Exploring the Potential Therapeutic Role of Citrullus Lanatus in Animal Model of Allergic Airway Inflammation

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Abstract

Objective: To investigate the anti-inflammatory properties of Citrullus lanatus in an ovalbumin-induced allergic airway inflammation model in mice.

Material and Methods: It was an experimental study, conducted from December 2022 to June 2023 at CMH Lahore Medical College, Lahore. For the study, twenty four BALB/c mice were randomly assigned into four groups with six mice in each group. Initially, for the purpose of sensitization an intraperitoneal (i.p) injection of 20 µg Ovalbumin (OVA) was given on 1st day and from day 14 to 21 intranasal challenge containing 1% OVA was given to all groups except of group I. The delayed hypersensitivity test was performed to confirm the presence of inflammation Group III received Citrullus lanatus extract, while Group IV was treated with methylprednisolone. The anti-inflammatory effects of both treatments were compared. Blood samples were taken and bronchoalveolar lavage fluid (BALF) was obtained to assess the total as well as differential leukocyte counts (TLC and DLC). Lungs were removed to examine any histological alterations.

Results: Citrullus lanatus significantly reduced the total leukocyte count (TLC) in both the blood (4.405 ± 0.201, $P<0.001$) as well as bronchoalveolar lavage fluid (BALF) (1.438 ± 0.108, $P<0.05$) of BALB/c mice. Additionally, C. lanatus demonstrated a strong anti-inflammatory effect in by lowering the differential leukocyte count in both the blood and BLAF. The reduction in TLC and DLC was comparable with the drug methylprednisolone which also significantly reduced these parameters. Histopathological changes observed in C. lanatus group also strongly favour its anti-inflammatory properties.

Conclusion: Citrullus lanatus has shown anti-inflammatory properties and may be useful as a complementary medicine for inflammatory conditions, particularly asthma.

Keywords: Citrullus Lanatus, Anti-inflammatory, Asthma

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Introduction

Dietary interventions involving functional foods and nutraceuticals are becoming increasingly important in the prevention of various diseases. Fruit and vegetable-rich diets are high in phytochemicals, flavonoids and minerals which are bioactive substances that target life-threatening conditions. [1] Watermelon, or Citrullus lanatus ©. lanatus), belongs to Cucurbitaceous family which is indigenous to West Africa, The nutritional quality of C. lanatus demonstrates that it is incredibly rich in minerals, vitamins, like phosphorus, iron, thiamine, riboflavin,

niacin, folate, ascorbic acid, vitamins A and B complex.[2] Additionally it is abundant in carotenoids, leutin, beta-carotene, and prolycopene. Red flesh contains lycopene, a carotenoid pigment with strong antioxidant qualities immune-modulatory and anti-inflammatory properties. [3] Because of its rich nutritional profile and associated health benefits, it is now being widely used in many diseases like macular diseases, diabetes, cardiovascular problems, nephrolithiasis, hepatitis, worm infestation, bacterial infections, pain and inflammation, impotence and cancers.[4]

Approximate number of people suffering worldwide from asthma is over 300 million, making it one of an important health concern[5]. Almost every 250th death globally is attributed to asthma, which also significantly raises the cost of healthcare by reducing the need for hospital administration and admissions. While most of the patients using currently available medicine for the treatment of asthma respond quite well to them, usually 5–10% of the patients do not respond well to current practice-based therapy. Persistent inflammation of the airways is a hallmark of asthma. Inflammatory cell infiltration, mucous cell hyperplasia leading to deposition of thickened mucous causing blockage in respiratory bronchioles, Laminin and type IV collagen causing thickening of respiratory basement membranes, bronchiolar smooth muscle hyperplasia and hypertrophy, airway edema, mast cell degranulation are among the symptoms.[6]

Corticosteroids are one of the most commonly used anti-inflammatory medications for the treatment of asthma. The adverse effects of this medication include adrenal suppression, decreased growth and metabolism of bone in children, myopathy, hyperglycemia, increased risk of cardiac ischemic and cardiac failure, mood swings, memory loss, peptic ulceration, gastritis, and pancreatitis osteoporosis and metabolic disorders.[7] Many efforts are being made to develop a novel, targeted, and more accurate treatment for asthma in light of these side effects of corticosteroids. This is why the current study's goal is to compare the anti-inflammatory properties of C. Lanatus and methylprednisolone using a rodent model. If it has anti-inflammatory properties, it might be a safe, affordable alternative for treating asthma.

Material and Methods

This was an experimental Study conducted at Pharmacology Department and Animal Research Lab of CMH Lahore Medical College, Lahore. The study was initiated after taking ethical letter of approval from ethics review committee of CMH Lahore Medical college (ERC number: 642/ERC/CMH/LMC). The duration of the study was six months from Dec 2022 to June 2023.

C. lanatus as a whole (Family: Cucurbitaceous; Watermelon) was sourced from local farmers directly. It was peeled, thinly sliced and seeds were removed. Slices were dried at room temperature. Once dried the pulp was ground and dipped in 90% ethanol for two days. The material was filtered using Whatman no. 1 filter, the filtrate was concentrated and then lyophilized at reduced pressure using a rotary evaporator (Hei-VAP, core heidolph, Germany). This extract was kept at -20°C till needed for pharmacological testing. The percentage yield of the extract was calculated to be 20%.[8]

BALB/c mice aging six to eight weeks were placed in the animal house of CMH Lahore Medical College Lahore. The humidity and room temperature of the environment was maintained at (45-65%) and (22-24 ^{o}C) respectively. Water and standard feed was given ad libitium and normal dark and light (12 hourly) cycle was maintained. Mice having any visible sign of disease or underweight were not included in the study.[9] Each group had six animals that were decided to be the sample.[10]

Using the lottery method, the BALB/c mice were randomly selected and divided into four groups of six. Computer-generated numbers were assigned to each mouse, and the mice were then placed in specific cages. On day 0, injection mixture of ovalbumin 20µg(OVA, Sigma-Aldrich, St. Louis, MO) and Aluminium hydroxide 2mg in 0.1ml phosphate-buffered saline (PBS), was administered intraperitoneally to induce allergic airway inflammation in all animals, except for Group I (control group), which received only PBS. This step served as sensitization.[11]

From day 15 to day 21, mice in Group II (disease group), Group III (C. lanatus group), and Group IV (methylprednisolone group) were challenged daily with ovalbumin solution via inhalation to induce allergic airway inflammation. Mice in Group I

(control group) were give normal saline inhalation instead of OVA.[12]

During the same period (day 15 to day 21), the following treatments were administered:

Group II (disease group): 0.2 ml normal saline was injected intraperitoneally.

Group III (C. lanatus group): received 200 mg/kg body weight of Citrullus lanatus ethanolic extract in 0.2 ml normal saline, intraperitoneally.[13]

Group IV (methylprednisolone group): received injection methylprednisolone (standard drug) at a dose of 15 mg/kg intraperitoneal 30 minutes before the intranasal challenge with 1% OVA.[13]

To test for delayed type hypersensitivity (DTH), ovalbumin was injected into the right ear's pinna to monitor the inflammatory response, while PBS was injected into the left ear's pinna as a control. The left and right ears were removed from the body and weighed as soon as the mice are sacrificed. The value of DTH was then be represented by the difference in the weight of the two ears.[12]

After sacrificing the mice 24 hours post challenging, using light ether vapors for anesthesia, blood samples were taken via cardiac puncture and stored in EDTA tubes for evaluation. The Sysmex XT-1800i automated hemocytometer assessed the total leukocyte count and differential leukocyte count (DLC) from the collected samples.

After euthanasia, bronchoalveolar lavage fluid (BALF) was obtained by instilling 0.2 ml of ice-cold phosphate-buffered saline (PBS) via the tracheal route. The BALF was then withdrawn and stored at -20 $^{\circ}$C for further analysis. The total leukocyte count in BALF was determined using a Neubauer hemocytometer. To determine the DLC in BALF, cytocentrifugation was performed on the BALF samples, followed by staining of the cells on glass slides using Wright-Giemsa stain. After methanol fixation, differential cell counts were conducted based on the cellular morphology observed under the microscope.[12,14]

Dissected lung tissues were fixed in 10% buffered formalin and then dehydrated using graded ethanol concentrations. The dehydrated tissues were embedded in paraffin wax, and 6 µm thick sections were prepared using a microtome. To assess inflammatory cell infiltration, the sections were stained with hematoxylin and eosin (H&E). Inflammatory cell infiltration was examined under a light microscope. The degree of changes was semi-quantified using a histopathological scoring system, where scores of 0, 1, 2, and 3 represented no changes, mild changes, moderate changes, and severe changes, respectively. An impartial, blinded histopathologist graded the extent of inflammatory cell infiltration.[15]

Results

Citrullus Lanatus (C. lanatus) was able to significantly decrease the total leukocyte cell and differential in both blood and BALF. In the inflammatory process, these observed parameters were noticeably elevated. In this instance blood parameters like TLC was observed to be high ($P<0.001$) in the diseased mice (6.406 ± 0.656) cells x 10^3 as opposed to the control group (3.92 ± 0.280) cells x 10^3. The group that received treatment with C. lanatus demonstrated a significant ($P<0.001$) decrease in TLC (4.405 ± 0.201) cells x 10^3 as compared to disease group. Absolute neutrophil count was higher ($P<0.001$) at (5.063 ± 0.418) x10^3 cells in the disease group than it was in the control group (2.613 ± 0.164) x10^3 cells. The absolute neutrophil count was significantly ($P<0.01$) decreased (3.80 ± 0.172) after C. lanatus administration. Similarly, lymphocyte counts showed a significant decrease ($P> 0.05$) in C. lanatus treated mice (1.238 ± 0.106) as compared to diseased mice (1.813 ± 0.181) and eosinophil counts also showed a significant decrease ($P>0.01$) in C. lanatus treated mice (0.462 ± 0.056) as compared to disease mice (0.800 ± 0.73).

All of these parameters also showed a significant decline when tested in BALF. In this regard TLC levels rose significantly ($P>0.001$) in diseased mice (2.050 ± 0.106) as compared to the control mice (0.950 ± 0.09). In the C. lanatus treated group, the TLC level was significantly lower ($P<0.001$), (1.438 ± 0.108) as compared to the disease group (2.050 ± 0.106) x10^3 cells. The percentages of neutrophil (1.50 ± 0.086) ($P<0.01$) and eosinophil (0.399 ± 0.625) ($P<0.01$) were lowered in C. lanatus treated groups than those of the disease group (1.713 ± 0.109) and (0.642 ± 0.982), respectively. However no significant

decrease in the lymphocyte percentages was observed in BALF of C. lanatus treated group (Fig 2). A delayed hypersensitivity test was also conducted to validate the inflammation and sensitization processes. The weight of the mice's ear pinna was found to differ significantly (P<0.01) between the diseased mice (1.55 ± 0.046) mg and the control mice (1.213± 0.063) milligrams. In C. lanatus treated mice, there was a significant (P<0.01) decrease in pinna weight (1.30 ± 0.065) mg as compared to disease group. Methylprednisolone dramatically lowered hematological parameters, such as TLC and DLC in both blood and BALF and the effect was comparable to the C. lanatus treated group (Fig.1D, 2D). Histopathological analysis showed a significant increase (P < 0.001) in inflammatory cell infiltration in the disease group (2.45 ± 0.147). Methylprednisolone (0.92 ± 0.08) and C. lanatus group (1.67 ± 0.07) treatment produced a significant reduction (P < 0.001) in the infiltration of inflammatory cells (Fig. 3).

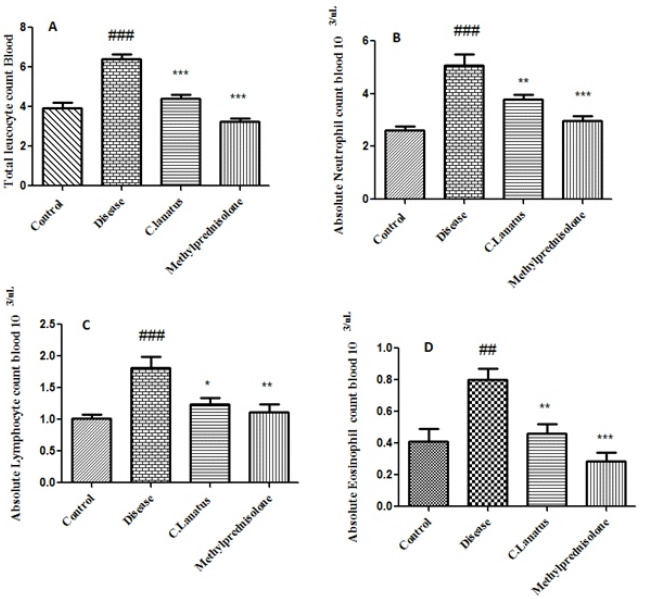

Figure-1: *The effects of C. lanatus and methylprednisolone on inflammation induced by ovalbumin are shown in the blood. The total number of inflammatory cells in the blood of mice is illustrated in Figure 1A. Figure 1B presents the absolute neutrophil count, while Figure 1C depicts the absolute lymphocyte count. Figure 1D shows the absolute eosinophil count.*

Data are presented as Mean ± SEM (n = 10). ###, ## indicates a statistically significant difference in the control and disease groups (P < 0.001). ***, **, and * shows statistical significance in the C. lanatus treated group and the disease group, with P < 0.001, P < 0.01, and P < 0.05, respectively. ***, **, and * also indicate statistically significant differences between the methylprednisolone-treated group and the disease group at P < 0.001, P < 0.01, and P < 0.05, respectively.

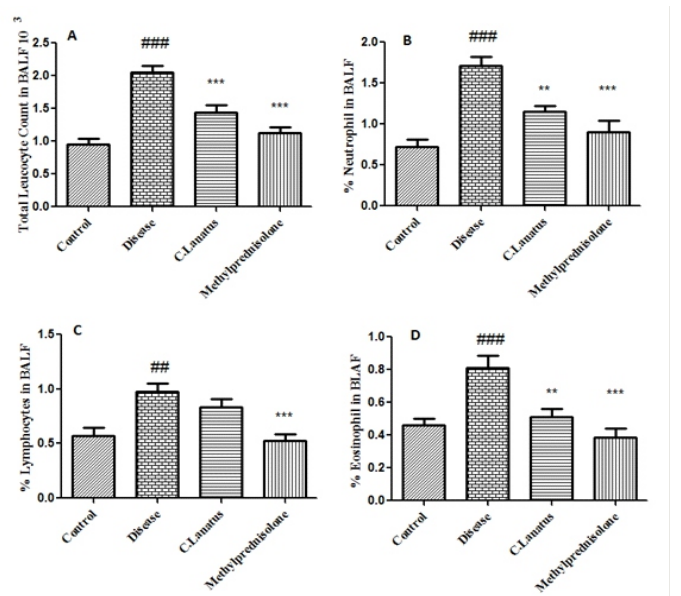

Figure-2: *Effects of C. lanatus and methylprednisolone on ovalbumin-induced inflammation in BALF are shown as follows. Figure 2A represents the total inflammatory cell count in the BALF of mice. Figure 2B shows the absolute neutrophil count, while Figure 2C depicts the absolute lymphocyte count. Figure 2D illustrates the absolute eosinophil count in the BALF of mice.*

Results are expressed as Mean ± SEM (n = 10). A P value < 0.001, and P< 0.01 are denoted by ###, ## indicates a statistically significant difference between the control and disease groups. P < 0.001 and P < 0.01 are represented by*** and **, respectively, indicating statistically significant differences between the C. lanatus treated group and the disease group. Similarly, P < 0.001, denoted by ***, respectively, show statistically significant differences between the methylprednisolone-treated group and the disease group.

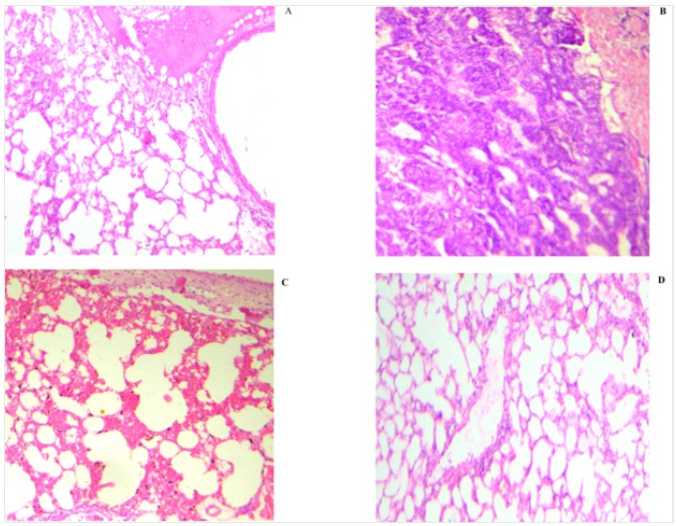

Figure-3: *3A showing normal histopathology of lung parenchyma of the control group. Fig-3B showing the effect of Ovalbumin in disease group, Fig-3C C. lanatus group and Fig-3D Methylprednisolone group, lung tissue stained with hematoxylin and eosin staining viewed under microscope with 40x magnification.*

Discussion

Asthma symptoms, including coughing, chest tightness, and wheezing, are caused by inflammation and airway remodeling. These effects arise from a complex interplay of immune, genetic, and environmental factors. A hallmark of asthma is the presence of leukocytes such as T lymphocytes, mast cells, and eosinophils into the airway walls. These inflammatory cells release mediators such as cytokines, chemokines, leukotrienes, and prostaglandins, which contribute to airway hyper-responsiveness, excessive mucus secretion, and airway constriction.[17]

The nutritional composition of C. lanatus is highlighted its rich content of minerals, vitamins, and antioxidants. The phytochemical profile describes beneficial chemicals including flavonoids, carotenoids, and phenolic acids and important active constituents like lycopene, beta-carotene contributes to its strong antioxidant, anti-inflammatory, antimicrobial properties and many other beneficial effects thus making it a valuable natural therapeutic agent. [18] Furthermore, it is helpful in preventing chronic diseases like cardiovascular disorders, diabetes, and cancers thus proving to be a natural plant-based substances for health improvement and gaining importance in integrative medicine.[19]

This study evaluated the anti-inflammatory effects of C. lanatus. Inflammation in the lungs was induced by ovalbumin, for the purpose of sensitization ovalbumin complexed with aluminum was injected intraperitoneally into mice, followed by intranasal ovalbumin challenges. This protocol mimicked key features of asthma, including elevated levels of inflammatory mediators especially IgE levels, Th2 cytokine release, and increased eosinophil, basophil and neutrophil infiltration, all of which are associated with inflammation.[20] Inflammation was confirmed by injecting ovalbumin into the right ear to assess delayed-type hypersensitivity (DTH). The weight difference between the left ear (control) and the right ear (injected with ovalbumin) was measured, with the right ear's weight significantly elevated, indicating successful induction of ovalbumin-induced inflammation. This protocol is widely used in studies and has been shown to effectively induce hypersensitivity. [12] Following ovalbumin sensitization, the disease group in this study exhibited a significant increase in neutrophils, eosinophils, lymphocytes, and total leukocyte count (TLC) in both blood and bronchoalveolar lavage fluid (BALF), consistent with the expected inflammatory response in asthma. These findings have been reported by Lee et al and other studies in which ovalbumin have been used to induce inflammation.[15] Upon administration of C. lanatus, these hematological and inflammatory markers were significantly reduced, highlighting its anti-inflammatory properties. The reduction in TLC, particularly the marked decrease in neutrophil and eosinophil counts in both blood and BALF, suggests that C. lanatus may modulate the inflammatory response, which play a key role in allergic inflammation in asthma.[20] Blood counts are valuable markers for monitoring asthma. Ke et al.'s study found a strong correlation between increased inflammatory biomarkers, such as TLC, neutrophils, eosinophils, and lymphocytes, and its heightened risk of respiratory disease and mortality in adults with asthma.[21]

Citrullus lanatus has been shown in previous studies to exhibit anti-inflammatory and antioxidant effects, in a study by Manivannan et al C. lanatus has exhibited these properties by detoxifying the harmful reactive oxygen species (ROS) by scavenging them,

decreasing the level of cyclooxygenase and DPPH.[22] As per these properties this effect has also been highlighted in our study by a decrease in histopathological scores depicting protective effect of C. lanatus in lung tissue damage.[20] The corticosteroid methylprednisolone, used as a positive control in this study, also significantly reduced these inflammatory markers, confirming the model's effectiveness. Remarkably, C. lanatus's anti-inflammatory effects were comparable to methylprednisolone, particularly in reducing eosinophil counts, which plays a critical role in asthma pathogenesis. This finding highlights the potential of C. lanatus in treating allergic airway diseases, either as an alternative or an adjunct to conventional corticosteroid therapy. The observed reduction in inflammatory mediators aligns with findings from other research.[12,16]

Conclusion

C. lanatus has demonstrated a capacity to reduce inflammation in allergic airway inflammation, indicating its potential as a future therapeutic agent. Further research is needed to explore its applicability in human treatments.

Conflict of Interest *None*

Funding Source *None*

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Authors Contribution

WAS, AQQ: Conceptualization of Project
WAS, AQQ: Data Collection
AQQ, AMR: Literature Search

AMR, AEZ: Statistical Analysis

WAS, AQQ, AMR, SZ: Drafting, Revision
AQQ, AMR: Writing of Manuscript

AEZ: Data Interpretation

RR: Critical Revision and Approval of Final Version