

# Methanolic Root Extract of *Lygodium flexuosum* Effectively Prevents Cigarette Smoke Induced Bronchitis: Experimental Study on Wistar Rats

Shweta Rathod\*, Tusharbindu Deasi, Pravin Tirgar

School of Pharmacy, R.K. University, Rajkot, Gujarat-360020, India

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## ABSTRACT

**Background:** Bronchitis is classified as a chronic obstructive pulmonary disease, which can manifest in either acute or chronic forms, contingent upon its severity. The primary etiology of this condition is cigarette smoking. *Lygodium flexuosum* (Lygodiaceae) is well known as a Choti Bhulan Climbing fern used as a traditional medicine.

**Objective:** The aim of our research was to examine the preventive potential of Methanolic extract of *Lygodium flexuosum* Root in cigarette smoke-induced bronchitis by investigating the biochemical, hematological, histological, and cytological approaches in wistar rats.

**Methods:** In this study, 30 rats were used. The animals were randomly divided into five subgroups, including normal control, negative control, the STD receiving Salbutamol 2 mg/kg, and two treatment groups receiving the *L. flexuosum* methanolic extract at 100 mg/kg and 200 mg/kg concentrations (Figure 1). The rats except for the Normal control (exposed to free air) were negative control and treatment groups exposed to cigarette smoke twice a day roughly 10 A.M and 3 P.M for continuous five days per week i.e. 20 days per month using special smoking chamber. Twenty days later a bronchitis model in the rats was achieved. From day 20 onward, plant extracts were administered orally once daily until day 28. The rats were sacrificed and blood, BALF from lung, serum samples of them collected for investigates biochemical, hematological, parameters and isolate the lungs for morphology, histology and cytology study. One-way ANOVA was used to examine the mean differences between the groups. Tukey's post hoc test was then used to determine any intergroup differences.

**Results:** Both doses of *L. flexuosum* could significantly ( $p < 0.001$ ) reduce the raised levels of Total WBC count specially Lymphocytes, Neutrophils and Eosinophil cells, CRP level, IL-6 and Total Albumin and total protein contains of lungs as compared to the negative control group.

**Conclusion:** The obtained results indicated the bronchitis protective properties of *L. flexuosum* methanolic extract.

**Keywords:** *L. flexuosum* root, Salbutamol, Anti-bronchitis, Cigarette smoke model, IL-6.

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**Conflict of interest:** None

## INTRODUCTION

The respiratory ailment known as bronchitis is typified by inflammation of the bronchial tubes, which frequently involves oxidative stress, Pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are elevated, and inflammatory cells are infiltrating. Smoke from cigarettes was causing 90% of the cases of bronchitis<sup>1</sup>. So, in present survey bronchitis in rats basically induced by CS model. This disease recognised as an excess of mucus due to the hypersecretion of goblet cell in lung<sup>2</sup>. According to the Indian medical system, the plant *L. flexuosum* may be "Rudra Jata" in Ayurveda. Black bhoolan has black hairy roots, while white bhoolan has white roots. The fibrous, adventitious roots emerge from the rhizome. Its roots and rhizome are mostly used to treat jaundice. In the southwestern ghats of India, its leaves are administered topically for seven days to treat jaundice<sup>3</sup>. But in this survey, we used for protective effect against bronchitis.

## MATERIALS AND METHODS

### Chemicals

Ethanol 90% was provided by Priyadarshini J L. College of Pharmacy, Nagpur. Salbutamol Tablet were purchased from local market. Anaesthetic ether, Buffer solution, and Formalin solution were obtained from the college laboratory. The staining agent used for cytology by PAP Staining agent.

### Instrument

Digital microscope (MOTICDM 1116120084), Centrifuge (REMI INSTRUMENT LTD Serial no. LXCI-7807), Water bath, Sonicator, Smoking chamber (Fabricated in the laboratory).

### Collection and Authentication of Selected Plant Material

From Shri Shail herbs, the entire *L. flexuosum* plant was gathered, chowk 66-a, vidya vihar colony, Pratap nagar, Nagpur, Maharashtra. Plants were collected in the month of January 2024. Authentication of plant was done at Rashtrasant Tukadoji Maharaj Nagpur University; Department of botany and authentication number is 2073.

### Preparation of Methanolic Extract of *L. flexuosum*

\*Author for Correspondence: smjadhav2511@gmail.com

Dried root (100 gm) of LF was defatted with petroleum ether (40°-60°) 500 ml for 7 days. Filtered and extract was evaporated by using water bath. Then Extracts of LF was prepared by 70% methanol solvent using Soxhlet apparatus process<sup>4</sup>.

#### Phytochemical Screening of *L. flexuosum* extract

Several tests, including the Hager's, Legal's, Lead Acetate, Ferric Chloride, Fehling's, Xanthoproteic, and Salkowski tests, were used to perform phytochemical screening on *L. flexuosum* extract. Alkaloids, glycosides, flavonoids, phenols, carbohydrates, proteins, and steroids were all detected, according to the test<sup>5</sup>.

#### Animals

Male, healthy animals were utilized. Kusum Life science A-3, MIDC Wasmata, dist. Hingoli 431512 M. S. India, provided the 150–200 g wistar rats. The animals were housed in sterile cages in rooms with a light-dark cycle of 12/12 hours, at a temperature of about 24±1°C and a humidity of 55±5%. Food and drink were freely available. All the experiments were performed by the Institutional Animal Ethics Committee (IAEC) Registration number-2117/PO/RcBiBt/s/20/CPCSEA.; Protocol no. PJLCP/2023-24/IAEC/01) established in accordance with directives from the Ministry of Animal Welfare Division, Government of India, New Delhi's Committee for Control and Supervision of Experiments on Animals (CCSEA). (Table 1)

#### CS Model for Induction of Bronchitis

Methanolic extract of *Lygodium flexuosum*, bronchitis was experimentally induced in Wistar rats 150–200 gm through exposure to cigarette smoke CS). Rats were divided into 5 groups as mentioned in table 1. The rats in the treatment and negative control groups were exposed to cigarette smoke twice a day, at around 10 a.m. and 3 p.m., five days a week, or 20 days a month, using a special smoking chamber, with the exception of the normal control group, which was exposed to free air. Twenty days later a bronchitis model in

Table 1: Grouping of Animals

S. No.	Animal groups	Treatment
1.	Normal Control	Fresh air
2.	Negative Control	4 Cigarettes per day for 5 days/weeks
3.	Standard (STD)	2mg/kg Salbutamol (p.o)
4.	LFME	CS +100mg/kg LFME (p.o.)
5.	LFME	CS +200mg/kg LFME (p.o.)

the rats was achieved. From day 20 onward, plant extracts were administered orally once daily until day 28<sup>6-8</sup>.

#### Blood Sample Collection and Analysis for Experimental Parameters

Twenty-four hours after the last CS exposure, the rats were sacrificed using light ether anaesthesia, BALF, lung specimens and Blood samples were collected from retro orbital plexuses into an ethylene diamine tetra acetic acid (EDTA) tube to prevent coagulation using light ether anaesthesia, in clean appendant tubes. Blood sample were subjected for estimation of:

- Hematological parameters: Total WBC count, Differential WBC count
- Serum Test: CRP
- Cytokine Test: IL-6
- Broncho-alveolar lavage fluid (BALF): Total Protein and Total Albumin
- Morphology of Lungs
- Cytology
- Histopathology

#### Plasma Separation

The blood is centrifuged to separate the plasma, which is the clear, yellowish liquid containing IL-6 and other components.

#### Sample Handling

It's crucial to centrifuge the sample within 30 minutes of collection to avoid analytical errors. The separated plasma



Figure 1: Collection of BALF (Broncho-alveolar lavage fluid)



Figure 2: Cytological study (Coplin jar used for slide fixation)

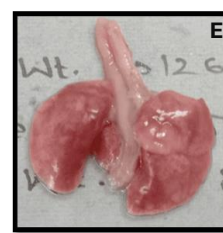
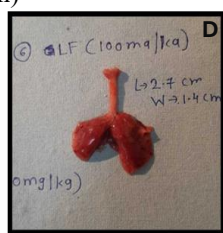
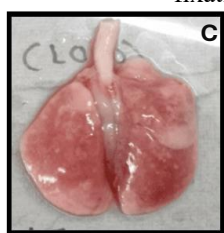
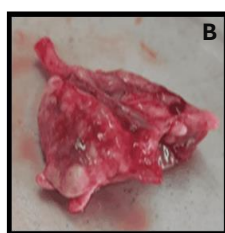
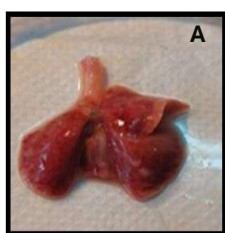


Figure 3: Morphology of Lungs in the (A) Normal control, (B) Negative control and (C) STD, (D) LFME (Low dose), (E) LFME (High dose)

Table 2: Hematological parameters of LFME

No. of Groups	Control	Negative Control	STD	LFME (100 mg/kg)	LFME (200mg/kg)
Total WBC Count	4640.0 ± 273.13	17817 ± 443.78	5416.7 ± 436.21	9400.0 ± 663.83	8116.7 ± 673.51
Neutrophil	25.83 ± 0.60	72.33 ± 0.88	29.833 ± 0.98	43.00 ± 2.82	40.33 ± 1.62
Lymphocytes	25.66 ± 1.64	65.33 ± 3.56	39.33 ± 1.54	53.16 ± 3.63	50.33 ± 3.55
Eosinophils	2.8 ± 0.47	7.8 ± 0.30	4.0 ± 0.36	6.83 ± 0.30	5.50 ± 0.34

Table 3: Values for Blood serum test: CRP

No. of Groups	Normal Control	Negative Control	STD	LFME (100 mg/kg)	LFME (200 mg/kg)
Total CRP Count	2.45 ± 0.35	16.83 ± 0.79	5.83 ± 0.79	12.33 ± 0.76	12.33 ± 0.76

should be stored refrigerated or frozen to maintain IL-6 stability.

#### ELISA (Enzyme-Linked Immunosorbent Assay)

This is a widely used method for IL-6 measurement. It involves coating a microplate with an anti- IL-6 antibody, adding the plasma sample, and then adding a detection antibody linked to an enzyme<sup>9,10</sup>.

#### Collection of Broncho-alveolar Lavage Fluid (BALF)

0.9% Saline solution (0.5 ml) was instilled through trachea into the lungs after sacrificing the animal and BALF was collected (total volume 1.5 ml) via tracheal cannulation. Every BALF sample was centrifuged at 500-1000 rpm and the supernatant layer collected was used for biochemical estimation and cytology study<sup>8</sup>. (Figure 1)

#### Preparation of BALF Smear

A tiny drop of the gathered BALF was put on a sanitized glass slide. Using a second slide held at a 45-degree angle, the drop was scrapethinly by the second slide across the first slide<sup>11,12</sup>.

#### Preparation of Smears from Tertiary Bronchi of Lung

The smear was prepared by dip cotton swab in BALF and rubbing on clean glass slide. Using a second slide held at a 45-degree angle, the scrapethinly by second slide across the first slide<sup>13,14</sup>.

#### Fixation

The smear slides were fixed immediately in a suitable fixative for about 30 minutes in the coplin jar shown in figure 2. The commonly used fixative is 90% ethanol. Subsequently, the fixed smears were stained using the PAP stain. The slides were gently rinsed with distilled water post-staining and allowed to air dry. stained smears were examined under the compound microscope. Examination was performed at magnification 10x. Different cell types, including macrophages, neutrophils, lymphocytes, eosinophils were identified<sup>15-17</sup>. (Figure 2)

#### Histopathology and Histo-morphology Evaluation

Histopathological study of lungs was carried out to study protective effects of extract LFME on smoke induce bronchitis complications on animals. Overnight, the collected lungs were preserved in a 10% formalin solution. They were dehydrated, embedded in paraffin wax, and sectioned at a thickness of 5 µm before being stained with haematoxylin and eosin (H & E) dye to create histo-slides. Light microscopy was used to analyse the produced slides' histomorphology<sup>18-20</sup>.

#### Statistical Analysis

Table 4: Broncho alveolar lavage fluid (BALF): Total Protein and Total Albumin

No. of Groups	Normal Control	Negative Control	STD	LFME (100 mg/kg)	LFME (200 mg/kg)
Total Protein	4.18 ± 0.18	7.03 ± 0.20	4.90 ± 0.11	6.55 ± 0.19	5.90 ± 0.08
Albumin	7.03 ± 0.20	11.25 ± 0.77	7.65 ± 0.20	8.63 ± 0.12	8.26 ± 0.07

Table 5: Determination of IL-6 level from Blood plasma

No. of Groups	Normal Control	Negative Control	STD	LFME (100 mg/kg)	LFME (200 mg/kg)
IL-6	2.66 ± 0.55	14.33 ± 0.42	5.16 ± 0.30	10.00 ± 0.36	8.50 ± 0.42

With the aid of Graph Pad Prism Version 5, the statistical analysis was carried out. Using one-way analysis of variance (ANOVA), all experimental groups were compared in order to determine statistical significance. The post-hock Tukey's multiple comparison was performed after each test. MEAN±SD p <0.05 was regarded as statistically significant for the data<sup>21,22</sup>.

## RESULTS

### Morphology of Lungs

Figure 3 Describe the cigarette smoke model was able to cause developed bronchitis in Wistar rats (B). Compared to a low dose of (D) LFME (100 mg/kg), a high dose (E) of LFME (200 mg/kg) demonstrated decreased oedema, redness, and inflammation.

### Hematological Parameters

A one-way ANOVA was used to examine the data, and then Tukey's Test was used. Mean ±SD (n=6) is used to express values. The criteria for determining statistical significance were \*p<0.05, \*\*p<0.01, and \*\*\*p<0.001. The treatment group and control group are contrasted with the negative control group. Figures 4,5, 6, and 7 show that both LFME dosages significantly reduce the total counts of WBC, neutrophils, lymphocytes, and eosinophils. (Table 2)

### Blood Serum Test: CRP

A one-way ANOVA was used to examine the data, and then Tukey's Test was used. Mean ± SD (n=6) is used to express values. The following criteria were used to assess statistical significance: \*p <0.05; \*\* p<0.01; \*\*\* p<0.001. The treatment group and control group are contrasted with the negative control group. Figure 8 shows that a high dose of LFME (200 mg/kg) significantly (\*\*\*p<0.001) lowers the CRP value compared to a low dose (100 mg/kg). (Table 3)

### Broncho Alveolar Lavage Fluid (BALF): Total Protein and Total Albumin

Table 6: Findings of Histopathology of lungs

S. No.	Groups	Eosinophilic Infiltration	Lymphocytic Infiltration	Others Changes	Grade of Infiltration
1	Normal control	Note seen	Not seen	Not seen	00
2	Disease control	Mild	Moderate to sever	Minimal Degree Hemorrhage	5
3	Standard	-	Minimal	-	1
4	LFME (100mg/kg)	Minimal	Mild to Moderate	Minimal Degree Hemorrhage	2
5	LFME (200mg/kg)	Minimal	Mild	Minimal Degree Hemorrhage	1

A one-way ANOVA was used to examine the data, and then Tukey's Test was used. Mean  $\pm$  SD (n=6) is used to express values. The following criteria were used to determine statistical significance: \*p <0.05; \*\* p<0.01; \*\*\* p<0.001. The treatment group and control group are contrasted with the negative control group. according to figures 9 and 10.

The levels of albumin and protein count in BALF are dramatically decreased by both dosages of LFME \*\* p<0.01; \*\*\*p<0.001. (Table 4)

#### Determination of IL-6 Level from Blood Plasma

A one-way ANOVA was used to examine the data, and then Tukey's Test was used. Mean  $\pm$  SD (n=6) is used to express

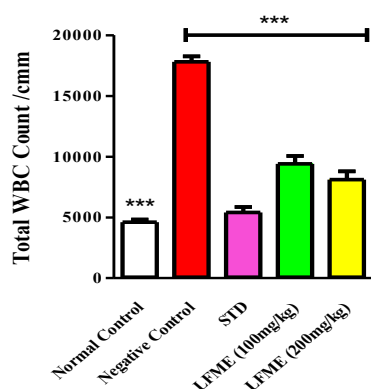


Figure 4: Total WBC count

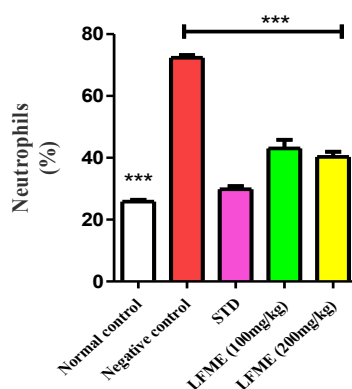


Figure 5: Neutrophils count

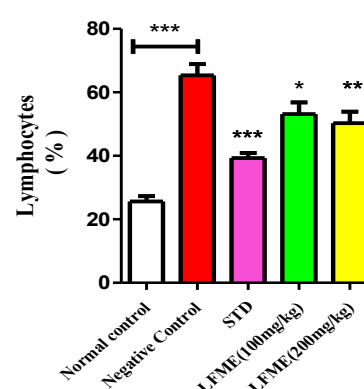


Figure 6: Lymphocytes count

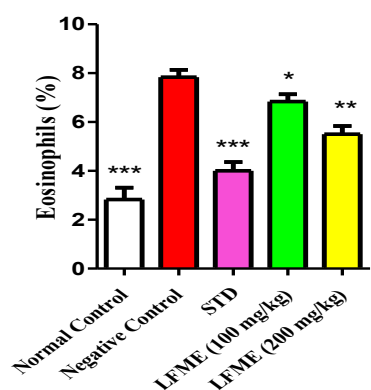


Figure 7: Eosinophils count

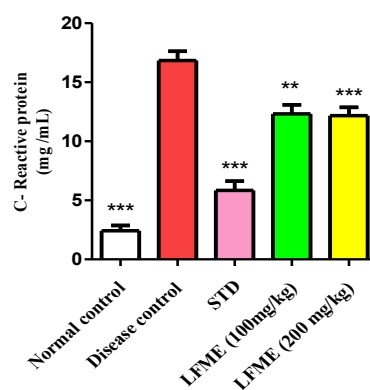


Figure 8: CRP count

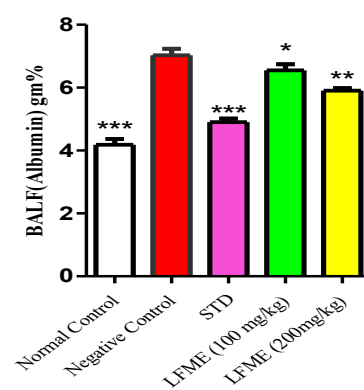


Figure 9: Total Albumin count in BALF

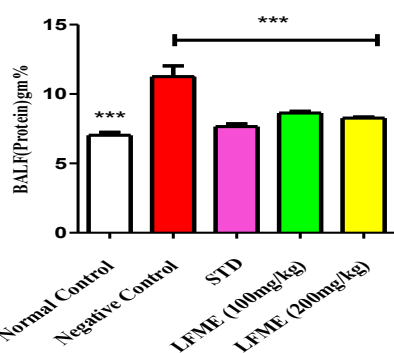


Figure 10: Total protein count in BALF

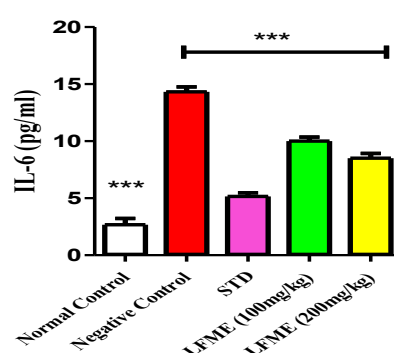


Figure 11: IL-6 level

values. The following criteria were used to assess statistical significance: \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ . The treatment group and control group are contrasted with the negative control group. Figure 11 shows that both LFME dosages considerably \*\*\* $p < 0.001$  lower blood IL-6 levels. (Table 5)

#### Findings of Histopathology of Lungs

Figure 12 and Table 6 Explain Histopathology analysis of Lungs of experimental animals. (A): Normal lung histology. No signs of inflammation, mucus hypersecretion, or fibrosis. (B): Marked inflammation of bronchial walls. Presence of inflammatory cells within the bronchial lumen and surrounding alveolar spaces. Possible thickening of bronchial walls due to inflammation. (C): Reduced inflammation compared to the Negative control group. Some thickening of bronchial walls but less severe than the Negative control group. (D): Moderate inflammation present. Mild improvement in the thickness of bronchial walls. (E): Further reduction in inflammation compared to LFME high dose. Bronchial walls appear less thickened, closer to normal histology<sup>23,24</sup>.

#### Cytological Study (BALF)

Cytological observations (magnification 10X) showing the effects of treatment on CS-induced cytological changes in the BALF are as follows.

#### Cytology Analysis of BALF of Experimental Animals Explain the Infiltration of Inflammatory Cells (Figure 13)

(A): The image likely shows a baseline condition where normal alveolar macrophages are present. Neutrophils, Lymphocytes, Eosinophils in range, indicating no inflammation. (B): This image probably displays an increased presence of neutrophils, lymphocytes, Eosinophils indicating an inflammatory response due to the induction process. Alveolar macrophages might be present in higher numbers or activated, showing signs of an immune response. (C): A reduction in neutrophils, Lymphocytes, Eosinophils compared to the induction group is expected, suggesting that the standard treatment is effective in reducing inflammation. Macrophages might appear more similar to the control group, indicating reduced activation and return towards normalcy. (D): Presence of neutrophils, Lymphocytes, Eosinophils less compared to the induction group, showing the effect of low-dose LFME treatment. Macrophages might show signs of reduced

activation compared to the induction group, but possibly not as normalized as the control group. (E): Even fewer neutrophils, Lymphocytes, Eosinophils present compared to the LFME low group, indicating a stronger anti-inflammatory effect of the high-dose LFME treatment. Macrophages might appear less activated and more similar to those in the control group<sup>25,26</sup>.

#### DISCUSSION

The present study explored the phytopharmacological potential of *Lygodium flexuosum* medicinal plants known in ethnomedicine for their anti-inflammatory and respiratory therapeutic properties. The investigation was designed to assess vivo anti-bronchitis efficacy. The experimental bronchitis model induced in animals showed typical pathological features including elevated total WBC count, serum CRP levels, increased total protein and albumin levels in BALF and significant histopathological damage to lung tissue. Treatment with graded dose of methanolic extract of LF resulted in notable amelioration of these parameters, indicating potent anti-inflammatory activity. Noteworthy reductions in IL-6 levels in treated groups compared to disease controls confirmed the immunosuppressive and cytokine-inhibitory potential of extract.

#### CONCLUSION

The findings of this study conclusively demonstrate that LFME exhibit significant \*\*\* $p < 0.001$  anti-inflammatory and therapeutic potential against bronchitis, largely due to their bioactive constituents—particularly flavonoids, phenol and tannins. The *in-vivo* results—evident through reduced CRP levels, normalization of hematological parameters, and improvement in cytokine profiles (e.g., IL-6)—confirmed their role in modulating immune responses and reducing airway inflammation. The BALF analyses provided strong evidence of lowered protein and albumin leakage, indicative of reduced vascular permeability and pulmonary inflammation. Histopathological examination of lung tissues revealed marked improvements in alveolar structure, reduced eosinophilic and lymphocytic infiltration, and minimized hemorrhagic damage in extract-treated groups. This was corroborated by cytological observations and BALF cell counts, which showed lower infiltration of

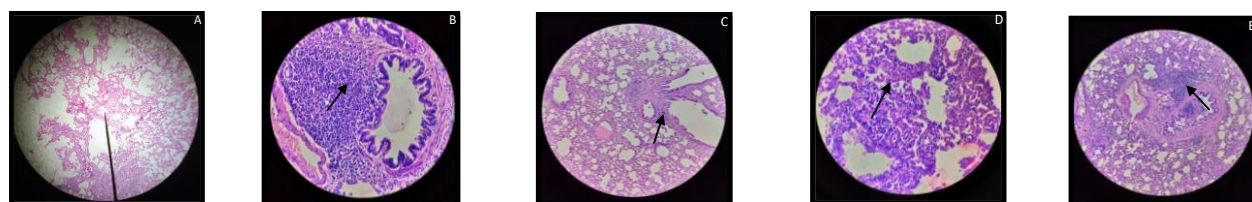


Figure 12: Histopathology analysis of Lungs of experimental animals observation (magnification 10X)

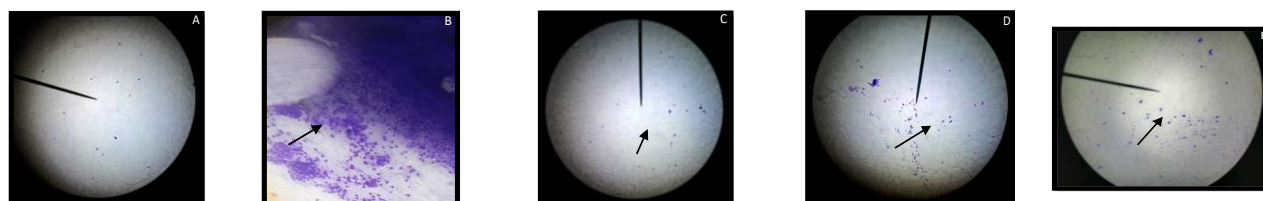


Figure 13: Cytology Analysis of BALF of experimental animals



inflammatory cells. The comprehensive results suggest that these plants, particularly their flavonoid-rich extracts, offer promising leads for the development of novel, plant-based anti-bronchitis and anti-inflammatory drugs. Future clinical validation and formulation development could translate these findings into effective, safe, and affordable therapeutic options.

### Acknowledgement

The Priyadarshini JL College of Pharmacy provided us with the facilities and environment we needed for our research, for which the authors are grateful.

### ABBREVIATIONS

*L. flexuosum*-*Lygodium flexuosum* CS-Cigarette smoke, BALF-bronchoalveolar fluid, CRP-C-reactive protein, IL-Interleukin, EDTA-ethylene diamine tetra acetic acid, PAP-Papanicolaou stain.

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