7.1 General Introduction

Man depends upon plants for his entire essentials requirement like food, clothing and shelter. Plants are also an important source of fine chemicals, which find their application in pharmaceutical industries across the globe (Singh, 1988). Plants have been the traditional source of raw materials and finished medicinals, since many centuries. A rich heritage of knowledge on preventive and curative medicines is available in ancient scholastic works. This is included in the Atharvana Veda, Charaka Samhita, Sushruta Samhita, etc. (WHO Regional Office for the Western Pacific, 1993; Pushpaganda, 1995).

Since disease, decay and death co-existed with life, the study of disease and its treatment must have also been contemporaneous with the dawn of human intellect (Kirtikar and Basu, 1991). In India, the Science of Ayurveda has provided a system of medical treatment. Most of the remedies for treating illnesses are being taken from plants. During the last few decades, much work has been done in the field of these natural products.

It is reported that in the modern times 41% prescriptions in U.S.A. and 90% in Europe for treating various ailments contain constituents from natural products. This shows an increasing trend of using natural products (Shah, 1982). Moreover, natural products have also served as lead molecules for the development of novel synthetic drugs. For example atropine for tropicamide, quinine for chloroquine, cocaine for procaine and tetracaine, etc.

India is a vast country, which often referred as a subcontinent for ‘Emporium of Medicinal Plants’ due to the occurrence of several thousand medicinal plants in different bioclimatic zones. Ayurveda and Siddha systems of medicine, which are 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).

The development of the science of phytopharmaceuticals and the hope for remedies for chronic diseases has generated new enthusiasm among researchers to
develop herbal medicines. Quite a considerable amount of work has been put for the study potential of herbal medicines. Modern science has accepted the plant kingdom as a source of new bio-dynamic constituents.

Scientific investigation regarding some folk medicines has resulted in *bona fide* drugs. Natural products have also been incorporated into many modern formulations. The most important drugs that have come from plant sources into clinical use are cinchona, opium, ergot, rauwolfia, etc. All were known to be healers in traditional medicine before their introduction to modern medicine. As the medicinal value of Indian traditional medicine cannot be ignored, researchers are gradually becoming interested in identification of active principles in their extracts with intensive follow-up study of their mechanisms of action.

**7.2 Introduction to Inflammation**

The word inflammation comes from the Latin word “inflammare” which means state of being inflamed or heat associated with redness and swelling. This is a complex, integrated host response found only in vertebrates. The inflammatory response has two facets:

i) inflammation and ii) repair.

Inflammation serves to destroy, dilute, or wall off the injurious agent and the tissue cells that may have been destroyed later. The second factor of the inflammatory response sets into motion. It is a complex series of events, which helps to heal and reconstitute the damaged tissue.

Repair begins during the active phase of inflammation, but reaches completion usually after the injurious influence has been neutralized. Destroyed cells and tissues are repaired thereby. Both inflammation and repair generally serve useful purpose. Without inflammation, bacterial infections would remain unencountered, wounds would never heal, and injured tissues and organs might be permanently defected. But inflammation may be potentially harmful. Inflammatory reactions underlie the genesis of crippling rheumatoid arthritis, life threatening sensitivity reaction, and some forms of fatal glomerular diseases.
7.3 History of inflammation (Spector et al., 1968; Movit et al., 1971)

“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 inflammation as a reaction of the body against injury.

Subsequently, Julius Colinteim in 1873 emphasized the role of vessels in the inflammatory process and Metchnikoff in 1892 emphasized mainly on the migration of Leucocytes and on phagocytosis. According to Rocha a Silva (1978), all the views developed by these eminent persons, with the four signs of Celsius in the background constituted ‘master leads’ to understand the whole pattern developed by the body to fight against aggression.

In late 19th Century, the science of immunology had been developed with the pioneering contributions from Jenner, Pasteur, Land Steiner, and so on. Thereafter, conclusive evidences have accumulated regarding body fluids and blood serum, which have a protective effect against a variety of invasive microorganisms. Lewis, 1927, proposed that either histamine or H – substances might be released from the skin in many forms of injury.

During 1930’s Henry Dale tried to explain the process of inflammation as an auto pharmacological phenomenon. According to him, most pathophysiologial events of inflammation are mediated by the release of acetylcholine, catecholamine, histamine, etc. In 1940’s by Menkin ,Rocha a Silva with their 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. On the other hand, in sixties, Florey and Majno with their associates studied the ultra structural alterations of the vessels during inflammatory processes with the help of electron microscope.

7.4 Pathophysiology of inflammation

Physical agents, chemical agents, infections and immunological reactions may bring about injury in its turn causes inflammation. Essentially there are two categories of inflammation: i) acute and ii) chronic.
7.5 Acute inflammation

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 (Anonymous, 1975). They are as follows:

7.5.1 Active hyperaemia

Immediately after the injury, the arterioles of the injured tissue contract 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. It also causes redness. In the area of engorged microcirculation, blood flows rapidly at first, later it becomes progressively slower and there might be a temporary static of blood.

7.5.2 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. The inflammatory exudates are much richer in plasma proteins than normal extra cellular fluids indicating the increased permeability of the vessels to macro
molecules. The increased leakage of fluid and electrolytes in acute inflammation is explained by the increased hydrostatic pressure of blood in small vessels in active hyperaemia. Exudation of plasma proteins from small vessels in acutely inflamed tissue requires an increase in permeability of endothelium. This is provided by the reversible opening up of relatively large gaps between endothelial cells.

7.5.3 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 normal blood flow, the red blood cells and white blood cells in the microvessels flow mainly in the central column of blood separated from the vessel wall by a clear layer of plasma (Axial streaming). In inflammation, when slowing of flow ensues, the axial streaming disappears, 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.

The adhesion may be due to neutralization of negative charges or reduction of charge density of the leukocytes. Divalent ions also play an important role and the chemostatic factors increase the adherence of neutrophils to endothelial cells. The marginated polymorphs extend between the junctions of the two endothelial cells and thereby disrupt it, then squeeze through it and the intercellular junction reforms rapidly.

Neutrophils migrate earlier and more rapidly than monocytes. Eosinophils accumulate mainly in immunologic inflammatory reaction. The neutrophil polymorphs are actively phagocytic but the migrated monocytes are not so, although they become more active when they change into macrophage. The process is similar for both. The particle to be ingested becomes attached to the surface of the leukocytes and a process known as ‘opsonisation’ occurs. Opsonin coats the foreign matter in such a way that leukocytes recognize it as a foreign body. The limiting membrane of the phagocytic vacuole fuses and then there is a discharge of the granule content into this phagolysosome.
The leukocytes become progressively degranulated and during this
degranulation, there is some leakage of hydrolytic enzyme and some metabolic
product into the external medium. Phagocytosis is an energy dependent process
that stimulates numerous intercellular events including increased oxygen
consumption, glycogenolysis, increased glucose oxidation and hydrogen peroxide
production. The hydrogen peroxide produced within the phagolysosome is
important in bacterial killing, which is the ultimate step in phagocytosis.

7.5.4 Consequences of acute inflammation

a) After termination of the injury, the blood flow and vascular permeability
becomes normal. Pavementing of leukocytes ceases, Cells and tissue
debris are digested by the enzymes. Migrated polymorphs die and
macrophages are drained. In short, normalization of the tissue is restored.

b) In certain inflammatory conditions (due to pyrogenic bacteria), severe
local toxic injury forms abscess in the tissue which is filled with
inflammatory exudates rich in polymorphs, bacteria and fragments of
necrotic tissue. Here, return to normal state is no longer possible since the
tissue has been destroyed and the abscess becomes enclosed in a wall of
granulation tissue, which eventually matures to real tissue.

c) Some acute inflammatory lesions do not subside. So the return to normalcy
is hampered. Formation of granulation tissue with consequent fibrosis or
scarring is very common. It complicates acute inflammation and there is
necrosis to tissue or excessive fibrin deposition and when acute
inflammation persists. It becomes a chronic one.

7.6 Chronic inflammation

Chronic inflammation is also characterized 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 the well being of the host. A chronic inflammation is caused by the
persistence of an irritant, which may be of biologic, physical, or chemical nature.
7.6.1 The histological marks of chronic inflammation

The irritant remains at the site due to inability of macrophages to digest it. The cycle of cellular infiltration, necrosis and fibrosis will continue as long as the irritant remains.

i) Infiltration of mononuclear cells, macrophages, lymphocytes and plasma cells:

When monocytes reach the extra-vascular tissue, they are transformed into much larger macrophages. Macrophages then undergo activation. In acute inflammation, if the injurious agent is not eliminated, macrophages persist for longer time.

ii) Proliferation of fibroblasts and small blood vessels: The complete mechanism given above is not fully clear but the factors derived from activated macrophages have been implicated in both fibroblasts and new vessel growth. Continued fibroblastic proliferation results in increased deposition of collagen, which causes scar formation with resultant deformities, adhesion between serosal surfaces, permanent fibrous replacement of damaged parenchyma and may result in permanent damage to tissue.

Chronic inflammation is more proliferative than an exudative one and necrosis commonly occurs and reoccurs. Formation of granulation tissue and connective tissue takes place. Thus, increasing amount of fibrous tissue will characterize a persistent, long term chronic process. Two types of chronic inflammation have been characterized; i) granulomatous and ii) basal.

Granulomas are small collections of inflammatory cells, principally modified macrophages, surrounded by a rim of lymphocytes. These modified macrophages are derived from monocytes and are known as epitheloid cells. Another feature of the granuloma is the presence of Langhans or foreign body type giant cells, which are formed by the coalescence and fusion of macrophages. Giant cells are associated with the presence of large amounts of indigestible materials and they often conglomerate around a foreign body. Fibroblasts, plasma cells and at times neutrophils can also be seen in a granuloma. Basal chronic inflammation is not highly cellular and produces relatively smaller lesions.
7.7 Cell Biology of Inflammation (Willoughby et al., 2000)

Inflammation is a critically important mechanism utilized by all tissues of the body as a primary defense against infection.

7.7.1 Accumulation of inflammatory Cells: The first stage of inflammation involves the accumulation of inflammatory cells in the micro vasculature in response to the initial infection either driven by molecules released from the organisms themselves or via generation of chemoattractants and chemokines from resident tissue cells, pulmonary capillaries or systemic venular endothelium. This represents one area of investigation.

7.7.2 Activation pathways: Once arrived, inflammatory cells contribute to the destruction of the infectious organism and the inflammatory process primarily by secretion of preformed and newly synthesized constituents. The biochemical and morphologic mechanisms involving activation and secretion from neutrophils and macrophages (both to the cell exterior as well as into the phagosome), with a particular emphasis on cell priming (i.e. mechanisms of sequential cooperative stimulation) and the signal pathways involved particularly those mediated through p38 MAP kinase should be considered.

7.8 Recognition and removal of Apoptotic cells:

Under normal circumstances, inflammatory cells are removed from the lesions during resolution of the inflammation. This follows programmed cell death (apoptosis) involving DNA fragmentation, nuclear alterations and changes in surface membranes without cell lysis which leads to recognition and phagocytosis by mature macrophages and adjacent tissue cells.

The processes appear highly abundant involving at least six different classes of receptors. The recognition and uptake of apoptotic cells also result in active suppression of pro-inflammatory cytokine, chemokine and eicosanoid production by macrophages, presumably also contributing to resolution, but perhaps in advertently enhancing opportunities for intracellular viral or bacterial pathogens in excess, leading to fibrosis.
7.9 Macrophage Maturation

Maturation of macrophages under the influence of different inflammatory stimuli results in ‘phenotypes’ that are characterized by the synthesis of specific protein markers, including new receptors for removal of apoptotic cells. The mechanisms of control of these pathways and their contribution to inflammatory cell clearance and/or progress of injury are yet another area of study.

Particular emphasis is on the generation of anti-inflammatory macrophages that are actively secreting suppressive mediators such as THFb, their potential induction by oxidized phospholipids or activators of PPARs and they have role in p38 MAP kinase inhibition.

7.10 Inflammatory Mediators

Finally, the complex elements of inflammation are orchestrated by the actions of a network of ‘mediators’. Of particular interest are lipid mediators, including the alkyl phospholipids, platelet activating factor (PAF) or oxidatively chain-shortened phospholipid analogues of PAF and the broad spectrum of arachidonate derivatives (eicosanoids). The co ordinate production of these by inflammatory cells, the role of co operation between cell types in their synthesis, the mechanisms of their secretion (release) and their interactive roles in inflammation are under investigation still.

![Fig. 7.2 Mediators of Inflammation](image-url)
7.10.1 Phospholipase A<sub>2</sub>

Arachidonic acid (AA) is a common precursor for eicosanoids such as prostaglandins, leukotrienes, etc. from membrane phospholipids. AA release is catalysed by a membrane associated enzyme, PLA<sub>2</sub>, which is also responsible for the production of platelet activating factor and other proinflammatory mediators (Chilton et al., 1984).

7.10.2 Cyclo-oxygenases

Cyclooxygenase (COX) pathway leads to the formation of PGs, thromboxanes and prostacyclins, a family of autocrine and paracrine mediators that contribute to many physiological and pathophysiological responses (see Fig. 4.2). Cyclooxygenase (COX; Prostaglandin endoperoxide synthase) catalyzes two separate enzyme reactions.

![Cyclooxygenase pathway](image)

**Fig. 7.3** Cyclooxygenase pathway

i) The bisoxygenation of arachidonic acid at carbon 11 and 15 (cyclooxygenase activity) and ii) the subsequent bi-electron reduction at 15-hydroperoxy group of PGG<sub>2</sub> (Peroxidase activity) to form another endoperoxide derivative, PGH<sub>2</sub> (Smith et al., 1996). These two reactions occur at distinct but structurally and functionally interconnected sites.
7.10.3 5-Lipoxygenase

Lipoxygenase (LOX) pathway leads to the formation of hydroperoxyeicosatetraenoic acid (HPETEs), leukotrienes (LTs) and lipoxins from arachidonic acid. Among these LTs are the most potent biologically active compounds.

LOXs have been classified based on their positional specificity of arachidonate oxygenation (Yamamota, 1992).

7.10.4 Platelet activating factor (PAF)

PAF is an extraordinarily potent mediator of endotoxic shock and inflammation (Hosford et al., 1990). It exerts its biological effects by activating the PAF receptor, accordingly stimulating protein kinase C and increasing intracellular Ca++. 

7.10.5 Myeloperoxidase (MPO)

Myeloperoxidase is the most abundant protein stored in azurophilic granules of neutrophils (polymorphonuclear leukocytes) which constitutes 5% and plays a central role in microbial killing and inflammatory tissue damage (Burner et al., 1999). MPO catalyses the reaction of hydrogen peroxide and chloride at plasma concentration levels, there by producing oxidative toxic products such as hypochlorous acid (HOCl) and free radical hydroxyl ion (Ramos et al., 1995).

7.10.6 Neutrophil elastase

NE, a neutrophil granule serine protease, is a key enzyme in tissue injury. The enzyme is a single chain polypeptide with a strong basic isoelectric pH (10 to 11) (Janoff, 1985).

7.10.7 Inducible Nitric Oxide Synthase

Cells synthesize nitric oxide (NO) by utilizing inducible nitric oxide synthase (iNOS), which converts L-arginine to L-citrulline and NO.NO plays an important role to induce apoptosis and necrosis (Sandowska-Krowicka et al., 1988) associated with chronic inflammatory process such as asthma and rheumatoid arthritis.
7.10.8 Cytokines

Interleukins (ILs), tumour necrosis factor (TNF), interferons, platelet-derived growth factor (PDGF), granulocyte-macrophage-colony-stimulating factor (GMCSF) and chemokines are collectively known as cytokines and are mediators of the immune system.

Cytokines, particularly IL-1 and TNF-α have been implicated as important mediators of inflammation and joint destruction in rheumatoid arthritis (Arend and Dayer, 1990).

7.11 Experimental models used for testing of anti-inflammatory activity

(Robert Turner A. 1965)

The inflammatory process involves a series of events that can be elicited by numerous stimuli, e.g. infectious agents, ischemia, antigen-antibody interactions, chemical, thermal or mechanical injury. The response is accompanied by the clinical signs of erythema, oedema, hyperalgesia and pain inflammatory responses which occur in three distinct phases, each apparently mediated by different mechanisms given as under.

- An acute, transient phase, characterized by local vasodilation and increased capillary permeability.
- A Sub-acute phase, characterized by infiltration of leukocytes and phagocytic cells.
- A chronic proliferative phase in which tissue degeneration and fibrosis occur.

*In vivo* methods for testing acute and sub-acute inflammation are

- UV – erythema in guinea pigs
- Vascular permeability
- Oxazolone induced ear oedema in rats and mice
- Croton oil induced ear oedema in rats and mice
- Paw oedema in rats.
7.12 Induction of paw oedema by chemical agents

- Pleurisy tests
- Granuloma pouch technique
- Hyaluronidase Inhibition
  The proliferative phase is measured by methods for testing granuloma formation, such as
  - Cotton wool granuloma
  - Glass rod granuloma
  - PVC sponge granuloma

Increase vascular permeability and cause fluid accumulation
*Eg.*: histamine, serotonin, dextran, eggwhite

Cause fluid accumulation by damaging the tissue
*Eg.*: formalin, kaolin

7.13 Experimental Models for Evaluation of Anti-inflammatory Activity

The various models available for testing anti-inflammatory activity with reasonable accuracy, minimum time and test compound consumption are described below:

7.13.1 Acute models of inflammation

7.13.1.1 Carrageenan-induced oedema model *(Nasrin et al., 2005)*

Acute hind paw oedema was induced either in mice or in rats by injecting 0.05 ml to 0.1 of 1 % w/v carrageenan which reaches a peak level at 3-5 hrs of carrageenan injection. Although oedema can be induced by many other phlogistic agents like dextrin, formaldehyde, 5-hydroxytryptamine, histamine, bradykinin and prostaglandin E₁ etc., for routine screening, acute carrageenan induced oedema test was employed.
7.13.1.2 U.V.light induced-erythema model (Iracema et al., 2005)

Exposure to U.V. radiation also induce acute erythema which is used as model for anti-inflammatory activity testing.

7.13.2 Chronic models of inflammation

7.13.2.1 Cotton pellet method (Victor et al., 2005; Gupta et al., 2005).

Chronic inflammation was induced by the implanatation of sterile cotton pellets (50 mg ± 1 mg) on the back or axilla of the rats aseptically. The peak effect was reached within 7 days.

7.13.2.2 Granuloma pouch method (Perez-Garcia et al., 2005; Isabel et al., 2004).

Pouch on the back of the rat was produced by injecting 20 ml of air and 1.0 ml of 1% croton oil in olive oil or 0.5ml of turpentine oil in the subcutaneous tissues in between the shoulder blades. The effect was seen after 7 days.

7.13.2.3 Formaldehyde-induced arthritis (Moura et al., 2005; Eun Mi et al., 2003).

Arthritis was induced by injecting 0.1 ml of 2% formaldehyde solution into the sub plantar region of one of the hind paws of rat on the first and third day of the 10 days experiment.

7.13.2.4 Adjuvant-induced arthritis (Lilly et al., 2005; Fan et al., 2005).

Chronic arthritis in rats was induced by injection of 0.5 mg of heat-killed Mycobacterium tuberculosis (Difco) suspended in 0.1 ml of liquid paraffin into one of the hind paws. The effect was observed till 21 days after injection.

7.14 Plants with 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, there have been no substantial progress has been made in achieving a permanent cure. The greatest disadvantage of the presently available potent synthetic drugs lie in their toxicity and reappearance of symptoms after discontinuation of treatment. The research of screening and development of drugs for their anti-inflammatory activity is therefore, an unending problem and there is need of finding out antirheumatic drugs from indigenous plants.

The literature survey reveals that 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 are mentioned in the table 7.1.

Table 7.1 Some plants with anti-inflammatory activity (The Useful plants of India, 1988; The Medicinal Plants of India, 1987; The Wealth of India, 1952).

<table>
<thead>
<tr>
<th>Plant species</th>
<th>Trade names in India</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconitum napellus</td>
<td>Aconite</td>
<td>Ranunculaceae</td>
</tr>
<tr>
<td>Alpinia officinarum</td>
<td>Rasna</td>
<td>Zingiberaceae</td>
</tr>
<tr>
<td>Azadirachta indica</td>
<td>Neem</td>
<td>Meliaceae</td>
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<tr>
<td>Balanites roxburghii</td>
<td>Gari</td>
<td>Simarubiaceae</td>
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<tr>
<td>Boerhaavia diffusa</td>
<td>Punarnava</td>
<td>Nyctaginaceae</td>
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<td>Boswellia serrata</td>
<td>Salaiguggal</td>
<td>Burseraceae</td>
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<td>Colchicum autumnale</td>
<td>Colchicum</td>
<td>Liliaceae</td>
</tr>
<tr>
<td>Commiphora mukul (Balsamodendron mukul)</td>
<td>Guggulu</td>
<td>Burseraceae</td>
</tr>
<tr>
<td>Curcuma longa</td>
<td>Turmeric</td>
<td>Zingiberaceae</td>
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<td>Delonix elata</td>
<td>Vatanarayana</td>
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<td>Leguminosae</td>
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<td>Hedychium spicatum</td>
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<td>Heliotropium curassavicum</td>
<td>Haatisura</td>
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<td>Asclepiadaceae</td>
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<td>Jassoon</td>
<td>Malvaceae</td>
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<td>Indigofera aspalathodes</td>
<td>Hakna</td>
<td>Febaceae</td>
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<td>Inula recemosa</td>
<td>Poshkar</td>
<td>Compositae</td>
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<td>Padma-pushkara</td>
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<td>Hulkshe</td>
<td>Labiatae</td>
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<td>Morus alba</td>
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<td>Myrtus communis</td>
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<td>Nepeta hindostana (Nepirin)</td>
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<td>Nakpatra</td>
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<td>Eugenia ooeinensis</td>
<td>Sandan</td>
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<td>Prosopis spicigera</td>
<td>Shami</td>
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<td>Psoralea coryligolia (bavachinine)</td>
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<td>Menispermaceae</td>
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<td>Verbena officinalis</td>
<td>Karaita</td>
<td>Verbenaceae</td>
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<td>Vitex negundo</td>
<td>Nirgundis</td>
<td>Verbenaceae</td>
</tr>
<tr>
<td>Withania somnifera</td>
<td>Ashwagandha</td>
<td>Solanaceae</td>
</tr>
</tbody>
</table>

**7.15 Treatment of inflammation**

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
  
  Naproixen, 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
- **Para aminophenol derivative:** Paracetamol

**Others:** Celecoxib, Rofecoxib, Valdecoxib and Nimesulide, Combination preparation of Nimesulide, Nabumetone
Some important NSAIDs with their structures were represented.
7.16 Selection of Animals

Wistar albino rats of either sex weighing between 150-200 g were obtained from National Institute of Nutrition (NIN), Hyderabad, Andhra Pradesh, India. The animals were housed under standard environmental conditions (temperature of 25 ± 2 °C with an alternating 12 h light-dark cycle and relative humidity of 50 ±15%), one week before the start and also during the experiment as per the rules and regulations of the Institutional Animal Ethics committee (AEC) and of the Regulatory body of the government (Regd no. 516/01/A/CPCSEA). They were fed with standard laboratory diet (supplied by Ratan Brothers, India) and water ad libitum during the experiment.

7.17 Experimental Protocol

The rats were given doses orally with extracts at different dose levels 18 h and 2 h prior to the induction of carrageenan subcutaneously (sc) into the subplantar tissue of the hind paw of each rat, 0.1 ml of 1% carrageenan suspension.

The drug effects were estimated by comparing the maximal oedema response during 6 h in the drug as extract treated group with that of vehicle treated group as control. Group I normal rats treated with Drug vehicle (1% Sodium CMC) and served as normal control and Group II rats were treated with Indomethacin 2.5x10^-5 moles/kg b.wt. All the doses were administered orally according to the body weight of the animals.

7.18 Evaluation of 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 h was determined. The results showed the ability of the model in detecting that the time course changes in the paw size was associated with carrageenan-induced rat paw oedema. The paw oedema was constantly increased during 4 h and reached peak of oedema at 4th hour. At the 5th and 6th hour, the oedema was gradually reduced. The percentage increase in paw oedema thickness was calculated by using following formula.
\[
\text{% Increase in paw thickness} = \frac{Y_t - Y_o \times 100}{Y_o}
\]

\(Y_t\) = Paw thickness at time (1, 2,3,4,5 and 6\(^{th}\)) after injection.

\(Y_o\) = Paw thickness at 0 hr (before injection)

Data were expressed in terms of mean values + S.E.M

The percentage increase in paw edema response during 6\(^{th}\) hr was determined. The percentage inhibition of paw edema thickness is calculated using the formula.

Percent inhibition = 100 x 1 - \(Y_1/Y_o\)

\(Y_1\) = Average increase in paw thickness in group treated with test compounds.

\(Y_o\) = Average increase in paw thickness in control

\text{Fig. 7.5} Progression of the carrageenan-induced rat paw edema over 6 h as monitored with Zeitlin’s apparatus.
Fig. 7.6 Zeitlin’s constant loaded lever (Paw thickness Measuring Devise)  
(Battu et al., 2000)

1) Place where the paws use to be kept to measure the thickness.

2) Constant load lever.

3) Graduated scale numbered between 1-10 and divided by 0.5 cm equal to 20 divisions.

4) Thread to pull down the lever with right leg in order to facilitate to keep the paw in between pointer 1 a and basement 1 b.
7.19 Effect of hexane fraction of *Elephantopus scaber* on Carrageenan-induced rat paw oedema

7.19.1 Objective

To evaluate the anti-inflammatory activity of hexane fraction of *Elephantopus scaber*.

7.19.2 Materials and Methods

Wistar albino rats of either sex (150-200 g, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The hexane fractions of *Elephantopus scaber* at different doses were administered *p.o.* in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig.7.7.

The extracts were administered orally in the following order:

- **Group-III** Received hexane fraction of *Elephantopus scaber* 125 mg/kg
- **Group-IV** Received hexane fraction of *Elephantopus scaber* 250 mg/kg
- **Group-V** Received hexane fraction of *Elephantopus scaber* 500 mg/kg

7.19.3 Results

Figure 7.7 shows that the Indomethacin and hexane extract of *Elephantopus scaber* inhibited the maximal oedema response by 45.30±2.41, 83.33±3.30, 72.87±4.06 and 57.11±2.02 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±17.64, 28.28±8.48, 38.66±11.60 and 46.39±13.92 respectively over 6 h when compared to the control group treated with drug vehicle.
7.19.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the hexane extract of *Elephantopus scaber* produced significant effect in reducing paw oedema at all three doses of 125,250 & 500 mg/kg.

**Table 7.2 Percentage inhibition of Carrageenan-induced paw oedema in rats by prophylactic treatment with the Hexane fraction of *Elephantopus scaber* and Indomethacin. ***P<0.001.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±17.64***</td>
</tr>
<tr>
<td>Group III</td>
<td>16.66±3.33***</td>
<td>28.28±8.48***</td>
</tr>
<tr>
<td>Group IV</td>
<td>27.12±4.06***</td>
<td>38.66±11.60***</td>
</tr>
<tr>
<td>Group V</td>
<td>42.88±2.02***</td>
<td>46.39±13.92***</td>
</tr>
</tbody>
</table>
**Fig.7.7** Effect of the Hexane fraction of *Elephantopus scaber* at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10^{-5} moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**ESH**: *Elephantopus scaber* Hexane fraction.
7.20 Effect of ethyl acetate fraction of *Elephantopus scaber* on carrageenan-induced rat paw oedema

7.20.1 Objective

To evaluate the anti-inflammatory activity of ethyl acetate fraction of *Elephantopus scaber*.

7.20.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The ethyl acetate fractions of *Elephantopus scaber* at different doses were administered *p.o* in sodium carboxy methyl cellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig. 7.8.

The extracts were administered orally in the following order

<table>
<thead>
<tr>
<th>Group</th>
<th>Received Ethyl acetate fraction of <em>Elephantopus scaber</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-VI</td>
<td>125 mg/kg</td>
</tr>
<tr>
<td>Group-VII</td>
<td>250 mg/kg</td>
</tr>
<tr>
<td>Group-VIII</td>
<td>500 mg/kg</td>
</tr>
</tbody>
</table>

7.20.3 Results

Figure 7.8 shows that the Indomethacin and ethyl acetate extract of *Elephantopus scaber* inhibited the maximal oedema response by 45.30±2.41, 80.57±5.55, 69.84±5.60 and 49.39±2.30 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±10.41, 32.68±5.78, 34.46±6.10 and 57.70±10.22 respectively over 6 h when compared to the control group treated with drug vehicle.
7.20.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the ethyl acetate extract of *Elephantopus scaber* produced significant effect in reducing paw oedema at all three doses of 125,250 & 500 mg/kg.

Table 7.3. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the ethyl acetate of *Elephantopus scaber* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±10.41***</td>
</tr>
<tr>
<td>Group VI</td>
<td>22.91±4.45***</td>
<td>32.68±5.78***</td>
</tr>
<tr>
<td>Group VII</td>
<td>30.15±5.60***</td>
<td>34.46±6.10***</td>
</tr>
<tr>
<td>Group VII</td>
<td>50.60±2.30***</td>
<td>57.70±10.22***</td>
</tr>
</tbody>
</table>
**Fig. 7.8** Effect of the ethyl acetate fraction of *Elephantopus scaber* at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10^{-5} moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**ESEA:** *Elephantopus scaber* Ethyl acetate fraction
7.21 Effect of ethanol fraction of *Elephantopus scaber* on carrageenan-induced rat paw oedema

7.21.1 Objective

To evaluate the anti-inflammatory activity of ethanol fraction of *Elephantopus scaber*.

7.21.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The ethanol fraction of *Elephantopus scaber* at different doses were administered *p.o.* in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig. 7.9.

The extracts were administered orally in the following order

- Group-IX  Received Ethanol fraction of *Elephantopus scaber* 125 mg/kg
- Group-X  Received Ethanol fraction of *Elephantopus scaber* 250 mg/kg
- Group-XI  Received Ethanol fraction of *Elephantopus scaber* 500 mg/kg

7.21.3 Results

Figure 7.9 shows that the Indomethacin and ethanolic extract of *Elephantopus scaber* at doses 125, 250 & 500 mg/kg inhibited the maximal oedema response by 45.30±2.41, 74.39±8.87, 51.96±4.77 and 48.48±0.95 respectively during the 6h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±13.35, 35.99±8.17, 50.91±11.56 and 48.79±11.08 respectively over 6 h when compared to the control group treated with drug vehicle.
7.21.5 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the ethanolic extract of *Elephantopus scaber* produced significant effect in reducing paw oedema at all three doses of 125,250 & 500 mg/kg.

Table 7.4. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Ethanol fraction of *Elephantopus scaber* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±13.35***</td>
</tr>
<tr>
<td>Group IX</td>
<td>25.61±2.78***</td>
<td>35.99±8.17***</td>
</tr>
<tr>
<td>Group X</td>
<td>48.03±4.77***</td>
<td>50.91±11.56***</td>
</tr>
<tr>
<td>Group XI</td>
<td>51.51±2.75***</td>
<td>48.79±11.08***</td>
</tr>
</tbody>
</table>
Fig.7.9 Effect of the ethanol fraction of *Elephantopus scaber* at 125,250 & 500 mg/kg along with Indomethacin (2.5x10^-5 moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**ESE:** *Elephantopus scaber* Ethanol fraction
7.22 Effect of methanol fraction of *Elephantopus scaber* on carrageenan-induced rat paw oedema

7.22.1 Objective

To evaluate the anti-inflammatory activity of methanol fraction of *Elephantopus scaber*.

7.22.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The methanol fraction of *Elephantopus scaber* at different doses were administered *p.o.* in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig. 7.10.

The extracts were administered orally in the following order:

- Group-XII: Received methanol fraction of *Elephantopus scaber* 125 mg/kg
- Group-XIII: Received methanol fraction of *Elephantopus scaber* 250 mg/kg
- Group-XIV: Received methanol fraction of *Elephantopus scaber* 500 mg/kg

7.22.3 Results

Figure 7.10 shows that the Indomethacin and methanolic extract of *Elephantopus scaber* significantly inhibited the maximal oedema response by 45.30±2.41, 79.24±2.59, 66.21±2.94 and 49.99±1.17 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±20.77, 33.98±12.01, 41.79±14.76 and 57.58±20.34 respectively over 6 h when compared to the control group treated with drug vehicle.
7.22.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the methanolic extract of *Elephantopus scaber* produced significant effect in reducing paw oedema at all three doses of 125,250 & 500 mg/kg.

Table 7.5. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Methanol fraction of *Elephantopus scaber* and Indomethacin. ***P<0.001

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0±</td>
<td>0.0</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±20.77***</td>
</tr>
<tr>
<td>Group XII</td>
<td>20.76±2.59***</td>
<td>33.98±12.01***</td>
</tr>
<tr>
<td>Group XII</td>
<td>33.79±2.94***</td>
<td>41.79±14.76***</td>
</tr>
<tr>
<td>Group XIV</td>
<td>48.32±1.07***</td>
<td>57.58±20.34***</td>
</tr>
</tbody>
</table>
Fig. 7.10 Effect of the methanol fraction of *Elephantopus scaber* at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10⁻⁶ moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**ESM:** *Elephantopus scaber* Methanol fraction
7.23 Effect of hexane fraction of *Celosia argentea* on carrageenan-induced rat paw oedema

7.23.1 Objective

To evaluate the anti-inflammatory activity of hexane fraction of *Celosia argentea*.

7.23.2 Materials and Methods

Wistar albino rats of either sex (150-200 g, n=6), Carrageenan and the Zeitlin Isotonic Lever, for measuring paw thickness, were used.

The hexane fraction of *Celosia argentea* at different doses were administered p.o. in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig.7.11.

The extracts were administered orally in the following order

Group-XV Received hexane fraction of *Celosia argentea* 125 mg/kg
Group-XVI Received hexane fraction of *Celosia argentea* 250 mg/kg
Group-XVII Received hexane fraction of *Celosia argentea* 500 mg/kg

7.23.3 Results

Figure 7.11 shows that the Indomethacin and hexane extract of *Celosia argentea* inhibited the maximal oedema response by 45.30±2.41, 79.24±2.59, 72.72±4.21 and 53.48±3.95 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±13.46, 27.52±6.30, 36.43±8.34 and 52.16±11.94 respectively over 6 h when compared to the control group treated with drug vehicle.
7.23.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the hexane extract of *Celosia argentea* produced significant effect in reducing paw oedema at all three doses of 125, 250 & 500 mg/kg.

Table 7.6 .Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Hexane fraction of *Celosia argentea* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±13.46***</td>
</tr>
<tr>
<td>Group XV</td>
<td>20.91±2.67***</td>
<td>27.52±6.30***</td>
</tr>
<tr>
<td>Group XVI</td>
<td>27.27±4.21***</td>
<td>36.43±8.34***</td>
</tr>
<tr>
<td>Group XVII</td>
<td>46.51±3.95***</td>
<td>52.16±11.94***</td>
</tr>
</tbody>
</table>
**Fig. 7.11** Effect of the hexane fraction of *Celosia argentea*, at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10^{-5} moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**CAH**: *Celosia argentea* hexane fraction.
7.24 Effect of ethyl acetate fraction of *Celosia argentea* on carrageenan-induced rat paw oedema

7.24.1 Objective

To evaluate the anti-inflammatory activity of ethyl acetate fraction of *Celosia argentea*.

7.24.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The ethyl acetate fraction of *Celosia argentea* at different doses were administered *p.o.* in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig.7.12.

The extracts were administered orally in the following order

Group-XVIII Received Ethyl acetate fraction of *Celosia argentea* 125 mg/kg

Group-XIX Received Ethyl acetate fraction of *Celosia argentea* 250 mg/kg

Group-XX Received Ethyl acetate fraction of *Celosia argentea* 500 mg/kg

7.24.3 Results

Figure 7.12 shows that the Indomethacin and ethyl acetate extract of *Celosia argentea* inhibited the maximal oedema response by 45.30±2.41, 79.39±4.15, 61.66±4.18 and 50.3±3.67 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±13.65, 34.19±7.93, 45.87±10.65 and 54.61±12.68 respectively over 6 h when compared to the control group treated with drug vehicle.
7.24.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the ethyl acetate extract of *Celosia argentea* whole plant produced significant effect in reducing paw oedema at all three doses of 125, 250 & 500 mg/kg.

Table 7.7. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the ethyl acetate fraction of *Celosia argentea* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0±0.54</td>
<td>0.0±0.33</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±13.65***</td>
</tr>
<tr>
<td>Group XVIII</td>
<td>20.60±4.15***</td>
<td>34.19±7.93***</td>
</tr>
<tr>
<td>Group XIX</td>
<td>38.33±4.18***</td>
<td>45.87±10.65***</td>
</tr>
<tr>
<td>Group XX</td>
<td>49.69±3.67***</td>
<td>54.61±12.68***</td>
</tr>
</tbody>
</table>
Fig. 7.12 Effect of the ethyl acetate fraction of *Celosia argentea*, at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10^5 moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan-induced rats.

**CAEA**: *Celosia argentea* ethyl acetate fraction.
7.25 Effect of ethanol fraction of *Celosia argentea* on carrageenan-induced rat paw oedema

7.25.1 Objective

To evaluate the anti-inflammatory activity of ethanol fraction of *Celosia argentea*.

7.25.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The ethanol fraction of *Celosia argentea* at different doses was administered p.o. in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig.7.13.

The extracts were administered orally in the following order

- **Group-XXI** Received ethanol fraction of *Celosia argentea* 125 mg/kg
- **Group-XXII** Received ethanol fraction of *Celosia argentea* 250 mg/kg
- **Group-XXIII** Received ethanol fraction of *Celosia argentea* 500 mg/kg

7.25.3 Results

Figure 7.13 shows that the Indomethacin and alcoholic crude extract of *Celosia argentea* inhibited the maximal oedema response by 45.30±2.41, 77.72±4.90, 56.81±3.92 and 40.30±1.18 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±16.02, 32.64±8.89, 48.71±13.28 and 64.23±17.51 respectively over 6 h when compared to the control group treated with drug vehicle.
7.25.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the alcoholic crude extract of *Celosia argentea* produced significant effect in reducing paw oedema at all three doses of 125,250 & 500 mg/kg.

Table 7.8. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Ethanol fraction of *Celosia argentea* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±16.02***</td>
</tr>
<tr>
<td>Group XXI</td>
<td>22.27±4.90***</td>
<td>32.64±8.89***</td>
</tr>
<tr>
<td>Group XXII</td>
<td>44.85±3.06***</td>
<td>48.71±13.28***</td>
</tr>
<tr>
<td>Group XXIII</td>
<td>59.7±1.18***</td>
<td>64.23±17.51***</td>
</tr>
</tbody>
</table>
Fig. 7.13 Effect of the ethanol fraction of *Celosia argentea*, at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10^{-5} moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

CAE: *Celosia argentea* ethanol fraction.
7.26 Effect of methanol fraction of *Celosia argentea* on carrageenan-induced rat paw oedema

7.26.1 Objective

To evaluate the anti-inflammatory activity of methanol fraction of *Celosia argentea*.

7.26.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The methanol fraction of *Celosia argentea* at different doses were administered *p.o.* in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig. 7.14.

The extracts were administered orally in the following order:

**Group-XXIV** Received methanol fraction of *Celosia argentea* 125 mg/kg
**Group-XXV** Received methanol fraction of *Celosia argentea* 250 mg/kg
**Group-XXVI** Received methanol fraction of *Celosia argentea* 500 mg/kg

7.26.3 Results

Figure 7.14 shows that the Indomethacin and methanolic extract of *Celosia argentea* inhibited the maximal oedema response by 45.30±2.41, 79.39±4.15, 67.87±3.73 and 56.51±2.89 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±14.11, 35.41±8.47, 44.18±10.61 and 50.57±12.14 respectively over 6 h when compared to the control group treated with drug vehicle.
7.26.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the methanolic extract of *Celosia argentea* produced significant effect in reducing paw oedema at all three doses of 125, 250 & 500 mg/kg.

Table 7.9 .Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Methanol fraction of *Celosia argentea* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±14.11***</td>
</tr>
<tr>
<td>Group XXIV</td>
<td>20.60±4.15***</td>
<td>35.41±8.47***</td>
</tr>
<tr>
<td>Group XXV</td>
<td>32.12±3.73***</td>
<td>44.18±10.61***</td>
</tr>
<tr>
<td>Group XXVI</td>
<td>43.48±2.89***</td>
<td>50.57±12.14***</td>
</tr>
</tbody>
</table>
Fig. 7.14 Effect of the methanol fraction of *Celosia argentea*, at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10⁻⁵ moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**CAM:** *Celosia argentea* methanol fraction.
7.27 Effect of hexane fraction of *Catharanthus pusillus* on Carrageenan-induced rat paw oedema

7.27.1 Objective

To evaluate the anti-inflammatory activity of hexane fraction of *Catharanthus pusillus*.

7.27.2 Materials and Methods

Wistar albino rats of either sex (150-200 g, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The hexane fraction of *Catharanthus pusillus* at different doses were administered *p.o.* in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig.7.15.

The extracts were administered orally in the following order

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXVII</td>
<td>Received hexane fraction of <em>Catharanthus pusillus</em> 125 mg/kg</td>
</tr>
<tr>
<td>XXVIII</td>
<td>Received hexane fraction of <em>Catharanthus pusillus</em> 250 mg/kg</td>
</tr>
<tr>
<td>XXIX</td>
<td>Received hexane fraction of <em>Catharanthus pusillus</em> 500 mg/kg</td>
</tr>
</tbody>
</table>

7.27.3 Results

Figure 7.15 shows that the Indomethacin and hexane extract of *Catharanthus pusillus* inhibited the maximal oedema response by 45.30±2.41, 82.65±5.43, 69.69±4.75 and 53.02±4.0 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±16.97, 29.85±8.61, 36.99±10.68 and 55.48±16.02 respectively over 6 h when compared to the control group treated with drug vehicle.
7.27.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the hexane extract of *Catharanthus pusillus* produced significant effect in reducing paw oedema at all three doses of 125, 250 & 500 mg/kg.

Table 7.10. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Hexane fraction of *Catharanthus pusillus* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0±0.54</td>
<td>0.0±0.33</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±16.97***</td>
</tr>
<tr>
<td>Group XXVII</td>
<td>17.51±5.32***</td>
<td>29.85±8.61***</td>
</tr>
<tr>
<td>Group XXVIII</td>
<td>30.30±4.75***</td>
<td>36.99±10.68***</td>
</tr>
<tr>
<td>Group XXIX</td>
<td>46.97±4.00***</td>
<td>55.48±16.02***</td>
</tr>
</tbody>
</table>
Fig. 7.15 Effect of the hexane fraction of *Catharanthus pusillus*, at 125,250 & 500 mg/kg along with Indomethacin (2.5x10^{-5} moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**CPH:** *Catharanthus pusillus* hexane fraction
7.28 Effect of ethyl acetate fraction of *Catharanthus pusillus* on Carrageenan-induced rat paw oedema

7.28.1 Objective

To evaluate the anti-inflammatory activity of ethyl acetate fraction of *Catharanthus pusillus*.

7.28.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The ethyl acetate fraction of *Catharanthus pusillus* different doses were administered *p.o* in sodium carboxy methyl cellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Figure 7.16.

The extracts were administered orally in the following order

- **Group-XXX** Received ethyl acetate fraction of *Catharanthus pusillus* 125 mg/kg
- **Group-XXXI** Received ethyl acetate fraction of *Catharanthus pusillus* 250 mg/kg
- **Group-XXXII** Received ethyl acetate fraction of *Catharanthus pusillus* 500 mg/kg

7.28.3 Results

Figure 7.16 shows that the Indomethacin and ethyl acetate extract of *Catharanthus pusillus* inhibited the maximal oedema response by 45.30±2.41, 80.9±3.16, 71.21±3.01 and 35.45±1.84 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±15.63, 30.48±8.10, 40.44±10.76 and 56.20±14.95 respectively over 6 h when compared to the control group treated with drug vehicle.
7.28.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the ethyl acetate extract of *Catharanthus pusillus* produced significant effect in reducing paw oedema at all three doses of 125, 250 & 500 mg/kg.

Table 7.11. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Ethyl acetate fraction of *Catharanthus pusillus* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0±0.54</td>
<td>0.0±0.33</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±15.63***</td>
</tr>
<tr>
<td>Group XXX</td>
<td>19.09±3.16***</td>
<td>30.48±8.10***</td>
</tr>
<tr>
<td>Group XXXI</td>
<td>28.79±3.01***</td>
<td>40.44±10.76***</td>
</tr>
<tr>
<td>Group XXXII</td>
<td>48.18±3.74***</td>
<td>56.20±14.95***</td>
</tr>
</tbody>
</table>
A) 

Mean±S.E.M, N=6

% Increase in rat paw oedema

Time(hrs)

Drug vehicle
Standard
CPEA 250 mg/kg
CPEA 500 mg/kg
CPEA 125 mg/kg

B) 

Mean±S.E.M, N=6

Total Oedema(AUC) as % of mean control response

Drug vehicle
Indomethacin
CPEA 125 mg/kg
CPEA 250 mg/kg
CPEA 500 mg/kg

Fig. 7.16 Effect of ethyl acetate fraction of *Catharanthus pusillus*, at 125, 250 & 500 mg/kg along with Indomethacin (2.5×10⁻⁵ moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

CPEA: *Catharanthus pusillus* ethyl acetate fraction
7.29 Effect of ethanol fraction of *Catharanthus pusillus* on Carrageenan-induced rat paw oedema

7.29.1 Objective

To evaluate the anti-inflammatory activity of ethanol fraction of *Catharanthus pusillus*.

7.29.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The ethanol fraction of *Catharanthus pusillus* at different doses were administered p.o. in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig.7.17.

The extracts were administered orally in the following order

- **Group-XXXIII**  Received ethanol fraction of *Catharanthus pusillus* 125 mg/kg
- **Group-XXXIV**  Received ethanol fraction of *Catharanthus pusillus* 250 mg/kg
- **Group-XXXV**  Received ethanol fraction of *Catharanthus pusillus* 500 mg/kg

6.27.3 Results

Figure 7.17 shows that the Indomethacin and alcoholic crude extract of *Catharanthus pusillus* inhibited the maximal oedema response by 45.30±2.41, 80.83±3.2, 58.33±3.29 and 42.27±3.84 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±17.96, 36.84±11.26, 46.14±14.10 and 58.53±17.89 respectively over 6 h when compared to the control group treated with drug vehicle.
6.27.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the ethanolic extract of *Catharanthus pusillus* produced significant effect in reducing paw oedema at all three doses of 125,250 & 500 mg/kg.

Table 7.12. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the ethanol fraction of *Catharanthus pusillus* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0±0.54</td>
<td>0.0±0.33</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±17.96***</td>
</tr>
<tr>
<td>Group XXXII</td>
<td>19.09±3.16***</td>
<td>36.84±11.26***</td>
</tr>
<tr>
<td>Group XXXIV</td>
<td>40.15±2.30***</td>
<td>46.14±14.10***</td>
</tr>
<tr>
<td>Group XXXV</td>
<td>57.72±3.84***</td>
<td>58.53±17.89***</td>
</tr>
</tbody>
</table>
**Fig. 7.17** Effect of ethanol fraction of *Catharanthus pusillus*, at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10^-5 moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**CPE:** *Catharanthus pusillus* ethanol fraction
7.30 Effect of methanol fraction of *Catharanthus pusillus* on Carrageenan-induced rat paw oedema

7.30.1 Objective

To evaluate the anti-inflammatory activity of methanol fraction of *Catharanthus pusillus*.

7.30.2 Materials and Methods

Wistar albino rats of either sex (150-200 gm, n=6), Carrageenan and the Zeitlin Isotonic Lever for measuring paw thickness, were used.

The methanol fraction of *Catharanthus pusillus* at different doses were administered p.o. in sodium carboxymethylcellulose suspension 18 h and 2 h prior to the induction of oedema by carrageenan injection. The maximal oedema response and the area under the time-course (AUC) as total oedema response are shown in Fig.7.18.

The extracts were administered orally in the following order

Group-XXXVI  Received methanol fraction of *Catharanthus pusillus* 125 mg/kg
Group-XXXVII Received methanol fraction of *Catharanthus pusillus* 250 mg/kg
Group-XXXVIII Received methanol fraction of *Catharanthus pusillus* 500 mg/kg

7.30.3 Results

Figure 7.18 shows that the Indomethacin and methanolic extract of *Catharanthus pusillus* inhibited the maximal oedema response by 45.30±2.41, 79.24±4.21, 64.69±2.65 and 51.81±2.71 respectively during the 6 h of the carrageenan-induced rat paw acute inflammation. The total oedema response (AUC) was inhibited by 58.77±16.58, 35.54±10.03, 42.29±11.93 and 56.01±15.80 respectively over 6 h when compared to the control group treated with drug vehicle.
7.30.4 Discussion

The results suggested that the standard drug Indomethacin significantly inhibited paw oedema compared to drug vehicle, where as the methanolic extract of *Catharanthus pusillus* produced significant effect in reducing paw oedema at all three doses of 125, 250 & 500 mg/kg.

Table 7.13. Percentage inhibition of Carrageenan induced paw oedema in rats by prophylactic treatment with the Methanol fraction of *Catharanthus pusillus* and Indomethacin. ***P<0.001.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage inhibition of the maximal paw oedema during 6 hours</th>
<th>Percentage inhibition of total AUC paw oedema during 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0.0±0.54</td>
<td>0.0±0.33</td>
</tr>
<tr>
<td>Group II</td>
<td>58.0±3.51***</td>
<td>58.77±16.58***</td>
</tr>
<tr>
<td>Group XXXVI</td>
<td>20.76±2.59***</td>
<td>35.54±10.03***</td>
</tr>
<tr>
<td>Group XXXVII</td>
<td>35.30±2.65***</td>
<td>42.29±11.93***</td>
</tr>
<tr>
<td>Group XXXVIII</td>
<td>48.18±2.71***</td>
<td>56.01±15.80***</td>
</tr>
</tbody>
</table>
**Fig. 7.18** Effect of methanol fraction of *Catharanthus pusillus*, at 125, 250 & 500 mg/kg along with Indomethacin (2.5x10^{-5} moles/kg body wt) on A) the maximal and B) the total paw oedema in carrageenan induced rats.

**CPM:** *Catharanthus pusillus* (Murray) G.Don. methanol fraction.
7.31 Discussion

The most widely used test to evaluate anti-inflammatory activity of any new compound is by testing its caliber in reducing the irritant induced oedema in experimental animals (Winter et al., 1962). The development of oedema in the paw of the rat after the injection of carrageenan has been described as biphasic event.

The initial phase which occurs between 0 and 2.5 h has been attributed to the action of histamine, serotonin and bradykinin on vascular permeability (Vinger et al., 1987). The oedema volume reaches its maximum approximately 3h post treatment and then begins to decline. The late phase, which is also a complement dependant reaction, has been shown to be a result of over production of prostaglandins in tissues (Di Rosa, 1974).

The methanolic extracts of *Celosia argentea* exhibited good anti-inflammatory activity when compared to the extracts of *Elephantopus scaber* and *Catharanthus pusillus*. Pharmacological investigations clearly indicated that anti-inflammatory activity in many plants have been attributed to their flavanoid and sterol contents (Mansour et al., 1990). Several flavanoids isolated from the medicinal plants have been discovered to possess significant anti-inflammatory activity (Duke, 1992).

Literature review reports the presence of flavanoids, triterpenoids, phytosterols and alkaloids in *Elephantopus scaber, Celosia argentea* and *Catharanthus pusillus*. These compounds may be responsible for the anti-inflammatory activity. 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. Among the selected three plant extracts, the methanolic extracts produced significant reduction of paw oedema.

Presence of higher ratio of the above mentioned compounds in *Celosia argentea* and also in other two plants *Elephantopus scaber* and *Catharanthus pusillus* may be responsible for potent activity.

Ethanolic, Methanolic extracts from the three selected species had produced significant activity at the lower to higher doses, where as the ethyl acetate and hexane extracts produced good reduction at the maximum dose. The
methanolic extract of *Elephantopus scaber* produced significant (P<0.001) reduction at 125, 250 & 500 mg/kg when compared to drug vehicle treated control group.

The ethanolic (125,250,500 mg/kg) and methanolic extract of *Celosia argentea* at three different doses produced significant (P<0.05) reduction at 125,250 and 500 mg/kg when compared to drug vehicle treated control group. The ethyl acetate and hexane extracts of *Celosia argentea* tested, at the doses 125,250 and 500 mg/kg were exhibited significant (p<0.001) activity, where as the dose 500 mg/kg exhibited a highly significant (p<0.001) effect when compared to drug vehicle treated control group.

The ethanolic (125,250 and 500 mg/kg) and methanolic extract of *Catharanthus pusillus* at three different doses produced significant (P<0.001) reduction at 125,250 and 500 mg/kg when compared to drug vehicle treated control group. The ethyl acetate and hexane extracts of *Catharanthus pusillus* tested, at the doses 125,250 and 500 mg/kg were exhibited significant (p<0.001) activity, where as the dose 500 mg/kg exhibited a highly significant (p<0.001) effect when compared to drug vehicle treated control group.

The percentage inhibition of the maximal paw oedema during 6 h for the hexane extracts of *Elephantopus scaber, Celosia argentea* and *Catharanthus pusillus* at 500 mg/kg were in the following order *Celosia argentea > Elephantopus scaber > Catharanthus pusillus*.

The percentage inhibition of the maximal paw oedema during 6 h for the ethyl acetate extracts of *Elephantopus scaber, Celosia argentea* and *Catharanthus pusillus* at 500 mg/kg were in the following order *Celosia argentea > Elephantopus scaber > Catharanthus pusillus*.

The percentage inhibition of the maximal paw oedema during 6 h for the ethanolic extracts of *Elephantopus scaber, Celosia argentea* and *Catharanthus pusillus* at 500 mg/kg were in the following order *Celosia argentea > Elephantopus scaber > Catharanthus pusillus*.

The percentage inhibition of the maximal paw oedema during 6 h for the methanolic extracts of *Elephantopus scaber, Celosia argentea* and *Catharanthus
pusillus at 500 mg/kg were in the following order Celosia argentea > Elephantopus scaber > Catharanthus pusillus.

The results clearly indicate that the pretreatment with the selected plant extracts and indomethacin have contained the increase in paw oedema due to the phlogistic agent. Among the selected three plant extracts methanolic extracts of Elephantopus scaber, Celosia argentea and Catharanthus pusillus produced highly significant reduction of paw oedema than crude, ethyl acetate and hexane extracts.

Further studies have to be conducted on chronic inflammation (Adjuvant induced arthritis model) to establish the mechanism of action of these extracts that exhibited significant activity. The exact bioactive principles responsible for the reduction in paw oedema induced by carrageenan remains to be explained. Furthermore, it is difficult, at this stage to draw any logical conclusion on the mechanism of anti-inflammatory action of such a diverse mixture of chemical compounds contained in the plants of Elephantopus scaber, Celosia argentea and Catharanthus pusillus.

Biochemical mediators involved in this inflammation process need to be investigated to assess the specific anti-inflammatory mechanisms of the extracts tested and also to identify the possible lead molecules involved during the inflammation process.