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Does gallic acid improve cardiac function by attenuation of oxidative stress and inflammation in an elastase-induced lung injury?

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ABSTRACT

Objective(s): Cardiovascular disease has an important role in mortality caused by lung injury. Emphysema is associated with impaired pulmonary gas exchange efficiency and airflow limitation associated with small airway inflammation. The aim was to evaluate the interactions between lung injury, inflammation, and cardiovascular disease. Since gallic acid has antioxidant and anti-inflammatory effects, we hypothesized that gallic acid protects the lung and the related heart dysfunction in elastase-induced lung injury.

Materials and Methods: Forty-eight Sprague-Dawley male rats were randomly divided into six groups: Control, Porcine pancreatic elastase (PPE) , PPE+GA, and 3 groups for different doses of gallic acid (GA 7.5, GA 15, GA 30 mg/kg). PPE was injected intra-tracheally on days 1 and 10 of the test. In each group, electrocardiography, hemodynamic parameters, oxidative stress, and bronchoalveolar lavage fluid were examined.

Results: PPE administration showed a decrease in HR and QRS voltage of electrocardiogram parameters, as well as in hemodynamic parameters (P<0.05, P<0.01, and P<0.001) and superoxide dismutase (SOD) (P<0.05). Tumor Necrosis Factor α (TNF-α) (P<0.001), interleukin 6 (IL-6) (P<0.001), interleukin 6 (MDA) (P<0.001), and the total number of white blood cells (P<0.001) showed an increase in PPE groups. Gallic acid preserved the values of hemodynamic properties, oxidative stress, inflammation, and electrocardiogram parameters in comparison to the PPE group.

Conclusion: Briefly, this study showed the valuable effect of gallic acid in cardiac dysfunction related to elastase-induced lung injury. These findings suggested that gallic acid, as a natural antioxidant, has a potential therapeutic effect on preventing oxidative stress, inflammation, and subsequent cardiovascular disease.

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Introduction

Emphysema is one of the main disorders associated with chronic obstructive pulmonary disease (COPD). Emphysema is associated with the loss of the alveolar wall and its irreversible enlargement, restriction of airflow, depletion of lung elastin (1), and reduction of the gas exchanging surfaces of the lung (2). There is a prevailing opinion that COPD exacerbation is associated with chronic inflammation (3). Inflammation plays a fundamental role in the development of emphysema (4). Inflammation of the lung is primarily caused by the gradual infiltration of inflammatory cells, mainly macrophages, responsible for the degradation of alveolar elastin by secretion of elastinolytic proteases (5, 6). Besides the well-known effects of emphysema on the lungs, the systemic effects of emphysema have also been described (7). Inflammatory state in emphysema is not limited to the lungs, but it also affects systemic circulation and can affect non-pulmonary organs (8, 9). Acute and chronic lung inflammation is an unknown risk factor for cardiovascular disease (10). Chronic lung disease also has significant effects on right ventricular function and pulmonary artery pressure. The highest increase in mortality caused by COPD is related to the involvement of the heart and cardiovascular dysfunction (11). The cardiovascular system consists of systemic circulation, and the two right and left ventricular pumps. Two basic principles to remember for ventricular function are the fact that the left ventricle pumps blood via the aorta and the right ventricle blood to the pulmonary artery. When blood is not fully oxygenated due to emphysema, it can lead to stress on the heart tissue and cause symptoms of heart failure. On the other hand, excess fluid in the lungs caused by left heart failure can make the breathing process more difficult for individuals with COPD (12). Some studies have suggested a link between pulmonary disease and heart dysfunction (13).

Since cardiac dysfunction plays a role in the overall complications of lung injury and chronic lung disease, it is essential to know how it plays a role in the treatment. There is a wide variety of plant-derived polyphenolic compounds. Their medicinal properties have received much attention in recent years. Gallic acid (3, 4, 5-trihydroxy benzoic acid) was highly regarded as a free radical scavenger and anti-oxidant (14). Gallic acid has anti-inflammatory (15), anti-oxidant (16), and anticancer effects (17).

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In light of these findings, the aim of the presented study was to evaluate the hypothesis that gallic acid may affect oxidative stress and inflammatory processes to reduce inflammation and improve heart function in the elastase-induced-emphysema model. Furthermore, the electrocardiography (ECG) and hemodynamic parameters were assayed to evaluate the cardioprotective effects of gallic acid on isolated rat hearts in elastase-induced emphysema.

Materials and Methods

Porcine pancreas elastase was purchased from Sigma-Aldrich (USA). Cytokine Elisa kits were purchased from ZellBio (Germany). Xylazine and ketamine were purchased from Alfasan (The Netherlands), Krebs salts from Merck (Germany), gallic acid, and heparin were bought from Sigma-Aldrich (USA). Male Sprague Dawley rats (weight range, 150 to 180 g) were classified into the 6 following groups (n=8): Control group, PPE group (intra-tracheal injection of 25 IU/kg body weight PPE on days 1 and 10 of the test) (18). Three groups treated with different doses of gallic acid (GA 7.5, GA 15, GA 30 mg/kg), were gavaged for 28 days (19), and the PPE group treated with GA intra-tracheal injection of PPE (25 IU/kg body weight) on days 1 and 10 of the test + Gallic acid (30 mg/kg/day), gavaged for 28 days. The experimental protocol was confirmed by the Animal Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (APRC-9801).

Experimental protocol

The rats were anesthetized via IP injection of 50 mg/kg ketamine and 10 mg/kg xylazine (20) and then intra-tracheally injected with (25 IU/kg body weight) of porcine pancreatic elastase in saline (control) on days 1 and 10 of the test. The rats were killed 28 days after instillation.

Histopathological examination

The left lobe of lungs was fixed in 10% formalin solution for 24 hr and then the tissues were stained with Masson's trichrome to evaluate the deposition of collagen fibers (21).

Extraction of alveolar bronchial lavage fluid

In the end, anesthesia was induced by a mixture of ketamine and xylazine. After ensuring deep anesthesia, the chest was opened and the lung's outer surface was rinsed with a small amount of saline and the trachea was cannulated. Then, 2 ml of phosphate-buffered saline (PBS) solution was administrated into the lung and immediately extracted with a suction syringe. This step was repeated for 5 series (22).

Investigation of inflammatory factors

For this purpose, the entire lavage fluid was centrifuged at 3000 rpm for 10 min at 4 ˚C. Then the supernatant was removed and kept at -80 ˚C until examination. The levels of IL-6 and TNF-α were measured using the ELISA (IBL, Germany) method according to the kit's instructions (23).

Measurement of the total number of white blood cells and differential counts in the alveolar bronchial lavage fluid

For this purpose, a mixture of lung lavage solution was mixed with the same volume of the torque solution, and the total number of WBCs (white blood cells) was determined on a hemocytometer. The smears were prepared using cell pellet suspension. Then, dried and stained with the Wright-Giemsa solution. The total and differential inflammatory cell counts were determined with 400 magnifications (22).

Electrocardiogram (ECG) recording

After anesthesia, lead II electrocardiogram was recorded by Bio-Amp and monitored by a Power Lab system (AD-Instruments, Australia) to determine heart rate, PR, QT, and RR interval, voltage of QRS, QRS interval and QTc (Bazett's formula: QT interval/square root of the RR interval) (24).

Measuring the hemodynamic parameters of isolated hearts using Langendorff setup

The animals were anesthetized with ketamine and xylazine. Heparin (1000 u/kg) was also used to prevent coagulation. Then the animals were connected to a ventilator (model: 7025, UGO BASILE), and the diaphragm was ruptured, a metal cannula (aortic cannula) inserted through the incision into the aorta, and the hearts were rapidly excised and mounted on a Langendorff setup with continuous retrograde perfusion using Krebs-Henseleit buffer consisting of glucose (11.1 mM), $NaHCO_3$ (25 mM), KCl (4.75 mM), $CaCl_2$ (1.75 mM), KH_2PO_4 (1.18 mM), $MgSO_4$ (1.2 mM), and NaCl (118 mM) equilibrated by 5% CO_2 and 95% O_2 at pH of 7.4. The cardiac parameters such as HR (Heart rate), LVDP (Left ventricular developed pressure), LVEDP (Left ventricular end-diastolic pressure), LVSP (Left ventricular systolic pressure), max dp/dt (Maximum rate of rise (+dp/dt)) and min dp/dt (Minimum rate of fall (-dp/dt)), RPP (Rate pressure product) (HR × LVDP), were monitored continuously by a Power Lab system (AD Instruments) (25).

Measurement of lipid peroxidation (MDA) and anti-oxidant enzyme (SOD) in heart tissue

At the end of the experiment, 100 mg of heart tissue was homogenized in PBS. After centrifugation, the supernatant was separated to measure MDA and SOD. Then MDA and SOD were measured according to the ZellBio kit (26).

Statistical analysis

The results were described as mean ± SEM. All groups were statistically compared by ANOVA followed by Tukey's multiple comparisons. $P<0.05$ was regarded as significantly different.

Results

Confirmation of PPE-induced systemic inflammation

The levels of TNF-α and IL-6 in BALF (bronchoalveolar lavage fluid) were examined in different groups to assess inflammatory changes (Figures 1A, 1B**)**. A significant increase in TNF-α and IL-6 was observed in the PPE group compared with the control (*P<0.001*). However, levels of TNF-α and IL-6 showed normal values in the PPE group using concomitant gallic acid (PPE+GA 30) ($P<0.001$).

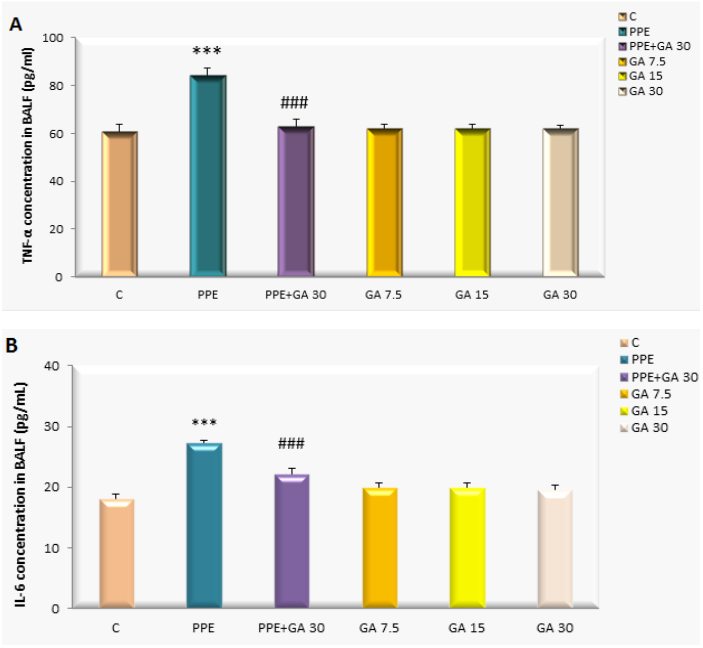

Figure 1. BALF contents of TNF-α and interleukine-6 in Control (C), PPE, PPE plus Gallic acid (GA 30), GA 7.5, GA 15, GA 30 mg/kg rats. ***P<0.001 vs the Control group; ###P<0.001 vs the PPE group. All groups were statistically compared by ANOVA followed by Tukey's multiple comparisons. Data are expressed as mean±SEM, n=8
BALF: bronchoalveolar lavage fluid; TNF-α: tumor necrosis factor α; PPE: porcine pancreatic elastase

Inflammation cell count

To confirm lung inflammation and subsequent systemic inflammation, WBC (white blood cell) counts were performed (Figures 2A, 2B). In the PPE group, the total number of WBC and the numbers of macrophages and lymphocytes were significantly higher compared with the control group but neutrophils in the PPE group were lower compared with the controls (P<0.001). The BALF WBC including macrophages and lymphocytes in the PPE group co-treated with gallic acid (GA 30) significantly decreased (P<0.001) with respect to the PPE group while the neutrophils count in this group treated with gallic acid (GA 30) increased significantly (P<0.001).

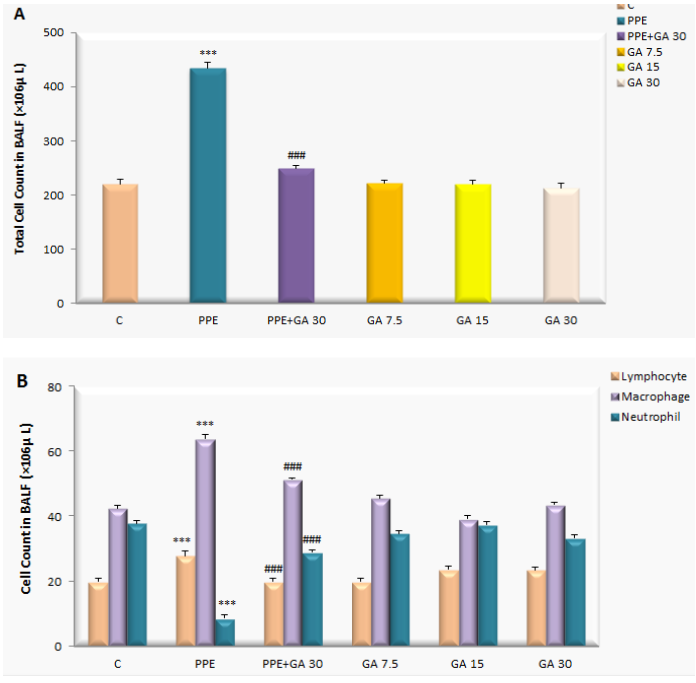

Figure 2. Total cell count and classification in bronchoalveolar lavage fluid (Control (C), PPE, PPE plus Gallic acid (GA 30), GA 7.5, GA 15, GA 30 mg/kg) rat. ***P<0.001 vs the Control group; ###P<0.001 vs the PPE group. Data are expressed as the mean±SEM, n=8. All groups were statistically compared by ANOVA followed by Tukey's multiple comparisons
PPE: porcine pancreatic elastase

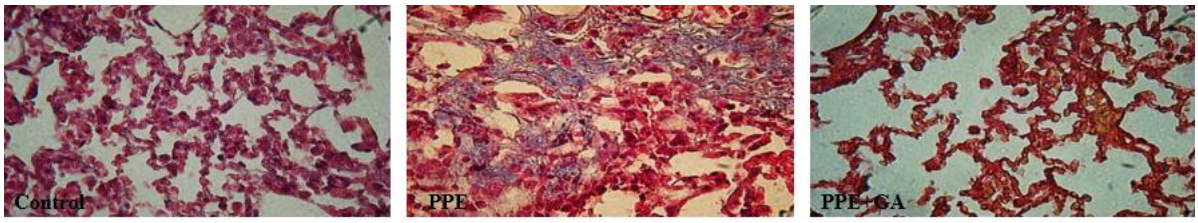

Figure 3. Lung histological changes in lung tissues of rat in Control, PPE, PPE+GA (30 mg/kg)
PPE: porcine pancreatic elastase; GA: gallic acid

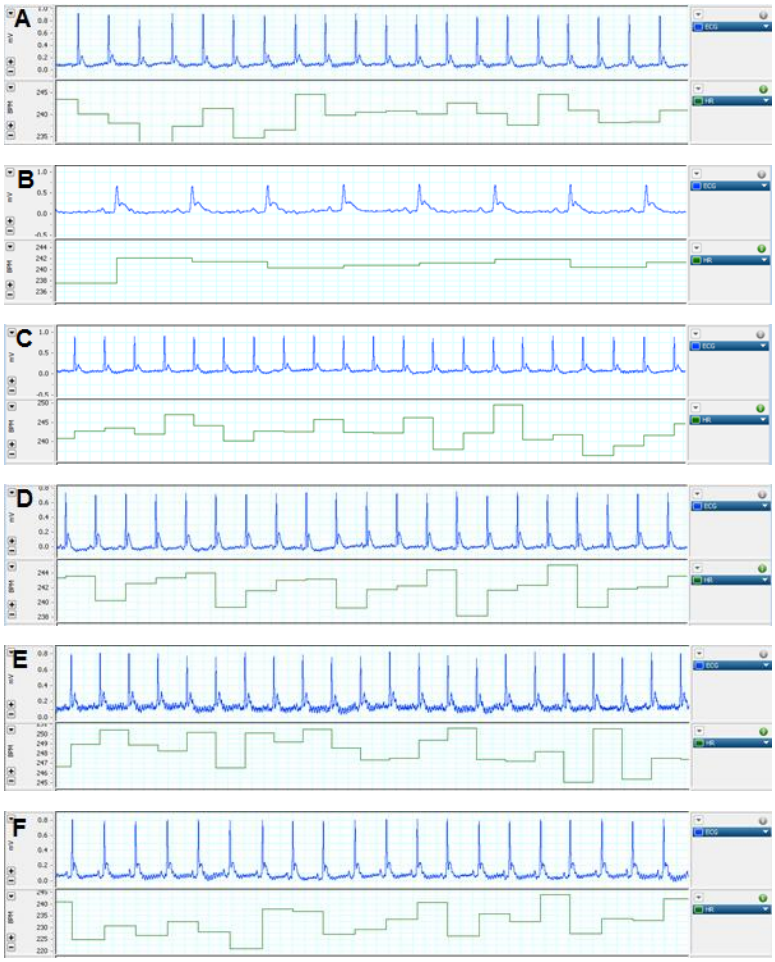

Figure 4. Electrocardiogram records from all rat groups. Control (4A), PPE (4B), PPE plus GA 30 (4C),GA 7.5 (4D), GA 15 (4E), and GA 30 mg/kg (4F). PPE: porcine pancreatic elastase; GA: gallic acid

Changes in lung histology

As shown in Figure 3, in the lung tissue of emphysematous rats (PPE group) the deposition of collagen fibers increased compared with the control group, but gallic acid was able to decrease the deposition rate of collagen compared with the emphysematous group (PPE).

Electrocardiographic parameters

To determine if PPE-induced emphysema has effects on the heart function, we compared cardiac electrocardiogram parameters between all groups. As shown in Table 1 and Figures 4A–4F, there was a decrease in HR (bpm) (P<0.001) and QRS complex (mv) (P<0.001) which is the negative inotropic indicator (myocardial contractility), and an increase in RR interval (S) (P<0.05), QRS Complex (S) (P<0.001), and QT interval (S) (P<0.05) in the PPE group. However, gallic acid could restore these changes significantly compared with the PPE group.

Hemodynamic parameters

In consideration of the possible preventive effect of gallic acid on intrinsic cardiac damage induced by PPE, the hemodynamic parameters in isolated rat hearts were examined. Figures 5 A–5G show that there is a decrease in + dp/dt (mmHg) (P<0.01), - dp/dt (mmHg) (P<0.05), rate pressure product (RPP) (P<0.001), LVDP (mmHg) (P<0.01), and LVSP (mmHg) (P<0.01). HR (P<0.001)

Table 1. Electrocardiogram records from all rat groups

Parameters	Control	PPE	PPE+GA 30	GA 7.5	GA 15	GA 30
HR (bpm)	249.56±2.17	209.11±3.47***	239.98±1.57##	250.17±3.67	249.76±2.53	249.49±2.91
PR interval (s)	0.023±0.008	0.023±0.001	0.024±0.001	0.023±0.008	0.024±0.001	0.023±0.009
QRS complex (s)	0.022±0.004	0.032±0.001***	0.025±0. 006##	0.024±0.009	0.024±0.008	0.024±0.009
QRS complex (mv)	0.556±0.08	0.515±0.05***	0.542±0.02##	0.550±0.07	0.560±0.07	0.561±0.07
QT interval (s)	0.072±0.006	0.075±0.006*	0.074±0.005	0.072±0.001	0.072±0.001	0.072±0.006
RR interval (s)	0.25±0.03	0.31±0.01*	0.26±0.002	0.25±0.03	0.25±0.03	0.25±0.03
QTc (s)	0.144±0.01	0.144±0.04	0.145±0.06	0.143±0.03	0.143±0.2	0.145±0.01

All groups were statistically compared by ANOVA followed by Tukey's multiple comparisons. Data are expressed as mean±SEM (n=8).* P<0.05, *** P<0.001 vs the Control, ## P<0.01 vs PPE. PPE: porcine pancreatic elastase. ; GA: Gallic acid; HR: Heart rate

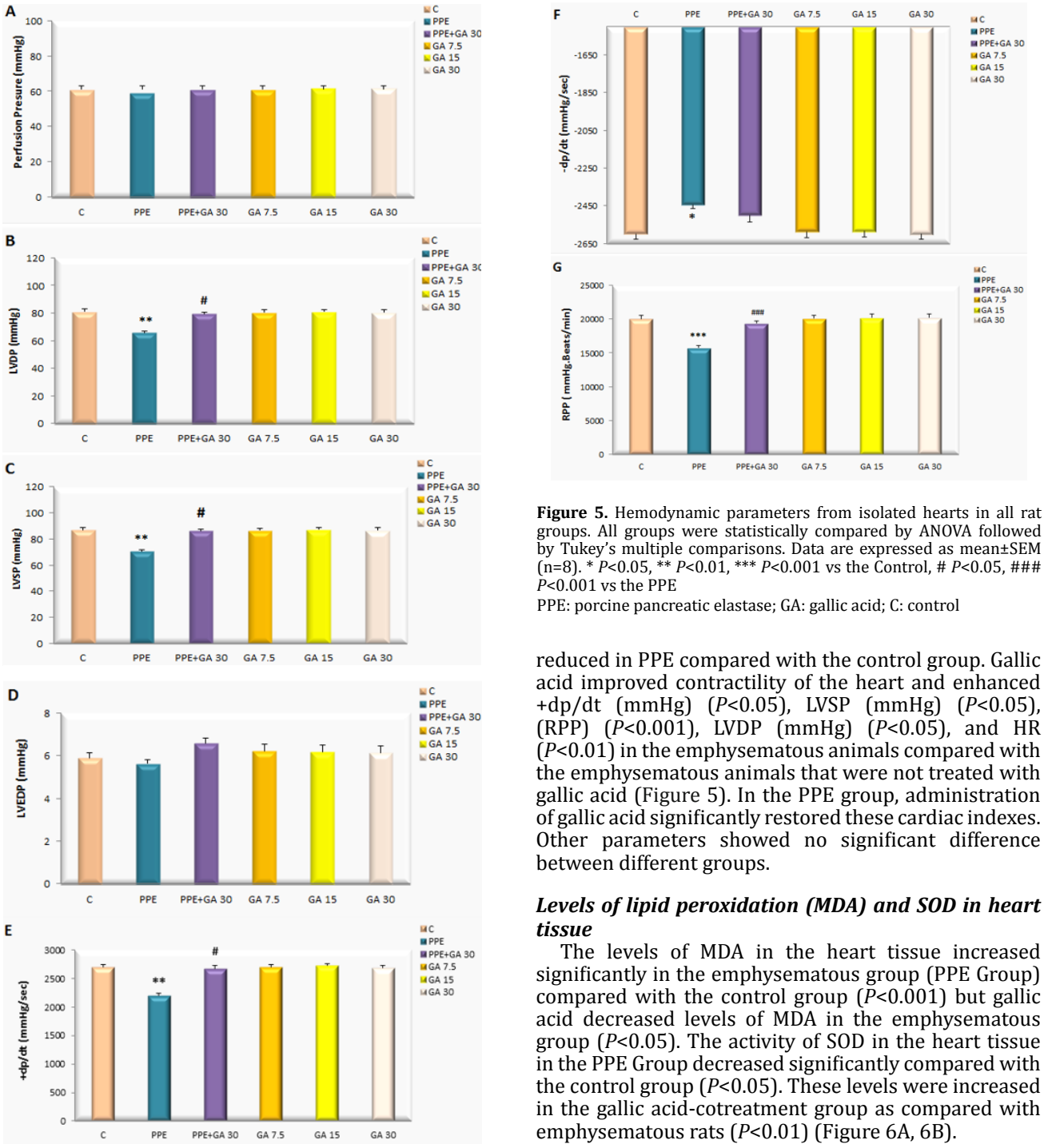

Figure 5. Hemodynamic parameters from isolated hearts in all rat groups. All groups were statistically compared by ANOVA followed by Tukey's multiple comparisons. Data are expressed as mean±SEM (n=8). * P<0.05, ** P<0.01, *** P<0.001 vs the Control, # P<0.05, ### P<0.001 vs the PPE

PPE: porcine pancreatic elastase; GA: gallic acid; C: control

reduced in PPE compared with the control group. Gallic acid improved contractility of the heart and enhanced +dp/dt (mmHg) (P<0.05), LVSP (mmHg) (P<0.05), (RPP) (P<0.001), LVDP (mmHg) (P<0.05), and HR (P<0.01) in the emphysematous animals compared with the emphysematous animals that were not treated with gallic acid (Figure 5). In the PPE group, administration of gallic acid significantly restored these cardiac indexes. Other parameters showed no significant difference between different groups.

Levels of lipid peroxidation (MDA) and SOD in heart tissue

The levels of MDA in the heart tissue increased significantly in the emphysematous group (PPE Group) compared with the control group (P<0.001) but gallic acid decreased levels of MDA in the emphysematous group (P<0.05). The activity of SOD in the heart tissue in the PPE Group decreased significantly compared with the control group (P<0.05). These levels were increased in the gallic acid-cotreatment group as compared with emphysematous rats (P<0.01) (Figure 6A, 6B).

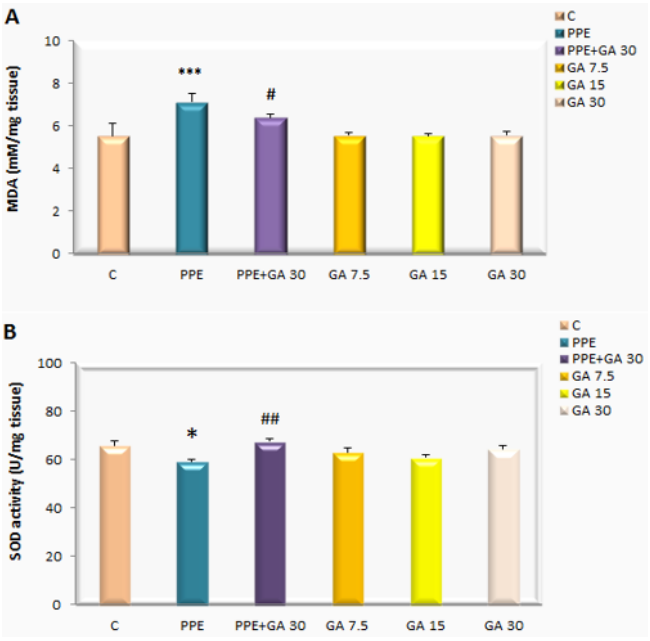

Figure 6. MDA levels and SOD in heart tissue rat in the groups of control, PPE, PPE+GA(30), GA (7.5, 15, and 30 mg/kg). *P<0.05 and ***P<0.001 vs control group, #P<0.05, ##P<0.01 vs PPE group. Data are expressed as mean±SEM (n=8)
MDA: malondialdehyde; SOD: superoxide dismutase; PPE: porcine pancreatic elastase; GA: gallic acid; C: control

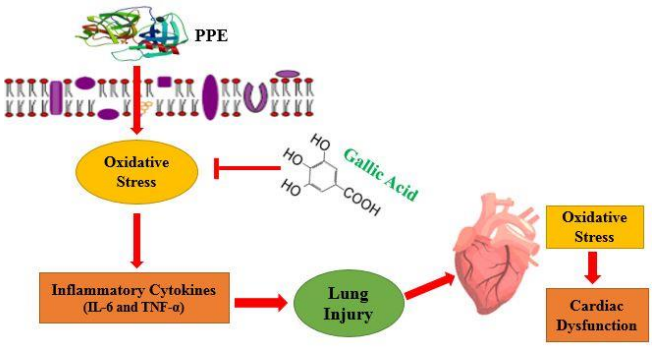

Figure 7. Schematic representation of the protective role of gallic acid against oxidative stress and inflammation pathway

Discussion

This study provided clear evidence that gallic acid protects the heart against injury induced by the animal emphysematous model. However, elastase instillation is not used as a causing agent of human emphysema, unlike smoke exposure, it offers the advantages of being inexpensive, easy to obtain (27) and more causing widespread lung injury (28). In addition, administrations of elastase results not only in lung injury but also in extra-pulmonary injury (29), which is more similar to the real-life consequences of COPD patients (30). Therefore, elastase-induced emphysema models can be useful for studying treatment strategies (27). In the present study, emphysema was induced by intra-tracheal injection of porcine pancreatic elastase which leads to lung injuries and systemic disorders such as dysfunction in the cardiac electrocardiogram and hemodynamic parameters. This study investigates changes in cardiac function affected in the emphysema model induced by elastase.

Several studies have pointed to the link between COPD (of which emphysema is a part) and cardiovascular disease, noting that systemic inflammation may be shared in both COPD and cardiovascular disease (8, 31, 32). Half of the patients with COPD die from cardiovascular dysfunction (33). Chronic inflammation is essential for COPD and has a considerable effect on the pathogenesis of disease and progression (34). Increased inflammatory cells in BALF have been documented both in PPE-induced emphysema and in patients with this disease (35). Numerous studies in COPD patients demonstrated some changes in different inflammatory cells, including lymphocytes and neutrophils (36, 37). A study showed increased number of infiltrated inflammatory cells into the lung in an animal model of COPD (38). Another study demonstrated that the activity of cytochrome oxidase was increased in circulating lymphocytes in patients with COPD. This disorder could also be observed in circulating lymphocytes in patients with other chronic inflammatory diseases (39). In one study, macrophages and neutrophils subsequently accumulated in the alveolar spaces and consequently in progressive airspace enlargement in the first month after elastase induction (40). However, neutrophils are important in the pathology of COPD. In the present study, the number of neutrophils in the BALF was very low, which is consistent with the findings of another study (41). After elastase injection, neutrophilic inflammation generally happens and is resolved after the first week (42, 43). The time period (28 days) estimated in this research work confirms the low number of neutrophils in BALF. The number of leukocytes in BALF was higher than the control group, and macrophages showed the highest increase compared with lymphocytes. In accordance with the findings in this study, other studies using the elastase model have shown that most BALF cells are macrophages (41, 43). A study showed that alveolar macrophages have high elastinolytic activity in the lungs of smokers instead of neutrophils, suggesting that macrophages cause induction and development of emphysema in smokers and also in animals exposed to cigarette smoke (44). The role of macrophages in COPD was determined by Retamales *et al.* (2001) who suggested that macrophages become activated and release pro-inflammatory cytokines such as TNF-α and interleukins which enhance lung inflammation and promote disease progression (35). Also, in another study, it was demonstrated that monocytes produce more TNF-α in COPD patients compared with the control group (45). A study demonstrated that IL-6 was transmitted from the lungs to the systemic circulation, as shown by differences in arteriovenous IL-6 levels due to increased lung inflammation and simultaneous lung permeability (46). Also, a study showed that serum levels of IL-6 were significantly increased during the exacerbation of the disease, which may be more involved in cardiovascular morbidity and mortality in COPD patients (47). TNF-α is an inflammatory cytokine mainly produced by inflammatory reactions (48).

Several studies have shown elevated levels of cytokines such as IL-6 and TNF-α in peripheral blood circulation in COPD patients (49-51). Another study showed that levels of TNF-α, IL-6, and IL-1β increased in sputum during emphysema in humans (52). Also, the present findings using an elastase-induced emphysema model indicate that the intra-tracheal administration of PPE can produce inflammation. Bronchoalveolar lavage fluid levels of TNF-α and IL-6 increased in emphysematous rats compared with the control group. We showed that gallic acid treatment reduced inflammatory cells such as macrophages and lymphocytes, and TNF-α and IL-6 levels, which probably affect the level of inflammatory cytokines. On the other hand, inflammation progression and oxidative stress are caused by the accumulation or overproduction of free radicals. Free radicals can cause lipid peroxidation (53). Malondialdehyde (MDA) is produced from peroxidation of lipids and is a marker of oxidative stress (54). The recent studies have shown that MDA is increased in people with COPD (55). Our study also showed a significant increase in MDA in emphysematous rats in comparison with the control group. Gallic acid significantly decreased the level of MDA. Decreased anti-oxidant levels or increased ROS levels induce oxidative stress. Anti-oxidant enzymes such as SOD have an important role in preventing oxidative stress (56). Our findings showed a significant decrease in the amount of SOD anti-oxidant enzyme in emphysematous rats but this enzyme is significantly increased by gallic acid.

On the other hand, Masson's trichrome staining was done to evaluate the deposition of collagen and elastic fibers, and the emphysematous group showed a significant increase in collagen fibers in the lung parenchyma. These findings confirm previous studies (41, 57). A few studies are investigating the effect of phenolic compounds in COPD. The inhibitory effect of polyphenolic compounds on elastase activity was shown by Bras *et al.* (58). Another study demonstrated that resveratrol decreases cytokine production by macrophages in COPD patients (59).

Gallic acid is a potent natural anti-oxidant with high content of phenolic compounds that have strong anti-inflammatory and anti-oxidant effects (60), and it has also cardioprotective effects (61). Several studies documented the cardioprotective effects of gallic acid when rat hearts were exposed to some materials such as isoproterenol and aluminum oxide (62, 63). In this regard, Ramezani-Aliakbari *et al.* (2017) showed that gallic acid has a protective role in ameliorating left ventricular function in the alloxan-induced diabetes model (64). The results obtained by a study showed that gallic acid could prevent the inflammation process in the respiratory and cardiovascular system induced by ambient particulate matters (24). A group demonstrated that gallic acid improves the cardiac function and electrocardiographic irregularities induced by doxorubicin (65). Badavi *et al.* (2016) showed that gallic acid increased the QRS voltage and decreased the QTc interval in a model of liver cirrhosis following induction of bile duct ligation (66). Also, another study reported that gallic acid pretreatment ameliorated $CaCl_2$-induced dysrhythmias (67). A study demonstrated that pre-treatment with gallic acid inhibited cardiotoxicity induced by isoproterenol (63). Also, another study reported that gallic acid increased the reduced hemodynamic parameters such as LVEDP, LVSP, LVDP, and RPP following I/R injury in hearts isolated from alloxan-induced diabetes mellitus (64). According to the results of this study, this is the first study that exhibited the significant adverse effects of elastase-induced emphysema on electrocardiogram and hemodynamic parameters. We observed that QRS complex voltage and heart rate reduced and following that QRS complex (s) and RR interval(s) showed a significant increase but the QT interval(s) showed a slight increase in emphysematous rats in comparison with the control group. Gallic acid significantly improved these parameters. Reduced QRS voltage causes the onset of factors such as myocardial injury (68). In the present study, we demonstrated a significant decrease in heart rate, LVDP, LVSP, +dp/dt, -dP/dt, and RPP in untreated rats of the PPE group, which is evidence of the development of severe myocardial injury. Gallic acid pretreatment preserves heart rate, LVDP, LVSP, +dp/dt, and RPP. Decreased LVDP and ±dp/dt (myocardial contraction and relaxation) is an index of reduction of contractile function (69). Also, LVSP can be considered as a marker for myocardial contraction (70). According to our findings, gallic acid increased myocardial contractility, improved hemodynamic parameters, and preserved ventricular function. This was shown by improvement in +dp/dt, resulting in increased cardiac output. Increased RPP is associated with enhancement of myocardial function and increased +dp/dt, which is considered an indicator of myocardial contractility (71).

Conclusion

Briefly, in the present study, it was found that gallic acid has a potent therapeutic effect on cardiac dysfunction caused by elastase-induced lung injury such as emphysema, which may be associated with its anti-oxidant and anti-inflammatory properties (Figure 7).

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Conflicts of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Tsukamoto M, Mori T, Wang KY, Okada Y, Fukuda H, Naito K, *et al*. Systemic bone loss, impaired osteogenic activity and type I muscle fiber atrophy in mice with elastase-induced pulmonary emphysema: Establishment of a COPD-related osteoporosis mouse model. Bone 2019;120:114-124.
2. MacNee W. Pathogenesis of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2:258-266.
3. Urban MH, Eickhoff P, Funk GC, Burghuber OC, Wolzt

M, Valipour A. Increased brachial intima-media thickness is associated with circulating levels of asymmetric dimethylarginine in patients with COPD. Int J Chron Obstruct Pulmon Dis 2017;12: 169-176.
4. Parr DG, White AJ, Bayley DL, Guest PJ, Stockley RA. Inflammation in sputum relates to progression of disease in subjects with COPD: a prospective descriptive study. Respir Res 2006 ;7:136.
5. Lombard C, Arzel L, Bouchu D, Wallach J, Saulnier J. Human leukocyte elastase hydrolysis of peptides derived from human elastin exon 24. Biochimie 2006;88:1915-1921.
6. Owen CA. Proteinases and oxidants as targets in the treatment of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2:373-385.
7. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 2003;21:347-360.
8. Sin DD, Man SP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003;107:1514-1519.
9. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination. Am J Med 2003;114:758-762.
10. Van Eeden S, Leipsic J, Paul Man SF, Sin DD. The relationship between lung inflammation and cardiovascular disease. Am J Respir Crit Care Med 2012;186:11-16.
11. Gupta NK, Agrawal RK, Srivastav AB, Ved ML. Echocardiographic evaluation of heart in chronic obstructive pulmonary disease patient and its co-relation with the severity of disease. Lung India 2011;28:105-109.
12. Leuchte HH, Baumgartner RA, Nounou ME, Vogeser M, Neurohr C, Trautnitz M, *et al*. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. Am J Respir Crit Care Med 2006;173:744-750.
13. Maclay JD, McALLISTER DA, MacNEE W. Cardiovascular risk in chronic obstructive pulmonary disease. Respirology 2007;12:634-641.
14. Đorović J, Marković JM, Stepanić V, Begović N, Amić D, Marković Z. Influence of different free radicals on scavenging potency of gallic acid. J Mol Model 2014 ;20:2345.
15. Ahmadi-Naji R, Heidarian E, Ghatreh-Samani K. Evaluation of the effects of the hydroalcoholic extract of *Terminalia chebula* fruits on diazinon-induced liver toxicity and oxidative stress in rats. Avicenna J Phytomed 2017;7:454-466.
16. Badhani B, Sharma N, Kakkar R. Gallic acid: a versatile anti-oxidant with promising therapeutic and industrial applications. RSC Adv 2015;5:27540-27557.
17. Faried A, Kurnia D, Faried LS, Usman N, Miyazaki T, Kato H, *et al*. Anticancer effects of gallic acid isolated from Indonesian herbal medicine, *Phaleria macrocarpa* (Scheff.) Boerl, on human cancer cell lines. Int J Oncol 2007;30:605-613.
18. Uniyal S, Dhasmana A, Tyagi A, Muyal JP. ATRA reduces inflammation and improves alveolar epithelium regeneration in emphysematous rat lung. Biomed Pharmacother 2018;108:1435-1450.
19. Badavi M, Sadeghi N, Dianat M, Samarbafzadeh A. Effects of gallic acid and cyclosporine a on anti-oxidant capacity and cardiac markers of rat isolated heart after ischemia/ reperfusion. Iran Red Crescent Med J 2014;16: 16424.
20. Dianat M, Radan M, Badavi M, Mard SA, Bayati V, Ahmadizadeh M. Crocin attenuates cigarette smoke-induced lung injury and cardiac dysfunction by anti-oxidative effects: the role of Nrf2 anti-oxidant system in preventing oxidative stress. Respir Res 2018;19:58.
21. Zaghloul MS, Said E, Suddek GM, Salem HA. Crocin attenuates lung inflammation and pulmonary vascular dysfunction in a rat model of bleomycin-induced pulmonary fibrosis. Life Sci 2019 ;235:116794.
22. Vosooghi S, Mahmoudabady M, Neamati A, Aghababa H. Preventive effects of hydroalcoholic extract of saffron on hematological parameters of experimental asthmatic rats. Avicenna J Phytomed 2013;3:279-287.
23. Gao ML, Chen L, Li YF, Xue XC, Chen L, Wang LN, *et al*. Synergistic increase of oxidative stress and tumor markers in PAH-exposed workers. Asian Pac J Cancer Prev 2014 ;15:7105-7112.
24. Radan M, Dianat M, Badavi M, Mard SA, Bayati V, Goudarzi G. Gallic acid protects particulate matter (PM 10) triggers cardiac oxidative stress and inflammation causing heart adverse events in rats. Environ Sci Pollut Res Int 2019 ;26:18200-18207.
25. Kheiry M, Dianat M, Badavi M, Mard SA, Bayati V. p-Coumaric acid protects cardiac function against lipopolysaccharide-induced acute lung injury by attenuation of oxidative stress. Iran J Basic Med Sci 2019 ;22:949-955.
26. Dianat M , Radmanesh E , Badavi M , Mard SA , Goudarzi G. Disturbance effects of PM 10 on iNOS and eNOS mRNA expression levels and anti-oxidant activity induced by ischemia–reperfusion injury in isolated rat heart: protective role of vanillic acid. Environ Sci Pollut Res Int 2016;23:5154-5165.
27. Wright JL, Cosio M, Churg A. Animal models of chronic obstructive pulmonary disease. Am J Physiol Lung Cell Mol Physiol 2008;295:L1-L15.
28. Antunes MA, Rocco PR. Elastase-induced pulmonary emphysema: insights from experimental models. An Acad Bras Cienc 2011;83:1385-1396.
29. Lüthje L, Raupach T, Michels H, Unsöld B, Hasenfuss G, Kögler H, *et al*. Exercise intolerance and systemic manifestations of pulmonary emphysema in a mouse model. Respir Res 2009 ;10:7.
30. Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J Chron Obstruct Pulmon Dis 2014;9:871-888.
31. Agusti À, Soriano JB. COPD as a systemic disease. COPD 2008 ;5:133-138.
32. Visca D, Aiello M, Chetta A. Cardiovascular function in pulmonary emphysema. Biomed Res Int 2013;2013:184678.
33. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, *et al*. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. JAMA 1994;272:1497-1505.
34. Chung K, Adcock I. Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. Eur Respir J 2008 ;31:1334-1356.
35. Retamales I, Elliott WM, Meshi B, Coxson HO, Pare PD, Sciurba FC, *et al*. Amplification of inflammation in emphysema and its association with latent adenoviral infection. Am J Respir Crit Care Med 2001;164:469-473.
36. Donovan C, Starkey MR, Kim RY, Rana BM, Barlow JL, Jones B, *et al*. Roles for T/B lymphocytes and ILC2s in experimental chronic obstructive pulmonary disease. J Leukoc Biol 2019 ;105:143-150.
37. Arellano-Orden E, Calero C, López-Ramírez C, Sánchez-López V, López-Villalobos JL, Arranz MA, *et al*. Evaluation of lung parenchyma, blood vessels, and peripheral blood lymphocytes as a potential source of acute phase reactants in patients with COPD. Int J Chron Obstruct Pulmon Dis 2019;14:1323-1332.
38. Lin J, Xu F, Wang G, Kong L, Luo Q, Lv Y, *et al*. Paeoniflorin attenuated oxidative stress in rat COPD model induced by cigarette smoke. Evid Based Complement Alternat Med 2016;2016:1698379.
39. Sauleda J, Garci´a-palmer FJ, Gonza´ lez GE, Palou A, A

gusti´ AG. The activity of cytochrome oxidase is increased in circulating lymphocytes of patients with chronic obstructive pulmonary disease, asthma, and chronic arthritis. Am J Respir Crit Care Med 2000;161:32-35.
40. Shapiro SD. Animal models for COPD. Chest 2000;117:223-227.
41. Taguchi L, Pinheiro NM, Olivo CR, Choqueta-Toledo A, Grecco SS, Lopes FD, *et al*. A flavanone from *Baccharis retusa* (Asteraceae) prevents elastase-induced emphysema in mice by regulating NF-κB, oxidative stress and metalloproteinases. Respir Res 2015;16:79-93.
42. Kawakami M, Matsuo Y, Yoshiura K, Nagase T, Yamashita N. Sequential and quantitative analysis of a murine model of elastase-induced emphysema. Biol Pharm Bull 2008 ;31:1434-1438.
43. Anciaes AM, Olivo CR, Prado CM, Kagohara KH, Pinto TD, Moriya HT, *et al*. Respiratory mechanics do not always mirror pulmonary histological changes in emphysema. Clinics 2011;66:1797-1803.
44. Ofulue AF, Ko M. Effects of depletion of neutrophils or macrophages on development of cigarette smoke-induced emphysema. Am J Physiol Lung Cell Mol Physiol 1999;277:L97-L105.
45. De Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM. Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. Am J Respir Crit Care Med 1996;153:633-637.
46. Tamagawa E, Suda K, Wei Y, Xing L, Mui T, Li Y, *et al*. Endotoxin-induced translocation of interleukin-6 from lungs to the systemic circulation. Innate Immun 2009 ;15:251-258.
47. Wedzicha JA, Seemungal TA, MacCallum PK, Paul EA, Donaldson GC, Bhowmik A, *et al*. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. Thromb Haemost 2000;84:210-215.
48. Pinto-Plata VM, Müllerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, *et al*. C-reactive protein in patients with COPD, control smokers and non-smokers. Thorax 2006 ;61:23-28.
49. Yao Y, Zhou J, Diao X, Wang S. Association between tumor necrosis factor-α and chronic obstructive pulmonary disease: a systematic review and meta-analysis. Ther Adv Respir Dis 2019 ;13:1753466619866096.
50. Fujita M, Ouchi H, Ikegame S, Harada E, Matsumoto T, Uchino J, *et al*. Critical role of tumor necrosis factor receptor 1 in the pathogenesis of pulmonary emphysema in mice. Int J Chron Obstruct Pulmon Dis 2016;11:1705-1712.
51. Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, *et al*. Inflammatory response and body composition in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:1414-1418.
52. Kersul AL, Iglesias A, Ríos Á, Noguera A, Forteza A, Serra E, *et al*. Molecular mechanisms of inflammation during exacerbations of chronic obstructive pulmonary disease. Arch Bronconeumol 2011;47:176-183.
53. Pashkow FJ. Oxidative stress and inflammation in heart disease: do anti-oxidants have a role in treatment and/or prevention? Int J Inflam 2011;2011:514623.
54. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351:2611-2618.
55. Montaño M , Cisneros J, Ramírez-Venegas A, Pedraza-Chaverri J, Mercado D, Ramos C, *et al*. Malondialdehyde and superoxide dismutase correlate with FEV(1) in patients with COPD associated with wood smoke exposure and tobacco smoking. Inhal Toxicol 2010;22:868-674.
56. Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 2012 ;125:773-781.
57. Anciães AM, Olivo CR, Prado CM, Kagohara KH, Pinto Tda S, Moriya HT, *et al*. Respiratory mechanics do not always mirror pulmonary histological changes in emphysema. Clinics (Sao Paulo) 2011;66:1797-1803.
58. Bras NF, Goncalves R, Mateus N, Fernandes PA, Ramos MJ, de Freitas V. Inhibition of pancreatic elastase by polyphenolic compounds. J Agric Food Chem 2010;58:10668-10676.
59. Culpitt SV, Rogers DF, Fenwick PS, Shah P, De Matos C, Russell RE, *et al*. Inhibition by red wine extract, resveratrol, of cytokine release by alveolar macrophages in COPD. Thorax 2003;58:942-946.
60. Akbari G. Molecular mechanisms underlying gallic acid effects against cardiovascular diseases: An update review. Avicenna J Phytomed 2020;10:11-23.
61. Appeldoorn CC, Bonnefoy A, Lutters BC, Daenens K, van Berkel TJ, Hoylaerts MF, *et al*. Gallic acid antagonizes P-selectin–mediated platelet–leukocyte interactions: implications for the French paradox. Circulation 2005;111:106-112.
62. El-Hussainy EH, Hussein AM, Abdel-Aziz A, El-Mehasseb I. Effects of aluminum oxide (Al_2O_3) nanoparticles on ECG, myocardial inflammatory cytokines, redox state, and connexin 43 and lipid profile in rats: possible cardioprotective effect of gallic acid. Can J Physiol Pharmacol 2016 ;94:868-678.
63. Prince PSM, Priscilla H, Devika PT. Gallic acid prevents lysosomal damage in isoproterenol induced cardiotoxicity in Wistar rats. Eur J Pharmacol 2009;615:139-143.
64. Ramezani-Aliakbari F, Badavi M, Dianat M, Mard SA, Ahangarpour A. Effects of gallic acid on hemodynamic parameters and infarct size after ischemia-reperfusion in isolated rat hearts with alloxan-induced diabetes. Biomed Pharmacother 2017;96:612-618.
65. Omóbòwálé TO, Oyagbemi AA, Folasire AM, Ajibade TO, Asenuga ER, Adejumobi OA, *et al*. Ameliorative effect of gallic acid on doxorubicin-induced cardiac dysfunction in rats. J Basic Clin Physiol Pharmacol 2018;29:19-27.
66. Badavi M, Barzegar F, Dianat M, Mard SA. Evaluation of the effect of gallic acid on QT interval prolongation and serum billirubin in rat model of liver cirrhosis. Res J Pharm Biol Chem Sci 2016;7:586-592.
67. Dianat M, Akbari G, Badavi M. Antidysrhythmic effects of aallic acid on $CaCl_2$-induced arrhythmia in rat. Int J Res Dev Pharm L Sc 2013;2:686-689.
68. Zhou R, Xu Q, Zheng P, Yan L, Zheng J, Dai G. Cardioprotective effect of fluvastatin on isoproterenol-induced myocardial infarction in rat. Eur J Pharmacol 2008;586:244-250.
69. Osada M, Netticadan T, Tamura K, Dhalla NS. Modification of ischemia-reperfusion-induced changes in cardiac sarcoplasmic reticulum by preconditioning. Am J Physiol 1998;274:H2025-2034.
70. Goyal S, Siddiqui MK, Siddiqui KM, Arora S, Mittal R, Joshi S, *et al*. Cardioprotective effect of 'Khamira Abresham Hakim Arshad Wala'a unani formulation in isoproterenol-induced myocardial necrosis in rats. Exp Toxicol Pathol 2010 ;62:61-74.
71. Giussani DA, Camm EJ, Niu Y, Richter HG, Blanco CE, Gottschalk R, *et al*. Developmental programming of cardiovascular dysfunction by prenatal hypoxia and oxidative stress. PLoS One 2012;7: 31017-31026.