Chapter-7

ANTI-INFLAMMATORY ACTIVITY
7.0 ANTI-INFLAMMATORY ACTIVITY

Inflammatory diseases including different types of rheumatic diseases are very common throughout the world. Although rheumatism is one of the oldest known diseases of mankind and affects a large population of the world, no substantial progress has been made in achieving a permanent cure (Handa et al., 1992). The greatest disadvantage of the presently available potent synthetic drugs lies in their toxicity and reappearance of symptoms after discontinuation of treatment. The research on screening and development of drugs for their activity is therefore, an unending process and there is hope of finding out antirheumatic drugs from indigenous plants. Various plant extracts and their isolated compounds have been already proved as good anti-inflammatory agents (Arathi and Leonard, 2005).

India is known as the 'Emporium of Medicinal Plants' due to the occurrence of several thousands of medicinal plants in different bioclimatic zones. Ayurveda and Siddha systems of medicine, the traditional heritage of India include many time tested medicinal plant drugs for various diseases to which there is no answer in modern medicine till today. The demands for Ayurvedic drugs or phytomedicines are increasing day by day globally (Yoganarasimham, 2000).

7.1 Introduction

The word inflammation comes from the Latin word “inflammare”, to burn. Inflammation is a response of the tissue to an infection, irritation (or) foreign substances. The characteristics of inflammation are numerous: reddening (visible), swelling (oedema), soreness (pain) and the corresponding histological changes (Neville et al., 2004).

Inflammatory response has two facets, inflammation and repair. Inflammation serves to destroy, dilute or wall off the injurious agent and the tissue cells that may have been destroyed. In turn, the inflammatory response sets into motion a
complex series of events, which heal and reconstitute the damaged tissue. Repair begins during the active phase of inflammation, but reaches completion usually after the injurious response had been neutralized. Destroyed cells and tissues are repaired therapy. Both inflammation and repair generally serve as useful purposes. Inflammatory reaction underlies the genesis of crippling rheumatoid arthritis, life threatening sensitivity reaction and some forms of glomerular diseases. Inflammation is normally beneficial, being part of a complex protective homeostatic mechanism.

7.2 History of inflammation (Almeida and Menezes, 2002; Saravana and Gandhimathi, 2012)

Inflammation was known as 'phlogosis' to the Greeks and as inflammation to the Romans. Nearly 2000 years ago Cornelous Celsius, a Roman doctor first described the four main signs of inflammation: rubor, tumor, calor and dolor. Galen in third century A.D. defined the inflammation as a reaction of the body against injury. Subsequently, Julius Colinteim in 1873 emphasised the role of vessels in the inflammatory process and E. Metchnikoff in 1892 emphasised mainly on the migration of Leucocytes and on phagocytosis. During 1930's Henry Dale tried to explain the process of inflammation as an autopharmacological phenomenon. According to him, most pathophysiological events of inflammation were mediated by the release of acetylcholine, catecholamine, histamine, etc. Menkin and Rocha a Silva with his co workers, in the fifties, demonstrated the role of the leukotrienes and kinins, in the process of inflammation. In the late sixties and seventies there came the Prostaglandin phase.

7.3 Pathophysiology of inflammation

Physical agents, chemical agents, infections and immunological reaction may bring about the injury which causes inflammation. Essentially there are two categories of inflammation, acute and chronic.
7.3.1 Acute inflammation (Neville et al., 2004)

The classical signs of acute inflammatory reaction are warmth, redness, pain, swelling and loss of function. Zweifach reviewed the vascular changes and phenomena which occur in acute inflammation after injury. They are as follows:

7.3.1.1 Active hyperaemia

Immediately after the injury, the arterioles of the injured tissue contracts followed by relaxation. As a result of that, the capillary network and post capillary venules become engorged with rapidly flowing blood, which warms the normal skin and also causes redness.

7.3.1.2 Exudation of Protein-rich fluid

After the onset of active hyperaemia the protein-rich fluid escapes from the blood vessels into the surrounding tissue and forms interstitial oedema.

7.3.1.3 Emigration of Leukocytes

One of the major hallmark of the inflammation is the migration of leukocytes (principally neutrophil and monocytes) derived from the blood in the injured area. In inflammation, the leukocytes in the venules passes into the peripheral stream, make contact with vascular endothelium and thereby get arrested on it, eventually forming a continuous layer. Neutrophils migrate earlier and more rapidly than monocytes.

7.3.2 Chronic inflammation (Panda et al., 2011)

Chronic inflammation is also characterised by pain, redness and swelling, but it does not subside in a period of days, but may instead have a relentless damaging course of several weeks, months or years, and may have far reaching effects on hosts well being. A chronic inflammation is caused by the persistence of an irritant, which may be of biologic, physical, or chemical nature. The histological marks of chronic inflammation are follows.

- Infiltration of mononuclear cells, macrophages, lymphocytes and plasma cells
• Proliferation of fibroblasts and small blood vessels.

The cycle of cellular infiltration, necrosis and fibrosis will continue as long as the irritant remains.

7.4 Experimental Models used for testing of Anti-inflammatory activity

Various models available for testing anti-inflammatory activity with reasonable accuracy, minimum time and less test substance consumption are described as below

7.4.1 Acute inflammation in animals

Acute inflammation condition is produced in the animals by adapting the following methods.

a) Carrageenan-induced rat paw oedema model (Battu et al., 2000)
b) U.V. light induced erythema model (Sun-Young et al., 2004)
c) Egg-white induced pedal inflammation (Felix et al., 2008)
d) Dextran-induced pedal inflammation (Mandal et al., 2003)

7.4.2 Chronic inflammation in animals

Chronic inflammation condition is produced in the animals by adapting the following methods.

a) Formaldehyde induced arthritis (Moura et al., 2005)
b) Cotton pellet test (Gupta et al., 2005)
c) Granuloma pouch test (Isabel et al., 2004)
d) Adjuvant-induced arthritis (Fan et al., 2005)

7.5 Plants with anti-inflammatory activity

The literature survey reveals that the plant species of about 96 genera belonging to 56 families have exhibited anti-inflammatory activity. Some of the plant sources used in traditional systems of medicine with pharmacologically/therapeutically proven anti-inflammatory and antirheumatic claims is mentioned in the table 7.1.

<table>
<thead>
<tr>
<th>Plant species</th>
<th>Family</th>
<th>Plant species</th>
<th>Family</th>
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<td>Aconitum napellus</td>
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<td>Morus alba</td>
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<td>Withania somnifera</td>
<td>Solanaceae</td>
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7.6 Treatment of inflammation (Vetrichtelvan and Jegadeesan, 2003).

For the treatment of inflammation Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used. Most commonly used drugs are:

- **Salicylates**: Aspirin
- **Propionic acid derivatives**: Ibuprofen, Ibuprofen + Paracetamol Combination. Flurbiprofen, Ketoprofen, Naproxen, Fenamates and Mefenamic acid
- **Pyrazolones**: Phenylbutazone and Oxyphenbutazone
- **Indole derivative**: Indomethacin
- **Arylacetic acid derivatives**: Diclofenac sodium, Diclofenac potassium, Diclofenac + Paracetamol Combination, Combination preparation of diclofenac and serratiopeptidase.
- **Oxicam derivatives**: Piroxicam, Tenoxicam and Meloxicam
- **Pyrrole-Pyrrole Derivatives**: Ketorolac
- **Paraaminophenol derivative**: Paracetamol
- **Others**: Celecoxib, Rofecoxib, Valdecoxib and Nimesulide, Combination preparation of Nimesulide, Nabumetone.
Figure-7.1: Some important NSAIDs with their structures were represented
7.7 Method used in the present study [Carrageenan-induced rat paw oedema model for assessment of acute inflammation]

Subcutaneous carrageenan injection to produce oedema in the rat paw is the most frequently used acute inflammatory animal model among the other models such as UV light induced erythema model etc. Various measuring systems used for the assessment of induced oedema in the paw include: volume (Santosh et al., 2008); paw thickness (Vanu et al., 2004); paw weight (Hamzah et al., 2006); and painfulness (Ching et al., 2009) to monitor the development of the induced oedema in the paw. The preferred routine system in our laboratory is measurement of dorsiventral paw thickness using zeitlin’s apparatus (Appendix - B) (Battu et al., 2000).

7.8 Materials

All the materials used for this experiment are of analytical grade. Carrageenan and Dimethyl sulphoxide (E. Merck) were purchased from Desai Chemicals, Visakhapatnam.

7.9 Animals

Sprague Dawley rats of either sex weighing between 200-250 gm were obtained from M/s. Mahavir Enterprises, Hyderabad, Andhra Pradesh, India. The animals were housed under standard environmental conditions (temp. 22 ± 1°C with an alternating 12 h light–dark cycle and relative humidity of 60 ± 5 %), one week before the start and also during the experiment as per the rules and regulations of the institutional ethics committee. They were fed with standard laboratory diet
supplied by M/s. Rayans biotechnologies Pvt. Ltd., Hyderabad, Andhra Pradesh, India. Food and water was allowed *ad libitum* during the experiment.

7.10 Preparation of solutions

7.10.1 Preparation of carrageenan suspension

One percent suspension of carrageenan sodium salt was prepared by sprinkling 100 mg of carrageenan powder on 10 ml of saline (0.9% NaCl) solution and set aside to soak for 1 hour. A homogenous suspension was then obtained by thorough mixing with a magnetic stirrer.

7.10.2 Preparation of Sodium CMC suspension

Stock suspension of sodium CMC was prepared by triturating the powder sodium CMC (1 g) finely in 2.5 ml of water containing tween 20. A 1:10 dilution of this stock solution made in distilled water was used for suspending the test and standard drugs.

7.10.3 Drug suspensions

Drug concentrations were prepared to maintain uniform dose volume, which was always given in a total equivalent to 0.1 ml per 100 gm rat. For instance, for a dose of 50 mg/kg, a 50 mg/ml suspension was prepared. Accordingly, a rat weighing 250 gm would be given 0.25 ml.

7.11 Induction of paw oedema

Oedema was induced in the rats by injecting subcutaneously 0.1 ml of 1% carrageenan suspension in saline into the sub-plantar tissue of the right hind paw of each rat. The left hind paw of the same rats was treated with 0.1 ml of saline alone in the same manner as control.
7.12 Measurement of oedema

Before induction of the oedema, the dorsiventral thickness of both the paws of each was measured using Zeitlin’s apparatus (appendix-B, figure A), which consists of a graduated micrometer, combined with a constant loaded lever system to magnify the small changes in paw thickness during the course of the experiment. The measurements were taken at 1 hour intervals after induction of the oedema for up to 6 hours. Oedema was monitored as the percentage increase in paw thickness in the carrageenan injected paw. To assess the effect of saline on the oedema produced, the percentage increase in paw thickness produced in the saline injected paw was subtracted from that of carrageenan injected left paw (Al-Aboubi et al., 1983).

\[
\text{Percentage increase in paw thickness} = \frac{Y_t - Y_0}{Y_0} \times 100
\]

\(Y_t = \) paw thickness at the time ‘t’ hours (after injection)

\(Y_0 = \) paw thickness at the time ‘0’ hours (before injection)

The percent increase in paw thickness during 6 hours was determined. The percent inhibition of paw oedema thickness is calculated using the formula

\[
\text{Percentage inhibition} = 100 \left(1 - \frac{Y_t}{Y_c}\right)
\]

\(Y_t = \) average increase in paw thickness in groups tested with test compounds

\(Y_c = \) average increase in paw thickness in control

7.13 Evaluation of this model

To evaluate this model, the percentage increase in paw thickness was plotted against the time (hour) and the maximal oedema response induced during the 6
hours was determined. The area under the time course curves (AUC) was also determined. The results showed the ability of the model in detecting the time course changes in the paw size was related with carrageenan induced rat paw oedema. The paw oedema was constantly increased during 4 hours and reached peak at 4th hour. At the 5th and 6th hour, the oedema was gradually reduced.

**Progression of the carrageenan-induced rat paw oedema over 6 h as monitored with Zeitlin's apparatus**

![Graph showing the progression of carrageenan-induced rat paw oedema over 6 hours](image)

**Figure 7.2: Progression of the carrageenan-induced rat paw oedema over 6 h as monitored with Zeitlin's apparatus.**

### 7.14 Drug effects

The rats were always pre-dosed orally with the extracts 1 hour (unless otherwise mentioned) prior to the induction of carrageenan. The drug effects were estimated by comparing the maximal oedema response during 6 hours (monitored as % increase in paw thickness) in the drug or extract treated group with that of drug vehicle treated group as control.
7.15 Effect of *Asparagus racemosus* ethanolic extracts on carrageenan induced rat paw oedema

7.15.1 Aim

To evaluate the anti-inflammatory activity of ethanolic extracts of the leaves of *Asparagus racemosus* (ARE)

7.15.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness were used. The ethanolic extracts of *A. racemosus* at different doses were administered p.o. in sodium carboxy methyl cellulose suspension 1 h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order

Group-III received ethanolic extract of *A. racemosus* 200 mg/kg

Group-IV received ethanolic extract of *A. racemosus* 400 mg/kg

Group- V received ethanolic extract of *A. racemosus* 800 mg/kg

7.15.3 Results

The results of anti-inflammatory activity of ethanolic extract of *A. racemosus* on carrageenan induced rat paw oedema are shown in Table 7.2. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.3. The standard drug indomethacin and the extracts at doses 200, 400 and 800 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 19.23 ± 9.68, 34.62 ± 8.88 and 46.15 ± 4.44
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by $37.16 \pm 2.53$, $13.30 \pm 5.42$, $23.85 \pm 5.43$ and $36.70 \pm 2.18$ respectively over 6 h when compared to the control group treated with drug vehicle.

### 7.15.4 Discussion

The results suggested that the ethanolic extract of *Asparagus racemosus* at the oral dose of 400 and 800 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

### Table 7.2: Percentage inhibition of carrageenan induced paw oedema in rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
<td>--</td>
<td>--</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Group II</td>
<td>Indomethacin</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55*</td>
<td>37.16 ± 2.53*</td>
</tr>
<tr>
<td>Group III</td>
<td>ARE</td>
<td>200</td>
<td>mg/kg</td>
<td>19.23 ± 9.68*</td>
<td>13.30 ± 5.42*</td>
</tr>
<tr>
<td>Group IV</td>
<td>ARE</td>
<td>400</td>
<td>mg/kg</td>
<td>34.62 ± 8.88*</td>
<td>23.85 ± 5.43*</td>
</tr>
<tr>
<td>Group V</td>
<td>ARE</td>
<td>800</td>
<td>mg/kg</td>
<td>46.15 ± 4.44*</td>
<td>36.70 ± 2.18*</td>
</tr>
</tbody>
</table>

Significance: *p<0.05, **p<0.01
Fig 7.3: Effects of the crude extracts of ARE 200, 400 and 800 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.16 Effect of *Asparagus racemosus* chloroform fractions on carrageenan induced rat paw oedema

7.16.1 Aim

To evaluate the anti-inflammatory activity of chloroform fractions of ethanolic extracts of the leaves of *Asparagus racemosus* (ARC).

7.16.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness, were used. The chloroform fractions of ethanolic extracts of *A. racemosus* at different doses were administered *p.o.* in sodium carboxy methyl cellulose suspension 1 h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order:

Group-VI received chloroform fraction of *A. racemosus* 200 mg/kg

Group-VII received chloroform fraction of *A. racemosus* 400 mg/kg

Group-VII received chloroform fraction of *A. racemosus* 800 mg/kg

7.16.3 Results

The results of anti-inflammatory activity of chloroform fraction of *A. racemosus* on carrageenan induced rat paw oedema are shown in Table 7.3. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.4. The standard drug indomethacin and the extracts at doses of 200, 400 and 800 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 15.38 ± 7.69, 26.92 ± 7.36 and 42.31 ± 7.36
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 11.47 ± 3.85, 19.72 ± 3.30 and 33.49 ± 3.92 respectively over 6 h when compared to the control group treated with drug vehicle.

7.16.4 Discussion

The results suggested that the chloroform fraction of *Asparagus racemosus* at the oral dose of 400 and 800 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

Table 7.3: Percentage inhibition of carrageenan induced paw oedema in rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
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<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
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<td>0.00</td>
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<tr>
<td>Group II</td>
<td>Indomethacin</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55**</td>
<td>37.16 ± 2.53**</td>
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<td>Group VI</td>
<td>ARC</td>
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<td>Group VIII</td>
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<td>42.31 ± 7.36**</td>
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Significance: *p<0.05, **p<0.01
Fig 7.4: Effects of the crude extracts of ARC 200, 400 and 800 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.17 Effect of *Asparagus racemosus* hexane fractions on carrageenan induced rat paw oedema

7.17.1 Aim

To evaluate the anti-inflammatory activity of hexane fractions of ethanolic extracts of the leaves of *Asparagus racemosus* (ARH).

7.17.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness were used.

The hexane fractions of ethanolic extracts of *A. racemosus* at different doses were administered *p.o.* in sodium carboxy methyl cellulose suspension 1 h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order

- Group-IX received hexane fraction of *A. racemosus* 200 mg/kg
- Group-XI received hexane fraction of *A. racemosus* 400 mg/kg
- Group-XI received hexane fraction of *A. racemosus* 800 mg/kg

7.17.3 Results

The results of anti-inflammatory activity of hexane fraction of *A. racemosus* on carrageenan induced rat paw oedema are shown in Table 7.4. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.5. The standard drug indomethacin and the extracts at doses of 200, 400 and 800 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 19.23 ± 3.85, 26.92 ± 7.36 and 38.46 ± 6.28
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 13.30 ± 5.21, 16.51 ± 3.71 and 26.15 ± 2.74 respectively over 6 h when compared to the control group treated with drug vehicle.

7.17.4 Discussion

The results suggested that the hexane fraction of *Asparagus racemosus* at the oral dose of 800 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
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<td>Group IX</td>
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<td>Group X</td>
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<td>Group XI</td>
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<td>38.46 ± 6.28**</td>
<td>26.15 ± 2.74**</td>
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</table>

Significance: *p<0.05, **p<0.01
Fig 7.5: Effects of the crude extracts of ARH 200, 400 and 800 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.18 Effect of *Aerva lanata* ethanolic extracts on carrageenan induced rat paw oedema

7.18.1 Aim

To evaluate the anti-inflammatory activity of ethanolic extracts of the leaves of *Aerva lanata* (ALE)

7.18.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness were used.

The ethanolic extracts of *A. lanata* at different doses were administered p.o. in sodium carboxy methyl cellulose suspension 1h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order:

- Group-III received ethanolic extract of *A. lanata* 200 mg/kg
- Group-IV received ethanolic extract of *A. lanata* 400 mg/kg
- Group- V received ethanolic extract of *A. lanata* 800 mg/kg

7.18.3 Results

The results of anti-inflammatory activity of ethanolic extract of *A. lanata* on carrageenan induced rat paw oedema are shown in Table 7.5. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.6. The standard drug indomethacin and the extracts at doses of 200, 400 and 800 mg/kg significantly inhibited the maximal oedema response by $50.00 \pm 4.55$, $15.38 \pm 7.69$, $30.77 \pm 4.44$ and $42.31 \pm 3.85$
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 10.55 ± 3.99, 20.18 ± 5.73 and 32.11 ± 1.98 respectively over 6 h when compared to the control group treated with drug vehicle.

7.18.4 Discussion

The results suggested that the ethanolic extract of *Aerva lanata* at the oral dose of 400 and 800 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

Table 7.5: Percentage inhibition of carrageenan induced paw oedema in rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
<td>--</td>
<td>--</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Group II</td>
<td>Indomethacin</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55**</td>
<td>37.16 ± 2.53**</td>
</tr>
<tr>
<td>Group III</td>
<td>ALE</td>
<td>200</td>
<td>mg/kg</td>
<td>15.38 ± 7.69*</td>
<td>10.55 ± 3.99*</td>
</tr>
<tr>
<td>Group IV</td>
<td>ALE</td>
<td>400</td>
<td>mg/kg</td>
<td>30.77 ± 4.44**</td>
<td>20.18 ± 5.73**</td>
</tr>
<tr>
<td>Group V</td>
<td>ALE</td>
<td>800</td>
<td>mg/kg</td>
<td>42.31 ± 3.85**</td>
<td>32.11 ± 1.98**</td>
</tr>
</tbody>
</table>

Significance: *p<0.05, **p<0.01
Fig 7.6: Effects of the crude extracts of ALE 200, 400 and 800 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.19 Effect of *Aerva lanata* chloroform fractions on carrageenan induced rat paw oedema

7.19.1 Aim

To evaluate the anti-inflammatory activity of chloroform fractions of ethanolic extracts of the leaves of *Aerva lanata* (ALC).

7.19.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness, were used.

The chloroform fractions of ethanolic extracts of *A. lanata* at different doses were administered *p.o.* in sodium carboxy methyl cellulose suspension 1h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order

- Group-VI received chloroform fraction of *A. lanata* 200 mg/kg
- Group-VII received chloroform fraction of *A. lanata* 400 mg/kg
- Group-VII received chloroform fraction of *A. lanata* 800 mg/kg

7.19.3 Results

The results of anti-inflammatory activity of chloroform fraction of *A. lanata* on carrageenan induced rat paw oedema are shown in Table 7.6. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.7. The standard drug indomethacin and the extracts at doses of 200, 400 and 800 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 15.38 ± 7.69, 22.22 ± 6.42 and 34.62 ± 3.85
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 14.22 ± 7.50, 16.51 ± 6.47 and 27.52 ± 2.18 respectively over 6 h when compared to the control group treated with drug vehicle.

**7.19.4 Discussion**

The results suggested that the chloroform fraction of *Aerva lanata* at the oral dose of 800 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

**Table 7.6: Percentage inhibition of carrageenan induced paw oedema in rats**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
<td>--</td>
<td>--</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Group II</td>
<td>Indomethacin 10 mg/kg</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55**</td>
<td>37.16 ± 2.53**</td>
</tr>
<tr>
<td>Group VI</td>
<td>ALC</td>
<td>200</td>
<td>mg/kg</td>
<td>15.38 ± 7.69*</td>
<td>14.22 ± 7.50*</td>
</tr>
<tr>
<td>Group VII</td>
<td>ALC</td>
<td>400</td>
<td>mg/kg</td>
<td>22.22 ± 6.42*</td>
<td>16.51 ± 6.47*</td>
</tr>
<tr>
<td>Group VIII</td>
<td>ALC</td>
<td>800</td>
<td>mg/kg</td>
<td>34.62 ± 3.85**</td>
<td>27.52 ± 2.18**</td>
</tr>
</tbody>
</table>

Significance: *p<0.05, **p<0.01
Fig 7.7: Effects of the crude extracts of ALC 200, 400 and 800 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.20  Effect of *Aerva lanata* hexane fracations on carrageenan induced rat paw oedema

7.20.1 Aim

To evaluate the anti-inflammatory activity of hexane fractions of ethanolic extracts of the leaves of *Aerva lanata* (ALH).

7.20.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness were used.

The hexane fractions of ethanolic extracts of *A. lanata* at different doses were administered *p.o.* in sodium carboxy methyl cellulose suspension 1 h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order

Group-IX received hexane fraction of *A. lanata* 200 mg/kg

Group-XI received hexane fraction of *A. lanata* 400 mg/kg

Group- XI received hexane fraction of *A. lanata* 800 mg/kg

7.20.3 Results

The results of anti-inflammatory activity of hexane fraction of *A. lanata* on carrageenan induced rat paw oedema are shown in Table 7.7. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.8. The standard drug indomethacin and the extracts at doses of 200, 400 and 800 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 15.38 ± 7.69, 19.23 ± 9.68 and 30.77 ± 4.44
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 10.55 ± 3.85, 15.14 ± 5.92 and 23.85 ± 1.18 respectively over 6 h when compared to the control group treated with drug vehicle.

7.20.4 Discussion

The results suggested that the hexane fraction of *Aerva lanata* at the oral dose of 800 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

### Table 7.7: Percentage inhibition of carrageenan induced paw oedema in rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
<td>--</td>
<td>--</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Group II</td>
<td>Indomethacin</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55**</td>
<td>37.16 ± 2.53**</td>
</tr>
<tr>
<td>Group IX</td>
<td>ALH</td>
<td>200</td>
<td>mg/kg</td>
<td>15.38 ± 7.69*</td>
<td>10.55 ± 3.85*</td>
</tr>
<tr>
<td>Group X</td>
<td>ALH</td>
<td>400</td>
<td>mg/kg</td>
<td>19.23 ± 9.68*</td>
<td>15.14 ± 5.92*</td>
</tr>
<tr>
<td>Group XI</td>
<td>ALH</td>
<td>800</td>
<td>mg/kg</td>
<td>30.77 ± 4.44**</td>
<td>23.85 ± 1.18**</td>
</tr>
</tbody>
</table>

Significance: *p*<0.05, **p**<0.01
Fig 7.8: Effects of the crude extracts of ALH 200, 400 and 800 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.21 Effect of *Abrus precatorius* ethanolic extracts on carrageenan induced rat paw oedema

7.21.1 Aim

To evaluate the anti-inflammatory activity of ethanolic extracts of the leaves of *Abrus precatorius* (APE)

7.21.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness were used.

The ethanolic extracts of *A. precatorius* at different doses were administered p.o. in sodium carboxy methyl cellulose suspension 1 h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order

Group-III received ethanolic extract of *A. precatorius* 50 mg/kg

Group-IV received ethanolic extract of *A. precatorius* 100 mg/kg

Group-V received ethanolic extract of *A. precatorius* 200 mg/kg

7.21.3 Results

The results of anti-inflammatory activity of ethanolic extract of *A. precatorius* on carrageenan induced rat paw oedema are shown in Table 7.8. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.9. The standard drug indomethacin and the extracts at doses of 50, 100 and 200 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 11.11 ± 6.05, 34.62 ± 11.54 and 50.00 ± 3.85
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 9.17 ± 6.55, 24.77 ± 5.02 and 35.78 ± 2.90 respectively over 6 h when compared to the control group treated with drug vehicle.

7.21.4 Discussion

The results suggested that the ethanolic extract of *Abrus precatorius* at the oral dose of 100 and 200 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
<td>--</td>
<td>--</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Group II</td>
<td>Indomethacin</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55**</td>
<td>37.16 ± 2.53**</td>
</tr>
<tr>
<td>Group III</td>
<td>APE</td>
<td>50</td>
<td>mg/kg</td>
<td>11.11 ± 6.05*</td>
<td>9.17 ± 6.55*</td>
</tr>
<tr>
<td>Group IV</td>
<td>APE</td>
<td>100</td>
<td>mg/kg</td>
<td>34.62 ± 11.54**</td>
<td>24.77 ± 5.02**</td>
</tr>
<tr>
<td>Group V</td>
<td>APE</td>
<td>200</td>
<td>mg/kg</td>
<td>50.00 ± 3.85**</td>
<td>35.78 ± 2.90**</td>
</tr>
</tbody>
</table>

Significance: *p<0.05, **p<0.01

Table 7.8: Percentage inhibition of carrageenan induced paw oedema in rats
Fig 7.9: Effects of the crude extracts of APE 50, 100 and 200 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.22 Effect of *Abrus precatorius* chloroform fractions on carrageenan induced rat paw oedema

7.22.1 Aim

To evaluate the anti-inflammatory activity of chloroform fractions of ethanolic extracts of the leaves of *Abrus precatorius* (APC).

7.22.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness, were used.

The chloroform fractions of ethanolic extracts of *A. precatorius* at different doses were administered *p.o.* in sodium carboxy methyl cellulose suspension 1 h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order

Group-VI received chloroform fraction of *A. precatorius* 50 mg/kg

Group-VII received chloroform fraction of *A. precatorius* 100 mg/kg

Group- VII received chloroform fraction of *A. precatorius* 200 mg/kg

7.22.3 Results

The results of anti-inflammatory activity of chloroform fraction of *A. precatorius* on carrageenan induced rat paw oedema are shown in Table 7.9. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.10. The standard drug indomethacin and the extracts at doses of 50, 100 and 200 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 16.67 ± 5.56, 27.78 ± 5.56 and 42.31 ± 3.85
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 11.01 ± 4.77, 23.85 ± 4.53 and 33.49 ± 2.84 respectively over 6 h when compared to the control group treated with drug vehicle.

**7.22.4 Discussion**

The results suggested that the chloroform fraction of *Abrus precatorius* at the oral dose of 100 and 200 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

**Table 7.9: Percentage inhibition of carrageenan induced paw oedema in rats**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
<td>--</td>
<td>--</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Group II</td>
<td>Indomethacin</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55**</td>
<td>37.16 ± 2.53**</td>
</tr>
<tr>
<td>Group VI</td>
<td>APC</td>
<td>50</td>
<td>mg/kg</td>
<td>16.67 ± 5.56*</td>
<td>11.01 ± 4.77*</td>
</tr>
<tr>
<td>Group VII</td>
<td>APC</td>
<td>100</td>
<td>mg/kg</td>
<td>27.78 ± 5.56**</td>
<td>23.85 ± 4.53**</td>
</tr>
<tr>
<td>Group VIII</td>
<td>APC</td>
<td>200</td>
<td>mg/kg</td>
<td>42.31 ± 3.85**</td>
<td>33.49 ± 2.84**</td>
</tr>
</tbody>
</table>

Significance: *p<0.05, **p<0.01
Fig 7.10: Effects of the crude extracts of APC 50, 100 and 200 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.23 Effect of *Abrus precatorius* hexane fractions on carrageenan induced rat paw oedema

7.23.1 Aim

To evaluate the anti-inflammatory activity of hexane fractions of ethanolic extracts of the leaves of *Abrus precatorius* (APH).

7.23.2 Materials and Method

Sprague Dawley rats of either sex (150-200 g, n=4), Carrageenan and the Zeitlin Isotonic Lever (Appendix - B) for measuring paw thickness were used.

The hexane fractions of ethanolic extracts of *A. precatorius* at different doses were administered p.o. in sodium carboxy methyl cellulose suspension 1 h prior to the induction of oedema by carrageenan injection and monitored the oedema progression as described in Appendix - B.

The extracts were administered orally in the following order

Group-IX received hexane fraction of *A. precatorius* 50 mg/kg
Group-XI received hexane fraction of *A. precatorius* 100 mg/kg
Group- XI received hexane fraction of *A. precatorius* 200 mg/kg

7.23.3 Results

The results of anti-inflammatory activity of hexane fraction of *A. precatorius* on carrageenan induced rat paw oedema are shown in Table 7.10. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig 7.11. The standard drug indomethacin and the extracts at doses of 50, 100 and 200 mg/kg significantly inhibited the maximal oedema response by 50.00 ± 4.55, 16.67 ± 5.56, 23.08 ± 6.28 and 34.62 ± 3.85
respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 37.16 ± 2.53, 10.09 ± 4.17, 19.72 ± 2.94 and 28.44 ± 2.12 respectively over 6 h when compared to the control group treated with drug vehicle.

7.23.4 Discussion

The results suggested that the hexane fraction of *Abrus precatorius* at the oral dose of 200 mg/kg, and a standard drug, indomethacin 10 mg/kg dose were found to be more effective when compared to drug vehicle treated group on maximal paw oedema and total oedema. The activity of the extracts is found to be dose dependant in reducing paw oedema at the two phases of inflammation.

Table 7.10: Percentage inhibition of carrageenan induced paw oedema in rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Dose</th>
<th>Units</th>
<th>Percentage inhibition of the maximal paw oedema during 6 h</th>
<th>Percentage inhibition of the total AUC paw oedema during 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Control</td>
<td>--</td>
<td>--</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Group II</td>
<td>Indomethacin</td>
<td>10</td>
<td>mg/kg</td>
<td>50.00 ± 4.55**</td>
<td>37.16 ± 2.53**</td>
</tr>
<tr>
<td>Group IX</td>
<td>APH</td>
<td>50</td>
<td>mg/kg</td>
<td>16.67 ± 5.56*</td>
<td>10.09 ± 4.17*</td>
</tr>
<tr>
<td>Group X</td>
<td>APH</td>
<td>100</td>
<td>mg/kg</td>
<td>23.08 ± 6.28*</td>
<td>19.72 ± 2.94*</td>
</tr>
<tr>
<td>Group XI</td>
<td>APH</td>
<td>200</td>
<td>mg/kg</td>
<td>34.62 ± 3.85**</td>
<td>28.44 ± 2.12**</td>
</tr>
</tbody>
</table>

Significance: *p<0.05, **p<0.01
Fig 7.11: Effects of the crude extracts of APH 50, 100 and 200 mg/kg respectively along with indomethacin 10 mg/kg on A) the maximal and B) the total paw oedema in carrageenan induced rats

Significance: *p<0.05, **p<0.01
7.24 General Discussion

The most widely used model to evaluate anti-inflammatory activity of any extract/compound is carrageenan induced paw oedema in rats (Winter et al., 1962; Battu et al., 2000). It is well known that carrageenan induced paw oedema is characterized by biphasic event with involvement of different inflammatory mediators. In the first phase (during the first 2 h after carrageenan injection), chemical mediators such as histamine and serotonin play role, while in second phase (3 - 4 h after carrageenan injection) kinins and prostaglandins are involved (Hernandez and Rabanal, 2002).

Ethanolic extract and its fractions chloroform and hexane of Asparagus racemosus (400 and 800 mg/kg) leaves had produced significant (p<0.01) reduction on maximal paw oedema and total oedema (AUC) when compared to drug vehicle treated where as the dose of 200 mg/kg significantly (p<0.05) inhibited the maximal oedema response and the total oedema response (AUC) during 6 h compared to the control group treated with drug vehicle.

Ethanolic extract of Aerva lanata (400 and 800 mg/kg) leaves had produced significant (p<0.01) reduction on maximal paw oedema and total oedema (AUC) when compared to drug vehicle treated group where as the chloroform and hexane fractions produced significant (p<0.01) reduction on maximal paw oedema and total oedema (AUC) at the maximum dose i.e. 800 mg/kg when compared to drug vehicle treated group.

Ethanolic extract and chloroform fraction of Abrus precatorius (100 and 200 mg/kg) seeds had produced significant (p<0.01) reduction on maximal paw
oedema and total oedema (AUC) when compared to drug vehicle treated group where as hexane fractions produced significant (p<0.01) reduction on maximal paw oedema and total oedema (AUC) at the maximum dose i.e. 200 mg/kg when compared to drug vehicle treated group.

The activity of the extracts is found to be dose dependant. Ethanolic extracts from the three selected species had produced significant (p<0.01) reduction at the middle and higher doses, where as the chloroform an hexane fractions produced significant (p<0.01) reduction at the maximum dose, hence better anti-inflammatory activity was found in ethanolic extract, the order of activity is in the following manner:

**Ethanolic extract > Chloroform fraction > Hexane fraction**

The percentage inhibition of the maximal and the total paw oedema during 6 h for the ethanolic extracts of *A. racemosus, A. lanata and A. precatorius* at maximal dose were in the following order

**A. precatorius > A. racemosus > A. lanata**

The results clearly indicated that the pretreatment with the selected plant extracts and indomethacin suppressed the increase in paw oedema produced by the phlogistic agent starting from the first hour and during all phases of inflammation, which is probably inhibition of different aspects and chemical mediators of inflammation.

Hence, the results of the present study suggests that the tested ethanolic extracts and its fraction chloroform and hexane of *A. racemosus, A. lanata and A. precatorius* have anti-inflammatory activity against carrageenan induced paw
oedema in rats. Literature survey revealed that flavonoids (Kim et al., 2000) and sterols (Navarro et al., 2001) contents present in the plants are responsible for their anti-inflammatory activity. Preliminary phytochemical analysis of the extracts and its fractions reveals the presence of flavonoids, triterpenoids and phytosterols in A. racemosus, A. lanata and A. precatorius, hence the “anti-inflammatory activity might be due to the presence of flavonoids and sterols compounds in the selected plant extracts”.

Further studies have to be conducted on chronic inflammation to establish the mechanism of action of these extracts that exhibited significant activity and also to identify the exact phytoconstituents involved during the inflammation process. The findings of this study supports the view, that the ethanolic extracts of plants are promising sources for potential anti-inflammatory activity.