, and mitigated oxidative damage, contributing to improved tissue recovery (19).

In this study, the LICI group exhibited a marked reduction in IL-10 expression, correlating with heightened inflammatory response and significant cardiac and aortic tissue damage. This drop in IL-10 levels aligns with increased inflammatory markers observed in other I/R models, emphasizing IL-10's role in protecting tissues against reperfusion-associated oxidative stress (20). However, treatment with CBD reversed this trend: IL-10 levels significantly increased in both the LICI+CBD and CBD-only groups, suggesting that CBD may exert its anti-inflammatory effects by upregulating IL-10 expression (20,21). This aligns with recent research showing CBD's potential to elevate IL-10 levels and modulate other cytokines in I/R injury and various inflammatory diseases (8, 21, 22).

The concurrent regulation of apoptotic and anti-inflammatory pathways by CBD highlights its therapeutic potential in complex injuries like I/R. In lung I/R, which often triggers secondary damage in organs like the heart, targeting multiple pathways becomes crucial. CBD's dual action-suppressing Bax-driven apoptosis while promoting Bcl-2-mediated cell survival and enhancing IL-10 levels positions it as a versatile therapeutic agent (23). This multifaceted mechanism of action not only preserves cell viability by reducing apoptosis but also dampens the inflammatory response, thereby addressing the primary mechanisms underlying I/R-induced tissue damage. This synergistic effect may have significant implications for the management of lung I/R injury, as well as other conditions involving similar ischemic and inflammatory profiles.

Our results align with Cao and Yang's study, demonstrating CBD's anti-apoptotic and anti-inflammatory effects in other models of I/R injury. For instance, studies on myocardial and hepatic I/R injuries report that CBD reduces infarct size and improves tissue recovery, primarily through modulation of Bax, Bcl-2, and IL-10 pathways (24,25). A study by Xiong et al. shows that CBD can enhance cardiac and hepatic cell survival, reduce apoptosis, and lower inflammatory cytokine levels, highlighting its broad-spectrum protective effects across various tissues (25).

This study has several limitations that should be considered. First, while animal models are invaluable for studying disease mechanisms and potential treatments, differences in physiology and immune response between animals and humans may limit the generalizability of these findings to clinical settings. The specific response to CBD, including pharmacokinetics and bioavailability, can vary across species, and thus, human trials are necessary to confirm these results. Second, the study utilized a relatively short reperfusion time, which may not capture the full extent of CBD's long-term protective effects on cardiac and aortic tissues. Extending the reperfusion duration in future studies could provide a more comprehensive understanding of CBD's therapeutic efficacy over time. Finally, this study focused on a select group of molecular markers, Bax, Bcl-2, and IL-10, while other pathways, such as oxidative stress markers (e.g., MDA, thiol, antioxidant enzymes) and pro-inflammatory cytokines (e.g., TNF-α), were not included. Future studies that integrate these additional markers could yield a more holistic view of CBD's protective mechanisms in lung I/R-induced cardiac injury.

Conclusion

Our findings contribute to the growing body of evidence that CBD offers protective effects in lung I/R-induced cardiac injury by regulating critical apoptotic and inflammatory pathways. By simultaneously reducing pro-apoptotic Bax expression, maintaining anti-apoptotic Bcl-2 levels, and upregulating anti-inflammatory IL-10, CBD emerges as a promising therapeutic approach to mitigate secondary cardiac damage in I/R scenarios. Future research, especially human clinical trials and studies incorporating additional inflammatory and oxidative markers, is necessary to fully elucidate CBD's therapeutic potential in managing ischemic injuries and their systemic impacts.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Ethical Approval

The protocols for Animal Research have been followed for this study: Reporting in Vivo Experiments (ARRIVE) 2.0 at all experiment stages. Permission was obtained from the university's local animal experimentation ethics committee (The number:508). In addition, this research received funding from the Scientific Research Projects Coordination Unit of a Suleyman Demirel University (grant number: TSG-2024-9515).

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Availability of Data and Materials

Data available on request from the authors.

Artificial Intelligence Statement

No artificial intelligence (AI) tools were used in this article.

Authors Contributions

HA: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

TC: Formal analysis; Investigation; Validation; Writing-original draft; Visualization

OBI: Formal analysis; Investigation; Validation; Visualization; Writing-original draft.

OO: Data curation; Formal analysis; Writing- review & editing.

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