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Original Research Article

The effect of carvacrol on lung inflammation of high-fat diet-induced obese male rats

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Abstract

Objective: The beneficial effects of carvacrol (CRV) have been demonstrated in various inflammatory conditions. Considering the inflammatory nature of obesity and associated lung disorders, this study investigated whether CRV could attenuate lung tissue damage induced by a high-fat diet (HFD) in male rats.

Materials and Methods: Twenty-four male Wistar rats (160 ± 10 g) were randomized into three groups (n=8 per group): Control, HFD, and HFD + CRV. Rats in the HFD groups were maintained on a high-fat diet for 12 weeks. In the HFD + CRV group, CRV was administered via intraperitoneal injection (50 mg/kg body weight) every other day during the final 4 weeks of the experimental period. Upon completion, lung tissues were excised. The lung mRNA expression of interleukin (*IL)-10, IL-6, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), tumor necrosis factor (TNF)-α* and *IL-1β* was quantified by real-time qPCR. Additionally, TNF-α protein concentrations in bronchoalveolar lavage fluid (BALF) were determined using an ELISA kit.

Results: Histopathological analysis revealed significant pulmonary damage in the HFD group compared to the control group. This damage was associated with the upregulation of *IL-1β, IL-6, TNF-α, VCAM-1*, and *ICAM-1* gene expression, alongside concurrent suppression of IL-*10*. Treatment with CRV significantly attenuated these histological changes and modulated the inflammatory markers.

Conclusion: The modulation of the inflammatory cascade by CRV likely contributes to its observed efficacy in preventing HFD-triggered lung tissue damage, as evidenced by the present findings.

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Introduction

Since 1975, the global prevalence of obesity has surged nearly threefold, with the number of affected individuals exceeding one billion by 2022. This epidemic presents critical socioeconomic implications for public health systems worldwide. Additionally, epidemiological forecasts point to an alarming trajectory, with expectations that over half of the global adult population will suffer from overweight or obesity by 2050 (Ahmed and Mohammed, 2025). Obesity gives rise to a wide spectrum of systemic complications that contribute to structural and functional impairments in multiple organs. These complications arise not only from excessive adipose tissue accumulation but also from the dysregulated secretion of adipocytes and pro-inflammatory cytokines by dysfunctional adipocytes (Aslani et al. 2017). Evidence suggests that obesity extends its pathological reach through a gut-origin pathway; by altering microbial composition and increasing intestinal permeability, obesity allows for the translocation of bacterial products such as lipopolysaccharide (LPS), into the systemic circulation. This process fosters chronic, low-grade inflammation that serves as a critical bridge to the multi-organ damage typically observed in obese subjects (Aslani et al. 2020; Babapour et al. 2021). The respiratory system exhibits a marked vulnerability to the inflammatory environment induced by obesity, which manifests through architectural remodeling, oxidative damage, and an excessive influx of both inflammatory cells and cytokines (Rezaei et al. 2023).

As a result, obesity increases the risk of several respiratory disorders (Koenig, 2001). As a naturally derived phenolic monoterpene, carvacrol (CRV) is prevalent in several aromatic plant species, most notably black cumin, oregano, sweet basil, thyme, and savory (Ahmadi et al. 2025; Bakour et al. 2024). The protective effects of CRV are largely attributed to its ability to modulate pivotal inflammatory signaling cascades—particularly the *TGF-β/Smad, MAPK/ERK*, and *PI3K/Akt/NF-κB* pathways—while concurrently reinforcing endogenous antioxidant defenses. Through these mechanisms, CRV attenuates the release of pro-inflammatory cytokines, thereby dampening the inflammatory response and limiting tissue damage (Mohammadzadeh et al. 2025; Dinanti et al. 2026; Pandi et al. 2026; Nazdikbin Yamchi et al. 2024). Given that obesity-linked pulmonary injury is largely driven by aberrant inflammatory signaling, agents possessing both anti-inflammatory and antioxidant activities, such as CRV, emerge as promising therapeutic candidates. Although CRV has gained recognition for its efficacy in various inflammatory respiratory conditions, its potential to counteract obesity-induced pulmonary inflammation remains largely uninvestigated. We hypothesized that CRV administration could mitigate high-fat diet (HFD)-provoked lung inflammation and histopathological damage by modulating inflammatory pathways and suppressing cytokine release.

Therefore, the present study aimed to investigate the ameliorative potential of CRV against HFD-induced pulmonary injury in male rats. To this end, we employed comprehensive histopathological evaluations, quantified mRNA transcript levels of key inflammatory markers (*IL-10, IL-6, ICAM-1, VCAM-1*, and *IL-1β*), and measured *TNF-α* protein concentrations within the bronchoalveolar lavage fluid (BALF).

Materials and Methods

Animals

All interventions involving animals were carried out following approval from the TBZMED ethics committee (IR.TBZMED.VCR.REC.1399.199).

Twenty-four male Wistar rats (150–170 g) were procured from the university's central animal facility. The animals were housed in standard laboratory cages (four per cage)

under controlled environmental conditions (12-hr light/dark cycle, a temperature of 20–24°C, and a relative humidity of 50–60%) .

Experimental design

Animals were randomly assigned to three experimental groups (n = 8/group; Figure 1). The Control group received a standard chow diet (11% fat, 22% protein, and 67% carbohydrates). The HFD group was fed a high-fat diet (32% fat, 48% carbohydrates, and 20% protein) for 12 weeks (Ahmadi et al. 2025; Bayazidi et al. 2022), sourced from Behparvar Co. (Tehran, Iran). The HFD + CRV group followed the same HFD regimen for 12 weeks and was concurrently treated with intraperitoneal (i.p.) carvacrol (50 mg/kg body weight) every other day during the final 4 weeks of the study. CRV was dissolved in a 1:5 (v/v) ethanol-saline solution (Nazdikbin Yamchi et al. 2024). After 12 weeks, the animals were euthanized via an intraperitoneal injection of ketamine (75 mg/kg) and xylazine (3 mg/kg) (Bayazidi et al. 2022). No fasting period was implemented prior to euthanasia, as the study did not include fasting-dependent metabolic assessments, such as blood glucose, insulin, or lipid profile measurements.

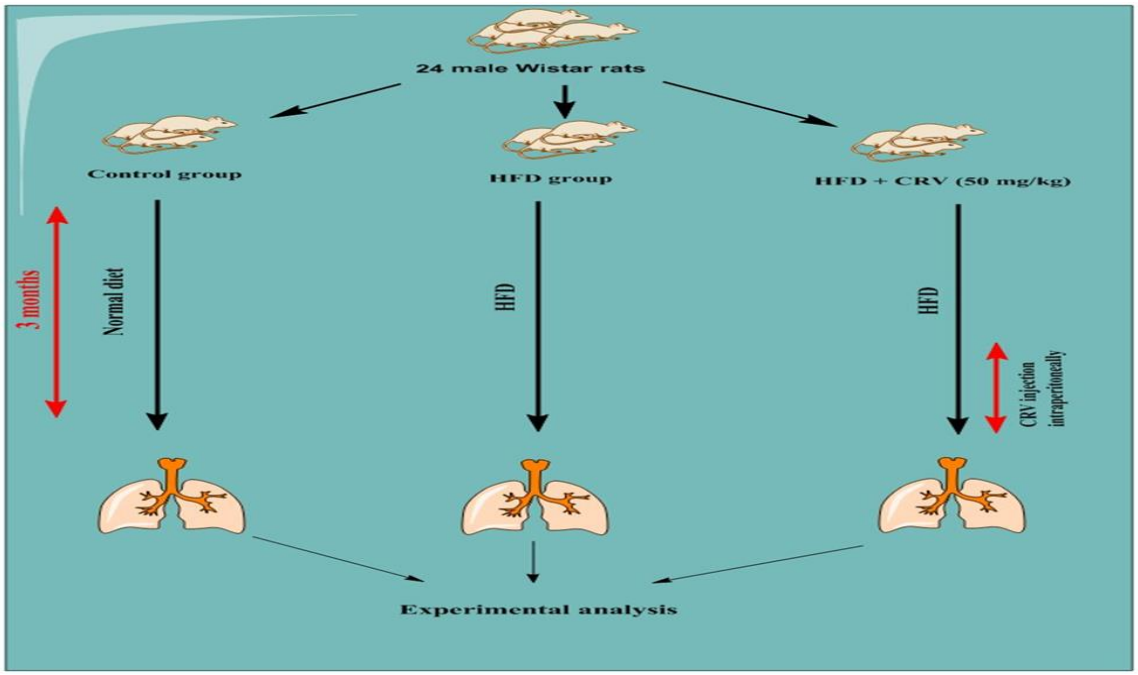


Figure 1. A schematic illustration of the study design

BALF collection

Following euthanasia, the lungs were partitioned: the right lung was dedicated to bronchoalveolar lavage fluid (BALF) collection, while the left lung was preserved for histopathological and gene expression analyses. For BALF retrieval, the trachea was cannulated and the right main bronchus was isolated. Three consecutive 1-mL aliquots of sterile normal saline (total volume: 3 mL) were instilled into the right lung and gently aspirated after each instillation. Following centrifugation, the supernatant was collected and stored at −80°C for future assays (Hassanzadeh-Khanmiri et al. 2024)

Histopathological changes

For histopathological assessment, tissue samples were excised from the lower lobe of the left lung and fixed in 10% neutral buffered formalin (Merck, Germany) . Following standard histological processing—involving dehydration in graded ethanol, clearing in xylene, and paraffin embedding— Sections of 4–5 µm

thickness were prepared from the paraffin-embedded tissues. The sections were stained with hematoxylin and eosin (H&E) and evaluated by a pathologist, using a light microscope (BX41; Olympus, Japan) (Hassanzadeh-Khanmiri et al. 2024). As no semiquantitative scoring system was employed, the histopathological findings are reported descriptively.

Gene expression analysis (qRT-PCR)

To this end, total RNA was extracted from the upper lobe of the left lung using the YTA total RNA extraction kit. The extracted RNA was subsequently converted into cDNA using a cDNA synthesis kit. Each resulting cDNA was utilized as a template for individual mRNA quantitative RT-PCR assays, employing the SYBR Green master mix (Cat No. YT2551, Iran). Expression levels of the target genes were normalized to β-actin as the reference gene, and relative fold changes were calculated using the $2^{-\Delta\Delta CT}$ method (Alaa et al. 2024). The primers were designed using Oligo 7 software (version 7.60) and are detailed in Table 1.

Table 1. The list of primers used for real-time PCR analysis

Gene	*Primer sequence (5'-3')*	
	Forward	Reverse
IL-6	*TCCTACCCCAACTTCCAATGCTC*	*TTGGATGGTCTTGGTCCTTAGCC*
TNF-α	*GACCCTCACACTCAGATCATCTTCT*	*TGCTACGACGTGGGCTACG*
ICAM-1	*GTGTGTGAAGGAGTGAATCTG*	*CCAACAGCAGCACATGTCAGA*
VCAM-1	*GTGTGTGAAGGAGTGAATCTG*	*CCAACAGCAGCACATGTCAGA*
IL-10	*TGAGAATAAAAGCAAGGCAGTGG*	*GTAGGCTTCTATGCAGTTGATGA*
IL-1β	*TGGACCTTCCAGGATGAGGACA*	*GTTCATCTCGGAGCCTGTAGTG*
β-actin	*TCCCTGGAGAAGAGCTACG*	*GTAGTTTCGTGGATGCCACA*

BALF TNF-α quantification (ELISA)

TNF-α levels in the BALF were determined using a rat ELISA kit, strictly following the manufacturer's protocols (Bayazidi et al. 2022; Atefipour et al. 2026).

Statistical analysis

The Shapiro–Wilk test was initially employed to verify data normality. Following confirmation of a normal distribution, inter-group differences were evaluated using one-way analysis of variance (ANOVA), supplemented by the Tukey–Kramer post hoc test. Data are expressed as mean ± SEM, with statistical significance defined at $p<0.05$.

Results

Pulmonary pathological changes occurred under prolonged HFD conditions

Compared to control group, lung tissue from HFD and HFD + CRV groups exhibited evidence of alveolar hemorrhage and mild interstitial pneumonitis, as denoted by red and black arrows, respectively. However, these diet-associated histopathological changes were significantly mitigated following CRV administration (Figure 2).

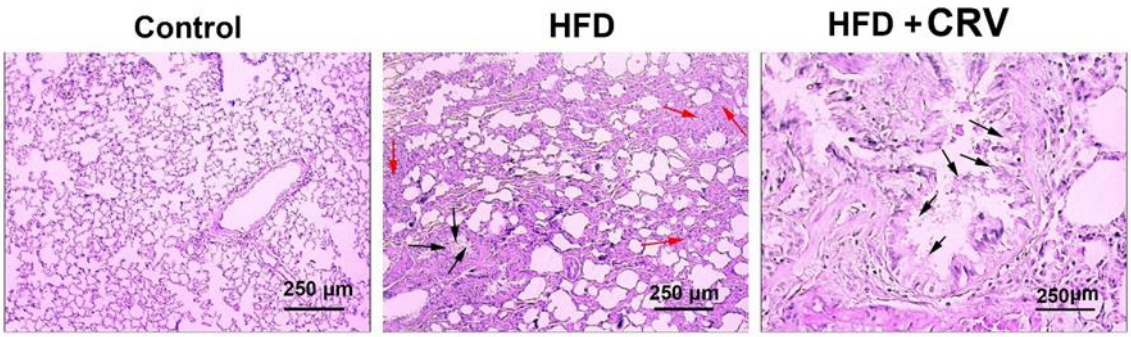


Figure 2. Bright-field images from lung tissue sections stained with H&E solution. Microscopic imaging showed a mild interstitial pneumonitis (Black arrows) and alveolar hemorrhage (Red rows) appearance in the lungs of HFD rats compared to the control group but CRV enhanced the histopathological alterations in lung tissue compared to the HFD group. Magnification *250 µm.*

Administration of CRV led to a significant downregulation of *ICAM-1 and VCAM-1* expression in HFD-fed rats

Analysis of *ICAM-1* and *VCAM-1* expression revealed a significant upregulation in the lung parenchyma of group HFD and HFD + CRV groups compared to the healthy group ($p<0.001$). In contrast, administration of CRV mitigated these molecular changes, resulting in a significant reduction in the expression of both adhesion molecules relative to the untreated HFD group ($p<0.05$) (Figure 3a, b).

Carvacrol modulates pulmonary mRNA expression of *IL-6, IL-10, TNF-α* and *IL-1β* in HFD-fed rats

The mRNA expression levels of *IL-1β, IL-6, TNF-α* and *IL-10* were significantly altered in the HFD and HFD + CRV groups compared to the control rats ($p<0.001$). Specifically, HFD induction led to a marked upregulation of pro-inflammatory cytokines (*IL-6* and *IL-1β*) and a concomitant decrease in the anti-inflammatory cytokine *IL-10*. Conversely, CRV administration significantly reversed these trends, resulting in the upregulation of *IL-10* and the downregulation of *IL-1β* and IL-6 expression relative to the untreated HFD group ($p<0.05$) (Figure 4a–d).

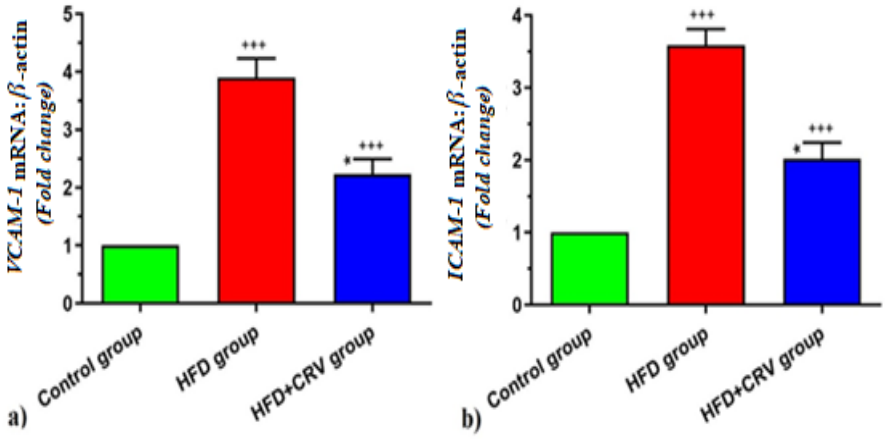


Figure 3. Real-time analysis of *VCAM-1*(a) and *ICAM-1*(b) expressions in the tissues of control, HFD and HFD + CRV groups (n = 6). Bars represent the mean ± SEM. Statistical differences between control and HFD groups: +++; $p<0.001$. Statistical differences between HFD group and HFD +CRV group: *; $p<0.05$.

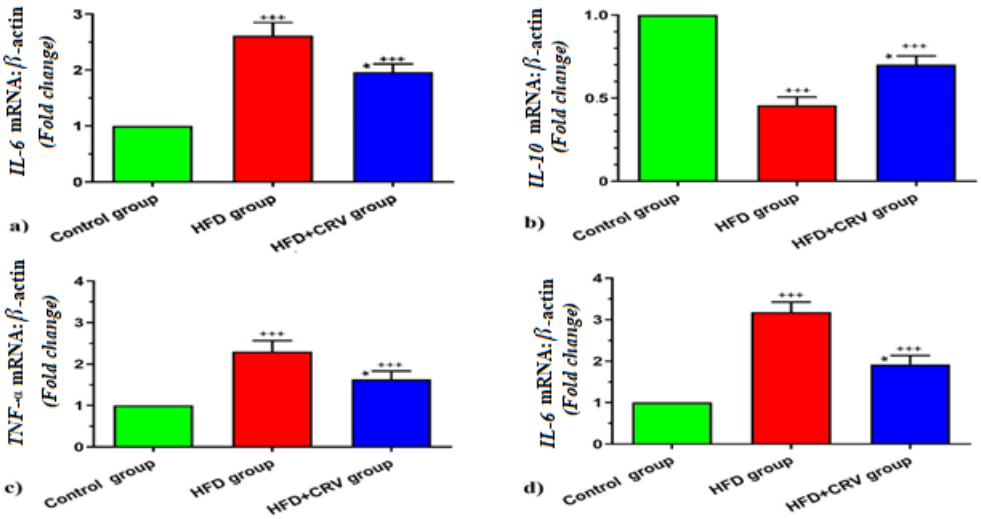


Figure 4. Measuring the transcription of *IL-1β* (a), *IL-10* (b), *TNF-α* (c) and *IL-6* (d) mRNA in the lung tissues of control, HFD and HFD + CRV groups (n = 6). Bars represent the mean ± SEM. Statistical differences between control and HFD groups: +++; p<0.001. Statistical differences between HFD group and HFD +CRV group: *; p<0.05.

HFD condition raised the BALF level of TNF-α

ELISA analysis revealed a significant elevation in *TNF-α* levels within the BALF of group HFD and HFD + CRV groups compared to the control group (p<0.001). Notably, CRV administration significantly attenuated this increase, resulting in markedly lower *TNF-α* concentrations in the HFD+CRV group relative to the untreated HFD group (p<0.05) (Figure 5).

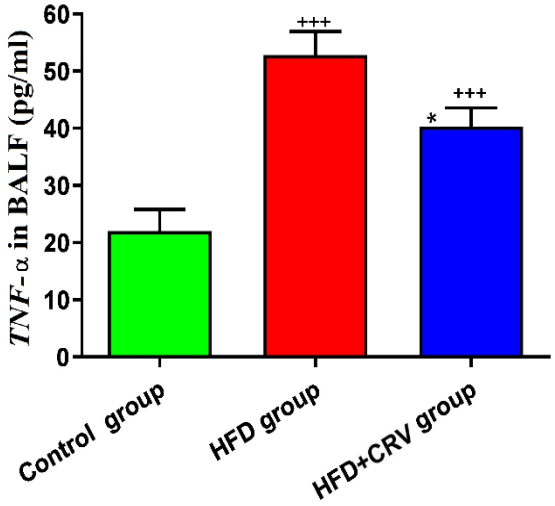


Figure 5. *TNF-α* levels in BALF in the lung tissues of control, HFD and HFD + CRV groups (n = 6). Bars represent the mean ± SEM. Statistical differences between control and HFD groups: +++; p<0.001. Statistical differences between HFD group and HFD +CRV group: *; p<0.05.

Discussion

High-fat diet (HFD) feeding is a well-established model for inducing obesity and investigating its pathophysiological consequences in various tissues (Ahmadi et al. 2025; Akhavanakbari et al. 2019). Our findings demonstrate that HFD-induced obesity exacerbated pathological damage and upregulated the mRNA expression of *IL-1β, VCAM-1, ICAM-1, TNF-α* and *IL-6* in lung tissue, while concurrently suppressing *IL-10* gene expression. Furthermore, ELISA analysis confirmed significantly higher *TNF-α* protein concentrations in the BALF of the HFD group compared to control rats. These findings corroborate existing literature demonstrating that obesity promotes pulmonary inflammation through both morphological damage and the upregulation of pro-inflammatory mediators. Collectively, these data underscore the high susceptibility of pulmonary tissue to systemic inflammatory dysregulation (Hancox 2016; Shoaran 2023; Zammit 2010). It is well-established in the literature that a HFD elevates inflammatory mediators within both lung tissue and BALF, which are critical in orchestrating the inflammatory response

observed in obesity (Shoaran et al. 2023). We observed a marked downregulation of pulmonary IL-10 mRNA in the HFD group. Consistent with the observations of Kondo et al. (2018), this result suggests that reduced IL-10 expression exacerbates airway inflammation by impairing its capacity to suppress pro-inflammatory cytokine release. This anti-inflammatory deficit likely potentiates airway inflammation in synergy with the upregulation of adhesion molecules; notably, Consistent with previous findings, we observed a significant upregulation of *ICAM-1*, *VCAM-1* within lung tissues. (Taghizadeh et al. 2022). As these molecules are essential for leukocyte recruitment and known to be induced by *TNF-α* and other pro-inflammatory mediators, their upregulation indicates an active influx of inflammatory cells into the pulmonary microenvironment (Kim et al. 2008; Taghizadeh et al. 2022). These results underscore how obesity-driven systemic inflammation and lung vascularity converge to drive profound pulmonary pathology and dysfunction, warranting further study into the mechanistic drivers of these severe outcomes (Shoaran et al. 2023). CRV exerts potent anti-inflammatory effects, as established in recent research (Khosravi et al. 2024; Mohammadi Mahjoob et al. 2024; Khazdair et al. 2024). Our findings demonstrate that CRV mitigates obesity-related lung injury, characterized by a decrease in *TNF-α* secretion within the BALF and a concomitant reduction in the transcriptional expression of *IL-6*, *ICAM-1*, *VCAM-1*, *TNF-α* and *IL-1β*. Furthermore, the capacity of CRV to restore *IL-10* expression suggests a protective, immunomodulatory role. These results corroborate previous reports that CRV modulates key pro-inflammatory pathways, such as *TGF-β/Smad, MAPK/ERK* and *PI3K/Akt/NF-κB* pathways, while simultaneously enhancing the pulmonary antioxidant milieu (Barnwal et al. 2018; Feng and Jia, 2014; Mousavi et al. 2020; Ozer et al. 2017; Memarzia et al. 2024). An important question raised by the present findings is whether the attenuation of HFD-induced pulmonary inflammation by CRV is mediated directly within the lung or arises secondarily from systemic metabolic or lipid-lowering actions. Carvacrol exhibits well-established direct anti-inflammatory capabilities, notably through the inhibition of *NF-κB* signaling pathways and the suppression of pro-inflammatory cytokine expression in both macrophages and airway epithelial cells. Conversely, systemic disturbances associated with HFD—including hyperlipidemia, insulin resistance, and adipose-derived inflammatory mediators—may serve as additional drivers of pulmonary inflammation. In this regard, CRV has previously been shown to ameliorate HFD-induced weight gain, visceral adiposity, and dyslipidemia (Ahmadi et al., 2025; Cho et al., 2012), suggesting a potential systemic pathway through which its pulmonary effects may be exerted. As body weight, food intake, and systemic metabolic parameters were not assessed in the present study, the relative contributions of direct pulmonary anti-inflammatory effects versus indirect metabolic mechanisms cannot be fully delineated. It is probable that both pathways contribute to the observed protection. Future investigations employing metabolic phenotyping, such as pathway-specific inhibition or pair-feeding protocols, are warranted to quantitatively differentiate these mechanisms. While our results provide insights into the effects of CRV in this specific model, several limitations should be acknowledged. First, this study utilized a single dosage; therefore, the dose-response relationship remains to be fully elucidated. Second, we did not evaluate the long-term persistence of these effects following the cessation of CRV administration. Future research involving multiple dose regimens and longitudinal studies is necessary to determine the sustained modulatory effects of CRV (Pashmforosh et al. 2025; Imran et

al. 2022). Notwithstanding these limitations regarding dose-response evaluation and systemic metabolic monitoring, our findings highlight a potential pulmonary protective role of CRV against obesity-driven inflammation. The observed attenuation of inflammatory mediators and adhesion molecules suggests that CRV may mitigate lung injury through the modulation of key molecular pathways, providing a foundational basis for further investigation into its role in managing the respiratory manifestations of obesity.

Given that CRV has been reported to attenuate HFD-induced weight gain, visceral adiposity, and dyslipidemia (Ahmadi et al. 2025; Cho et al. 2012), indirect systemic contributions cannot be discounted. Since body weight, food intake, and metabolic parameters were not evaluated in the current study, the relative contribution of direct versus indirect mechanisms remains to be fully elucidated; it is likely that a synergistic interplay between both pathways confers the observed protection. Future research utilizing comprehensive metabolic phenotyping, such as pathway-specific inhibition or pair-feeding protocols, is warranted to quantitatively delineate these effects

Overall, the present study demonstrates that CRV effectively attenuates obesity-induced pulmonary inflammation and histopathological injury by modulating key inflammatory cytokines and adhesion molecules. These findings highlight the potential of CRV to alleviate respiratory complications associated with obesity. While the current results provide a mechanistic basis for these observations, further research is warranted to characterize the dose-response profile and evaluate the long-term efficacy and persistence of these effects in diverse experimental model. Such investigations will be essential to elucidate the therapeutic role of CRV in managing obesity-related respiratory issues.

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Conflicts of interest
The authors have declared that there is no conflict of interest.

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Ethical Considerations
The Local Ethics Committee approved this study of Tabriz University of Medical Sciences

Code of Ethics
IR.TBZMED.VCR.REC.1399.199).

Authors' Contributions
JR, RA, YK and MA: Literature search, Proposal writing, Data collection, Analysis of data, Interpretation of data, Manuscript preparation, Review of manuscript.
HS, RMH, MRA, AASH, and AD: Data collection, Interpretation of data, Manuscript preparation, Review of manuscript.

Abbreviations
BALF: bronchoalveolar lavage fluid, CRV: carvacrol, ERK: extracellular-signal-regulated kinase, HFD: high-fat diet, ICAM-1: intercellular adhesion molecule 1, IL: interleukin, LPS: lipopolysaccharide, MAPK: mitogen-activated protein kinase, NF-κB: nuclear factor kappa B, PI3K/Akt: phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), TGF-β/ Smad: Transforming growth factor-beta superfamily member, TNF- α: tumor necrosis factor alpha, VCAM-1: vascular cell adhesion molecule 1

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