BMC Pulmonary Medicine

RESEARCH

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The effect of bempedoic acid on histopathologic changes associated with natural aging in rat lungs

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Abstract

Background The process of aging is characterized by a series of physiological, cellular, and immunological changes in tissues. Bempedoic acid is an antioxidant, anti-inflammatory, and cholesterol-lowering drug that does not belong to the statin class. The objective of this study was to assess the impact of bempedoic acid on age-related histopathological alterations in rat lungs.

Methods A total of 40 Wistar-Albino male rats (275–357 g) were included in the study, with 10 rats in each experimental group [Young control (YC), Young + Bempedoic acid (YD), Elderly control (EC), Elderly + Bempedoic acid (ED)]. Bempedoic acid (30 mg/kg/day) was administered orally for one month. The rats were housed under controlled conditions to minimize external stressors. The Geropathological Grading System (GGP) was used to standardize the evaluation of age-related findings in the lungs. Some lesions were classified as either present or absent, whereas others were evaluated on a scale of 0–4 according to their severity. Composite lesion scores were calculated for each rat. Additionally, the presence and severity of emphysema in the rat lungs were recorded.

Results Although the median composite lesion score was higher in the elderly groups, the difference was not statistically significant ($p = 0.7$). The distribution of cells associated with passive congestion, heart failure, and atelectasis was higher in the elderly drug group ($p = 0.024$ and $p = 0.015$, respectively). The prevalence of perivascular inflammation was significantly higher in the elderly control group compared to the other groups. Moreover, no cases of moderate-to-severe perivascular inflammation were observed in the elderly drug group ($p = 0.019$). The prevalence of severe emphysema was higher in the elderly control group compared to the other groups, whereas no cases of severe emphysema were observed in the elderly drug group ($p = 0.044$).

Conclusion It is hypothesized that statins, a class of antihyperlipidemic drugs, exert a protective effect against aging due to their ability to correct oxidative damage. Similarly, bempedoic acid's effect on fat oxidation and cholesterol metabolism may be associated with its protective role in the lungs.

Keywords Bempedoic acid, Antiaging, Lung, Histopathological

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Introduction

Aging can be defined as a progressive and widespread dysfunction that leads to a decline in stress adaptation responses and an increased risk of age-related diseases. The global population is aging rapidly, and with advancing age, physiological functions are negatively affected, resulting in various pathologies in multiple organs.

Aging results from damage to cells and tissues over time. This damage begins in the early stages of life and continues throughout the lifespan. With aging, degenerative changes that are characteristic of natural aging at both the cellular and organ levels (shorter telomeres, increased expression of cellular aging markers, increased DNA damage, oxidative stress, and apoptosis) reach pathological levels. These changes contribute to impaired stress adaptation responses, higher risk of age-related diseases, and increased mortality rates. Physiological, cellular, and immunological alterations associated with aging play key roles in the development of various lung diseases. Notably, lung aging is strongly linked to the onset and progression of chronic pulmonary diseases including chronic obstructive pulmonary disease (COPD), lung cancer, and idiopathic pulmonary fibrosis [1]. With age, the number of alveoli and alveolocapillary surface area decreases, leading to development of senile emphysema. In recent years, age-related changes in lung tissue have become a significant research focus [2].

Bempedoic acid (ETC-1002, 8-hydroxy-2,2,14,14 tetramethyl-penta-decanedioic acid) is a non-statin drug with cholesterol-lowering properties. It is well absorbed orally, reaches its maximum plasma concentration in 3.5 h and is administered once a day due to its long half-life of approximately (-21 h-) [3]. It has been used effectively to lower low-density lipoprotein (LDL) cholesterol in patients with heterozygous familial hypercholesterolemia who do not achieve sufficient LDL reduction with ezetimibe + statins alone. Bempedoic acid inhibits cholesterol and fatty acid synthesis by suppressing the enzyme adenosine triphosphate (ATP)-citrate lyase (ACL) and activating adenosine monophosphate (AMP)-activated protein kinase (AMPK) [4]. Studies have shown that it can reduce plasma triglyceride levels (up to 64%) and, total cholesterol concentrations (up to 50%), and improve glucose tolerance. In the liver, bempedoic acid decreases cholesterol and triglyceride levels by increasing fatty acid oxidation and by inhibiting fatty acid synthesis. Hepatic gene expression analyses indicate that it suppresses the expression of inflammatory genes involved in lipid metabolism and significantly upregulates genes related to fatty acid oxidation [5, 6]. Additionally, bempedoic acid has been reported to reduce the risk of major cardiovascular events and non-fatal myocardial infarction, attenuate the expression of pro-inflammatory genes in the aortic tissue, and reduce the i-NOS/Arg1 ratio [7]. As a collective effect, it has been shown to cause weight loss and improve the lipid profile.

Previous studies have demonstrated that statins, a class of cholesterol-lowering drugs, possess antioxidant and anti-inflammatory properties, in addition to their lipid-lowering effects. Statins have been suggested to exert protective effects against aging by mitigating oxidative damage [8, 9]. Similarly, various studies have shown that bempedoic acid reduces systemic inflammation [10, 11]. Therefore, its influence on fatty acid oxidation and the cholesterol cascade, both crucial pathways in the body, may also play a role in its protective effects in the lungs. A clearer understanding of these mechanisms could provide valuable insights into the preventive potential of bempedoic acid against oxidative stress, cellular destruction, atherosclerosis, and pulmonary conditions such as pulmonary hypertension and fibrosis.

This study aimed to evaluate whether bempedoic acid exerts a protective effect against aging and age-related pathologies, based on histopathological findings in the lungs.

Material and method

Ethical approval

The experimental protocol was conducted in accordance with the European Communities Council Directive November 24, 1986 (86/609/EEC- Official Journal of the European Communities), the Guide for the Care and Use of Laboratory Animals (8th Edition, 2011), and the relevant regulations of the Scientific and Technological Research Council of Turkey. The study protocol was reviewed and approved by the Local Ethics Committee of Experimental Animal Studies at Kocaeli University (Approval No: KOU HADYEK 11/3-2023; date: 26-12-2023). This study complied with the ARRIVE guidelines for reporting animal experiments.

Study design

A total of 40 male Wistar Albino rats (275–350 g), 10 in each group, were obtained from the Experimental Medicine Research Unit of Kocaeli University and assigned to one of four groups [Young control (YC), young + drug (bempedoic acid) (YD), elderly control (EC), and elderly drug (bempedoic acid) (ED)].

This prospective study was conducted over a six-month period, from December 2023 to May 2024. Rats aged 4–6 months were used for the young animal groups, while naturally aged rats older than 24 months were used for the elderly groups. Bempedoic acid was administered to the drug-treated at a dose of 30 mg/kg/day for one month.

Housing and environmental conditions

Rats were housed in controlled laboratory environments under standard conditions: temperature (22 ± 2 °C), humidity (45%), and a 12-hour light/dark cycle (lights on from 07:00 AM to 07:00 PM). They were fed standard laboratory chow and provided water ad libitum. To prevent social isolation-induced stress, cages were arranged to allow interactions between animals. Stress-inducing methods such as gavage were avoided. Instead, bempedoic acid (30 mg/kg) was dissolved in the drinking water of the treatment groups to ensure consistent daily administration.

Lung collection and Preparation

At the end of the study, the animals were anesthetized with intraperitoneal injection of ketamine (90 mg/kg, Ketalar®; Pfizer, Istanbul, Turkey) and xylazine (10 mg/kg, Xylazin Bio®; Bioteva, Czech Republic). Euthanasia was carried out using a lethal dose of sodium thiopental (Pentothal® Sodium; Abbott Laboratories, Italy). Following a median sternotomy, the lungs were harvested and rinsed with 0.9% saline for further examination.

Histological examination

A blinded pathologist scored both the right and left lungs and the average of these scores was recorded as the lesion score. For morphological evaluation, lung tissues were fixed in 10% formalin, embedded in paraffin, sectioned at a thickness of 4 µm, and stained with hematoxylin and eosin (H&E).

Geropathology grading platform (GGP)

To date, studies of agents aimed at slowing aging in mice and humans have primarily measured the lifespan. However, this method is costly and time consuming. Therefore, new endpoints and methods are required for preclinical testing and screening of therapeutics designed for slow aging. To address this need, a new scoring system called the geropathological grading platform has been developed [12, 13].

GGP is a reliable scoring system used to assess the presence and severity of age-related lesions in the heart, lungs, liver, and kidneys, particularly in animal aging studies [12]. Specific lesions were defined in each organ. Some specific lesions were scored as either present or absent (0–1), while others were graded on a scale from 0 to 4 based on the severity of the lesion (0 = absent, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe). The total score of specific lesions identified in each organ was calculated using the composite lesion score (CLS). Lung-specific lesions included acidophilic alveolar macrophage pneumonia, alveolar histiocytosis, foam cells, heart failure cells (chronic passive congestion), interstitial pneumonia, perivascular inflammation, bronchial/bronchiolar inflammation, airway metaplasia or hyperplasia, vascular hypertrophy, pulmonary fibrosis, atelectasis, lymphoid aggregates (peribronchiolar, perivascular, and/or pleural/subpleural), and tumors. In this study, a geropathology grading platform was used to evaluate age-related findings in the lungs in a standardized manner. The composite lesion score was calculated for each rat and the presence and extent of emphysema in the rat lungs were recorded.

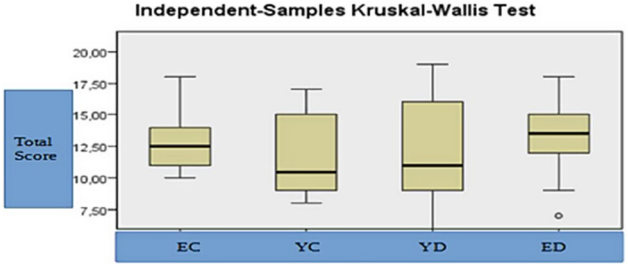

Fig. 1 Distribution of Geropathologic Grading System (GGP) composite lesion score according to groups

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 (SPSS, Chicago, IL, USA). Categorical variables were expressed as numbers (percentages) and continuous variables as median (25th -75th percentiles). The chi-square test was used for intergroup comparisons of categorical variables. Comparisons of GGP lung-specific pathologic lesions and median composite lesion scores between the groups were assessed using the Kruskal-Wallis test, and a two-sided p-value < 0.05 was considered statistically significant.

Results

The comparison of pathological features between the groups revealed significant differences in terms of heart failure cells, perivascular inflammation, airway metaplasia, hyperplasia, and atelectasis. Although the median composite lesion score was higher in the elderly groups according to GGP, the difference was not statistically significant (YC: 10.5; YD: 11; EC: 12.5; ED: 13.5; $p = 0.7$) (Fig. 1) (Table 1).

Among the GGP scoring parameters, heart failure cell distribution related to passive congestion and atelectasis were found to be higher in the ED group ($p = 0.024$ and $p = 0.015$, respectively) (Fig. 2).

Perivascular inflammation was significantly higher in the EC group compared to the other groups; moderate and severe perivascular inflammation were not observed in the ED group ($p = 0.019$) (Figs. 3 and 4).

A significant difference in the prevalence of emphysema was observed between groups. The prevalence of severe emphysema was higher in the elderly control

Table 1 Comparison of histopathological findings between groups according to GGP

	YC	YD	EC	ED	*P*
Alveolar acidophilic macrophage pneumonia	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	1
Alveolar histiocytosis	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	1
Foamy cells	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	1
Heart failure cell	0 (0–1)	0 (0–0)	0 (0–0,25)	1 (0–2,25)	**0,024**
Interstitial pneumonia	2 (1,75 – 3)	2 (2–3)	2 (2–2,25)	1,5 (1–2)	0,1
Perivascular inflammation	1(1–1,25)	1 (1–2)	2 (1,75 – 3)	2 (1–2)	**0,019**
Bronchial/bronchiolar inflammation	2 (2–3)	2 (1–3)	2 (1,75 – 3)	2,5 (1,75 – 3)	0,95
Airway metaplasia and hyperplasia	1 (1–1)	1 (1–1,25)	1,5 (1–2)	1 (1–1)	**0,036**
Vascular hypertrophy	1 (0,75 – 2)	1 (1–3)	1 (0–2)	1 (0–1,25)	0,29
Pulmonary fibrosis	1 (1–2)	1,5 (1–2)	1 (1–1,25)	1 (1–2)	0,79
Atelectasis	0 (0–0)	0 (0–0,25)	0 (0–0)	1 (0–1)	**0,017**
Lymphoid aggregates	2 (2–3)	1 (1–3)	1,5 (1–3)	2,5 (1,75 – 3)	0,31
Tumor	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	1
Composite lesion score	10,5 (9–15,5)	11 (8,75 – 16,5)	12,5 (11–15)	13,5 (11,25 – 15,25)	0,704

Abbreviations: YC: Young Control; YD: Young + Drug; EC: Elderly Control; ED: Elderly + Drug

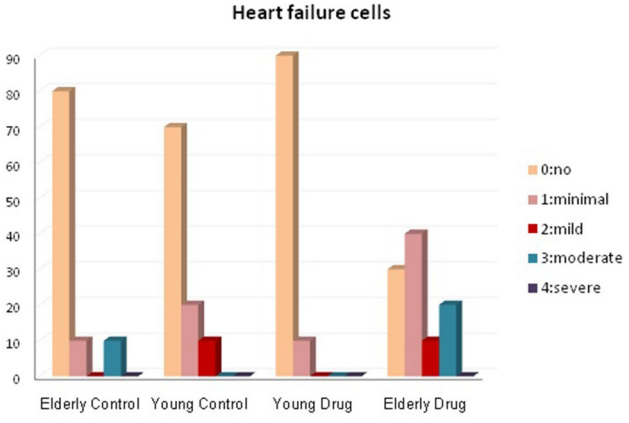

Fig. 2 Distribution of heart failure cells among groups

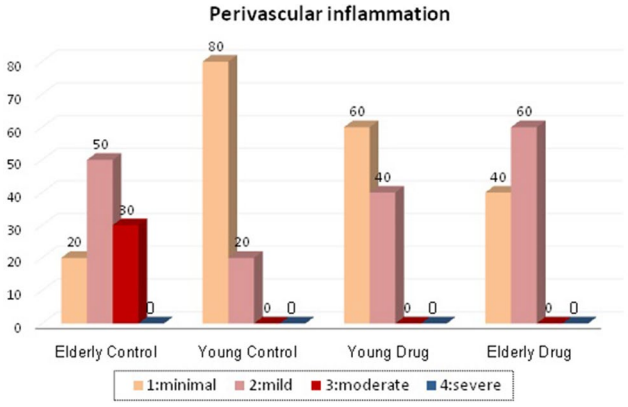

Fig. 3 Comparison of perivascular inflammation between groups

group than in the other groups, while severe emphysema was not observed in the ED group ($p = 0.044$). (Figs. 5 and 6).

Discussion

The present study revealed that, although the median GGP composite lesion scores were higher in aged rats, the difference was not statistically significant. Among the changes associated with aging in rats receiving bempedoic acid, passive congestion-related heart failure cell distribution and atelectasis were found to be higher compared to the other groups. Notably, the incidence of perivascular inflammation was lower in the drug received group. Beyond the GGP assessment, the distribution of emphysema demonstrated that the severe emphysema observed in the elderly control group was absent in the elderly drug group. Although previous studies have examined the effects of statins, this study is the first to investigate the impact of bempedoic acid on natural lung aging.

Several studies have evaluated the effects of statins on ageing. Xia et al. showed that atorvastatin attenuates cellular aging caused by oxidative stress and 5-Fluorouracil in human intestinal epithelial cells and human umbilical cord endothelial cells [14]. Similarly, in a study by Kuwahara et al., it was shown that atorvastatin or pitavastatin increased the expression of the anti-aging klotho protein synthesized in the kidneys and improved atherosclerosis in rats with chronic nitric oxide synthesis inhibition [15]. Previous studies have demonstrated that simvastatin induces the expression of key molecules involved in the regulation of aging and aging-related disorders in endothelial progenitor cells [16]. Janic et al. showed that short-term low-dose fluvastatin and valsartan have the potential to induce the expression of longevity genes [17].

In our literature review, no studies examined the effects of bempedoic acid on aging. The mechanism of action of bempedoic acid is similar to that of statins as it blocks the metabolic pathway of cholesterol biosynthesis [18].

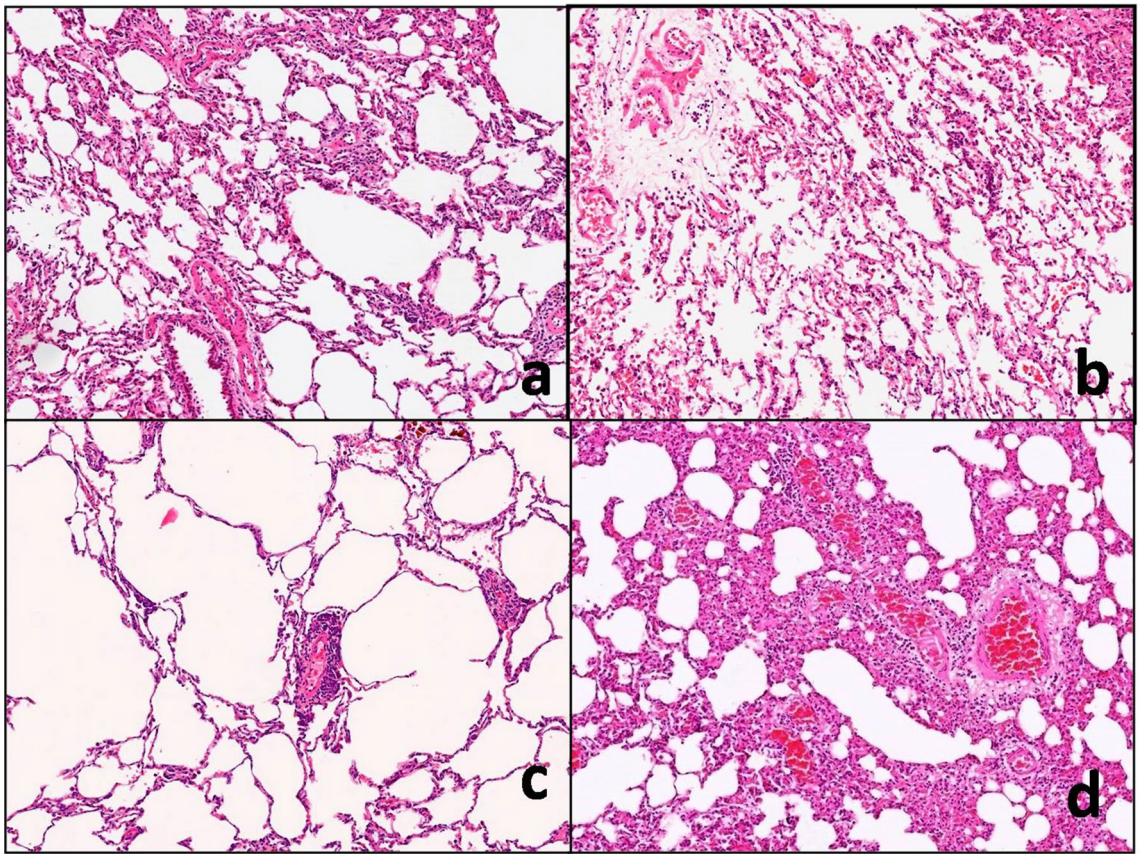

Fig. 4 Perivascular inflammation. While perivascular lymphoid infiltration was not observed in young control (**a**) and young drug groups (**b**), it was more intense in elderly control group (**c**) than in elderly drug group (**d**). (H&E x10)

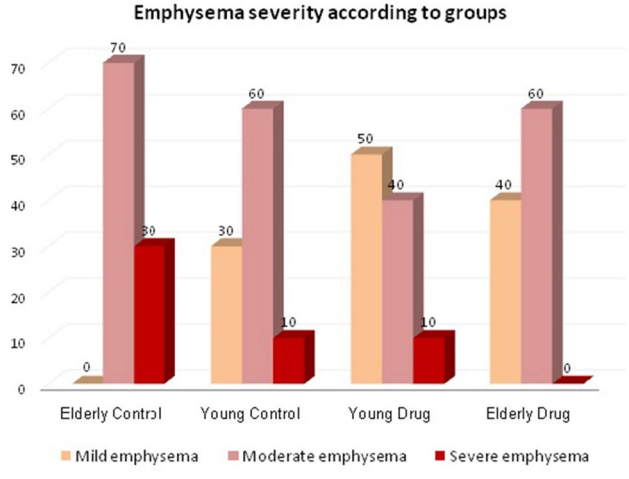

Fig. 5 Severity of emphysema by groups

Since similar metabolic pathways are involved, this raises the possibility that bempedoic acid may have allow us to think that it may have antioxidant and antiaging properties, similar to statins. In our study, a notable finding was the lower perivascular inflammation in the group receiving bempedoic acid.

In addition to their lipid-lowering effects, statins are known to have anti-inflammatory and antioxidant effects in various diseases [19, 20]. In COPD patients, inflammatory cells such as neutrophil elastase, macrophage elastase, matrix metalloproteinases, and particularly reactive oxygen radicals generated by cigarette smoke exposure contribute to alveolar destruction and emphysema. Statins are known to inhibit the expression of tumor necrosis factor α (TNF-α), interleukin 1β, interleukin 6, vascular cell adhesion molecule-1 (VCAM-1), and, E-selectin in endothelial cells, and the interaction between intercellular adhesion molecule-1 (ICAM-1). Proinflammatory cytokines such as TNF-α and interleukin 1β play a key role in the pathophysiology of emphysema [21]. Similarly, Lee et al. showed that simvastatin reduced lung parenchymal destruction, inflammatory cell counts, and pulmonary hypertension caused by chronic cigarette smoking [22]. In addition, Schenk et al. showed that statins significantly prolonged the time to the first COPD exacerbation in COPD patients and reduced the exacerbation rate [23]. Notably, no severe emphysema was observed in the elderly group receiving bempedoic acid in our study.

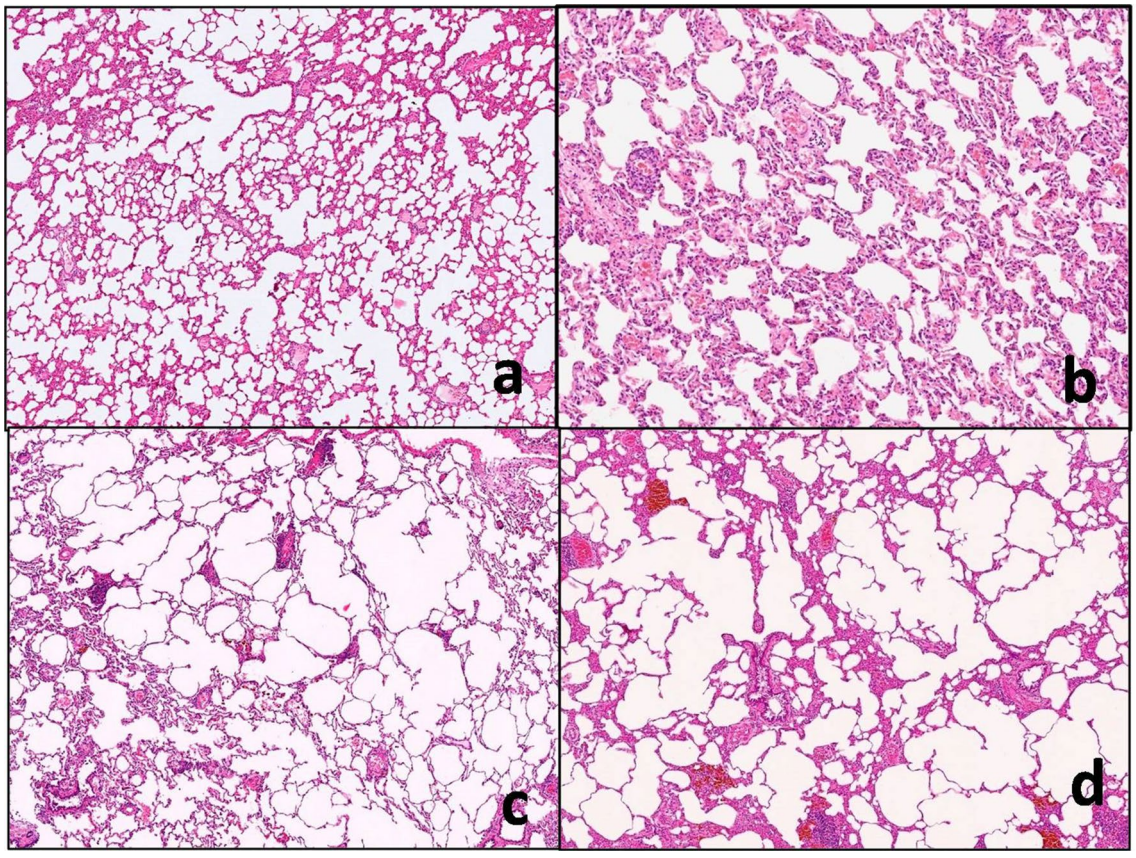

Fig. 6 Emphysema. While alveolar distortion was less in young control (**a**) and young drug groups (**b**), it was more intense in elderly control group (**c**) than in elderly drug group (**d**). (H&E x10)

This study had several limitations. First, the sample size was limited to 40 rats due to funding constraints. Second, this study was designed as a pathology-focused investigation that led to the use of the geropathology grading platform, a validated scoring system for assessing age-related histopathological changes. However, the serum levels and gene expression data for various inflammatory and oxidative markers were not included. Therefore, future studies should incorporate these markers. Third, bempedoic acid was administered for one month in the drug group, which may be a short duration, especially for observing long-term effects, such as emphysema.

Despite these limitations, the present study had several strengths. We used a validated and standardized scoring system to evaluate the effects of aging on multiple organs, which enhanced the reliability of our findings. Furthermore, this study is the first to examine the impact of bempedoic acid on natural lung aging in rats, making a significant contribution to the field.

Conclusion

Statins are believed to exert protective effects against aging by mitigating oxidative stress and inflammatory responses. Similarly, the effects of bempedoic acid on fat oxidation and cholesterol metabolism may be linked to its protective role in lungs. A more detailed understanding of these mechanisms could provide valuable insights into its potential protective effects against cytopathological processes such as oxidative damage, cell destruction, atherosclerosis, pulmonary hypertension, and fibrosis. However, further research is needed to clarify the effects of bempedoic acid on especially inflammation and emphysema.

Author contributions

All of the authors declare that they have all participated in the preparation, design, execution, and analysis of the paper, and that they have approved the final version.

Funding

There was no funding source for this study.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval

The experimental protocol was conducted in compliance with the European Communities Council Directive November 24, 1986 (86/609/EEC- Official Journal of the European Communities), the Guide for the Care and Use of

Laboratory Animals (8th Edition, 2011), and the relevant regulations of the Scientific and Technological Research Council of Turkey. The study protocol was reviewed and approved by the Local Ethics Committee of Experimental Animal Studies at Kocaeli University (Approval No: KOU HADYEK 11/3-2023; date: 26-12-2023). This study complied with the ARRIVE guidelines for reporting animal experiments.

Consent for publication
Not applicable.

Disclosure
Our study received the first-place award for oral presentation at the 27th International Turkish Thoracic Society Congress, held in Kyrenia, Cyprus, from April 29 to May 3, 2024.

Competing interests
The authors declare no competing interests.

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Received: 26 November 2024 / Accepted: 18 March 2025
Published online: 28 March 2025

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