1.1 HERBAL MEDICINE

Ever since the birth of mankind there has been a relationship between life, disease and plants. Primitive men started studying diseases and treatments (Lyons and Pertrucelli, 1987). There is no record that people in prehistoric times used synthetic medicines for their ailments but they tried to make use of the things they could easily procure. The most common thing they could find was their in environment i.e. the plants and animals (Singh and Abarar, 1990). They started using plants and found that majority of plants were suitable as food, where as other were either poisonous or medicinally useful (Fuller and Henrick, 1985). By their experience, this knowledge of herbal remedies was transferred to generation as folk medicine. So the history of herbal medicine is as old as human history.

Herbal medicine is still the mainstay of about 75–80% of the world’s population, mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. It is estimated that approximately one quarter of prescribed drugs contain plant extracts or active ingredients obtained from or modeled on plant substances. Aspirin, atropine, artemisinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine and vinblastine are a few important examples of what medicinal plants have given us in the past. Most of these plant-derived drugs were originally discovered through the study of traditional cures and folk knowledge of indigenous people and some of these could not be substituted despite the enormous advancement in synthetic chemistry. Consequently, plants can be described as a major source of medicines, not only as isolated active principles to be dispensed in standardized dosage form but also as crude drugs for the population.

Today in many countries modern medicine has displaced plants with many synthetic products but almost 30% of pharmaceutical preparations are still obtained directly or indirectly from plants. The modern era has seen some decline in use of medicinal plants and their extracts as therapeutic agent, particularly in developed countries, many of which either been discarded by the medical profession or now given in the form of isolated compound. The strategy of isolating the active principles
from the medicinal plants and manufacturing a pharmaceutical preparation then became popular. Modern medicines and herbal medicines are complimentarily being used in areas for health care program in several developing countries including India. Of late, the interest in the plant products surfaces all over the world due to the belief that many herbal medicines are known to be free from side effects. It is the fact that the discovery of the new synthetic drug is time consuming & an expensive affair. The utility of the synthetic drug is always accompanied with its single or multiple adverse effects and in some cases the curatives are not available.

Herbs had been used by all cultures throughout history but India has one of the oldest, richest and most diverse cultural living traditions associated with the use of medicinal plants. In the present scenario, the demand for herbal products is growing exponentially throughout the world and major pharmaceutical companies are currently conducting extensive research on plant materials for their potential medicinal value. In many journals, national and international, increasing number of research publications based on herbal drugs (Adithan, 1996; Tandon et al., 2004).

Plants have provided mankind a large variety of potent drugs to alleviate suffering from diseases in spite of spectacular advances in synthetic drugs in recent years, some of the drugs of plant Origin have still retained their importance. The use of plant-based drugs all over world is increasing. Inspite of the tremendous advances made in the modern medicine there are still a large number of ailments for which suitable drugs are yet to be found. Today, there is an urgent need to develop safer drugs for the treatment of inflammatory disorders, diabetes, liver diseases, and gastrointestinal disorder. Hence, there is a growing interest in the pharmacological evaluation of various plants used in Indian traditional systems of medicine.

However, the folkloric use of crude drugs is often empirical and is based on observation from clinical trials without experimental support. The need for exhaustive systemic research into indigenous drugs cannot be overemphasized.
1.2 INFLAMMATION

A human or animal must defend itself against multitude of different pathogens including viruses, bacteria, fungi, and protozoan and metazoan parasites as well as tumours and a number of various harmful agents which are capable to derange its homeostasis. For this, a plenty of effector mechanisms capable of defending the body against such antigens and agents have developed and these can be mediated by soluble molecules or by cells. If infection occurs as a consequence of the tissue damage, the innate and, later, the adaptive immune systems are triggered to destroy the infectious agent.

Inflammation is the body's reaction to invasion by an infectious agent, antigen challenge or even just physical, chemical or traumatic damage. It is the non-specific immune response that occurs in response to any type of bodily injury. It is a stereotype response that is identical irrespective of the stimuli (either pathogenic organism, foreign body, ischemia, physical trauma, ionizing radiation, electrical energy, or extreme temperature). The effect of inflammation is divided into two fold i.e.

- To destroy or remove the causative agent.
- To repair the damage tissue.

For the first, one mesodermal cells of blood or tissue come to the picture but for the second on fixed cells of the tissue takes part. Children, old people or those with poor resistance of the body are more predisposed to inflammatory changes than healthy young adults.

PURPOSE - A protective host response to injury - vascular, cellular, chemical: the delivery of plasma and cells to the wound to:

- stop injury with edema which dilutes toxins
- remove bacteria and cell debris by phagocytosis
- initiate healing and repair
- wall off infection
Cardinal Signs of Inflammation:

The four principal effects of acute inflammation were described nearly 2,000 years ago by Celsus:

Redness (rubor): due to dilatation of small blood vessels within the damaged area.

Heat (calor): due to increased blood flow (hyperaemia) through the region, resulting in vascular dilatation and the delivery of warm blood to the area. Systemic fever, which results from some of the chemical mediators of inflammation, also contributes to the local temperature.

Swelling (tumor): results from oedema, the accumulation of fluid in the extra vascular space as part of the fluid exudate, and to a much lesser extent, from the physical mass of the inflammatory cells migrating into the area.

Pain (dolor): results partly from the stretching and distortion of tissues due to inflammatory oedema and, in particular, from pus under pressure in an abscess cavity. Some of the chemical mediators of acute inflammation, including bradykinin, the prostaglandins and serotonin, are known to induce pain.

Loss of function: Loss of function, a well-known consequence of inflammation, was added by Virchow (1821-1902) to the list of features drawn up by Celsus. Movement of an inflamed area is consciously and reflexly inhibited by pain, while severe swelling may physically immobilise the tissues.

According to different criteria, inflammatory responses can be divided into several categories. The criteria include:

1. Time -- hyperacute (peracute), acute, subacute, and chronic inflammation
2. The main inflammatory manifestation - alteration, exudation, proliferation
3. The degree of tissue damage - superficial, profound (bordered, not bordered)
4. Characteristic picture - nonspecific, specific
5. Immunopathological mechanisms
   - allergic (reaginic) inflammation,
   - inflammation mediated by cytotoxic antibodies,
   - inflammation mediated by immune complexes,
   - delayed-type hypersensitivity reactions.
The main features of the inflammatory response are: **vasodilation**, i.e. widening of the blood vessels to increase the blood flow to the infected area; **increased vascular permeability**, which allows diffusible components to enter the site; **cellular infiltration** by chemotaxis, or the directed movement of inflammatory cells through the walls of blood vessels into the site of injury; **changes** in biosynthetic, metabolic, and catabolic **profiles** of many organs; and **activation** of cells of the immune system as well as of complex enzymatic systems of blood plasma. Of course, the degree to which these occur is normally proportional to the severity of the injury and the extent of infection.

Inflammation can be divided into several phases. The earliest, gross event of an inflammatory response is temporary vasoconstriction, i.e. narrowing of blood vessels caused by contraction of smooth muscle in the vessel walls, which can be seen as blanching (whitening) of the skin. This is followed by several phases that occur over minutes, hours and days later, outlined below.

1. The **acute vascular response** follows within seconds of the tissue injury and last for some minutes. This results from vasodilation and increased capillary permeability due to alterations in the vascular endothelium, which leads to increased blood flow (**hyperaemia**) that causes redness (**erythema**) and the entry of fluid into the tissues (**oedema**).

2. If there has been sufficient damage to the tissues, or if infection has occurred, the **acute cellular response** takes place over the next few hours. The hallmark of this phase is the appearance of granulocytes, particularly neutrophils, in the tissues. These cells first attach themselves to the endothelial cells within the blood vessels (**margination**) and then cross into the surrounding tissue (**diapedesis**). During this phase erythrocytes may also leak into the tissues and a haemorrhage can occur (e.g. a blood blister). If the vessel is damage, fibrinogen and fibronectin are deposited at the site of injury, platelets aggregate and become activated, and the red cells stack together in what are called "rouleau" to help stop bleeding and aid clot formation. The dead and dying cells contribute to pus formation.
3. If the damage is sufficiently severe, a **chronic cellular response** may follow over the next few days. A characteristic of this phase of inflammation is the appearance of a mononuclear cell infiltrate composed of macrophages and lymphocytes. The macrophages are involved in microbial killing, in clearing up cellular and tissue debris, and they also seem to be very important in remodelling the tissues.

4. Over the next few weeks, **resolution** may occur, meaning that the normal tissue architecture is restored. Blood clots are removed by fibrinolysis, and if it is not possible to return the tissue to its original form, **scarring** results from infilling with fibroblasts, collagen, and new endothelial cells. Generally, by this time, any infection will have been overcome. However, if it has not been possible to destroy the infectious agents or to remove all of the products that have accumulated at the site completely, they are walled off from the surrounding tissue in **granulomatous tissue**. A **granuloma** is formed when macrophages and lymphocytes accumulate around material that has not been eliminated, together with epitheloid cells and gigant cells (perhaps derived from macrophages) that appear later, to form a ball of cell.

Inflammation is often considered in terms of **acute inflammation** that includes all the events of the acute vascular and acute cellular response (1 and 2 above), and **chronic inflammation** that includes the events during the chronic cellular response and resolution or scarring (3 and 4).

The phenomenon of inflammation is divided into three phases namely:

- a) Vascular Phenomenon
- b) Cellular response
- c) Repair
Phytopharmacological action of *Pergularia daemia* with special reference to its actions and mechanism of action as diuretic and anti-inflammatory agent.

Inflammation

- **Vascular Phenomenon**
  - Hyperemia
  - Vascular Dilatation and Stasis

- **Cellular**
  - Exudation of Plasma

- **Repair**
  - Emigration of leucocytes and RBC (diapedesis)
  - Phagocytosis

- **Proliferation**
  - 1) Fibroblastic
  - 2) Vascular

- **Regeneration**
CLASSIFICATION OF ANTI-INFLAMMATORY DRUGS

I. Steroidal Anti-inflammatory Drugs
1. Natural Opium Alkaloids Morphine, Codeine
2. Semisynthetic Opiates Diacetyl Morrhine (Heroin) Ethyl Morphine, Pholcodeine.
3. Many others like Hydromorphone, oxymorphone, Hydrocodone, Oxy codone
4. Synthetic Opioids Pethidine (mepiridine), Fentanyl, Methadone, Dextropropoxyphene, Ethoheptazine.
5. Many others like Alphoprodine, Anileridine, Dextromoramide, Alfentanil, Sufentanil

II. Non-steroidal Anti-inflammatory Drugs

Classification

A. Analgesic and anti-inflammatory
1. Salicylates Aspirin, Salicylamide, Benoxylate, Difulnisal
2. Pyrazolone derivatives Phenyl butazone, Oxyphenbutazone
3. Indole derivatives Indomethacinc, Sulindac
4. Propionic Acid derivatives Diclofenac Sodium, naproxen, Ketoprofen, Fenoprofen, Flubiprofen
5. Anthranilic Acid derivatives Mephenamic acid, Enfenamic acid.
6. Aryl acetic acid derivatives Diclofenac, Tolmetin
7. Oxicam derivatives Piroxicam, Tenoxicam
8. Pyrrolo-pyrrole derivatives Keturolac

B. Analgesic but poor anti-inflammatory
1. Para-Aminophenol Paracetamol derivatives
2. Pyrazolone derivatives Metamizol, Propiphenazone
3. Benzoxazocine derivative Nefopam
1.3 DIURETICS

Diuretic is any drug that increases the flow of urine. Diuretics increase the rate of urine flow and sodium excretion and are used to adjust the volume and/or composition of body fluids. Diuretics promote the removal from the body of excess water, salts, poisons, and accumulated metabolic products, such as urea. Diuretics not only alter the excretion of Na⁺ but also may modify renal handling of other cations (e.g., K⁺, H⁺, Ca²⁺, and Mg²⁺), anions (e.g., Cl⁻, HCO₃⁻, and H₂PO₄⁻), and uric acid. In addition, diuretics may alter renal hemodynamics indirectly. They serve to rid the body of excess fluid (edema) that accumulates in the tissues owing to various disease states.

Diuretics help to
- Lower high blood pressure
- Reduce fluid retention, edema, swollen ankles
- Provide relief from the pain and burning sensation associated with cystitis

In medicine diuretics are used to treat
- Heart Failure
- Hypertension
- Liver Cirrhosis
- Kidney Diseases
- Pulmonary and Systemic Edema

Diuretics increase the excretion of Na⁺ and water. They decrease the reabsorption of Na⁺ and (usually) Cl⁻ from the filtrate, increased water loss being secondary to the increased excretion of NaCl (natriuresis). This can be achieved by:
- a direct action on the cells of the nephron
- indirectly, by modifying the content of the filtrate

Classes of diuretics
- Carbonic Anhydrase Inhibitors e.g. Acetazolamide, Dichlorphenamide
- Loop Diuretics e.g. Furosemide, Ethacrynic acid
- Thiazides e.g. Chlorothiazide, Benztiazide
- Potassium-sparing diuretics e.g. Spironolactone
- Osmotic e.g. Mannitol, Glycerol