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Original Article

Effects of combined epigallocatechin gallate and chlorogenic acid on metabolic parameters and pulmonary remodeling in a metabolic syndrome model: A preclinical study

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Abstract

Metabolic syndrome (MetS) may contribute to pulmonary fibrotic remodeling through metabolic dysregulation, oxidative stress, and inflammatory signaling. Epigallocatechin gallate (EGCG) and chlorogenic acid (CGA) have antioxidant, anti-inflammatory, and metabolic regulatory properties, but their combined effects on systemic and pulmonary peroxisome proliferator-activated receptor gamma (PPARγ) levels and pulmonary fibrosis in MetS remain insufficiently characterized. The aim of this study was to evaluate the effects of combined EGCG and CGA administration on metabolic parameters, plasma and lung tissue PPARγ levels, and histological pulmonary fibrosis severity, as well as to examine the relationships between PPARγ levels and fibrosis severity in a rat model of MetS. A post-test-only control group design was used, with 30 male Sprague-Dawley rats randomly allocated to healthy control, untreated MetS, and MetS treated with combined EGCG-CGA groups (n=10 each). MetS was induced using a high-fat, high-sucrose diet and intraperitoneal streptozotocin. Treated rats received EGCG 300 mg/kg/day and CGA 200 mg/kg/day by oral gavage for nine weeks. Metabolic parameters, plasma and lung tissue PPARγ levels, and pulmonary fibrosis severity assessed using the modified Ashcroft score were evaluated. Compared with controls, untreated MetS rats had higher body weight, fasting blood glucose, triglyceride levels, and Ashcroft scores, but lower high-density lipoprotein (HDL) cholesterol and plasma and lung PPARγ levels (all $p<0.001$). Compared with untreated MetS rats, EGCG-CGA significantly improved metabolic markers ($p<0.001$) and reduced the Ashcroft score from 5 to 4 (19.6%; $p=0.012$). Plasma and lung PPARγ levels were significantly increased in EGCG-CGA-treated rats than in untreated MetS rats (64.4±35.1 vs 17.0±4.9 ng/mL and 46.0±7.2 vs 27.9±4.9 ng/mg protein, respectively; both $p<0.001$). Plasma and lung PPARγ were positively correlated ($r=0.805$; $p<0.001$), whereas both were negatively correlated with Ashcroft score ($r=-0.749$ and $r=-0.912$, respectively; both $p<0.001$). In conclusion, combined EGCG-CGA was associated with improved metabolic profiles, increased systemic and pulmonary PPARγ levels, and lower histological pulmonary fibrosis severity in MetS rats.

Keywords: Metabolic syndrome, pulmonary fibrosis, PPARγ, EGCG, chlorogenic acid

Introduction

Metabolic syndrome (MetS) is not merely a clustering of cardiometabolic abnormalities; it represents a sustained inflammatory and oxidative milieu that may affect distant organs, including the lung [1]. The syndrome is commonly characterized by central obesity, insulin

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resistance, dysglycemia, atherogenic dyslipidemia, and elevated blood pressure. Beyond its established association with cardiovascular diseases and type 2 diabetes, MetS promotes chronic low-grade inflammation through adipose tissue dysfunction, excess circulating free fatty acids, and altered secretion of pro-inflammatory mediators such as tumor necrosis factor-α and interleukin-6 [2,3]. These metabolic disturbances also increase systemic oxidative stress, which may further amplify inflammatory signaling and tissue injury in organs beyond the classical cardiometabolic axis. Therefore, MetS should be viewed as a systemic inflammatory-metabolic condition with potential consequences for organ remodeling and functional decline [4,5].

Pulmonary fibrosis is a maladaptive tissue repair process characterized by excessive extracellular matrix deposition, alveolar septal thickening, fibroblast activation, myofibroblast persistence, and distortion of normal lung architecture [6]. Although fibrotic lung remodeling can develop from various triggers, common pathways include transforming growth factor-β signaling, oxidative stress, inflammatory cell recruitment, and sustained activation of profibrotic fibroblast programs. In the context of MetS, hyperglycemia, dyslipidemia, lipotoxicity, and adipokine imbalance may intensify lung fibroinflammatory signaling through reactive oxygen species generation, nuclear factor-κB activation, and transforming growth factor-β-related pathways [6]. This systemic metabolic burden may create a permissive biological environment for pulmonary remodeling, even in the absence of a primary pulmonary insult. Therefore, MetS-associated pulmonary fibrosis represents a relevant preclinical model for examining how metabolic injury contributes to structural lung changes [7,8].

Peroxisome proliferator-activated receptor gamma (PPARγ) is of particular interest because it lies at the intersection between metabolic homeostasis and fibrotic tissue remodeling. As a ligand-activated nuclear receptor, PPARγ regulates lipid metabolism, glucose homeostasis, insulin sensitivity, adipocyte differentiation, and inflammatory responses. In fibrotic conditions, reduced PPARγ activity has been associated with enhanced fibroblast activation, myofibroblast differentiation, extracellular matrix accumulation, and persistence of profibrotic signaling [9]. Conversely, activation of PPARγ-related pathways has been linked to attenuation of inflammatory and fibrogenic responses in several experimental models [9]. Within the lung, this receptor may serve as a biological bridge between systemic metabolic dysregulation and local tissue remodeling [7,10]. Assessment of PPARγ in both circulating and pulmonary compartments may therefore help determine whether systemic metabolic alterations are accompanied by corresponding changes within fibrotic lung tissue.

Epigallocatechin gallate (EGCG) and chlorogenic acid (CGA) are polyphenolic compounds with biological activities that may be relevant to MetS-associated pulmonary remodeling. EGCG, a major catechin in green tea, has been extensively investigated for its antioxidant, anti-inflammatory, and metabolic regulatory properties, whereas CGA, a major phenolic acid found in coffee and green coffee, has been reported to modulate glucose and lipid metabolism, oxidative stress, and inflammatory responses [11]. Although their molecular actions are diverse, both compounds have been linked to pathways involved in metabolic homeostasis and tissue remodeling, including adenosine monophosphate (AMP)-activated protein kinase-related signaling, oxidative stress regulation, inflammatory cytokine modulation, and PPARγ-associated pathways [12-14]. These overlapping biological properties provide a rationale for evaluating EGCG and CGA in combination in MetS-associated pulmonary injury. However, the available evidence does not establish synergistic effects between these compounds or indicate that their biological effects are mediated through a single shared mechanism.

Despite this biological rationale, the effects of combined EGCG and CGA administration on MetS-associated pulmonary remodeling remain insufficiently characterized. Previous experimental studies have largely evaluated EGCG or CGA individually and have examined metabolic, inflammatory, or fibrotic responses across different experimental models [12-14]. Moreover, limited evidence is available regarding the relationship between circulating and pulmonary PPARγ levels and the severity of pulmonary fibrosis within the same MetS model. This is particularly relevant because PPARγ may represent a biological interface between systemic metabolic dysregulation and local fibrotic remodeling in the lung. Accordingly, it remains unclear whether plasma PPARγ levels are associated with pulmonary PPARγ levels and whether PPARγ levels in either compartment are related to the severity of fibrotic lung remodeling. Therefore, the

aim of this study was to evaluate the effects of combined EGCG and CGA administration on metabolic parameters, plasma and lung tissue PPARγ levels, and histological pulmonary fibrosis severity, and to examine the relationships between PPARγ levels and fibrosis severity in a rat model of MetS.

Methods

Study design and setting

This controlled preclinical study was conducted to evaluate the effects of combined EGCG and CGA administration on metabolic parameters, PPARγ levels, and pulmonary fibrosis severity in a rat model of MetS. Thirty male Sprague-Dawley rats (*Rattus norvegicus*) were randomly allocated, using computer-generated random numbers, to three experimental groups (n=10 per group): healthy control, untreated MetS, and MetS treated with combined EGCG and CGA (EGCG-CGA). A post-test-only control group design was used. The primary outcomes were plasma PPARγ levels, lung tissue PPARγ levels, and pulmonary fibrosis severity assessed using the modified Ashcroft score. Secondary outcomes included body weight, fasting blood glucose, triglyceride levels, and high-density lipoprotein cholesterol levels.

Animals and housing conditions

Sprague-Dawley rats, aged 10–12 weeks, were used in this study. Male rats were selected to reduce variability related to hormonal cycling. Animals were acclimatized for one week before the experimental procedures and housed under standard laboratory conditions, with room temperature maintained at 20–24°C, relative humidity at 50–60%, and a 12-hour light–dark cycle (light phase, 06:00–18:00; dark phase, 18:00–06:00). Rats were housed individually in standard laboratory plastic cages with adequate ventilation. Food and water were provided ad libitum. Animals were monitored daily for general condition, feeding behavior, activity, signs of stress, illness, or other abnormalities. Rats were excluded if they developed severe illness, marked stress, or incomplete outcome measurement during the study period. No mortality or dropout occurred during the experiment.

Experimental groups

The animals were divided into three groups. The control group received a standard diet and did not undergo MetS induction or EGCG-CGA treatment. The MetS group received a high-fat, high-sucrose (HFHS) diet combined with intraperitoneal streptozotocin (STZ) injection but did not receive EGCG-CGA treatment. The MetS plus EGCG-CGA group underwent the same MetS induction protocol and subsequently received combined EGCG-CGA treatment for nine weeks. Initiation of the intervention only after confirmation of MetS ensured that EGCG-CGA was evaluated as a treatment following establishment of the metabolic phenotype rather than as a preventive intervention.

Induction of metabolic syndrome (MetS)

MetS was induced using HFHS diet combined with STZ injection. Rats in the MetS groups received an HFHS diet for at least eight weeks, followed by intraperitoneal STZ injection at a dose of 30 mg/kg body weight. The induction phase was continued for up to 10 weeks to achieve the predefined MetS phenotype. The MetS phenotype was defined by the presence of obesity and metabolic abnormalities, including body weight >500 g, triglyceride level >175 mg/dL, high-density lipoprotein (HDL) cholesterol level <45 mg/dL, and fasting blood glucose >126 mg/dL. Body weight was used as an indicator of obesity, fasting blood glucose as an indicator of diabetes-like hyperglycemia, and triglyceride and HDL cholesterol levels as indicators of dyslipidemia.

Combined EGCG and CGA administration

After the MetS phenotype was established, rats in the treatment group received combined EGCG-CGA by oral gavage using a gastric tube once daily for nine weeks. EGCG (Sigma-Aldrich, USA) was administered at a dose of 300 mg/kg body weight/day, while CGA (Sigma-Aldrich, USA) was administered at a dose of 200 mg/kg body weight/day. The daily dose was adjusted according to each rat's body weight during the intervention period. Body weight was therefore monitored

regularly throughout treatment. The intervention was administered as a combined EGCG-CGA regimen rather than as separate single-compound treatments. The nine-week treatment period was predefined in the experimental protocol to provide sustained exposure after establishment of the MetS phenotype and to assess subsequent metabolic and pulmonary responses.

Assessment of metabolic parameters

Body weight, fasting blood glucose, triglyceride level, and HDL cholesterol level were measured to evaluate the effect of EGCG-CGA treatment. Body weight was measured using a calibrated digital scale. Animals were fasted before blood sampling according to the experimental protocol. Fasting blood glucose was measured using a glucometer, whereas triglyceride and HDL cholesterol levels were determined using standard enzymatic-colorimetric laboratory methods.

Measurement of PPARγ levels

The levels of PPARγ were measured in plasma and lung tissue using enzyme-linked immunosorbent assay (ELISA). Plasma PPARγ concentration was expressed as ng/mL, whereas lung tissue PPARγ expression was expressed as ng/mg protein. At the end of the nine-week intervention, rats were fasted for 8–12 hours before terminal sampling. General anesthesia was induced using intraperitoneal ketamine (80–100 mg/kg body weight) and xylazine (5–10 mg/kg body weight). Blood (approximately 3–5 mL) was subsequently collected by cardiac puncture. Blood samples were centrifuged to collect the plasma. Lung tissue samples were collected after euthanasia, processed into tissue homogenates, and the supernatant was used for analysis. ELISA analysis was conducted using a rat-specific PPARγ ELISA kit following manufacturer's protocol (Bioassay Technology Laboratory, Shanghai, China). Briefly, 40 µL of sample was added to each well, followed by PPARγ antibody and streptavidin–HRP, then incubated at 37°C for 60 min. After washing, substrate solutions were added and incubated at 37°C for 10 min in the dark. The reaction was stopped, and optical density was read at 450 nm using a microplate reader.

Histopathological assessment of pulmonary fibrosis

Lung tissue specimens were collected at the end of the experimental period for histopathological evaluation. Following collection, the specimens were fixed in 10% neutral-buffered formalin, dehydrated through graded alcohol solutions, cleared in xylene, and embedded in paraffin. Paraffin-embedded tissue sections were subsequently prepared and stained with hematoxylin and eosin for microscopic examination.

Pulmonary fibrosis severity was evaluated semi-quantitatively using the modified Ashcroft scoring system, with scores ranging from 0 to 8. Lower scores represented absent or minimal fibrotic changes, whereas progressively higher scores reflected increasing alveolar septal thickening, fibrotic remodeling, and distortion of the normal lung architecture. Histopathological evaluation and fibrosis scoring were independently performed by two pathologists.

Statistical analysis

The distribution of continuous variables was assessed using the Shapiro-Wilk test and data were presented as mean ± standard deviation. Comparisons among the three groups were performed using one-way analysis of variance (ANOVA) when parametric assumptions were met. For non-parametric data, the Kruskal-Wallis test was used, followed by appropriate pairwise post hoc analysis. Correlations between the levels of plasma PPARγ, lung tissue PPARγ, and pulmonary fibrosis severity scores were analyzed using Spearman correlation. A p-value less than 0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Effects of EGCG-CGA on metabolic parameters

No mortality or dropout occurred during the study period; therefore, all 30 animals were included in the final statistical analysis. The MetS model was validated by comparing metabolic parameters between the control and untreated MetS groups. The results confirmed the occurrence of MetS (**Table 1**).

Compared with the control group, untreated MetS rats had markedly higher body weight, fasting blood glucose, and triglyceride levels, together with lower HDL cholesterol (**Table 1**). Mean body weight was 53.3% higher in the MetS group than in the control group (550.7±13.2 g vs 359.1±27.9 g; $p<0.001$). Fasting blood glucose was 222.3% higher in the MetS group than in the control group (299.1±70.4 mg/dL vs 92.8±14.4 mg/dL; $p<0.001$). Triglyceride level was 276.3% higher, whereas HDL cholesterol was 45.9% lower in the MetS group than in the control group (both $p<0.001$; **Table 1**).

Table 1. Comparison of metabolic parameters among control rats, untreated metabolic syndrome (MetS) rats, and MetS rats treated with combined epigallocatechin gallate and chlorogenic acid (EGCG-CGA)

Parameter	Control Mean±SD	Untreated MetS Mean±SD	MetS + EGCG-CGA Mean±SD	Overall *p*-value*
Body weight (g)*	359.1±27.9[a]	550.7±13.2[b]	450.0±25.6[c]	<0.001
Fasting blood glucose (mg/dL)*	92.8±14.4[a]	299.1±70.4[b]	154.3±19.0[c]	<0.001
Triglyceride (mg/dL)*	79.9±9.6[a]	300.7±73.3[b]	145.5±31.0[c]	<0.001
HDL cholesterol (mg/dL)**	51.4±7.0[a]	27.8±4.7[b]	41.0±2.1[c]	<0.001

CGA: chlorogenic acid; EGCG: epigallocatechin gallate; HDL: high-density lipoprotein; MetS: metabolic syndrome
* Analyzed using one-way ANOVA followed by Tukey's post hoc test
** Analyzed using the Kruskal-Wallis test followed by Mann-Whitney U pairwise comparisons with Bonferroni correction (α=0.017)
[a, b, c] Different superscript letters within the same row indicate statistically significant differences between groups in post hoc pairwise comparisons

Compared with untreated MetS rats, EGCG-CGA-treated rats showed a more favorable metabolic profile, reflected by lower body weight, fasting blood glucose, and triglyceride levels, as well as higher HDL cholesterol (**Table 1**). Body weight was 18.3% lower in EGCG-CGA-treated rats than in untreated MetS rats (450.0±25.6 g vs 550.7±13.2 g; $p<0.001$). Fasting blood glucose and triglyceride levels were 48.4% and 51.6% lower, respectively, in EGCG-CGA-treated rats than in untreated MetS rats (154.3±19.0 vs 299.1±70.4 mg/dL and 145.5±31.0 vs 300.7±73.3 mg/dL, respectively; both $p<0.001$). Conversely, HDL cholesterol was 47.5% higher in EGCG-CGA-treated rats than in untreated MetS rats (41.0±2.1 mg/dL vs 27.8±4.7 mg/dL; $p<0.001$) (**Table 1**). Although all metabolic parameters differed significantly between untreated MetS and EGCG-CGA-treated rats, the treatment group remained significantly different from the control group for all metabolic variables (**Table 1**).

Effects of EGCG-CGA on pulmonary fibrosis severity

Pulmonary fibrosis severity was assessed using the modified Ashcroft score. The score differed significantly among the three groups ($p<0.001$) (**Table 2**). The mean Ashcroft fibrosis score was lowest in the control group (2.7±0.7), highest in untreated MetS rats (5.1±0.9), and lower in EGCG-CGA-treated rats than in untreated MetS rats (4.1±0.7). Post hoc analysis showed significant differences between control and MetS groups ($p<0.001$), control and EGCG-CGA groups ($p=0.001$), and MetS and EGCG-CGA groups ($p=0.012$). The reduction from 5.1 to 4.1 corresponded to an approximately 19.6% decrease in fibrosis severity after EGCG-CGA administration.

Table 2. Effects of combined epigallocatechin gallate and chlorogenic acid (EGCG-CGA) on pulmonary fibrosis severity assessed using Ashcroft fibrosis score

Study group	n	Ashcroft score		*p*-value	
		Mean±SD	Median (IQR)	Overall Kruskal-Wallis test	Post hoc comparisons*
Control	10	2.7±0.7	3.0 (1.0)	$p<0.001$	Control vs MetS: $p<0.001$
Untreated MetS	10	5.1±0.9	5.0 (1.0)		Control vs MetS + EGCG-CGA: $p=0.001$
MetS + EGCG-CGA	10	4.1±0.7	4.0 (1.0)		MetS vs MetS + EGCG-CGA: $p=0.012$

CGA: chlorogenic acid; EGCG: epigallocatechin gallate; MetS: metabolic syndrome
* Analyzed using Kruskal-Wallis test

Effects of EGCG-CGA on plasma and lung PPARγ levels

PPARγ levels differed significantly among the three groups in both plasma and lung tissues (**Table 3**). The overall group differences were significant for both plasma and lung PPARγ levels (both $p<0.001$). Post hoc analyses found that plasma PPARγ was 70.4% lower in untreated MetS rats than in control rats (17.0±4.9 vs 57.3±3.8 ng/mL; $p<0.001$). In contrast, plasma PPARγ was 279.6% higher in EGCG-CGA-treated rats than in untreated MetS rats (64.4±35.1 vs 17.0±4.9 ng/mL; $p<0.001$), with no significant difference between the EGCG-CGA and control groups ($p=0.481$) (**Table 3**).

A similar pattern was observed in lung tissue, where PPARγ expression was 59.3% lower in untreated MetS rats than in control rats (27.9±4.9 vs 68.6±3.7 ng/mg protein; $p<0.001$) (**Table 3**). Lung PPARγ expression was 64.9% higher in EGCG-CGA-treated rats than in untreated MetS rats (46.0±7.2 vs 27.9±4.9 ng/mg protein; $p<0.001$), although it remained significantly lower than in the control group ($p<0.001$) (**Table 3**).

Table 3. Comparison of plasma and lung tissue PPARγ levels among control rats, untreated metabolic syndrome (MetS) rats, and MetS rats treated with combined epigallocatechin gallate and chlorogenic acid (EGCG-CGA)

Group	PPARγ levels			Post hoc comparison	% change[b]	Post hoc *p*-value
	Mean±SD	Median	IQR			
Plasma[a]						
Control	57.3±3.8	56.6	6.3	Control vs MetS	-70.4%	<0.001
Untreated MetS	17.0±4.9	15.5	9.8	Control vs MetS + EGCG-CGA	+12.4%	0.481
MetS + EGCG-CGA	64.4±35.1	49.4	39.4	MetS vs MetS + EGCG-CGA	+279.6%	<0.001
Lung tissue[a]						
Control	68.6±3.7	68.3	6.4	Control vs MetS	-59.3%	<0.001
Untreated MetS	27.9±4.9	28.5	10.2	Control vs MetS + EGCG-CGA	-32.9%	<0.001
MetS + EGCG-CGA	46.0±7.2	45.9	12.2	MetS vs MetS + EGCG-CGA	+64.9%	<0.001

EGCG-CGA: epigallocatechin gallate and chlorogenic acid combination; MetS: metabolic syndrome.
[a] Analyzed using the Kruskal-Wallis test, followed by pairwise Mann-Whitney U tests with Bonferroni correction (α=0.017).
[b] Percentage changes were calculated relative to the first group listed in each pairwise comparison.

Correlation between PPARγ levels and pulmonary fibrosis severity

Spearman correlation analysis was performed to evaluate the correlation between the levels of plasma PPARγ, lung tissue PPARγ, and pulmonary fibrosis severity (**Table 4**). Plasma PPARγ showed a strong positive correlation with lung tissue PPARγ ($r=0.805$; $p<0.001$; 95% CI: 0.627 to 0.903). Both plasma and lung tissue PPARγ were inversely correlated with Ashcroft scores (**Table 4**). Plasma and lung tissue PPARγ levels had a strong negative correlation with Ashcroft score, with $r=-0.749$; $p<0.001$, and $r=-0.912$; $p<0.001$, respectively (**Table 4**). These findings indicate that higher PPARγ expression was inversely correlated with fibrosis severity, with the strongest correlation observed for lung tissue PPARγ.

Table 4. Spearman correlation analysis between peroxisome proliferator-activated receptor gamma (PPARγ) levels and pulmonary fibrosis severity

Variable pair	Spearman *r*	95% confidence interval	*p*-value
Plasma PPARγ vs lung tissue PPARγ	0.805	0.627 to 0.903	<0.001
Plasma PPARγ vs Ashcroft score	-0.749	-0.873 to -0.532	<0.001
Lung tissue PPARγ vs Ashcroft score	-0.912	-0.958 to -0.822	<0.001

Discussion

MetS is increasingly recognized as a systemic metabolic-inflammatory condition that may extend beyond traditional cardiometabolic complications and contribute to structural remodeling of distant organs, including the lung. In the present study, combined EGCG-CGA administration was associated with improved metabolic parameters, higher plasma and lung tissue PPARγ protein levels, and lower histological pulmonary fibrosis severity in rats with MetS. The induction

protocol produced a clear MetS phenotype, as shown by increased body weight, fasting blood glucose, and triglyceride levels, together with reduced HDL cholesterol. This metabolic alteration was accompanied by lower plasma and lung tissue PPARγ protein levels and higher Ashcroft scores, indicating that the model involved both systemic metabolic disturbance and pulmonary structural remodeling. EGCG-CGA administration was associated with lower body weight, fasting glucose, triglyceride levels, and Ashcroft score, as well as higher HDL cholesterol and PPARγ protein levels in both plasma and lung tissue. However, most parameters in the treated group did not fully return to control group values, indicating a partial rather than complete restoration. Plasma and lung tissue PPARγ showed inverse correlations with Ashcroft score, with the strongest relationship observed between lung tissue PPARγ and fibrosis severity. These findings support a biologically plausible association between PPARγ-related responses and reduced fibrotic remodeling, without establishing pathway causality [9,15].

The establishment of a valid MetS model is central to interpreting the present findings. Compared with control rats, untreated MetS rats showed a 53.3% increase in body weight, a 222.3% increase in fasting blood glucose, a 276.3% increase in triglyceride levels, and a 45.9% reduction in HDL cholesterol. These changes indicate the development of obesity, diabetes-like hyperglycemia, and dyslipidemia, which are key metabolic features of MetS. The model also showed a marked reduction in plasma PPARγ protein levels and a significant increase in Ashcroft score, suggesting that metabolic injury was accompanied by molecular and structural pulmonary changes. This pattern is consistent with the concept that MetS is not confined to cardiometabolic risk, but may create a systemic oxidative-inflammatory environment capable of affecting distant organs, including the lung [5]. Hyperglycemia and dyslipidemia may promote reactive oxygen species generation, advanced glycation end-product signaling, lipid-associated inflammation, and nuclear factor-κB activation [2,5]. These processes can amplify profibrotic signaling and contribute to fibroblast activation, extracellular matrix deposition, and alveolar septal thickening [6]. Therefore, the pulmonary fibrosis observed in the untreated MetS group provides experimental support that this model is appropriate for studying MetS-related pulmonary remodeling [16].

EGCG-CGA administration was associated with significant improvement in the metabolic profile of MetS rats. Treated rats showed lower body weight, fasting blood glucose, and triglyceride levels, together with higher HDL cholesterol compared with untreated MetS rats. The magnitude of change was most evident for triglyceride and fasting glucose, which decreased by 51.6% and 48.4%, respectively, while HDL cholesterol increased by 47.5%. These findings suggest that the combined polyphenolic intervention modified several metabolic abnormalities induced by the MetS protocol. EGCG and CGA have been linked to metabolic regulation through antioxidant activity, modulation of inflammatory signaling, improved insulin sensitivity, AMPK-related pathways, and lipid metabolism regulation [17,18]. In this study, the improvement in systemic metabolic parameters may have reduced the metabolic and inflammatory burden contributing to lung remodeling. However, the treated group remained significantly different from the control group for all metabolic variables, indicating that EGCG-CGA produced partial metabolic improvement rather than full normalization. Because the study did not include EGCG-only and CGA-only arms, these findings should be interpreted as the effect of combined administration, not as evidence of synergy between the two compounds [5]. Accordingly, the contribution of each compound to the observed metabolic effects cannot be distinguished from the present design.

PPARγ may represent a biologically relevant bridge between metabolic regulation and pulmonary fibrotic remodeling in this model. Untreated MetS rats showed markedly lower PPARγ levels in both plasma and lung tissue, while EGCG-CGA administration increased PPARγ expression in both compartments. Plasma PPARγ increased from 17.0±4.9 ng/mL in untreated MetS rats to 64.4±35.1 ng/mL in treated rats, whereas lung tissue PPARγ increased from 27.9±4.9 to 46.0±7.2 ng/mg protein. The plasma response reached a level not significantly different from control values, while lung tissue PPARγ remained lower than controls, indicating partial restoration in the pulmonary compartment. This distinction is important because tissue-level PPARγ may more closely reflect local pulmonary biological responses than circulating PPARγ levels. The correlation analysis further showed that plasma PPARγ was positively

correlated with lung tissue PPARγ, while both plasma and lung tissue PPARγ were negatively correlated with Ashcroft score. Although this study did not use a PPARγ antagonist, knockout model, or gene-silencing approach, the strong inverse correlation between PPARγ levels and Ashcroft score supports a biologically plausible link between PPARγ-associated responses and reduced fibrotic remodeling [9,15]. Therefore, PPARγ should be discussed as a possible mechanistic bridge, not as a confirmed causal mediator.

The reduction in pulmonary fibrosis severity after EGCG-CGA administration was supported by both semiquantitative scoring and histopathological findings. Untreated MetS rats exhibited more pronounced fibrotic remodeling, characterized by higher Ashcroft scores, alveolar septal thickening, interstitial fibrosis, inflammatory cell infiltration, and disruption of normal alveolar architecture. In contrast, EGCG-CGA-treated rats had a lower mean Ashcroft score than untreated MetS rats (4.1±0.7 vs 5.1±0.9), representing an approximately 19.6% lower fibrosis score, together with less extensive septal thickening and greater preservation of alveolar architecture. Nevertheless, residual histological abnormalities remained evident, indicating attenuation rather than complete resolution of pulmonary fibrotic remodeling. These findings are biologically consistent with the reported antioxidant, anti-inflammatory, and antifibrotic properties of polyphenols, including modulation of transforming growth factor beta-related signaling and fibroblast activation [14,17,18]. Experimental evidence also supports the potential role of EGCG and CGA in attenuating fibrotic or fibroinflammatory responses through pathways related to oxidative stress, epithelial-mesenchymal transition, TGF-β signaling, and extracellular matrix remodeling [19,20]. However, these pathways were not directly assessed in the present study and should therefore be regarded as biologically plausible mechanisms rather than demonstrated mediators of the observed histopathological differences.

Some limitations of the study should be acknowledged. The study did not include EGCG-only or CGA-only groups, so the individual contribution of each compound cannot be separated. Fibrosis assessment was mainly based on Ashcroft scoring and did not include additional molecular or biochemical fibrosis markers such as TGF-β1, α-SMA, collagen I/III, hydroxyproline, western blot, or qPCR. The study measured PPARγ levels rather than direct receptor activity or downstream PPARγ signaling, limiting mechanistic interpretation. Finally, as a preclinical study, these findings cannot be directly translated into clinical efficacy or safety in humans. Future studies should include single-compound and combined-treatment groups, dose-response evaluation, pathway-specific PPARγ validation, additional fibrotic and inflammatory markers, and longer follow-up protocols.

Conclusion

EGCG-CGA co-administration was associated with improved metabolic parameters, increased plasma and lung PPARγ levels, and reduced histological pulmonary fibrosis severity in rats with MetS. The inverse correlations between PPARγ expression and Ashcroft score suggest a possible PPARγ-associated antifibrotic response in this preclinical model. These findings support the relevance of PPARγ as a potential biological link between metabolic dysfunction and pulmonary fibrotic remodeling. Further studies using EGCG-only and CGA-only comparison groups, dose-response protocols, additional fibrotic markers, and pathway-specific validation are required to clarify the mechanistic contribution of PPARγ in MetS-related pulmonary fibrosis.

Ethics approval

All animal procedures were approved by the Health Research Ethics Committee of Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia, with approval number 400/222/K.3/102.7/2025. All procedures were conducted with efforts to minimize animal discomfort during handling, metabolic syndrome induction, oral intervention, blood sampling, tissue collection, and euthanasia.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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