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EVALUATION OF ANTIASTHMATIC ACTIVITY OF SEED EXTRACTS OF APIUM GRAVEOLENS LINN

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ABSTRACT: anti-asthmatic potential is one of them In view of this, the present study was undertaken to investigate the anti-asthmatic potential of the seeds of *Apium graveolens* Linn. In this study first, extract was prepared using Soxhlet apparatus with continuous heat extraction method in 95% v/v ethanol. The total yield obtained from extraction was found to be 34% w/w. Then Preliminary Phytochemicals Screening was carried out for by using different types of chemical tests. The result of phytochemical screening shows that ethanolic extract contained flavonoids, steroids and terpenoids. Then Acute Oral Toxicity study for determination of LD50 was done by Dose Fixation method according to OECD guideline (AOT 425). This was performed in Swiss Albino mice. The observation of this study confirmed that, LD50 of the compound was to be greater than 2000mg/kg for the test compound. Any dose below 2000mg/kg could be used as a dose for animals and evaluation of anti-asthmatic activity was carried out at doses of 50, 100 and 200 mg/kg body weight by using milk induced leukocytosis and eosinophilia. Total Leukocyte Count and Differential Leukocyte Count were done by Haemocytometry and Field Staining Method respectively. Statistical analysis carried out by Student t-test, one way ANOVA and followed by Dunnett's test using PRISM Software (Graph Pad PRISM Version 5.03). The ethanolic extract showed significant inhibition against leukocytosis and eosinophilia induced by milk as compared to disease control, among three doses the 100mg dose showed significant * ($P < 0.05$) effect of EEAG on milk induced Leucocytosis and eosinophilia. Group of mice which were pre-treated with EEAG (200 mg/kg p.o.) demonstrate significant *** ($P < 0.05$) effect of EEAG on milk induced Eosinophilia.

Keywords: *Apium graveolens* Linn, anti-asthmatic activity, leukocytosis, Swiss Albino mice.

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1. INTRODUCTION:

Introduction to Herbal Medicine:

Herbal medicine is the most widely used system of medicine in the world today. They are made exclusively from plants. According to World Health Organization, medicinal plants would be the best source to obtain a variety of drugs. About 80% of individuals from developed countries use traditional medicine, which has compounds derived from medicinal plant.[1]

Herbal medicines are in great demand in both developed and developing countries as a source of primary health care owing to their attributes having wide biological and medicinal activities, high safety margins and lesser costs. Herbal molecules are safe and would overcome the resistance produced by the pathogens as they exist in a combined form or in a pooled form of more than one molecule in the protoplasm of the plant cell. Even with the advent of modern or allopathic medicine, Balik and Cox (1996) have noted that a number of important modern drugs have been derived from plants by indigenous people.[2]

Plant drug have been the major source for treatment of disease for a long time. They have been used in traditional used in traditional medicine on basis of experience and practice. With the advent of modern systems of medicine need has been felt to investigate the active constituents present in these plants. Various molecules have been isolated, characterized and tested for their related pharmacological activities.[3] The active molecules have provided significant leads in the development of more effective synthetic molecules.[4]

Traditional use of medicine is recognized as a way to learn about potential future medicines. Researchers have identified number of compounds used in mainstream medicine which were derived from "ethno medical" plant sources. Plants are used medicinally in different countries and are a source of many potent and powerful drugs.[5]

1.2 *Apium graveolens* Linn.

Apium graveolens Linn. (Apiaceae), celery, is a native of Eurasia and is grown mainly in coastal regions. Celery is widely cultivated in the temperate zones as an important garden crop and the bleached leaf stalks are

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relished as a popular vegetable. *Apium graveolens* Linn. is one of the ingredients in 8 of the 33 Indian poly herbal formulations with reputed life protecting activity. The characteristic odour of celery essential oil is due to a series of phthalide derivatives. Vegetables and fruits are considered to be good sources of functional ingredients.

2. MATERIALS AND METHOD

➢ MATERIALS

Fresh seeds of *Apium graveolens* Linn. were collected from Grocerry Shop Mandleshwar, District Khargone, M.P. The plant was authenticated by Dr. S.K. Mahajan, Head of Department of Botany, P.G. College, Khargone, M.P. Dexamethasone IP was obtained from Mahima Life Sciences Pvt Ltd, , EDTA 5% w/v, WBC diluting fluid, , Cedar wood oil was obtained Biolab Diagnostics (I) Pvt Ltd and Anhydrous $CaCl_2$, 95% Ethanol, Diethyl ether was obtained from Loba Chem Pvt Ltd Mumbai

2.1 EXPERIEMENTAL WORK:

Experimental Animals

Swiss Albino mice (15-25 g) of either sex were purchased from the Institute of Animal Health & Veterinary. Biologicals, Rasalpura, Mhow (M.P.). They were housed in group of six under standard laboratory conditions of temperature (25 ± 2°C). Animals were provided standard laboratory diet (Maize 60%, Soya flex 20%, Wheat grain 18.5%, Common salt 1%, Mineral mixture 0.5%) and free access to drinking water. The experimental mice were maintained under a constant 12 hrs light and dark cycle. Animal were acclimatized to the new experimental environment for 5days (Quarantine period) before initiating the study. Laboratory animal handling and experimental procedures were performed according to CPCSEA guidelines and the registration number of 1575/PO/a/11/CPCSEA in Charak Institute of Pharmacy,Madleshwer,M.P.

Methods

- Fresh seeds of *Apium graveolens* L. were collected from Grocerry Shop Mandleshwar, District Khargone, M.P.
- Extract was prepared using soxhlet apparatus with continuous heat extraction method in 95% v/v ethanol.

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- Preliminary Phytochemicals Screening was carried out by following methods.
- ➢ Identification of Flavonoids by Shinoda test and Lead acetate test.
- ➢ Identification of Alkaloids by Dragendroff's test and Mayer's test.
- ➢ Identification of steroids by Liebermann's reaction.
- ➢ Identification of Terpenoids by Salkowski reaction.
- ➢ Identification of Tannins by Ferric chloride solution test &Lead acetate test.
- ➢ Identification of carbohydrates by Molisch's test.
- ➢ Swiss Albino mice (15-25 g) of either sex were procured from the Institute of Animal Health & Veterinary. Biologicals, Rasalpura, Mhow (M.P.).
- ➢ Acute Toxicity study for determination of LD_{50} was done by Dose Fixation method according to OECD guideline (AOT 425).
- ➢ Anti-asthmatic activity done by animal model [Milk-induced Leukocytosis and Eosinophila in mice (In vivo)].
- ➢ Total Leukocytes Count and Differential Leukocytes Count were done by Haemocytometry and Field Staining Method respectively.
- ➢ Statistical analysis done by Student t-test, one way ANOVA and followed by Dunnett's test using PRISM Software (Graph Pad PRISM Version 5.03).

2.2 EXPERIMENTAL WORK & RESULTS:

- **Collection and preparation of plant material**

Fresh seeds of *Apium graveolens* Linn. were collected from Grocerry Shop Mandleshwar, District Khargone, M.P. The plant was authenticated by Dr. S.K. Mahajan, Head of Department of Botany, P.G. College, Khargone, M.P. After taxonomic and ethnomedicinal identification & authentification of collected plant *Apium graveolens* Linn. fresh seeds were collected.

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- **Preparation of extract**

Extract was prepared using Soxhlet apparatus with continuous heat extraction method. About 50gm of powdered seeds was taken to prepare first batch of extract. The powder was packed in 5 layers of muslin cloth and sealed to make a pocket. About 300 ml of 95% v/v ethanol was added and the extraction continued for 36 hrs at 55-60°C. Extract was collected in a beaker which was covered with aluminium foil. The whole procedure was repeated to make 6 such batches of extract to get the yield. The combined extracts were concentrated on a water bath at 40°C under atmospheric pressure. The semisolid dark brownish residue material thus obtained was dried again in a desiccator over anhydrous calcium-chloride and using commercially available adsorbents. The total yield obtained from extraction was found to be 34 % w/w. Extract was preserved in refrigerator for phytochemical screening, acute oral toxicity study and evaluation of anti-asthmatic activity. [55]

- **Preliminary Phytochemicals Screening**
- **Tests for Identification of Flavonoids**

A) Shinoda test: A small amount of extract was taken in a test tube to which 5ml 95% ethanol was added, then few drops of concentrated HCl was added slowly. Then 0.5g Mg turnings were added. Occurrence of pink color confirmed the flavonoids.

B) Lead acetate test: Small quantity of residue was taken in a test tube to which lead acetate solution was added. Yellow color precipitate formed which confirmed the presence of flavonoids presence.

- **Test for identification of Alkaloids**

A small amount of extract was taken in a test tube and diluted with 2ml of dilute HCl. This solution was properly shaken and filtered. This filtrate was used for performing the following tests:

A) Dragendroff's test: Quantity of 2 - 3 ml of filtrate was taken in a new test tube. Small amount of dragendroff's reagent was added. Appearance of Orange -brown sediment was not appeared. This shows the absence of alkaloids.

B) Mayer's test: Quantity of 2 to 3 ml of filtrate was taken in a test tube followed by the addition of Mayer's reagent. A white precipitate was not formed which inferred the absence of alkaloids.

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- **Test for identification of steroids**

Liebermann's reaction: Quantity of 3 ml of extract was taken in a clean test tube. In this 3 ml of acetic anhydride was added. This was heated and cooled. Then few drops of conc. H2SO4 were added Appearance of blue color. Confirmed the presence of steroids

- **Test for identification of Terpenoids**

Salkowski reaction: Quantity of 2ml of extract was taken in a test tube. 2ml of chloroform was added in followed by 2ml of conc. H2SO4 was added in the test tube slowly and shaken well. Appearance of Greenish - yellow fluorescence confirms the presence of terpenoids.

- **Tests for identification of Tannins**

A) Ferric chloride solution test: A small amount of extract was taken in a test tube. 2ml ethanol was added and mixed well followed by adding 1ml of 5% ferric chloride reagent. Appearance of Deep blue black color confirms the absence of tannins.

B) Lead acetate test: A small amount of extract was taken in a test tube and alcohol was added to it the mixture was shaken properly and 2 ml lead acetate was added, no precipitates has formed which confirms the absence of tannins.

- **Test for carbohydrates**

Molisch's test: In 2-3 ml of extract few drops of molisch's reagent (alpha napthol solution in alcohol) was added. The mixture was shaken well & concentrated sulphuric acid was added from the sides of the test tube. Formation of violet ring at the junction of two liquids was observed. This inferred the absence of carbohydrates. [56]

- **Determination of LD_{50} of the EEAG in mice by Acute Toxicity Studies :**

Dose Fixation - Acute oral toxicity study was done according to OECD guideline (AOT 425). It was done for the test compound in female mice procured the Institute of Animal Health & Veterinary. Biologicals, Rasalpura, Mhow, Dist. Indore, M.P. Limit test was performed in 3 animals. A dose of 2000mg/kg was selected. One animal was administered a dose of 2000mg/kg on first day. The animal was observed for 24 hours. The animal showed no signs

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of discomfort or symptoms so, the same dose was given to one more animal, the next day. The procedure was repeated in 3 animals for 3days. All the animals survived without any symptom. Based on the above observation, LD_{50} of the compound was confirmed to be greater than 2000mg/kg for the test compound. Any dose below 2000mg/kg could be used as a dose for animals.

- **Determination of In-vivo Anti-asthmatic activity of the prepared extract by using the model [Milk-induced Leukocytosis and Eosinophila]:**

Swiss Albino mice were divided into six groups having six animals in each group. Each group numbered in Roman as I (Normal control group), II (Disease control group), III (Standard group), IV, V& VI (Test groups). Fasting blood sample collection done by retro-orbital plexus under slight diethyl ether anaesthesia. Blood collected in EDTA coated eppendoff tubes which was properly labeled. Mice of the normal control group (I group) were administered distilled water (10ml/kg, p.o.), whereas animals belonging to group III administered standard drug dexamethasone (50mg/kg, i.p.). Animals belonging to group IV, V and VI administered EECPF in the doses of 50,100 and 200mg/kg p.o., respectively. Animals belonging to groups II, III, IV,V and VI administered boiled and cooled cow milk in doses of (4ml/kg s.c.).Cow milk was boiled at temperature 70°C for 20 minutes. All the test drugs were administered 1 hour before milk administration. Total leukocytes and eosinophils counts were carried out in each group pre administration of test compound and 24 hours after milk administration. Difference in total Leukocytes and Eosinophiles count pre and post 24 hour drug administration were calculated.[57]

Total Leukocytes Count by Haemocytometry

Anticoagulated blood was drawn by WBC pipette up to 0.5 marks. The excess blood from outsides of the pipette was wiped by using cotton. Diluting fluid was drawn up to 11 marks. The contents was mixed in the pipette and after 5 minutes charged the counting chamber. The cells were allowed to settled down for 2-3 minutes. One of the 'W' marked areas (each having 16 small squares) was focused by using low power objective (10X).The cells were counted in the entire four 'W' marked corners. Number of white blood cells /cu mm of whole blood were calculated.

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- **Differential Leukocytes Count by Field Staining**

A thin smear was prepared by spreading a small drop of blood evenly on the cleaned, dried glass slide. A lead marker pencil was used for making an identification number on the glass slide. Then the dried blood smear was fixed with methanol for 2-3 minutes to prevent distortion of the cells and adhesion of the blood film on the glass slide. The fixed smear was dipped in Field Stain 'B' for 5 seconds. Then smear was washed with tap water. Now, smear was dipped in the Field Stain 'A' for 5 seconds. Then smear was washed with tap water. The stained glass slide was placed vertically on the rack. The smear was dried in air and examined the smear under oil immersion objective (100X) by using cedar wood oil. Different types of WBCs (Neutrophiles, Lymphocytes, Monocytes Eosinophiles and Basophiles) were identified and their % was calculated.[58]

3. RESULTS

3.1 Extraction Process

The total yield obtained from extraction was found to be 34 % w/w.

3.2 Preliminary Phytochemical Screening

The phytochemical screening shows that ethanolic extract contained flavonoids, steroids and terpenoids. Refer table no.1.

Phytochemicals present in the ethanolic extracts of seed of *Apium graveolens* Linn.							
Plants	**Part**	**Flavonoid**	**Alkaloid**	**Steroid**	**Terpenoid**	**Tannin**	**Carbo hydrate**
***Apium graveolens* L.**	**Seed**	+	-	+	+	-	-
Note: "+" = present; "-" = absent							

Table No. 1 Results of Preliminary Phytochemical Screening of EEAG.

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3.3 Acute Toxicity Study

Observation All the animals survived without any symptom or toxicity during the observations up to 24 hrs. Based on the above observation, LD_{50} of the compound was confirmed to be greater than 2000mg/kg for the test compound.

Inference Any dose below 2000mg/kg could be used as a dose for animals. The biological evaluation of anti-asthmatic activity was carried out at doses of 50, 100 and 200 mg/kg body weight.

3.4 Statistical Analysis

The results of this study were analyzed on the basis of mean ± SEM from 6 animals. Statistical analysis was carried by using Student t-test, one-way analysis of variance (ANOVA) Test and by the Dunnett's test using Prism Software. $P < 0.05$ was considered significant. Refer table no. 9 to 11 and graph no. 1 to 6.

Groups	Treatment	Number of leukocytes (cu.mm)		
		Before treatment	After treatment	Difference
1	Normal Control(10ml/kg DW p.o.)	12500±1744	11183±1527	1850±84.7
2	Diseases Control (10ml/kg DW + 4ml/kg milk s.c.)	9367 ± 1591	15417±1896	6050± 458
3	Standard (Dexa 50mg/kg i.p. + 4ml/kg milk s.c.)	10517±1530	3617 ± 540	6900±1647
4	EEAG 50 + Milk(4ml/kg s.c.)	10667±1903	9933 ± 1468	2133±465
5	EEAG 100 + Milk(4ml/kg s.c.)	10033±1912	8933 ± 1796	2433± 531
6	EEAG 200 + Milk(4ml/kg s.c.)	11567±1985	10583±1675	1617± 207

Table No.2 Effect of the ethanol extract of seed of *Apium graveolens* L. (EEAG) on Total Leukocyte Count. All values are expressed as mean±SEM of a sample size of n=6, level of significance chosen was *p<0.05.

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Groups	**Treatment**	**Number of differential leukocytes (cu.mm)**		
		Neutrophils	**Lymphocytes**	**Eosinophiles**
1	Normal Control(10ml/kg DW p.o.)	25 ± 3.095	74 ± 3.177	00 ± 00
2	Diseases Control (10ml/kg DW + 4ml/kg milk s.c.)	26 ± 2.432	72 ± 2.104	00 ± 0.166
3	Standard (Dexa 50mg/kg i.p. + 4ml/kg milk s.c.)	28 ± 2.551	70 ± 2.056	00 ± 0.166
4	EEAG 50 + Milk(4ml/kg s.c.)	25 ± 3.263	75 ± 3.25	00 ± 0.166
5	EEAG 100 + Milk(4ml/kg s.c.)	19 ± 3.422	81 ± 3.562	00 ± 0.166
6	EEAG 200 + Milk(4ml/kg s.c.)	28 ± 3.270	71 ± 3.191	00 ± 0.166

Table No.3 Differential Leukocyte Count pre drug administration.

All values are expressed as mean±SEM of a sample size of n=6, level of significance chosen was *p<0.05.

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Groups	**Treatment**	**Number of differential leukocytes (cu.mm)**		
		Neutrophils	**Lymphocytes**	**Eosinophiles**
1	Normal Control(10ml/kg DW p.o.)	023 ± 2.812	75 ± 2.432	00 ± 0.341
2	Diseases Control (10ml/kg DW + 4ml/kg milk s.c.)	21 ± 0.792	75 ± 1.021	03 ± 0.619
3	Standard (Dexa 50mg/kg i.p. + 4ml/kg milk s.c.)	68 ± 7.46	32 ± 7.467	00 ± 00
4	EEAG 50 + Milk(4ml/kg s.c.)	30 ± 4.064	68 ± 3.782	01 ± 0.5
5	EEAG 100 + Milk(4ml/kg s.c.)	22 ± 3.015	76 ± 2.98	01 ± 0.42
6	EEAG 200 + Milk(4ml/kg s.c.)	28 ± 5.258	71 ± 5.256	00 ± 0.21

Table No.4 Effect of the ethanol extract of seeds of *Apium graveolens* L. (EEAG) on Differential Leukocyte Count. (Post drug administration)

All values are expressed as mean±SEM of a sample size of n=6, level of significance chosen was *p<0.05.

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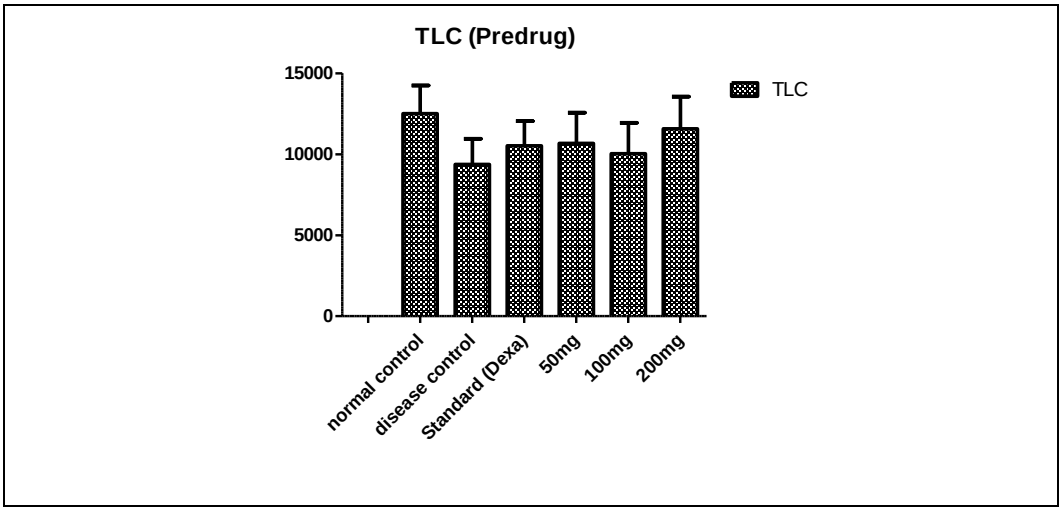
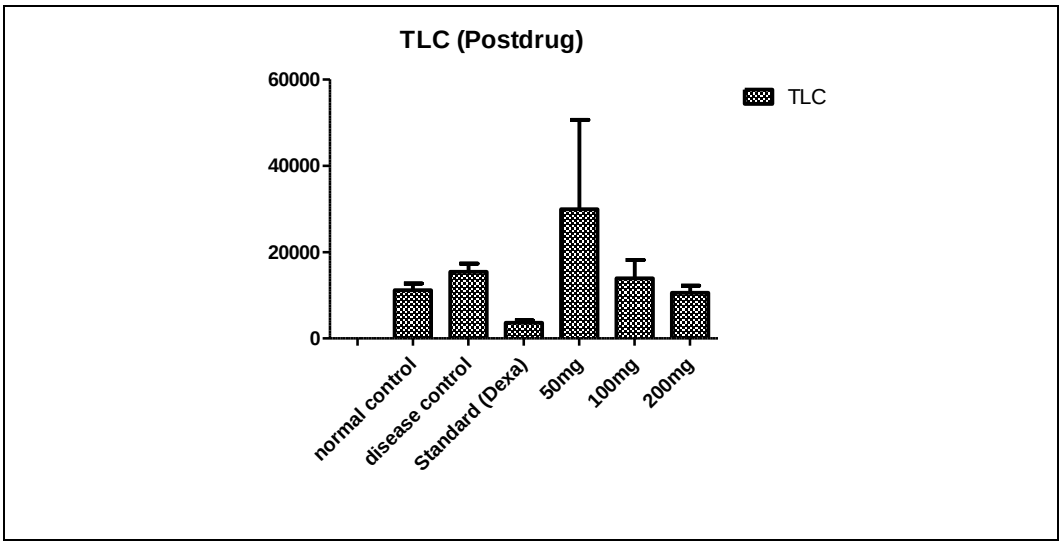
3.5 Comparison of Total Leukocytosis Pre Vs Post



Graph No. 1 Total Leukocytes Pre Drug Administration.



Graph No. 2 Total Leukocytes Post Drug Administration

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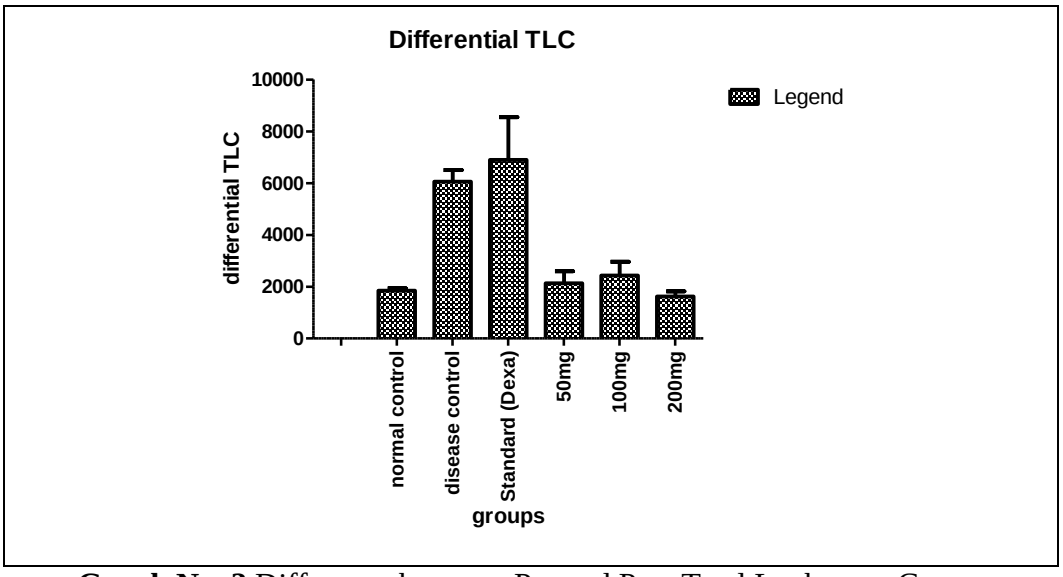
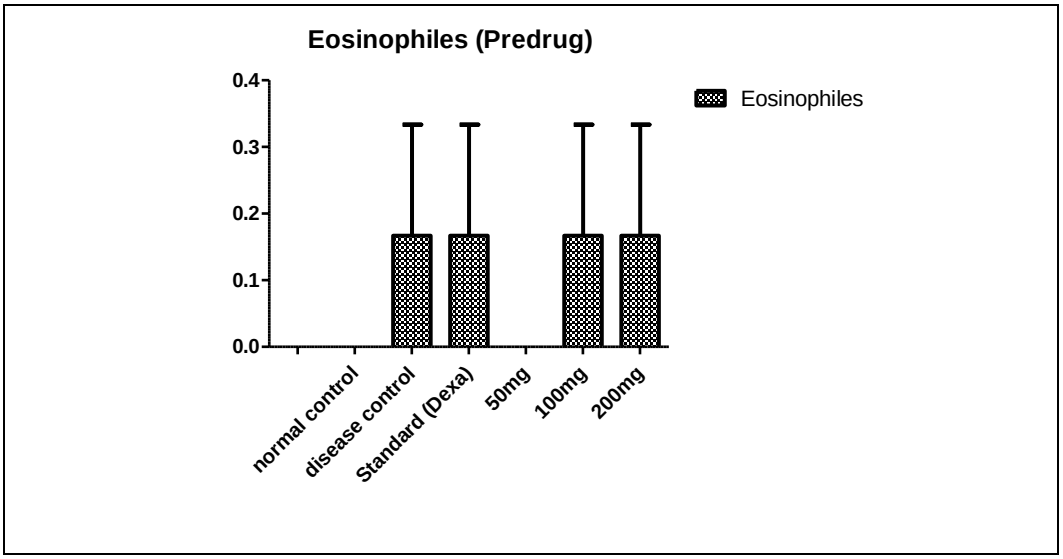


Graph No. 3 Difference between Pre and Post Total Leukocyte Count.

3.6 Comparation of Eosinophiles Pre vs Post



Graph No.4 Eosinophiles Pre Drug Administration.

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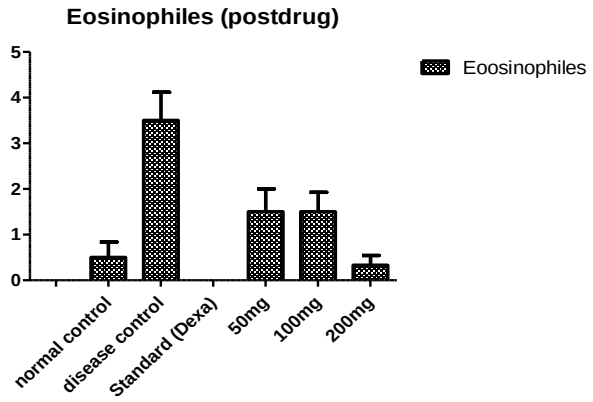
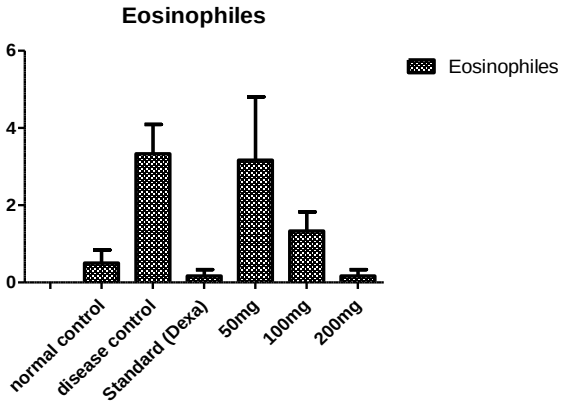


Graph No.5 Eosinophiles Post Drug Administration.



Graph No.6 Difference between Pre and Post Eosinophiles

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4. SUMMARY & CONCLUSION: In the present study it is found that asthmatic inflammation due to leukocytes are responsible for releasing of various inflammatory mediators such as histamine cytokinin etc. Infilteration of leukocytes in surrounding tissue in asthamatic inflammation causes increased inflammation stress which is observed as main pathogenic character of asthma. In the present study it was found that the inhibition of leukocytosis was significant in animals treated with the *Apium graveolens* L.as compared to disease control group. These results suggest that *Apium graveolens* L. suppresses the milk induced leukocytosis and eosinophilia by stabalising the oxidative stress in the surrounding tissues. The study results show that, the group of mice pretreated with *Apium grveolens* L. seeds extract given by oral route inhibits the milk induced eosinophil count. This may probably indicates that *Apium graveolens* L. seeds may helps to decrease type I hypersensitivity in asthmatic mice. This study reveals that *Apium graveolens* L. possessed anti-asthamatic activity which may be beneficial in the management of bronchial asthma as an alternative drug therapy. The anti-asthamatic activity of *Apium graveolens* L. seeds may be due to anti-oxidant properties and phytochemicals such as Flavonoids and Steroids present in it. It is concluded that *Apium graveolens* L.seeds have anti-asthamatic activity against milk induced leukocytosis and eosinophilia.

It is concluded from current results that either increament of doses of current extract or evaluation of anti-asthmatic activity from different parts of *Apium graveolens* L. may results in introduction of better extracts with more anti-asthmatic activity. A further study on this plant may results in introduction of new potent & safer anti-asthmatic agent.

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