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Comparative effects of salbutamol, montelukast, prednisolone, and combination therapy on renal function and oxidative stress in ovalbumin-induced asthmatic rats

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ABSTRACT

Background: In addition to hyperresponsive airways and reversible airflow restrictions, bronchial asthma is also associated with systemic oxidative stress, which can negatively affect extra-pulmonary organs, including the kidneys. **Objective:** The purpose of this study was to determine the effects of salbutamol, montelukast, prednisolone, and their combinations on renal oxidative stress, antioxidant status, renal function indices, electrolyte balance, and kidney histology in ovalbumin-induced asthmatic Sprague-Dawley rats. **Methods:** A total of 64 female Sprague-Dawley rats were randomly assigned to eight groups: the negative control group, the positive control group, the salbutamol group, the montelukast group, the prednisolone group, the salbutamol/prednisolone group, and the prednisolone/montelukast group. The asthma was induced using ovalbumin sensitization and aerosol challenge. A 28-day course of oral treatment was administered. Upon completion of the study, serum and kidney samples were analyzed for malondialdehyde, hydrogen peroxide, nitric oxide, antioxidant enzymes, urea, creatinine, sodium, potassium, chloride, and histopathological changes. **Results:** Ovalbumin sensitisation produced renal oxidative and structural injury, the untreated asthmatic group showing glomerular distortion, tubular damage, inflammatory infiltration, and elevated malondialdehyde and hydrogen peroxide. Antioxidant responses were treatment-specific: salbutamol raised superoxide dismutase (1.16±0.09) and catalase activities (0.50±0.04), while salbutamol/prednisolone reduced both (0.58±0.03 and 0.26±0.01, respectively) ($p<0.05$); glutathione peroxidase was largely unchanged ($p>0.05$). The salbutamol/montelukast and prednisolone/montelukast combinations attenuated lipid peroxidation (0.55±0.07; 0.25±0.06, respectively), and hydrogen peroxide fell across most regimens. Serum changes were modest, reflecting altered tubular ion handling rather than overt renal failure. Histologically, prednisolone afforded the strongest single-agent protection and montelukast moderate protection, with prednisolone/montelukast yielding the best overall preservation of renal architecture. **Conclusion:** As a result of these findings, it appears that asthma exacerbates renal oxidative stress and that drug treatment has variable effects on the kidney. Combinations containing montelukast attenuated oxidative injury comparatively better than prednisolone/montelukast, whereas prednisolone/montelukast was associated with less favorable renal biochemical changes.

Keywords: Bronchial asthma, Kidney oxidative stress, Salbutamol, Montelukast, Prednisolone, Ovalbumin-induced asthma model.

INTRODUCTION

Symptoms of bronchial asthma include hyperresponsive bronchi, reversible airflow limitation, and recurrent wheezing, breathlessness, chest tightness, and coughing [1]. In addition to affecting the lungs, asthma is increasingly recognized as a systemic disease caused by persistent inflammation and oxidative stress [2]. This inflammatory response is mediated by eosinophils, neutrophils, macrophages, mast cells, and lymphocytes that release cytokines, leukotrienes, and reactive oxygen species [3,4]. Asthma is characterized by oxidative stress, which occurs when oxidants and antioxidants are imbalanced [5,6]. Anbar *et al* [7] and Rajizadeh *et al* [8] speculate that the kidney may be particularly susceptible to inflammation and oxidative stress.

Increasing oxidative stress associated with asthma alters renal physiology through lipid peroxidation, endothelial dysfunction, and antioxidant depletion [9]. Increased malondialdehyde levels, reduced activities of superoxide dismutase and catalase in inflammatory disease states, may cause renal

injury [10,11]. Renal dysfunction may initially appear as subtle biochemical changes or oxidative changes before obvious changes in serum urea and creatinine [12,13]. Thus, kidney tissue antioxidants, oxidants, electrolytes, and histology may provide a more sensitive assessment of asthma's extra-pulmonary consequences.

Asthma medications themselves may influence systemic oxidative stress as well as renal function [9]. A selective beta-2 adrenergic agonist, salbutamol, can provide effective bronchodilation. However, it may also alter sodium and potassium handling in the kidneys and, under some conditions, increase tissue injury and oxidative stress [9]. Prednisolone, a corticosteroid, suppresses inflammatory activity, although prolonged use may interfere with oxidative metabolism and affect renal function [14-16]. Studies have demonstrated that montelukast reduces renal oxidative stress, neutrophil infiltration, and lipid peroxidation and improves renal histology, suggesting renoprotective effects in asthma-related systemic inflammation [17-19].

Although salbutamol, montelukast, and prednisolone are individually well characterised as bronchodilatory, anti-leukotriene, and anti-inflammatory agents, respectively, their renal consequences appear to diverge in direction and mechanism, ranging from adaptive antioxidant induction and electrolyte perturbation to genuine renoprotection. These agents are, moreover, frequently co-administered in clinical asthma management, yet the renal repercussions of such combinations remain poorly defined, and it is not established whether concurrent suppression of inflammatory and leukotriene-mediated pathways confers additive protection or, conversely, unmasks unfavourable biochemical effects on the kidney. The present study was therefore designed to interrogate this gap by comparing the effects of salbutamol, montelukast, prednisolone, and their combinations on renal oxidative–antioxidant balance, biochemical function, electrolyte handling, and histoarchitecture in ovalbumin-induced asthmatic rats.

MATERIALS AND METHODS

Chemicals and reagents

All chemicals and reagents used were of analytical grade and obtained from reputable suppliers in India and China. Ovalbumin from LOBA CHEMIE (product code P0010-80, CAS (9006-59-1), and aluminium hydroxide (product code 00910, CAS 21645-51-2).

Ethical approval and experimental animals

This study was conducted in accordance with internationally accepted guidelines for the care and use of laboratory animals, as outlined by the National Research Council (NRC) [20]. Ethical approval was obtained from the University of Benin College of Medical Sciences Ethics Board before commencement of the study (Approval number: CMS/REC/2024/570). A total of 64 female Sprague-Dawley rats obtained from the Department of Anatomy at the University of Benin were used in the experiment. The animals were housed in a well-ventilated, temperature-controlled room under standard laboratory conditions and were provided standard rat chow and water ad libitum. The rats were allowed to acclimatize for 2 weeks before the experiment began.

Experimental design

After acclimatization, the animals were randomly assigned to 8 groups of 8 rats and studied over 7 weeks, comprising 2 weeks of acclimatization, 1 week of sensitization, and 4 weeks of ovalbumin challenge and drug treatment.

The groups were designated as follows:

- Group 1 (Negative control): non-asthmatic and untreated
- Group 2 (Positive control): ovalbumin-induced asthmatic rats, untreated
- Group 3: ovalbumin-induced asthmatic rats treated with salbutamol (1 mg/kg p.o.)
- Group 4: ovalbumin-induced asthmatic rats treated with montelukast (10 mg/kg p.o.)
- Group 5: ovalbumin-induced asthmatic rats treated with prednisolone (3 mg/kg p.o.)
- Group 6: ovalbumin-induced asthmatic rats treated with salbutamol + prednisolone
- Group 7: ovalbumin-induced asthmatic rats treated with salbutamol + montelukast
- Group 8: ovalbumin-induced asthmatic rats treated with prednisolone + montelukast

The combination therapy groups received the same doses as the monotherapy groups. Throughout the 28-day ovalbumin challenge, all medications were administered orally once daily.

Induction of experimental asthma

Adapted from Aloamaka and Nzoputam [9]. Experimental asthma was induced in Groups 2-8. Following acclimatization (14 days), 1 mg ovalbumin emulsified with 20 mg aluminum hydroxide in normal saline was injected intraperitoneally on days 14 and 21. To induce asthmatic responses, sensitized animals were exposed to aerosolized ovalbumin for 15 min, twice weekly for 28 days. Negative control animals received normal saline instead of ovalbumin.

Drug administration

In the 28-day challenge phase, salbutamol, montelukast, and prednisolone were administered orally once daily. Treatment groups received salbutamol, montelukast, and prednisolone, either individually or in combination. Based on previous experimental studies and established therapeutic relevance, drugs were selected and dosed.

Sample collection

After the experimental period, the animals were fasted overnight and euthanized under chloroform vapor anesthesia. By cardiac puncture, blood samples were collected into plain sample bottles, allowed to clot, and centrifuged to obtain serum. Icy-cold normal saline was used to rinse and dry both kidneys after carefully excising them. For histopathological examination, one kidney from each animal was fixed in 10% neutral buffered formalin, while the other was weighed and homogenized in ice-cold phosphate buffer.

Preparation of kidney homogenate

Kidney tissue homogenates were prepared using standard procedures. Briefly, renal tissue was homogenized in cold phosphate buffer, centrifuged, and the supernatant obtained was used to estimate total protein concentration, oxidative stress markers, and antioxidant enzyme activities.

Determination of kidney oxidative stress markers and antioxidant enzymes

Coomassie Brilliant Blue G-250 dye was used to measure total protein concentration in kidney tissue [21]. A thiobarbituric acid reactive substance method was used to measure malondialdehyde concentration [22]. Hydrogen peroxide concentration in kidney homogenates was determined spectrophotometrically following standard biochemical procedures [23]. The Griess reaction was used to estimate nitrite concentration indirectly [24]. Superoxide dismutase activity was assessed by measuring its ability to inhibit epinephrine autooxidation [25]. Catalase activity was determined using Aebi's method by monitoring hydrogen peroxide decomposition spectrophotometrically [26]. The peroxide substrate was utilized to determine glutathione peroxidase activity [27].

Determination of renal function indices and serum electrolytes

Using standard diagnostic methods, serum was analyzed for renal function markers. Standard laboratory procedures were used to determine serum electrolyte concentrations, including sodium, potassium, and chloride.

Histopathological examination of kidney tissue

Hematoxylin and eosin-stained kidney tissues embedded in paraffin wax and sectioned after 10% neutral buffered formalin fixation. Sections stained for renal histoarchitecture were examined under a light microscope for glomerular distortion, tubular degeneration, vascular congestion, inflammation, and interstitial changes. Photomicrographs were captured for documentation.

Statistical analysis

Data were expressed as the mean±standard error of the mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc multiple comparison test in GraphPad Prism. Differences were considered statistically significant at $p<0.05$.

RESULTS

Effects of montelukast, salbutamol, prednisolone, and their combinations on kidney tissue total protein, superoxide dismutase, catalase, and glutathione peroxidase

The result showed no significant difference between the negative and positive control groups in kidney tissue total protein concentration (Figure 1A) or glutathione peroxidase activity (Figure 1D), except for the salbutamol/prednisolone-treated groups, which showed a significant increase in total protein. There was a significant increase in superoxide dismutase (Figure 1B), and catalase activity (Figure 1C) in the salbutamol-treated group ($p<0.05$). Compared with the negative control, montelukast, prednisolone, salbutamol/prednisolone, and salbutamol/montelukast showed no significant differences. A significant decrease in superoxide dismutase and catalase activities was observed in the salbutamol/prednisolone-treated group ($p<0.05$).

Malondialdehyde, hydrogen peroxide, and nitric oxide changes in asthmatic rats treated with salbutamol, montelukast, prednisolone, and their combinations

The positive control and montelukast-treated groups showed significantly higher malondialdehyde levels (Figure 2A) than the negative control groups ($p<0.05$). Comparatively, salbutamol, prednisolone, salbutamol/prednisolone, salbutamol/montelukast, and prednisolone/montelukast did not show any significant differences. The salbutamol/montelukast and prednisolone/montelukast groups significantly decreased malondialdehyde ($p<0.05$). Compared with the negative control, the positive control, prednisolone, and the salbutamol/prednisolone groups showed significantly increased hydrogen peroxide concentration (Figure 2B), whereas the salbutamol, montelukast, salbutamol/montelukast, and prednisolone/montelukast groups did not differ significantly. As compared with the positive control, hydrogen peroxide was significantly decreased in the salbutamol, montelukast, salbutamol/prednisolone, and salbutamol/montelukast groups ($p<0.05$). Compared with the negative control, no significant difference in nitric oxide concentration (Figure 2C) was observed ($p>0.05$); however, nitric oxide concentration was significantly higher in the prednisolone, salbutamol/prednisolone, salbutamol/montelukast, and prednisolone/montelukast groups compared with the positive control group.

Effects of Salbutamol, Montelukast, Prednisolone, and Their Combination Therapies on Serum Urea, Creatinine, Sodium, Potassium, and Chloride Levels in Ovalbumin-Induced Asthmatic Rats

The prednisolone/montelukast-treated group had significantly lower serum urea concentrations (Figure 3A) than negative controls ($p<0.05$). The positive control group, salbutamol, montelukast, prednisolone, and salbutamol/prednisolone showed no significant difference ($p>0.05$) from the negative control group. Montelukast, prednisolone, salbutamol/montelukast, and prednisolone/montelukast significantly decreased serum urea compared to the positive control ($p<0.05$). Compared to both negative and positive controls, prednisolone/montelukast significantly increased serum creatinine (Figure 3B), and prednisolone significantly decreased it ($p<0.05$). The positive control, salbutamol group, montelukast group, salbutamol/prednisolone group, and salbutamol/montelukast group did not differ significantly from the negative control ($p>0.05$). Prednisolone treatment reduced serum potassium levels (Figure 3C) compared with the negative control ($p<0.05$), with no significant difference in the other groups relative to the negative control ($p>0.05$). Neither serum sodium (Figure 3D) nor chloride concentrations (Figure 3E) differed significantly from the negative control groups ($p>0.05$); however, compared with the positive control group, sodium increased significantly, and chloride decreased significantly ($p<0.05$). N=4±SEM. $^{\alpha}p<0.05$ compared with the negative control; $^{\Phi}p<0.05$ compared with the positive control.

Effect of Salbutamol, Montelukast, Prednisolone, and Their Combination Therapies on Renal Histoarchitecture in Asthmatic Rats

Compared with the negative control group (1), the positive control group (2) demonstrated inflammatory cell infiltration (IC), glomerular distortion, and tubular damage to the renal architecture (Figure 4). Despite persistent inflammation, salbutamol (3) showed mild improvement, montelukast (4) provided moderate protection with reduced inflammation, while prednisolone (5) markedly improved renal morphology. Combination therapy was more effective: salbutamol/prednisolone (6) demonstrated minimal inflammation and near-normal structure; salbutamol/montelukast (7) showed moderate improvement; and prednisolone/montelukast (8) demonstrated the best preservation of renal architecture with minimal inflammation.

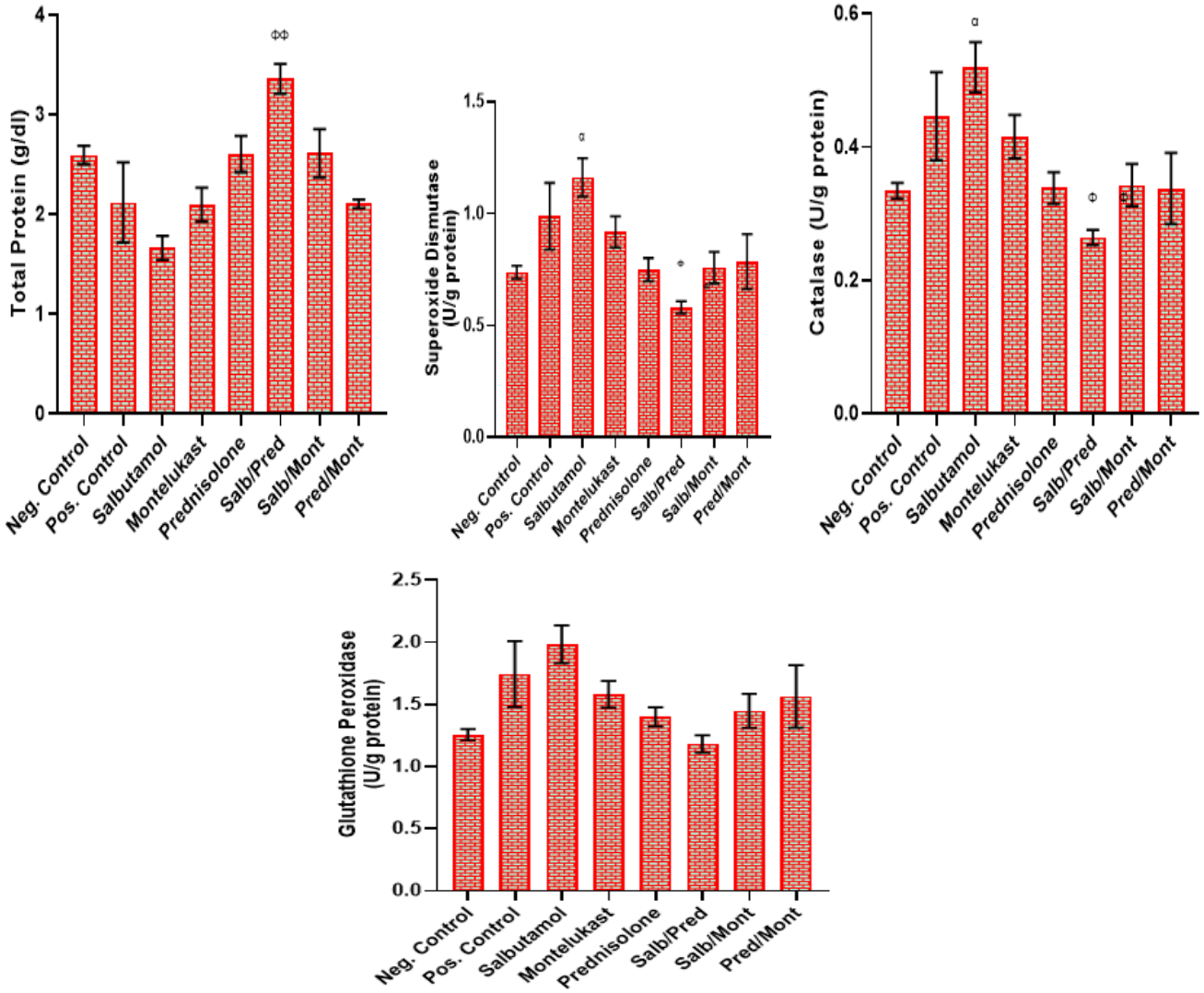

Figure 1: Effect of salbutamol, montelukast, prednisolone, and their combinations on kidney tissue (1A) total protein concentration and antioxidant enzyme activities ((1B) superoxide dismutase, (1C) catalase, and (1D) glutathione peroxidase) in asthmatic rats. N=4±SEM. $^{\alpha}p<0.05$ compared with the negative control; $^{\Phi}p<0.05$ compared with the positive control.

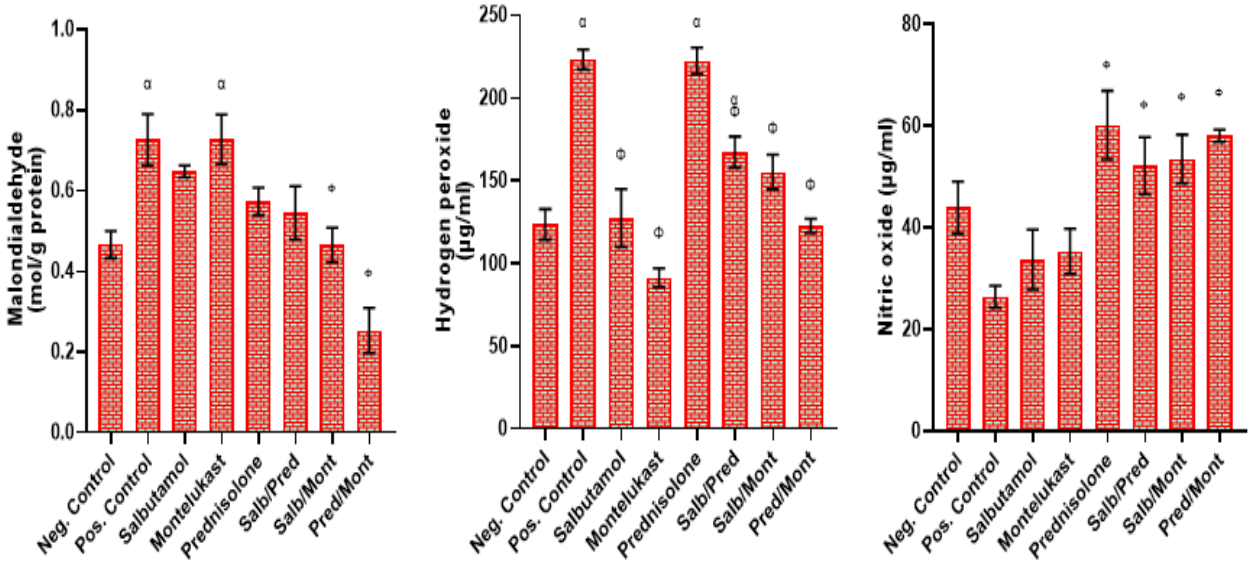

Figure 2: Effect of salbutamol, montelukast, prednisolone, and their combinations on kidney tissue (2A) malondialdehyde, (2B) hydrogen peroxide, and (2C) nitric oxide concentrations in asthmatic rats. N=4±SEM. $^{\alpha}p<0.05$ compared with the negative control; $^{\Phi}p<0.05$ compared with the positive control.

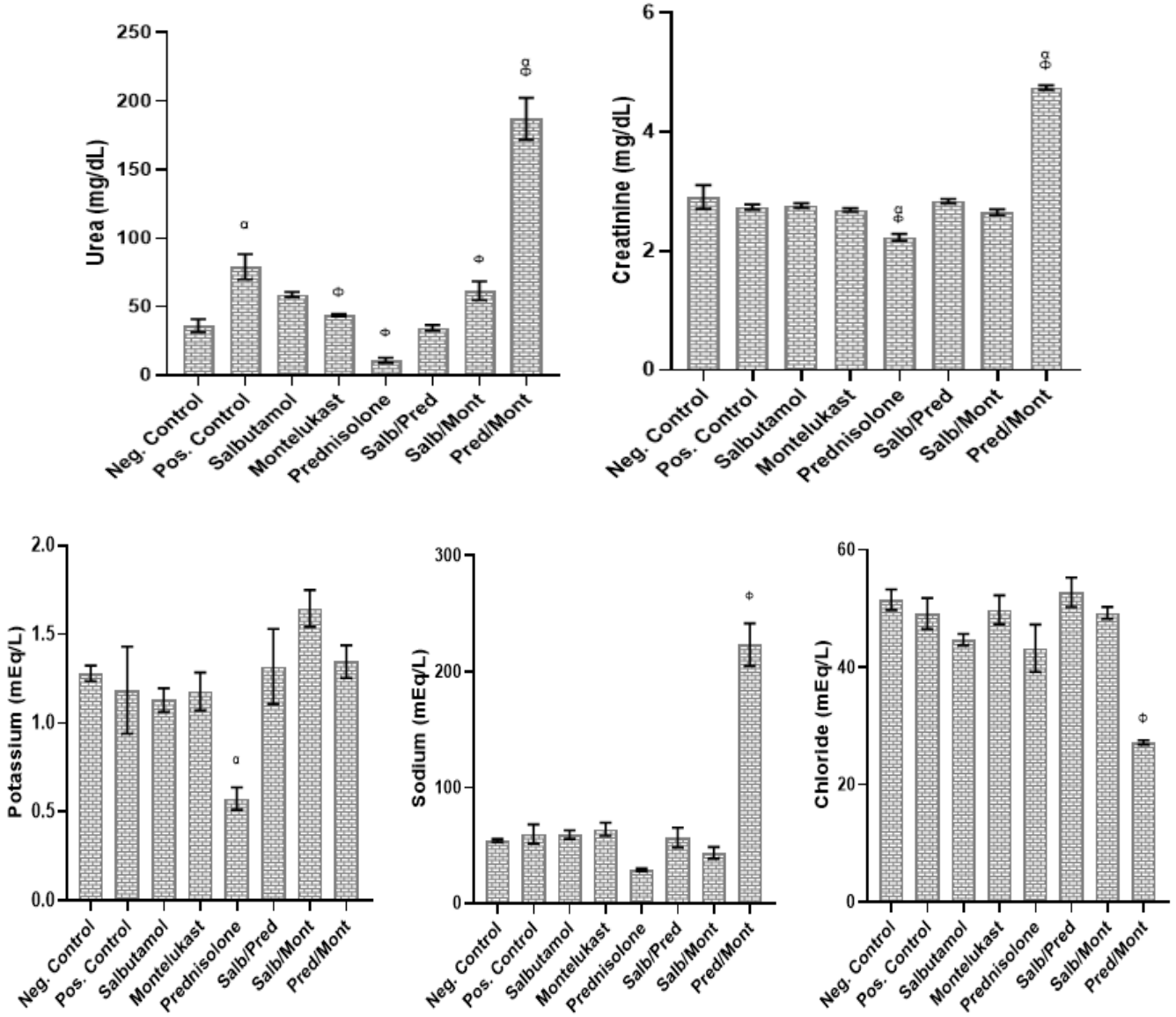

Figure 3: Effect of salbutamol, montelukast, prednisolone, and their combinations on serum (3A) urea, (3B) creatinine, (3C) potassium, (3D) sodium, and (3E) chloride concentrations in asthmatic rats.N=4±SEM. $^{\alpha}p<0.05$ compared with the negative control; $^{\Phi}p<0.05$ compared with the positive control.

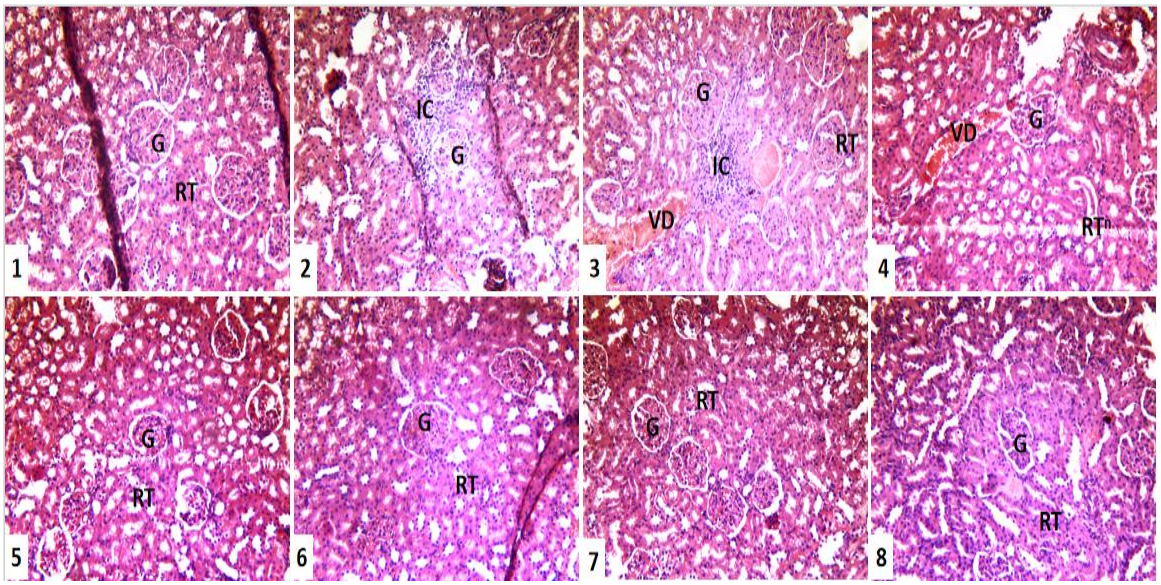

Figure 4a: Histopathological evaluation of renal tissue across experimental groups (H&E staining, x100)

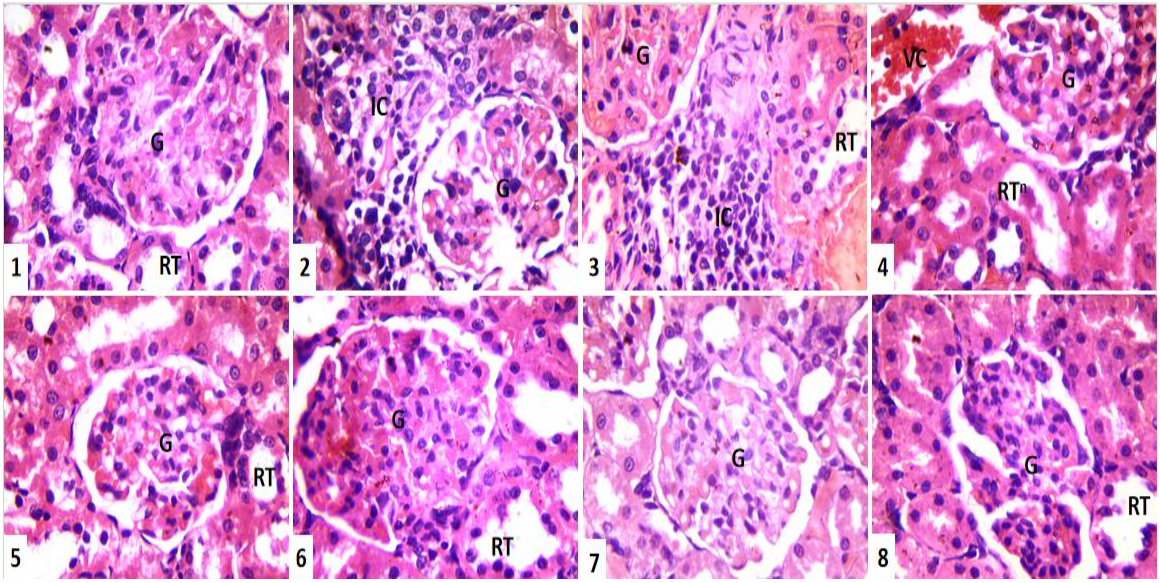

Figure 4b: Histopathological evaluation of renal tissue across experimental groups (H&E staining, x400)
Photomicrographs demonstrating kidney sections from (1) positive control, (2) salbutamol-treated, (3) montelukast-treated, (5) prednisolone-treated rats, (6) salbutamol/prednisolone-treated rats, (7) salbutamol/montelukast-treated rats, and (8) prednisolone/montelukast-treated rats.

DISCUSSION

In the present study, asthma induction resulted in renal injury characterized by histopathological changes, oxidative imbalance, and modest changes in biochemical indices, indicating that asthma is an inflammatory and oxidative systemic disorder [4,9,28,29]. The findings are in agreement with reports that chronic inflammation, reactive oxygen species generation, and reduced antioxidant defenses contribute to asthma-related renal injury [7,9,30]. Renal involvement occurs during systemic oxidative stress [7,31,32]. Considering the kidney's metabolic activity and vascular and tubular integrity, it is especially susceptible to oxidative and inflammatory damage [33]. The present findings confirm earlier findings that asthma-related inflammation can also cause nephroinflammatory damage [8,30,34].

The treatment modified these lesions differently. Salbutamol monotherapy caused only mild histological improvement, with persistent inflammatory infiltration and incomplete restoration of renal structure. The limited effect is understandable, since salbutamol is primarily a bronchodilator rather than a direct renoprotector [9.28]. Aside from influencing inflammatory mediators and electrolyte transport, its renal benefits are weaker than those of anti-inflammatory drugs[9]and excessive beta-2-adrenergic stimulation has been linked to tissue damage and oxidative stress [35-39]. There was better preservation of glomerular and tubular morphology with montelukast. According to studies, montelukast has antioxidant, anti-inflammatory, and renoprotective properties by blocking cysteinyl leukotriene receptor 1, suppressing leukotriene-mediated inflammation, and reducing oxidative damage [7,17,40,41]. Based on its corticosteroid suppression of inflammatory cells and cytokines, prednisolone produced the strongest renoprotection among monotherapies [3,15,42]. During prolonged exposure, corticosteroids may alter oxidative metabolism and reduce inflammation-driven oxidative injury [14,16,43]. Prednisolone/montelukast showed the best structural preservation in combination therapies, suggesting additive benefits from suppressing generalized inflammation and leukotriene-mediated pathways simultaneously [7,15].

The kidney tissue did not show any gross protein depletion, suggesting the induced injury was not severe enough to cause such a phenomenon. A higher total protein level in the salbutamol/prednisolone group may indicate improved cell integrity, according to Khaldi *et al* [44] And Nwogueze *et al* [45] Oxidative stress can damage cellular proteins and impair tissue metabolism. Antioxidant enzyme results indicate different patterns of redox response. There was a significant increase in superoxide dismutase and catalase levels in the salbutamol-treated group, suggesting an adaptive response to persistent oxidative stress. Based on the findings of Aloamaka and Nzoputam [9] antioxidant enzymes were upregulated in regimens containing salbutamol. The presence of this enzyme is essential to the antioxidant defense of the kidney, and a rise in its activity could be indicative of continued production of reactive oxygen species [46,47]. As a result of the lower oxidative demand associated with salbutamol/prednisolone, superoxide dismutase and catalase levels were reduced relative to the positive control. It is possible that, as inflammation and oxidant generation decline, compensatory enzyme induction is no longer necessary, so that lower enzyme activity suggests the restoration of redox balance rather than the enhancement of injury [8,46] Interestingly, glutathione peroxidase activity showed little difference between the groups, suggesting that glutathione is less sensitive than other antioxidant systems. As reported by Kaviani *et al* [18] Montelukast increased glutathione peroxidase activity in other nephrotoxic models, possibly due to differences in disease models, injury severity, or treatment duration.

In asthmatic rats, malondialdehyde was present at levels that indicated oxidative membrane damage and confirmed previous reports linking asthma to increased lipid peroxidation and reduced antioxidant protection [11]. Despite histological improvements, montelukast alone was insufficient to suppress lipid peroxidation in this model fully. Salbutamol/montelukast and prednisolone/montelukast groups, on the other hand, showed significant reductions in oxidative membrane damage, suggesting that combination therapy is more effective than individual therapy. It has been reported by Kavian *et al* [18] that montelukast reduces lipid peroxidation and inflammation induced by oxidative injury in renal tissue and other organs. In contrast to Aloamaka and Nzoputam [9], who found that salbutamol/prednisolone increased malondialdehyde levels. Asthma severity, dosage, treatment duration, or a balance between anti-inflammatory protection and drug-induced oxidative reactions may explain the discrepancy, suggesting renal oxidative effects of combination therapy are context-dependent and should be interpreted cautiously across studies.

Among the treatment groups, salbutamol, montelukast, salbutamol/prednisolone, salbutamol/montelukast, and prednisolone/montelukast had lower hydrogen peroxide than the positive control. The results are consistent with the literature, which shows that montelukast reduces oxidative stress by suppressing inflammatory mediators and lipid peroxidation [7,18]. Therefore, even where antioxidant enzyme responses varied, hydrogen peroxide levels

were reduced overall. The nitric oxide findings support improvements in renal vascular and inflammatory function. However, salbutamol/prednisolone, salbutamol/montelukast, and prednisolone/montelukast showed higher nitric oxide levels than the positive control, suggesting partial restoration of nitric oxide bioavailability. The beneficial effects of nitric oxide on tissue perfusion and vascular tone are reduced in inflammation. Treatment increases may indicate reduced oxidative quenching and improved endothelial function [5,6]. In some nephrotoxic models, montelukast also normalizes nitric oxide-mediated inflammatory responses, contributing to its renoprotective properties [18].

Histological and oxidative indices showed more modest changes than serum markers of renal function. In general, serum urea remained close to the negative control levels in most groups, suggesting that asthma induction did not cause severe impairment of nitrogenous waste excretion. There was partial improvement in disease-related disturbances with montelukast, prednisolone, salbutamol/montelukast, and prednisolone/montelukast. Compared with the negative control group, the prednisolone/montelukast group showed elevated urea levels, suggesting treatment-related metabolic effects. Montelukast lowers serum urea in nephrotoxic models [48], while corticosteroids alter protein catabolism and nitrogen metabolism [49], complicating interpretation. Similarly, Aloamaka and Nzoputam [9] reported elevated serum urea without significant changes in creatinine or electrolytes. Prednisolone is shown to have an anti-inflammatory renoprotective effect [50,51], suggesting urea levels may be reflective of combined renal and extra-renal influences rather than frank renal failure in this study. Although the histological and oxidative findings in the prednisolone/montelukast group were favorable, creatinine levels were higher in this group due to reduced protein metabolism compared with urea. Despite the small sample size, this increase suggests that structural protection does not always translate into normalized serum renal markers. It is possible that histological and biochemical recovery may not occur simultaneously in early or moderate injury states. Aloamaka and Nzoputam [9] reported that asthmatic models have lower serum creatinine levels compared to individuals who undergo certain treatment-related renal changes.

There was a mild change in electrolyte levels. Compared to the negative control, prednisolone, salbutamol/prednisolone, salbutamol/montelukast, and prednisolone/montelukast increased potassium; salbutamol, prednisolone, salbutamol/prednisolone, and prednisolone/montelukast increased sodium; and salbutamol and prednisolone/montelukast increased chloride. As a result, electrolyte imbalances may not be the cause of tubular ion handling effects. By altering sodium and potassium transport through renal tubular mechanisms [37] Salbutamol may alter potassium balance, while corticosteroids may affect it. In the absence of marked deterioration in other renal markers, electrolyte changes suggest pharmacologic effects rather than worsening renal injury.

CONCLUSION

In conclusion, asthma induction in Sprague-Dawley rats results in renal structural injury and oxidative stress, confirming systemic effects beyond the airways. Prednisolone provided significant histological protection, whereas montelukast exhibited substantial antioxidant and renoprotective effects. Although salbutamol provided limited renal protection, it triggered adaptive antioxidant responses instead of suppressing oxidative damage. Despite mixed results in serum functional markers, such as urea and creatinine, prednisolone/montelukast produced the best histological and oxidative profiles.

Abbreviations

G: glomerulus; RT: renal tubules; IC: inflammatory cells; VC: vascular congestion; VD: vascular dilation.

Author Contributions

AEOO and EFO contributed to the conceptualization and design of the study and to data acquisition. AEOO conducted the literature review and performed the statistical analysis. Both authors took part in the interpretation of the results and the preparation of the manuscript. AEOO acts as guarantor of the manuscript. Both authors read and approved the final version submitted for publication.

Data Availability Statement

The data that support the findings of this study are available and will be made available upon request.

Use of AI in Drafting of Manuscript

During the preparation of this work, the author(s) used Jenni AI, ChatGPT, and Grammarly in order to improve the clarity and quality of written communication. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflict of Interest

The authors declared no conflict of interest.

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