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Avena sativa's Therapeutic Potential: Exploring Antiasthmatic Effects in Guinea Pig Asthma Model

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Abstract

Avena sativa (oat) has emerged as a potential therapeutic candidate for asthma, a global health challenge characterized by chronic airway inflammation. This research investigates the anti-asthmatic potential of the Hydro-Alcoholic Extract of *Avena sativa* (HAEAS) in a guinea pig asthma model induced by histamine and ovalbumin. The study explores the influence of HAEAS on oxidative stress markers, leucocytes, eosinophils, and histopathological changes in lung tissues. Results reveal that HAEAS, particularly at 400 mg/kg, significantly increases the latent period and percentage protection in histamine-induced bronchospasm. In ovalbumin-sensitized guinea pigs, HAEAS demonstrates a notable reduction in total leucocyte count, eosinophils, neutrophils, and macrophages in bronchoalveolar lavage fluid. Moreover, HAEAS exhibits antioxidative effects by increasing superoxide dismutase levels and decreasing malondialdehyde levels. Histopathological analysis demonstrates a decrease in inflammatory cell infiltration, hyperplasia, and bronchoconstriction. This study highlights the potential of *Avena sativa* as a novel therapeutic avenue for asthma, offering anti-inflammatory and antioxidant benefits.

Keywords: *Avena sativa*, Asthma, Anti-Inflammatory, Antioxidative, Guinea Pig Model, Histamine, Ovalbumin

1. Introduction

Asthma, a chronic inflammatory disorder of the airways, poses a global health challenge characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The complexity of asthma involves a myriad of cells and elements contributing to chronic inflammation, leading to increased airway hyperresponsiveness. The inflammatory profile includes T-lymphocytes of the T-helper (Th) type 2 phenotype, eosinophils, macrophages/monocytes, and mast cells. Notably, exacerbations may exhibit an 'acute-on-chronic' inflammation with increased eosinophils and sometimes neutrophils[1].

Bronchial asthma, a result of intricate genetic and environmental interactions, affects approximately 7-10 % of the global population. In India alone, a staggering 40 million individuals grapple with asthma, with

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urbanization and industrial pollution contributing to an alarming rise. Children are not spared, with an escalating incidence attributed to environmental changes. The burden of respiratory diseases, including asthma, is poised to surge, making it imperative to explore novel therapeutic avenues[2]. The prevalence of asthma worldwide continues to rise, with an estimated 300 million affected individuals. Projections indicate a 50% increase in asthma prevalence every decade, with an anticipated additional 100 million asthma cases by 2025[3]. The disease's pathophysiology involves chronic airway inflammation, cytokine release, and the predominance of the T-helper 2 (Th2) phenotype, marked by the overproduction of interleukins IL-4, IL-5, and IL-13[4].

Histamine and cysteinyl leukotrienes play pivotal roles in asthma pathology, contributing significantly to symptoms such as airflow obstruction, mucus secretion, bronchoconstriction, and inflammatory cell infiltration. Mast cells, activated by allergen-IgE interactions, release histamine, leukotrienes, and other mediators, orchestrating early and late-phase allergic responses in both upper and lower airways[5]. Leukotrienes, particularly leukotriene D4, trigger smooth muscle contractions in the trachea, exacerbating inflammation in asthma. Cysteinyl leukotriene receptors (CysLT1 and CysLT2) further contribute to pro-inflammatory activities, influencing endothelial cells and mast cells[6].

Despite advancements in modern medicine, current asthma treatments often provide only symptomatic relief, prompting a search for alternative and complementary therapeutic options. The escalating incidence of asthma in India, particularly among children, underscores the urgency of exploring novel interventions[7].

In this context, the role of *Avena sativa* (oat) emerges as a potential therapeutic candidate. Herbal remedies, deeply rooted in traditional medicine, are gaining attention globally[8]. Oats, rich in diverse chemical constituents, including avenanthramides, possess pharmacological activities such as immune modulation, antioxidant effects, and the potential to control childhood asthma. With its historical use in addressing nervous exhaustion, insomnia, and weakness of the nerves, oats present a promising avenue for exploring anti-asthmatic properties.

This research aims to evaluate the anti-asthmatic potential of the Hydro-Alcoholic Extract of *Avena sativa* (HAEAS) in a guinea pig asthma model. Through inducing asthma using histamine and ovalbumin, the study will delve into the influence of HAEAS on oxidative stress markers, leucocytes and eosinophils levels, and histopathological changes in lung tissues. This investigation is crucial in expanding our understanding of herbal interventions in managing asthma, offering a potential alternative or complement to existing therapeutic approaches.

2. Materials and Methods

2.1 Chemicals

Histamine (HIS) and Ovalbumin (OVA) was purchased from the Sigma Aldrich. All other chemicals and reagents were used in the experiments were of analytical grade and the same were purchased from the GMP certified companies through local vendors

2.2 Animals

The study utilized adult Guinea pigs (*Cavia porcellus*) weighing between 400 to 450 g, sourced from Mahaveera Enterprises in Hyderabad. The animals were housed in polypropylene cages at a controlled temperature of 25±2 °C, following an 8-hour light/8-hour dark cycle. Their diet consisted of a standard feed supplemented with water infused with carrot extracts for additional vitamin C. Prior to the initiation of the experimental protocol, a 10-day acclimatization period was implemented to ensure the animals adapted to laboratory conditions. The research adhered to approved procedures, with the experimental protocols receiving ethical clearance from the Institutional Animal Ethical Committee at SIMS College of Pharmacy, Guntur, under approval no. 04/IAEC/SIMS/2023.

2.3 Collection of Plant Material

Powder of the seeds of *Avena sativa* plant were collected from Brahma Natural Products of Vijayawada (A.P). The powder was then sieved and fine powder was collected for preparation of methanolic extract.

2.4 Preparation of Plant Extract

The powder (100 g) was subjected to continuous hot extraction with water and ethanol at a ratio of 1:1 in soxhelet apparatus at 40°C for 24 h. The residue obtained after extraction process was dried using rotary flash evaporator to get completely dried product. The percentage yield of extract was determined as 6.45%.

2.5 Grouping of Animals

All the 24 animals were randomly assigned to eight groups containing 3 each. The treatment of the groups are as follows:

- Group I: Histamine dihydrochloride 2% (Nebulization)
- Group II: Histamine dihydrochloride 2% (Nebulization)+Chlorpheniramine maleate 2mg/kg (Oral)
- Group III: Histamine dihydrochloride 2% (Nebulization)+HAEAS 200 mg/kg (Oral)
- Group IV: Histamine dihydrochloride 2% (Nebulization)+HAEAS 400 mg/kg (Oral)
- Group V: Ovalbumin solution 1mg (Nebulization)
- Group VI: Ovalbumin solution 1mg (Nebulization)+Dexamethasone (10 mg/kg) (Oral)
- Group VII: Ovalbumin solution 1mg (Nebulization)+HAEAS 200 mg/kg (Oral)
- Group VIII: Ovalbumin solution 1mg (Nebulization)+HAEAS 400 mg/kg (Oral)

HAEAS dose was selected based on the acute toxicity study reported by Sivakumar *et al*[9].

2.6 Treatment Procedure

All animals, randomly allocated into eight groups of three each, underwent a 14-day treatment regimen. Group I received Histamine Dihydrochloride at a 2% concentration, administered via nebulization. Group II was subjected to a combination of Histamine Dihydrochloride (2%) and Chlorpheniramine Maleate (2 mg/kg), with nebulization as the route of administration. In Group III, animals were treated with Histamine Dihydrochloride (2%) combined with Hydro Alcoholic Extract of *Avena sativa* (HAEAS) at 200 mg/kg, delivered through nebulization for histamine and oral ingestion for HAEAS dissolved in water. Group IV received the same histamine concentration but with a higher HAEAS dose of 400 mg/kg, administered using the same routes. Ovalbumin solution at 1mg was nebulized for Group V, while Group VI received Ovalbumin solution (1mg) combined with Dexamethasone (10 mg/kg), with nebulization for both substances. In Group VII, Ovalbumin solution (1 mg) was nebulized alongside HAEAS at 200 mg/kg, while Group VIII received Ovalbumin solution (1mg) with a higher HAEAS dose of 400 mg/kg, both administered through nebulization for ovalbumin and orally for HAEAS. Chlorpheniramine maleate and Dexamethasone were administered via the intra-peritoneal route. This comprehensive treatment strategy was designed to assess the impact of various substances and combinations on the study parameters within the specified timeframe.

2.7 Induction of Asthma using Histamine

In this study, guinea pigs were selected based on their propensity to develop typical histamine asthma within three minutes, three days prior to the experiment. These animals were acclimated to the histamine chamber, and following a 24-hour fasting period, they were exposed to a fine mist of 2% histamine dihydrochloride aerosol. The histamine, dissolved in normal saline, was generated using a nebulizer at a pressure of 300 mm Hg in a histamine chamber constructed of perplex glass (24 x 14 x 24 cm). Progressive signs of difficulty in breathing leading to convulsions, asphyxia, and death were observed, and the time between the appearance of initial convulsion signs was recorded as the Pre-Convulsion Time (PCT). The criterion for evaluation was the time for the onset of dyspnea. Twelve animals each were divided into four groups, and 30 minutes before exposure, chlorpheniramine maleate (2 mg/kg) and extracts (200 and 400 mg/kg) were orally administered. Upon the commencement of PCT, animals were promptly removed from the chamber and placed in fresh air for recovery. Percent protection was calculated based on the animals that did not develop typical asthma within six minutes[10].

The protection offered by treatment was calculated using the following formula:

$\%protection = (1–T1/T2) \times 100$

T1 = The mean of PCT before administration of test drugs.

T2 = The mean of PCT after administering of test drugs.

2.8 Induction of Asthma using Ovalbumin

In this study, four groups of guinea pigs with a weight range of 300-350 g were sensitized for the evaluation of the anti-inflammatory effects of HAEAS. Sensitization was achieved by intraperitoneal injection of 100 µl Ovalbumin (OVA) solution, comprising 2 mg ovalbumin emulsified in 10 mg Aluminum Hydroxide ($AlOH_3$) dissolved in 10 ml normal saline (0.9% w/v NaCl) at the commencement of the experiment. On day 14, a booster dose of 100 µl solution (1 mg ovalbumin dissolved in saline) was administered intraperitoneally. Simultaneously,

a control group of naïve animals (n = 3) received sham-sensitization with 100 µl normal saline. Subsequently, from day 21 to day 30, sensitized guinea pigs underwent daily challenges with aerosolized ovalbumin (1% w/v dissolved in Phosphate-Buffered Saline, PBS) for 10 min. Preceding each challenge, both naïve and test groups were treated with normal saline (10 ml/kg, p.o.), HAEAS (200 and 400 mg/kg, i.p.), or dexamethasone (3 mg/kg, p.o.) 30 min after intraperitoneal injection or 1 h after oral administration[11].

2.9 Bronchoalveolar Lavage Fluid (BALF) Collection and Analysis

Following immediate blood collection, the experimental procedure involved the meticulous exposure of the trachea, taking care to prevent contamination of luminal contents with blood and minimize damage to lung tissues. Subsequently, the trachea was cannulated to facilitate the collection of bronchoalveolar fluid through aspiration. To ensure the integrity of the lung tissues, they were carefully flushed with three consecutive 5 ml portions of Phosphate-Buffered Saline (PBS), and the resultant fluid was aspirated following gentle massage. From the fluid Leucocytes, neutrophils, macrophages, and eosinophil cells were then analyzed under a microscope (Olympus CX23)[11].

2.10 Serum Preparation

Blood was obtained for clinical biochemistry in clot activator tubes. The serum was separated by centrifugation of blood samples approximately at 5000 rpm for 10 minutes at 250C. The clear, clean serum was put into plastic tubes with labels and stored in the freezer at -4 °C for further use[12].

2.11 Tissue Homogenate Preparation

The lung samples from all experimental rats were sliced into pieces and homogenised in ice-cold 0.067 M phosphate buffer using a tissue homogeniser (Dynaken, Malaysia) to give 20% homogenate. After homogenisation, the samples were centrifuged at 4000 rpm for 10 min at 4°C in a cold centrifuge. The subsequent supernatants were kept at -20 °C and used for oxidative parameter estimations. Oxidative parameters like SOD[13], MDA[14] were analysed.

2.12 Histopathological Analysis

For histopathological analysis, the Lungs tissues were fixed in 10% formalin, dehydrated on treatment with a series of different concentration of ethanol, cut into sections and embedded in paraffin wax. Specimen slides with 5 µm thick tissue sections were prepared using a semi-automatic rotatory microtome (M/s Biocraft, India). Hematoxylin and eosin stains were used to stain these slides, and a light microscope (BX 43, Olympus, India) was used to take photomicrographs.

2.13 Statistical Analysis

The statistical analysis was done using SPSS V26 software. All data are expressed as mean ± standard deviation. The statistical significance is calculated via one-way ANOVA, with Tukey's post hoc test for the biochemical data, and Dunnet's multiple comparison tests for cell culture and animal experiment data. The results have been expressed in $p < 0.05$, 0.01, and 0.001 for statistical significance.

3. Results

3.1 Effect of HAEAS in Histamine Induced Bronchospasm in Guinea Pigs

3.1.1 Effect of HAEAS on Latent Period

The study found that the Chlorpheniramine Maleate 2 mg/kg (CPM) treated animals showed significant increase in the latent period compared to the Histamine dihydrochloride (2%) (HIS) treated animals. Whereas the HAEAS treated animals at a dose of 400 mg/kg body weight significantly increased the latent period compared to the HIS treated animals (Figure 1(A)).

3.1.2 Effect of HAEAS on Percent Protection

The study found that the CPM treated animals showed significant increase in the % protection compared to the HIS treated animals. Whereas the HAEAS treated animals at a dose of 400 mg/kg body weight significantly increased the % protection compared to the HIS treated animals (Figure 1(B)).

3.2 Effect of HAEAS in Ovalbumin Sensitization in Guinea Pigs

3.2.1 Effect of HAEAS on Total Leucocyte (TLC) in BALF

The effect of HAEAS on TLC of Ovalbumin (OVA) showed decrease in the TLC in BALF of OVA sensitized guinea pigs. Dexamethasone at 10 mg/kg significantly

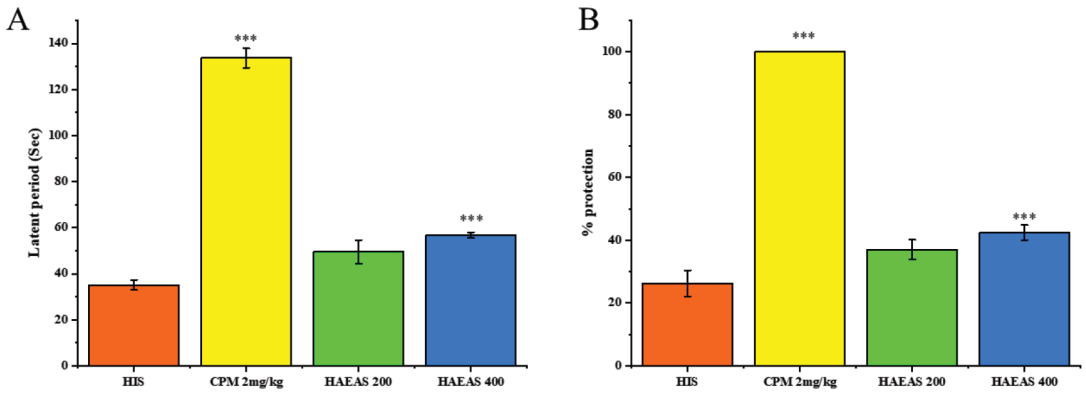


Figure 1. Effect of HAEAS on **(A)** Latent Period. **(B)** % Protection.
The values were presented as Mean ± SEM (n = 3); ONE WAY ANOVA test was done using Tukey's post hoc test and considered P<0.05, 0.01, 0.001 were significant. *** P<0.001 when compared to Histamine (HIS) Control.

decreased the leucocyte infiltration in lungs compared to OVA group. Whereas, HAEAS 200 and 400 significantly decreased the TLC infiltration in BALF (Figure 2(A)).

3.2.2 Effect of HAEAS on % Inhibition

The effect of HAEAS on % inhibition of Ovalbumin (OVA) induced leucocyte infiltration showed decrease, while Dexamethasone at 10 mg/kg significantly increased the % inhibition of leucocyte infiltration in lungs compared to OVA group. Whereas, HAEAS 200 and 400 significantly increased the % inhibition of leucocyte infiltration in BALF (Figure 2(B)).

3.2.3 Effect of HAEAS on Eosinophils

The effect of HAEAS on eosinophils of Ovalbumin (OVA) group showed decrease in the eosinophils in BALF of OVA sensitized guinea pigs. Dexamethasone at 10 mg/kg significantly decreased the eosinophilic infiltration in lungs compared to OVA group. Whereas, HAEAS 200 and 400 significantly decreased the eosinophilic infiltration in BALF. (Figure 3(A))

3.2.4 Effect of HAEAS on Neutrophils

The effect of HAEAS on neutrophils of Ovalbumin (OVA) group showed decrease in the neutrophils in BALF of OVA sensitized guinea pigs. Dexamethasone at 10 mg/kg oral route ??? significantly decreased the neutrophils infiltration in lungs compared to OVA group. Whereas, HAEAS 400 significantly decreased the neutrophils infiltration in BALF. (Figure 3(B))

3.2.5 Effect of HAEAS on Macrophages

The effect of HAEAS on macrophages of Ovalbumin (OVA) group showed decrease in the macrophages in BALF of OVA sensitized guinea pigs. Dexamethasone at 10 mg/kg significantly decreased the macrophages

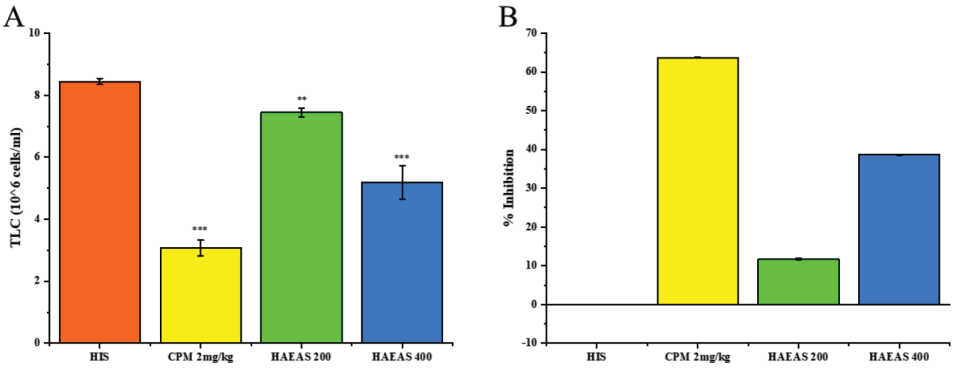


Figure 2. Effect of HAEAS on **(A)** TLC in BALF. **(B)** % inhibition.
The values were presented as Mean ± SEM (n = 3); ONE WAY ANOVA test was done using Tukey's post hoc test and considered P<0.05, 0.01, 0.001 were significant. *** P<0.001 when compared Ovalbumin (OVA) Control.

infiltration in lungs compared to OVA group. Whereas, HAEAS 400 significantly decreased the macrophages infiltration in BALF. (Figure 3(C))

3.3 Effect of HAEAS on Oxidative Stress Markers

3.3.1 Effect of HAEAS on Superoxide Dismutase (SOD)

The study found the animals treated with OVA were found to have decreased SOD. Dexamethasone treated animals significantly increased the SOD levels compared to the OVA treated group. Treatment of HAEAS to the OVA treated rats showed significant increase in the levels of SOD at doses of 200 and 400 mg/kg body weight (Figure 4(A)).

3.3.2 Effect of HAEAS on Malondialdehyde (MDA)

The study found the animals treated with OVA were found to have increased MDA. Dexamethasone treated animals significantly decreased the MDA levels compared to the OVA treated group. Treatment of HAEAS to the OVA treated rats showed significant decrease in the levels of MDA at doses of 200 and 400 mg/kg body weight. (Figure 4(B))

3.3.3 Effect of HAEAS on Histopathology of Lung

Massive infiltration of inflammatory cells in the interstitial space was observed indicating the airway inflammation in the sensitized group (Figure 5). The sensitized group also showed emphysema, hyperplasia, and necrosis. The HAEAS 200 and 400 treated group showed decreased inflammatory cell infiltration compared to the sensitized group. The treatment with the HAEAS prevented hyperplasia and bronchoconstriction in sensitized + HAEAS treated animals.

4. Discussion

The study's findings reveal interesting insights into the effects of Chlorpheniramine Maleate (CPM) and Hydro

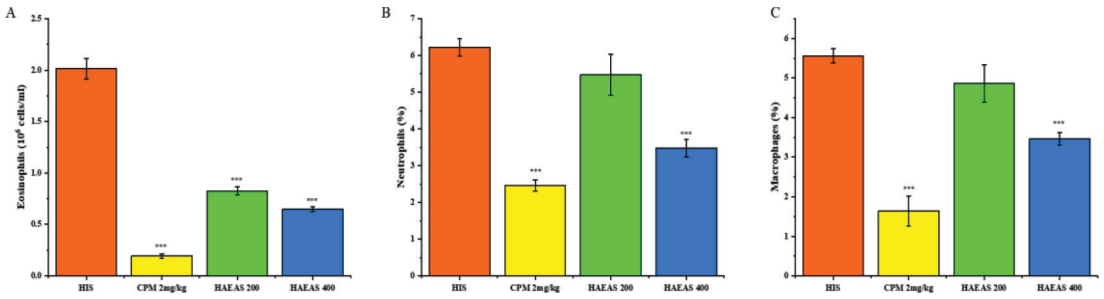


Figure 3. Effect of HAEAS on **(A)** Eosinophils. **(B)** Neutrophils. **(C)** Macrophages.
The values were presented as Mean ± SEM (n = 3); ONE WAY ANOVA test was done using Tukey's post hoc test and considered P<0.05, 0.01, 0.001 were significant. *** P<0.001 when compared Ovalbumin (OVA) Control.

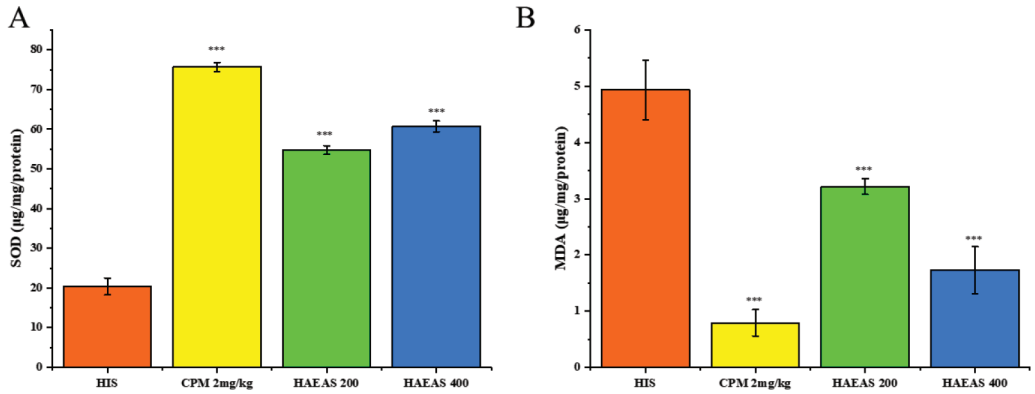


Figure 4. Effect of MEAL on **(A)** SOD. **(B)** MDA.
The values were presented as Mean ± SEM (n = 3); ONE WAY ANOVA test was done using Tukey's post hoc test and considered P<0.05, 0.01, 0.001 were significant. *** P<0.001 when compared Ovalbumin (OVA) Control.

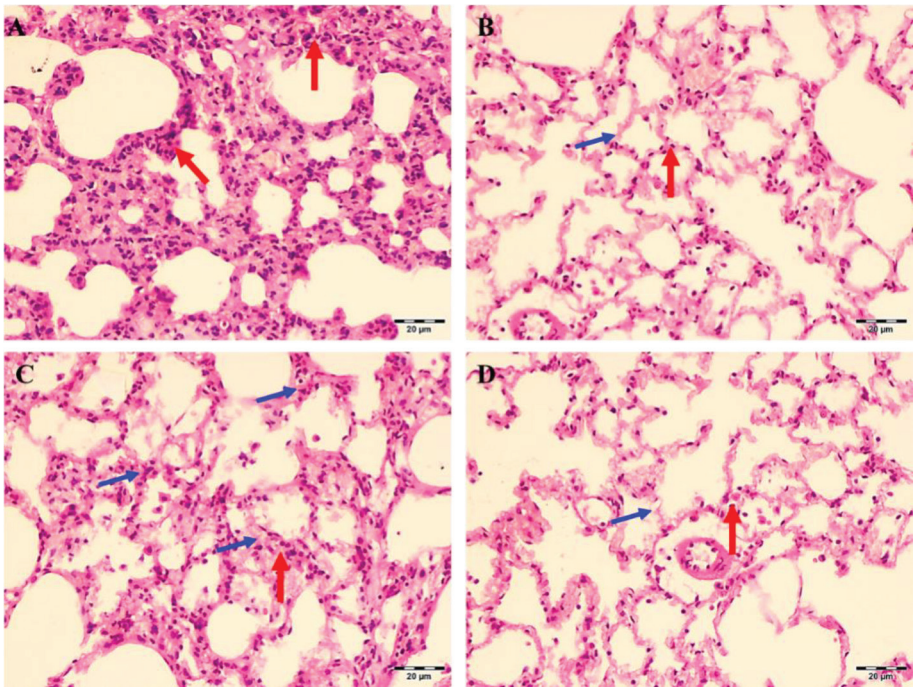


Figure 5. Effect of HAEAS on the HE stained sections of Lung **(A)**. OVA. **(B)**. DEX 10mg/kg. **(C).** HAEAS 200, **(D)**. HAEAS400) Cellular infiltration (red arrows), intrapulmonary bronchial smooth muscle (blue arrows**).**

Alcoholic Extract of *Avena sativa* (HAEAS) on the latent period when compared to Histamine dihydrochloride (HIS) treatment. The latent period refers to the time between the application of a stimulus and the observable response, and variations in this period can provide valuable information about the substances' impact on certain physiological processes.

The results indicate that CPM, administered at a dose of 2 mg/kg, led to a significant increase in the latent period when compared to the HIS-treated animals. This suggests that CPM may possess antihistaminic properties, as evidenced by its ability to delay or mitigate the effects induced by histamine[15]. The prolonged latent period implies a potential suppression of the histaminergic response, highlighting CPM's efficacy in modulating histamine-induced reactions.

On the other hand, the study also observed that the Hydro Alcoholic Extract of *Avena sativa* (HAEAS), administered at a dose of 400 mg/kg body weight, significantly increased the latent period compared to the HIS-treated animals. This finding suggests that HAEAS may possess anti-allergic or anti-inflammatory properties. The delayed onset of the histamine-induced response in HAEAS-treated animals implies a potential protective effect against histamine-mediated reactions. In terms of percentage protection, CPM-treated animals showed a substantial increase compared to HIS-treated animals, highlighting CPM's efficacy in preventing histamine-related adverse effects. Furthermore, HAEAS at 400 mg/kg demonstrated a significant rise in percentage protection, suggesting a protective effect against histamine-induced reactions.

It's noteworthy that *Avena sativa*, commonly known as oats, has been associated with various health benefits, including anti-inflammatory and antioxidant properties[9]. The observed effects on the latent period could be attributed to the presence of bioactive compounds in *Avena sativa*, and further investigations into the specific mechanisms involved would be valuable.

The intricate interplay of eosinophils, neutrophils, and macrophages in asthma underscores the complexity of the disease and the necessity for a nuanced understanding of immune responses[16]. The findings of this study provide compelling evidence for the anti-inflammatory and antioxidative effects of the HAEAS in an OVA-sensitized guinea pig model. The observed decrease in TLC in BALF of OVA-sensitized animals treated with HAEAS suggests a notable attenuation of leucocyte infiltration. This effect was further supported by the significant increase in the percentage inhibition of leucocyte infiltration in BALF, particularly at doses of 200 and 400 mg/kg, highlighting the potential of HAEAS to mitigate allergic

airway inflammation. The distinct effects of HAEAS on eosinophils, neutrophils, and macrophages further underscore its ability to modulate specific inflammatory cell types associated with allergic responses. Notably, HAEAS at 400 mg/kg demonstrated significant efficacy in reducing eosinophilic, neutrophilic, and macrophagic infiltration in BALF. Previous studies have suggested that plant-derived extracts may exert anti-inflammatory effects by influencing the recruitment and activation of these immune cells[17].

The study's exploration of oxidative stress markers, particularly SOD and MDA, provides crucial insights into the complex interplay of antioxidant defenses and oxidative damage in the context of asthma[18]. The observed decrease in SOD levels and increase in MDA levels in animals treated with Ovalbumin (OVA) indicate a potential imbalance in the redox status, highlighting the presence of oxidative stress in the sensitized guinea pig model. This aligns with the broader understanding of asthma, where oxidative stress plays a pivotal role in perpetuating airway inflammation and structural changes. The significant increase in SOD levels in Dexamethasone-treated animals compared to the OVA group suggests the anti-inflammatory agent's effectiveness in enhancing antioxidant defenses, reinforcing the link between inflammation and oxidative stress in asthma. Furthermore, the treatment of animals with the hydroalcoholic extract of HAEAS demonstrated a noteworthy increase in SOD levels at doses of 200 and 400 mg/kg body weight, indicating a potential antioxidative role for HAEAS in mitigating the impact of oxidative stress. Conversely, the significant decrease in MDA levels with HAEAS treatment at these doses suggests a potential protective effect against lipid peroxidation. These findings underscore the importance of exploring natural compounds, such as HAEAS, as potential therapeutic agents in asthma, with the modulation of SOD and MDA providing valuable markers for assessing the redox balance in the asthmatic airways.

Histological examination revealed a massive infiltration of inflammatory cells, emphysema, hyperplasia, and necrosis in the lungs of sensitized animal[19]. However, treatment with HAEAS, particularly at doses of 200 and 400 mg/kg, resulted in a visible decrease in inflammatory cell infiltration, prevention of hyperplasia, and bronchoconstriction. These histopathological changes align with the observed anti-inflammatory effects of HAEAS and further support its potential therapeutic use in allergic airway inflammation.

5. Conclusion

In conclusion, the current study demonstrates that HAEAS possesses significant anti-inflammatory and antioxidative properties, as evidenced by its impact on inflammatory cell infiltration, modulation of specific leucocyte subtypes, and regulation of oxidative stress markers. The ability of HAEAS to mitigate histopathological changes in the lungs further strengthens its potential as a therapeutic agent for allergic airway disorders. However, additional studies are warranted to elucidate the chemicals responsible for the protective activity and the precise molecular mechanisms involved and to assess the long-term safety and efficacy of HAEAS in diverse experimental and clinical settings.

6. Future Prospectus

Further research is essential to elucidate molecular mechanisms and assess long-term safety and efficacy

7. Acknowledgement

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