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Original Article

Solitary and Synergistic Influences of Eugenol and Curcumin against Induced Bronchial Asthma in Male Rats

Hani M. Abdelsalam

ABSTRACT

Background and Aim: Asthma crosstalk has recently gained growing scientific attention, especially in the terrifying existence of COVID-19 that affected specifically the function of the respiratory system and led to death. Thus, this study aimed to determine how and if natural products as eugenol (Eug) and curcumin (Cur) can appoint the promising recovery and treatment of induced bronchial asthma. **Methods:** Forty male albino rats were included and randomly divided into five groups: Group I (control group), Group II (asthma group), Group III (Eug+Asthma group), Group IV (Cur+Asthma group), and Group V (Eug+Cur+Asthma group). Complete blood count (CBC) and biochemical estimation of serum urea, creatinine, and blood urea nitrogen (BUN) levels, lipid profile, and high-sensitivity C-reactive protein (hs-CRP) and pulmonary tissue homogenate levels were performed to evaluating inflammatory markers (IL-1β, IL-4, and TNF-α). **Results:** Eug and Cur significantly improve urea, creatinine, and BUN levels and lipid profile. Moreover, restoring the normal levels of CBC and inflammatory markers (hs-CRP, IL-1β, IL-4, and TNF-α) ameliorates the stress of asthma on the function of the respiratory system. **Conclusion:** Solitary and synergistic therapeutic effects of Eug and Cur on experimental induced asthma model owes principally to promoting the improvement of kidney and pulmonary functions by reducing inflammatory stress.
Key words: Eugenol, Curcumin, Asthma, Inflammatory markers, Experimental model.

INTRODUCTION

Asthma is a chronic inflammatory malady of the airways and distinguished by variational and recurring signs and airflow congestion and bronchospasm. The communal symptoms of asthma include wheezing, coughing, chest tightness, and shortness of breath. According to the report of the WHO, nearly 300 million individuals were newly identified with asthma annually, and around 250,000 deaths were linked with this disease.[1]

The pathogenesis of chronic obstructive lung disorders, such as asthma and chronic obstructive pulmonary disease, is complex. It involves both airway inflammation and oxidant/antioxidant flaw.[2,3] Reactive oxygen species have been revealed to be associated with the pathogenesis of asthma by inducing bronchial hyperreactivity.[4] Oxygen radicals can cause asthma pathology by oxidation or nitration of proteins, lipids, or DNA to cause dysfunction of these molecules. Moreover, the physiological antioxidant system is weakened in asthma, possibly because of inflammation.[5]

Ovalbumin (OVA)-induced eosinophilic asthma exhibited characteristic features such as airway inflammation (with significant eosinophil infiltrates), airway hyperresponsiveness, and airway transformation (with increased mucus secretion of epithelial goblet cells).[6]

Curcumin is a lively ingredient extracted from the perennial herb *Curcuma longa* (turmeric). It has powerful antifibrotic, antioxidant, anti-inflammatory, antiviral, and antitumor properties.[7] Anti-inflammatory effects of Curcumin take place by hindering the release of proinflammatory cytokines and regulating the activity of adhesion molecules.[8] Previous studies have shown that curcumin may relieve asthma in a mouse model by inhibiting T-helper 17 cells and augmenting the activity of regulatory T cells.[9] Simultaneously, curcumin could diminish airway inflammation in asthmatic animal models.[10] Subhashini *et al.* demonstrated that OVA-induced airway inflammation was decreased by curcumin involved in the suppression of p38 MAPK, ERK 42/44, and JNK 54/56 activation in mice.[11]

Eugenol (4-allyl-2-methoxyphenol) is a yellow viscous oil at normal temperature. Previous studies have reported biological activities of eugenol, counting antibacterial,[12] antifungal,[13] and anti-allergic[14] properties. The anti-asthmatic influence of eugenol has been recently reported in a mouse model where eugenol was shown to affect the vitamin D3-upregulated protein 1/NF-κB pathway.[15] Recently, eugenol has paid the attention of many researchers because of its anti-inflammatory and chemoprotective special effects and antioxidant

Hani M. Abdelsalam

Department of Zoology, Faculty of Science, Zagazig University, EGYPT.

***Correspondence**

Hani Mohamed Abdelsalam
Faculty of Science, Zagazig University, Zagazig, 44519, Asharquia, EGYPT.

Phone: 00201008051012

Email: hani.abdelsalam@su.edu.eg

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activity[16] due to the presence of phenolic group in its structure. Because of wide pharmacological and biological activities, studies on eugenol and plant species that include this substance are still a priority in research. Relating to the inflammatory process, several studies demonstrate the anti-inflammatory activity of eugenol. It was shown that eugenol stimulated a reduction in carrageenan-induced pleural volumes in mice.[17] Furthermore, eugenol causes suppression of proinflammatory markers, such as cyclo-oxygenase-2, necrosis factor-κB, interleukin-6, leukotriene C4, and 5-LOX.[18]

MATERIALS AND METHODS

Experimental Animals

Forty healthy adult male Wistar albino rats weighing 160–180 g were obtained and maintained at the Breeding Animal House of the Faculty of Medicine, Zagazig University, Egypt. Animals were kept for acclimatization in plastic cages with stainless steel wire-bar lid at a controlled temperature (23°C ±1°C) and humidity (55% ±5%) in an artificially illuminated room (12:12-h light: dark cycle), completely free from chemical contamination. They were fed standard laboratory food and allowed to access it and drink water freely. All rats received humane care in compliance with the Ethical Committee of Zagazig University and compliant with the National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animals.

Experimental Design

The animals were assigned to the following groups:

Group I (control group): Eight rats were included and received no treatment for 3 weeks.

Group II (asthma group) (animal sensitization): Eight rats were included and sensitized, as shown in Figure 1, and concisely 1 mg/kg OVA[18] (Sigma Chemical Ltd., UK) plus 100 mg Al(OH)3 (Sigma Chemical Ltd., UK) was administered intraperitoneally (i.p.), and rats were exposed to 2% OA aerosol with airflow of 8 L/min for 20 min/day in a 0.8 m^3 chamber, with normal breathing in animals. Saline was used instead of the OVA solution in the control rats.[19]

Group III (Eug+Asthma group): Eight rats were included and sensitized as the abovementioned group; then, on day 15, eugenol (pure 95 %) was purchased from the National Institutes for Food and Drug Control (Beijing, China) and administered by gavage at the doses of 100 mg/kg body weight[20] for 6 days based on individual weekly body weight.

Group IV (Curcumin+Asthma group): Eight rats were included and sensitized as the abovementioned group; then, on day 15, curcumin (100 mg/kg) was administered daily by gastric lavage.[21] Curcumin was purchased from Sigma-Aldrich Chemical Company (Cairo, Egypt). The required daily dose was suspended in 2 mL corn oil.

Group V (Eugenol+Curcumin+Asthma group): Eight rats were included and sensitized as the abovementioned group; then, on day 15, eugenol and curcumin were administered by gavage at the doses of 100 mg/kg body weight for 6 days based on individual weekly body weight.

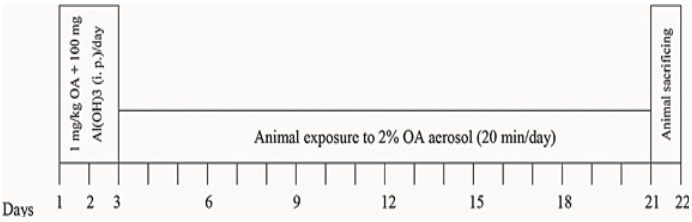

Figure 1: Sensitization method of rats by ovalbumin, 1 mg/kg + 100 mg Al(OH)3 as adjuvant and treatment of animals.

At the end of the experiment, blood samples were collected;[22] then, rats in all groups were sacrificed with intraperitoneal injection of 25 mg/kg sodium thiopental.[23] The lungs were collected and processed for light microscope examination.

Experimental Procedures

Collection of blood samples

Collection of blood sample took place from the retro-orbital venous plexus, under mild anesthesia, using a heparinized capillary tube inserted into the medial epicanthus of the rat's eye.[22] Clean graduated centrifuge tube is used to collect the blood samples, allowed to clot at room temperature for ten min, and then centrifuged using REMI cool centrifuge at 3 thousand rpm for twenty min. The supernatant serum was harvested in a dry clean tube for determination of biochemical factors. Biochemical measurements were carried out in the Central Research Laboratory (CRL), Faculty of Medicine, Zagazig University.

Complete blood count (CBC) analysis

CBC analysis was conducted using an automated analyzer: Excbio Analyzer (European Union, 2019), which counts and measures blood cells by detecting and measuring changes in electrical resistance when the cells in the conductive liquid passes through a small aperture of the machine and, hence, impedes the current and cause a measurable pulse. The volume of the cells is directly proportional to the height of the pulse, while the number of pulses specifies particle count, and the magnitude of the electrical pulse created is proportional to the cell's volume.

Determination of inflammatory factors in lung homogenate

The collected rat lung tissue (0.65 g) was ground and centrifuged at 5000 × g for 10 min at 4°C for preparation of lung homogenate. The IL−1β, IL−4 and TNF−α levels in rat lung homogenate were detected using the respective ELISA kits from Sigma−Aldrich, Merck KGaA, according to the manufacturer's instructions.

Biochemical estimation of serum urea, creatinine, and blood urea nitrogen (BUN) levels

Serum urea level was estimated by quantitative colorimetric method using QuantiChrom™ assay kits (BioAssay Systems, USA). The BUN was measured using a commercial kit (BUN II reagent kit; Wako Pure Chemical Industries).[24]

Biochemical estimation of serum lipid profile

Triglyceride, total cholesterol, HDL-cholesterol, and LDL-cholesterol levels were evaluated enzymatically using assay kits (Sigma Chemical Co, St Louis, MO, USA). VLDL-cholesterol level was calculated as triglyceride/5, and LDL-cholesterol level was calculated using the following equation: LDL-cholesterol= total serum cholesterol–(HDL + VLDL).[25]

Estimation of high-sensitivity C-reactive protein (hs-CRP)

C-reactive protein level was determined by immune turbidimetric assay (Iatron, Tokyo, Japan).[26]

Statistical Analysis of Data

The data of the present study were expressed as mean ± standard deviation. Statistical analysis was performed using the Statistical Package for the Social Sciences software version 13.00 (Chicago, Illinois, USA). Statistical significance was applied by one-way analysis of variance for

differences between the means of studied groups. P< 0.05 were reflected a statistical significance.

RESULTS

Effects of Eugenol and Curcumin on Hematological Parameters

All measured hematological parameters listed in Table 1 were significantly higher in the asthma group compared to the control group (P < 0.05), although lymphocyte level declined. In the Asthma+Eug, Asthma+Cur, and Asthma+Eug+Cur groups, all indices were significantly decreased (P <0.05), but the eosinophil and basophil levels increased only in the Asthma+Eug group compared to those in the asthma group, while platelet count decreased in the Asthma+Eug, Asthma+Cur, and Asthma+Eug+Cur groups compared to those in the asthma group, but it was not statistically significant.

Estimation of hs-CRP, TNF-α, IL-1β, and IL-4 Levels

Inflammatory markers (hs-CRP, TNF-α, IL-1β, and IL-4) exhibited statistically significantly higher mean in the asthma group compared to those in the control group (P < 0.05). Moreover, these markers significantly decreased (P < 0.05) in all treated groups (Asthma+Eug, Asthma+Cur, and Asthma+Eug+Cur) compared to those in the asthma group, as presented in Table 2.

Biochemical Estimation of Serum Urea, Creatinine, and BUN Levels

The asthma group exhibited statistically significantly higher mean serum urea, creatinine, and BUN levels compared to the control group (P < 0.05). Asthma+Eug and Asthma+Cur groups revealed significant lower levels compared to the asthma group. Moreover, a statistically significant decrease of serum urea, creatinine, and BUN levels was evident in the Asthma+Eug+Cur group compared to those in all studied groups, other than the control group (P < 0.05). Statistical results of various studied groups are presented in Table 3.

Estimation of Serum Lipid Profile

The asthma group exhibited statistically significantly higher mean total cholesterol and LDL-cholesterol compared to the control group (P < 0.05). The Asthma+Eug and Asthma+Cur groups revealed significant lower mean total cholesterol, triglyceride, and LDL-cholesterol levels compared to the asthma group (P > 0.05). Moreover, statistically significant decreased serum lipid profile levels was evident in the Asthma+Eug+Cur group compared to those in all studied groups, other than the control group (P < 0.05). Statistical results of various studied groups are presented in Figure 2.

DISCUSSION

Asthma is a disease of chronic airway inflammation causing symptoms of paroxysmal airflow obstruction, airway hyperresponsiveness to irritative

Table 1: Hematological profile of various studied groups.

	Groups				
Indices	Control	Asthma	Asthma+Eug	Asthma+Cur	Asthma+Eug+Cur
RBCs (10^6/μL)	7.57 ± 0.43	8.28 ± 0.33	7.08 ± 0.34[b]	6.83 ± 0.4[b]	6.19 ± 0.37[abc]
Hb (g/dL)	13.83 ± 0.5	15.14 ± 0.47[a]	13.79 ± 0.5[b]	14.07 ± 0.78	12.64 ± 0.81[b]
MCV (fL)	53.82 ± 1.49	55.76 ± 0.71	52.39 ± 1.23[b]	51.21 ± 0.99[ab]	49.91 ± 1.33[ab]
MCH (pg/cell)	19.10 ± 1.34	19.42 ± 1.46	18.39 ± 0.99	15.78 ± 0.66[ab]	14.55 ± 0.78[a b c d]
MCHC (g/dL)	32.68 ± 1.24	35.78 ± 0.84[a]	31.77 ± 0.97[b]	33.30 ± 1.22[b]	30.43 ± 1.29[abd]
Monocyte count (10^3/μL)	0.5 ± 0.06	1.54 ± 0.35[a]	0.77 ± 0.04a[b]	0.65 ± 0.06[ab]	0.54 ± 0.09[bcd]
Lymphocyte count (10^3/μL)	7.35 ± 0.62[a]	5.98 ± 0.59[a]	4.82 ± 0.67[a]	4.99 ± 0.26[ab]	4.16 ± 0.61[abd]
Neutrophil count (10^3/μL)	2.19 ± 0.47	4.960 ± 0.71[a]	2.746 ± 0.41[b]	3.455 ± 0.56[ab]	1.914 ± 0.48[bcd]
Eosinophil count (10^3/μL)	0.40 ± 0.11	2.24 ± 0.5[a]	3.46 ± 0.45[ab]	1.008 ± 0.16[ab]	1.82 ± 0.39[acd]
Basophil count (10^3/μL)	0.17 ± 0.04	0.42 ± 0.06[a]	1.46 ± 0.3[ab]	0.27 ± 0.09	0.53 ± 0.05[abcd]
Platelet count (10^5/μL)	602.5 ± 29.3	732.3 ± 44.61[a]	646.7 ± 36.57	717.3 ± 27.68[a]	659.4 ± 42.04

All values are expressed as mean ± SD, n = 8. [a]Significant vs control group, [b]Significant vs asthma group,[c]Significant vs Asthma+Eug group, [d]Significant vs Asthma+Cur group (*P* < 0.05). A one-way ANOVA followed by *post hoc* Tukey test multiple comparisons between groups.

Table 2: High-sensitivity C-reactive protein (hs-CRP), TNF-α, IL-1β, and IL-4 levels in various studied groups.

	Groups				
Variables	Control	Asthma	Asthma+Eug	Asthma+Cur	Asthma+Eug+Cur
hs-CRP (mg/dL)	4.46 ± 0.37	23.93 ± 2.48[a]	13.61 ± 2.29[ab]	17.31 ± 1.44[ab]	8.44 ± 1.05[abcd]
TNF-α (pg/mL)	12.32 ± 1.33	46.89 ± 1.45[a]	27.38 ± 1.22[ab]	33.69 ± 1.94[ab]	17.56 ± 1.46[abcd]
IL-1β (pg/mL)	36.75 ± 1.18	154 ± 2.57[a]	75.10 ± 3.37[ab]	94.12 ± 2.23[ab]	55.41 ± 1.34[abcd]
IL-4 (pg/mL)	2.63 ± 0.31	7.21 ± 0.23[a]	4.45 ± 0.35[ab]	5.44 ± 0.29[ab]	3.44 ± 0.26[abcd]

All values are expressed as mean ± SD, n = 8. [a]Significant vs control group, [b]Significant vs asthma group, [c]Significant vs asthma+Eug group, [d]Significant vs Asthma+Cur group (P < 0.05). A one-way ANOVA followed by *post hoc* Tukey test multiple comparisons between groups.

Table 3: Serum urea, creatinine, and BUN levels in various studied groups.

Variables	Groups				
	Control	Asthma	Asthma+Eug	Asthma+Cur	Asthma+Eug+Cur
Urea (mg/dL)	24.61± 1.3	75.5 ± 1.1[a]	35.35 ± 1.58[ab]	48.22 ± 2.42[ab]	27.41 ± 2.03[abcd]
Creatinine (mg/dL)	0.57 ± 0.02	0.84 ± 0.04[a]	0.73 ±0.04[ab]	0.6 ± 0.06[b]	0.55 ± 0.04[bc]
BUN (mg/dL)	21.79 ± 1.53	83.32 ± 1.8[a]	54.65 ± 1.98[ab]	64.04 ± 2.41[ab]	47.61 ± 1.8[abcd]

All values are expressed as mean ± SD, n = 8. [a]Significant vs control group, [b]Significant vs asthma group, [c]Significant vs asthma+Eug group, [d]Significant vs asthma+Cur group (P < 0.05). A one-way ANOVA followed by *post hoc* Tukey test multiple comparisons between groups.

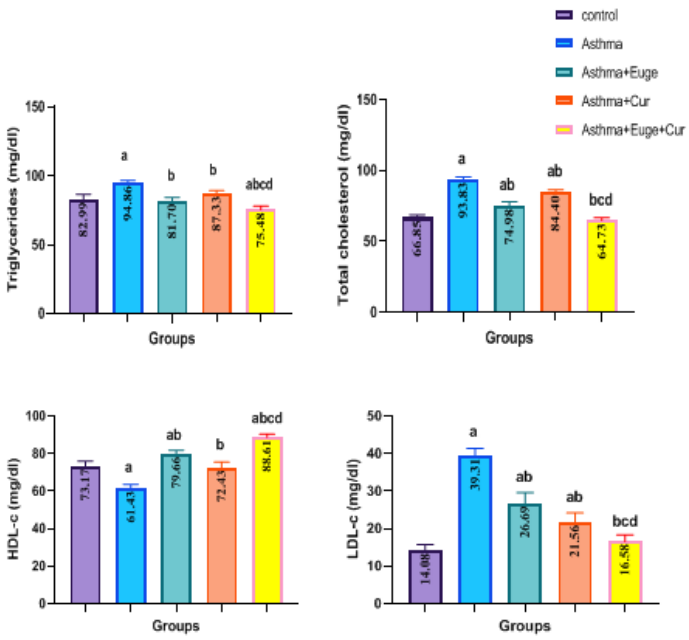

Figure 2: Serum Lipid profile in various studied groups.
All values are expressed as mean ± SD, n = 8. [a]Significant vs control group, [b]Significant vs asthma group, [c]Significant vs asthma+Eug group, [d]Significant vs asthma+Cur group (*P* < 0.05). A one-way ANOVA followed by *post hoc* Tukey test multiple comparisons between groups.

stimuli, wheezing, chest tightness, and coughing.[27] These symptoms develop against a background of allergic inflammation, characterized by infiltration of mast cells, eosinophils, and lymphocytes into the airway wall and causing mucus hypersecretion.[28] We intended to explore therapeutic potentials of single and combined eugenol and curcumin on the asthma experimental model.

The findings of the present study showed that red blood cell (RBC) count and their related indices (Hb, MCH, MCV, and MCHC) were increased in asthmatic rats. Erythrocytes count is raised during asthma due to contracted and inflamed airway tracts; thus, airflow declines and less oxygen arrives the lungs; moreover, asthma restrict oxygen-carrying capacity of RBCs, which makes the bone marrow produce more RBCs. Although the increase in RBC count in the asthma group was not significant compared with that in the control group. An increase in RBC count and Hb level in asthma cases might be due to increased erythropoietin production. Erythropoietin is the principal stimulator of erythropoiesis and induced under hypoxic conditions.[29] The erythrocyte count improves due to the stabilized effect of curcumin on the cell membrane of RBCs and restores various blood variables; moreover, it protects against lipid peroxidation and hemolysis of RBCs induced by H_2O_2.[30]

Curcumin markedly reduced the hemolysis and lipid peroxidation of erythrocytes and acts as a scavenger of NO by blocking the enzyme that produces it, thus exerting promoter activity.[31] NO and its producer iNOS downregulate neutrophil migration through downregulation of vascular cell adhesion molecule.[32]

In the present study, counts of all types of WBCs were elevated, but lymphocyte levels were decreased compared to that in the control group, while eugenol and curcumin treatments alter these investigations 180°. These results were in accordance with the results of Shakeri *et al.*[33] who showed increased total WBC, eosinophil, neutrophil, and monocyte levels, but a decrease in lymphocyte count in asthma compared to control animals. In the induction of an asthma model (sensitization) in rat, the decrease in lymphocyte count could probably be due to cell margination rather than destruction. It is also possible that eugenol contains agents that stimulate the bone marrow to produce neutrophils and release them into the blood.[34] Treatment with curcumin and dexamethasone decreased total WBC, eosinophil, neutrophil, and monocyte levels but increased lymphocyte count. Reduction in eosinophil, neutrophil, and monocyte levels in the asthma group treated with curcumin was observed by Shakeri *et al.*[33] who suggested that it occurred due to the anti-inflammatory effect of the plant. Therefore, this plant may have preventive effect on asthma by reducing inflammatory cells and airway inflammation. These findings are in line with those of Moghaddam *et al.*[35] who demonstrated that oral supplementation of dietary curcumin results in a marked reduction of total leukocyte and neutrophil counts induced by extrinsic and intrinsic inflammatory models in a dose-dependent manner in mice.

It is deduced that the inhibitory effect of eugenol and curcumin is in favor of anti-inflammatory effect of extract, which may be subsequently improved hyperresponsiveness and function of respiratory airways. The data of this investigation agree with the results obtained by Adamko *et al.* based on the increase in the number of mast cells, eosinophils, lymphocytes, neutrophils, and macrophages in the mucosal layer of the airway tract in patients with asthma.[36] Moreover, it is interpreted by Bloemen *et al.*, who stated that asthma is characterized by an inflammatory state resulting in activation of lung tissue cells and attraction and infiltration of leukocytes from the blood. The accumulation of eosinophilic leukocytes is a prominent feature of inflammatory reactions that occur in allergic asthma. The increase in number of eosinophils is important since it correlates in time with an increase in bronchial hyperresponsiveness.[37]

This study explained the increase in platelet number of sensitized rats; as in previous studies, platelet activation has been demonstrated in different inflammatory lung diseases, including asthma.[38] Release of mediators contained in all types of platelet granules, such as PAF and TGF-β, can occur after activation that helps improve the inflammation process during asthma. Eugenol and curcumin prevented the increase in platelet numbers in sensitized animals, which can support the

observations made in former studies to express the anti-inflammatory effect of saffron.[39]

Curcumin reduced platelet adhesion via modulation of the endothelium.[40] Taken together, these results demonstrated the preventive effect of eugenol and curcumin on WBC count, eosinophil percentage, and platelet number in the blood of sensitized rats, which can indicate the prophylactic effect of eugenol and curcumin on asthma.

Alveolar macrophages are richly present in the alveoli, distal airspaces, and conducting airways and have been considered the first line of defense against numerous agents. They produce both Th1 (TNF-α) and Th2 cytokines (IL-6 and IL-10), along with other inflammatory mediators, including nitric oxide and products of arachidonic acid metabolism, such as PGE2 and LTB4. Cytokine networks between alveolar-capillary cell membranes are pivotal in the initiation and propagation of the inflammatory response, leading to pulmonary injury.[41]

Biochemical investigations revealed that the inflammatory markers (hs-CRP, TNF-α, IL-1β, and IL-4) exhibited statistically significantly higher mean in the asthma group compared to the control group. This is explained by Possa *et al*., who stated that OVA is a well-known allergen for generating Th2 and eosinophil cell-mediated inflammatory responses.[42] Pan and Dong,[15] who used OVA to induce allergic asthma, demonstrated that eugenol administration suppressed OVA-induced eosinophilia in the lung, stopped the elevation of interleukin-4 and interleukin -5 levels, and reduced the necrosis factor-*κ*B signaling pathways. According to the authors, the inflammatory response reduction had a pivotal role in the anti-asthmatic effect of eugenol, resulting in the decrease in airway resistance.[15] Mediators, including proinflammatory cytokines and various chemokines, participate in the pathogenesis of asthma and have become key foci for new therapeutic approaches in treating this disease.[43]

IL-4 is responsible for the inhibition of Th1 and Th2 cell differentiation and expansion and has an important role in IgE production.[44] TNF-α is a major mediator of severe asthma, and it is demonstrated that soluble TNFR and antibodies against TNF-α[45] are effective in animal models of asthma, while eugenol and curcumin reduced the TNF-α levels in our model. CRP constitutes an inflammatory marker comprising an important inflammation-sensitive plasma protein generated by the liver.[46] Increased hs-CRP levels may be associated with allergic inflammation, particularly eosinophilic inflammation, and degree of airway obstruction in patients with asthma.[47] It was recently reported that increased hs-CRP levels are associated with respiratory symptoms in patients with asthma.

Moreover, it must state that different proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, and IL-18, have been synthesized by the activated proteins hs-CRP. The levels of these cytokines have increased due to asthmatic inflammation.[48]

The present results verified that eugenol and curcumin significantly suppressed the production of proinflammatory markers such as hs-CRP, IL-1β, IL-4, and TNF-α in OVA-challenged asthmatic rats. Eugenol was previously reported to inhibit the proinflammatory mediators (NO production and COX 2 expression) in lipopolysaccharide-induced RAW264.7 macrophages[49] and TNF-induced NF-kB activation in ML1-a cells.[50] These results are consistent with,[51] who suggested that eugenol has been shown to downregulate the TNF-α and IL-6 levels by inhibiting the activation of NF-κB pathway in acute lung injury model. The overproduction of reactive oxygen species and unbalanced glutathione redox status induce the activation of signal transduction pathways, including NF-κB pathway, which in turn regulates the transcription of inflammatory cytokines (TNF-α, IL-1β, and IL-6).[52] Yeh *et al*. demonstrated that eugenol inhibits the inducible nitric oxide synthase (iNOS) expression from macrophages in response to lipopolysaccharide- (LPS-), culminating in the reduction of NO levels. Additionally, eugenol also decreased the tumor necrosis factor-*α* and interleukin-1*β* and necrosis factor-*κ*B, ERK1/2, and p38 MAPK signaling pathways.[53] The authors suggested that anti-inflammatory effect of eugenol had main importance, since it was associated with the lessening of interleukin-1*β*, IL-6, and tumor necrosis factor-*α* levels causing a reduction of inflammatory cell.[54]

After treatment with different curcumin preparations, a decrease in cytokine production in rats was apparent. This might be attributed to the anti-oxidative and neutrophil inhibitory activity of curcumin.[55] Curcumin anti-oxidative influence and reduction in cytokine level were also revealed by,[56] who assessed the effectiveness of curcumin-loaded solid lipid nanoparticles for treatment of rheumatoid arthritis in rats. Curcumin also reduced the levels of immune cells (neutrophils and WBC) and proinflammatory cytokines–TNF-α, IL-1, and IL-6, which were close to that in healthy controls.[55] Moreover,[57] explained that curcumin also inhibited COX-2 expression in mouse macrophage cell line exposed to LPS,[58] inhibiting the production of TNF-α. Inactivation of two transcription factor genes, activator protein-1 (mediating cell proliferation) and nuclear factor-κB (mediating immune activity, inflammation, collagenase, and cell proliferation) may explain the inhibitory effects of curcumin on proinflammatory gene expression and suppression of inflammation.

Interestingly, a decline in proinflammatory markers indicated the improvement in lung function in animals treated with eugenol and curcumin, counteracting the allergen-induced bronchial hyperresponsiveness and blocking inflammatory cell infiltration (eosinophil, lymphocyte, and neutrophil) into the airways.

Huang *et al*.[59] found that patients with asthma were more likely to have chronic kidney disease (CKD) compared with controls. It is known that increased muscular contractions, which are a characteristic feature of acute asthma, are correlated with rhabdomyolysis, and rhabdomyolysis is further linked with acute renal failure.[60]

The asthma group exhibited significantly higher mean serum urea, creatinine, and BUN levels compared to the control group. The Asthma+Eug and Asthma+Cur groups revealed significant lower levels compared to the asthma group. Moreover, a significant decrease in serum urea, creatinine, and BUN levels was evident in the Asthma+Eug+Cur group compared to all studied groups other than the control group. Ejaz *et al*.[61] elucidated these findings, where he documented that there was significantly higher creatinine, urea, and BUN levels in patients with asthma compared to those in normal controls and concluded that there might be a relation between the pathogenesis of asthma and renal failure.

Pretreatment of rat with eugenol markedly protected the kidney against acute kidney injury and oxidative stress, as evidenced by the significant decrease in serum urea, creatinine, and LDH levels.[62] Eugenol significantly decreased plasma creatinine and BUN levels. A decline in creatinine clearance is one of the important evaluation parameter observed in diabetic nephropathy. Eugenol has improved the creatinine clearance in diabetic animals. This suggests improvement in kidney function. Reduction of plasma protein due to extra breakdown and excretion in urine is detected in diabetic condition. Treatment with eugenol have reversed this condition.[63]

Curcumin significantly and dose-dependently improved creatinine and urea clearance and decreased serum creatinine and BUN levels.[64] Long-term curcumin administration improves metabolic dyslipidemia and shows renoprotective effects in adenine-induced CKD.[65] Curcumin significantly decreased serum creatinine and urea levels and attenuated histopathological alterations in methotrexate-intoxicated rats.[66] Consistent with these results, treatment with curcumin significantly decreased creatinine and BUN levels and reduced histopathological

changes associated with 5/6 nephrectomized rats.[7] Di Tu *et al*.[67] found that curcumin at 300 mg/kg/day is effectively against renal function injury and reduced serum creatinine, BUN, and urine albumin levels and podocyte loss and suggested that curcumin attenuated the apoptosis level in kidney tissues by upregulating the Bcl-2 expression and declining the protein expression levels of Bax and caspase-3. In contrast, curcumin stimulates the transcription of genes, which induce the expression of antioxidant systems, such as glutathione peroxidase, glutathione-S-transferase, catalase, and superoxide dismutase.[68] Therefore, it can be concluded that curcumin possibly reduces leukocyte infiltration and functional disturbances in the rat kidney via supporting the kidney against oxidative stress.[69]

In this study, the asthma group exhibited statistically significantly higher mean total cholesterol and LDL-cholesterol compared to the control group. The Asthma+Eug and Asthma+Cur groups revealed significantly lower mean total cholesterol, triglyceride, and LDL-cholesterol levels compared to the asthma group. Moreover, statistically significantly decreased serum lipid profile levels was evident in the Asthma+Eug+Cur group compared to those in all studied groups other than the control group. These data are proved by,[59] who assessed the association between asthma and serum LDL and HDL levels. Furthermore,[70] found that high LDL levels were associated with concurrent asthma and airway obstruction and specific airway resistance. Vinding *et al*.[71] found that high HDL levels were associated with improved specific airway resistance, reduced bronchial hyperresponsiveness, and lower risk of aeroallergen sensitization. They also found that high triglyceride levels were associated with aeroallergen sensitization and a trend of increased exhaled nitric oxide. Villeneuve[72] found that LDL with proinflammatory effects could affect endothelial dysfunction and endothelial cell damage and promote the development of asthma.[73] Immoderate cholesterol load can motivate the innate immune system, a reaction that was only recently originate in the lungs. Cholesterol can manufacture lipid rafts in the plasma membrane. Studies have found that cholesterol levels in lipid rafts are significantly lower and may play an important role in the pathogenesis of asthma.[74] Meanwhile, a large epidemiological survey showed that total cholesterol and triglyceride levels were negatively correlated with the prevalence of asthma,[73] which is consistent with our experimental results. Hypercholesterolemic rats that had received eugenol had significantly lower mean serum levels of total cholesterol, triglycerides, LDL-cholesterol, and VLDL-cholesterol and significantly higher mean serum levels of HDL-cholesterol than those in hypercholesterolemic saline-treated rats and clarified that the lipid-lowering effect of eugenol and its active component in an experimental animal model of hypercholesterolemia is probably mediated through inhibition of hepatic cholesterol biosynthesis and reduction of lipid absorption in the intestine.[75] The lipid-lowering effect brought about by administration of eugenol might have been caused by reactivation of lipolytic enzymes for early clearance of lipids from the circulation in triton-induced hyperlipidemia. Our results are consistent with those of Vallianou *et al*.[76]

Curcumin might decrease absorption of cholesterol and increase the activity of cholesterol-7α-hydroxylase.[77] This hypocholesterolemic effect of curcumin may be attributed to its stimulatory effect on hepatic cholesterol-7α-hydroxylase enzyme, an enzyme that regulates cholesterol catabolism.[78] Curcumin was also reported to modulate (decrease) 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase enzyme activity to decrease serum and liver cholesterol, triglyceride, and free fatty acid levels.[79] The present results are in line with,[80] who noted that serum cholesterol, triglyceride, LDL, and VLDL levels were significantly decreased by curcumin treatment. Moreover, the results agree with those of Neerati *et al*., who examined the potential beneficial effects of curcumin capsules on blood lipids in patients with type 2 diabetes mellitus treated with glyburide. The results showed that, in the curcumin-treated group, the serum cholesterol, LDL, VLDL, and triglyceride levels were significantly decreased, and HDL levels were significantly increased.[81] Ding *et al*. showed that doses of 40 and 80 mg/kg curcumin were administered to diabetic rats, and results showed decrease in serum fasting blood sugar, insulin, cholesterol, triglyceride, and LDL levels and insulin resistance in the curcumin-treated diabetic rats. The causes of these effects of curcumin were reported as a decrease in lipid-regulating enzymes (HMG-COA reductase) in adipose tissue and hepatic gluconeogenic enzymes (glucose 6 phosphatase and phosphoenolpyruvate carboxykinase) and sterol regulatory element-binding protein cycle regulation.[82]

CONCLUSION

Eugenol and curcumin have a tremendous impact in recovery and amelioration of progressive symptoms of asthma by improving the inflammatory markers levels and counts of different types of WBCs and the global necessity in the presence of COVID-19 that affects mainly the respiratory system. Moreover, they have a considerable force in amending kidney functions and lipid profile in patients with asthma.

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CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest.

Ethical approval and consent to participate

All rats received humane care in compliance with the Ethical Committee of Zagazig University and in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals.

Availability of data materials

On Mendeley Data (https://data.mendeley.com/datasets/publish-confirmation/zzm3ft89s5/1)

ABBREVIATIONS

Eug: Eugenol; **Cur:** Curcumin; **OVA:** Ovalbumin; **CBC:** Complete Blood Count; **BUN:** Blood Urea Nitrogen; **hs-CRP:** High-Sensitivity C-Reactive Protein.

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