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A Review on Inflammation & its Management by Ayurvedic Formulations

Rishabh Utreja* and Akriti Sharma

Department of Pharmacology, Himalayan Institute of Pharmacy and Research, Rajawala Selaqui, Dehradun, Uttarakhand, India

Corresponding author: Department of Pharmacology, Himalayan Institute of Pharmacy and Research, Rajawala Selaqui, Dehradun, Uttarakhand, India

ABSTRACT

When a cell or tissue undergoes mechanical, chemical or any other distress from an external object or stimuli the defense mechanism mainly leucocytes acts up in the form of inflammation. There is a variety of steroidal and non-steroidal drugs are helpful in management of acute as well as chronic inflammation. The major issues with treatment of chronic inflammation is the toll that drugs take on gastrointestinal system as well as renal system. Prolonged consumption of NSAIDs is associated with lesions in stomach as well as load on kidneys. There is a need for alternative therapy so as to minimize these adverse effects. The drugs derived from natural resources are generally well tolerated & have low toxicity. The article highlights the signs, causes, type, mediators & mechanism of acute and chronic inflammation & its management using the ayurvedic drugs.

Keywords: Inflammation, NSAIDs, Leucocytes, Curcumin

INTRODUCTION

INFLAMMATION

Inflammation is characterized as the local reaction of any living mammalian tissue to trauma from any agent. It is the defense reaction of body for the eradication or cut off the spread of injurious agent, followed by elimination of the necrosed or dead cells and tissues. It happens through cascade of events. The cascade contains increased permeability in micro vessels, attachment of circulating cells & agents to the vessels in the location of injury, movement of abundant cell types, growth of new tissue and blood vessels ^[1]. Inflammation may release or generate a distinct number of pro-inflammatory & inflammatory mediators like serotonin, bradykinins, prostaglandins (PGs), histamines, and nitric oxide (NO). These substances give to the classic clinical depiction of heat (calor), redness (rubor), pain (dolor), swelling (tumor) and reduced function associated with inflammation and may produce hyperalgesia ^[2].

SIGNS OF INFLAMMATION

Redness (rubor): -The small blood vessels in the damaged area dilate which leads to the inflamed tissue to appear red.

Swelling (tumor): - Inflammatory fluid exudate in extravascular space & the physical mass of the inflammatory cells migrating to the inflamed area results in edema.

Heat (calor): - Increased blood flow (hyperemia) through the inflamed region results in vascular dilation and the delivery of warm blood to the area.

Pain (dolor): - Inflammatory edema causes the stretching and distortion of tissues, also chemical mediators like bradykinins & prostaglandins contribute to nociception.

Loss of Function (Functio Laesa): - The swelling caused by inflammation immobilizes the affected area & the movement is inhibited by the pain.

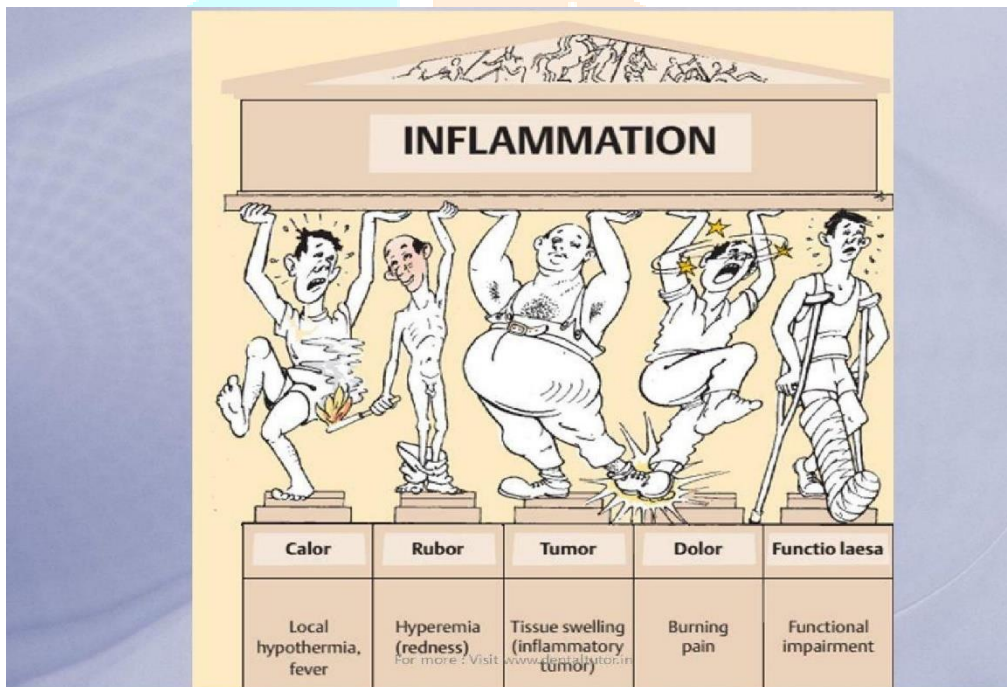


Figure 1: Signs of inflammation

Depending where the inflammation has occurred may define the number of the signs that are observable. Inflammation of skin may show all the five signs depending on the intensity of the inflammation. In the inflammation of lungs (pneumonitis) there is no pain due to absence of sensory nerves endings nearby. While symptoms of acute inflammation are among the five major signs the symptoms of chronic inflammation might be very varied and hard to assess. Symptoms like chest pain, fever, fatigue, rash, mouth sores, abdominal pain, joint pain may be signs of chronic inflammation ^[3].

CAUSES OF INFLAMMATION

Inflammation may be caused by:

1. Microorganisms like viruses, fungi, bacteria, parasites and their toxins.
2. Immunological agents like cell-mediated and antigen antibody reactions.
3. Physical agents like cold, heat, mechanical trauma, radiation etc.
4. Chemical substances like poisons -chemo toxins (organic as well as inorganic).
5. Inert bodies such as dust, hay, etc. (Mohan et.al 2000).

TYPES OF INFLAMMATION

The defense capacity of host as well as the duration of the response of the cell or tissue determines if the inflammation is acute or chronic.

A. ACUTE INFLAMMATION: It is the early body reaction of the body and lasts less than 2 weeks. This kind of inflammation resolves quickly followed by healing of the affected area. The three major characteristics of acute inflammation are:

1. There is buildup of plasma & fluid at affected area;
2. Platelets get activated in intravascular spaces; and
3. Neutrophils polymorph as inflammatory cells.

Acute inflammation is a swift self-limiting process characterized by increased movement of leukocytes and plasma into infected site, facilitated by vasoactive amines and eicosanoids ^[4]. The traditional traits of acute inflammation are redness, pain, heat, swelling and loss of function ^[5]. Pro-inflammatory and Inflammatory mediators such as leukotrienes & prostaglandins play a vital role in the primitive inflammatory response ^[6]. At times the acute inflammation progresses to chronic inflammation due to hyper secretion of pro-inflammatory mediators ^[7]. The acute inflammatory response of the host to any stimuli or agent is an unceasing process and can be divided into two events:

1. Vascular events
2. Cellular events

1. Vascular Events: The promptest response to tissue injury is modification in the microvasculature (arterioles, venules and capillaries). These modifications include: i. Hemodynamic changes and ii. Altered vascular permeability.

i. Hemodynamic Changes: There is an alteration in the vascular flow and diameter of small blood vessels in the injured tissue as an inflammatory response. The order of these alterations is as under: 1. Immediate vascular response no matter what type of cell injury is of transient vasoconstriction of arterioles. In cases of mild injury, the blood flow is re-established in 3-5 secs while in case of severe injuries the vasoconstriction can last for about 5 minutes. 2. After vasoconstriction follows persistent progressive vasodilatation of the arterioles, other components of the microcirculation like capillaries & venules are also affected but to a lesser extent. The change is observable within 1/2 an hour of injury. The increased blood volume in micro

vascular bed of the inflamed area is caused by vasodilation, which also causes redness and warmth at the location of inflammation. 3. Progressive vasodilatation elevates the local hydrostatic pressure which results in exudation of fluid into the extracellular space which causes swelling at the site of inflammation. 4. There is increased concentration of red cells which leads to retardation or stasis of microcirculation and thus, raised blood viscosity. 5. After stasis or retardation, there is leucocytic margination or change in the orientation of leucocytes (mainly neutrophils) along the vascular endothelium. The neutrophils stick to the vascular endothelium fleetingly, and then move and migrate through the gaps between the endothelial cells into the extravascular space. This progression is known as emigration. Lewis experiment demonstrates the Triple response or the hemodynamic changes in inflammation. Lewis used a blunt point to cause changes in the skin of inner side of forearm by firmly stroking it. The reaction hence observed is known as red line response or triple response & comprises of the following (Fig. 2): i) Red line appears almost instantly within a few seconds after stroking due to the local vasodilatation of venules and capillaries. ii) The adjacent arterioles vasodilate and cause flare, which is the bright reddish appearance or flush surrounding the red line. iii) Wheal is the oedema or swelling around skin that occurs due to exudation of fluid into the extravascular space. These features comply with the classical indications of inflammation—redness, heat and swelling, which is followed by fourth indication pain.

ii. Altered Vascular Permeability: There is accumulation of oedema fluid in and around the inflamed tissue, in the interstitial compartment which comes from blood plasma which escaped via endothelial wall of the peripheral vascular bed. Initially, vasodilatation and elevation in hydrostatic pressure lead to escape of fluid by transudation. But increased vascular permeability of microcirculation causes characteristic inflammatory oedema. Starling's hypothesis explains the appearance of inflammatory oedema or swelling due to increased vascular permeability of micro vascular bed.

Starlings hypothesis hypothesises that in normal conditions the fluid balance is maintained by two opposing sets of forces: i) Intravascular hydrostatic pressure and colloid osmotic pressure of interstitial fluid that causes the outward movement of fluid from microcirculation ii) Hydrostatic pressure of interstitial fluid & Intravascular colloid osmotic pressure that cause inward movement of interstitial fluid into circulation. The remaining fluid in interstitial compartment is drained away with help of lymph nodes & since this equilibrium is maintained normally there is no oedema. (Fig. 2, A)., The endothelial lining of microvasculature becomes leakier in case of inflamed tissues. The intravascular colloid osmotic pressure declines and osmotic pressure of the interstitial fluid increases which results in the excessive outward flow of fluid into the interstitial compartment which can be observed as exudative inflammatory oedema (Fig. 2, B).

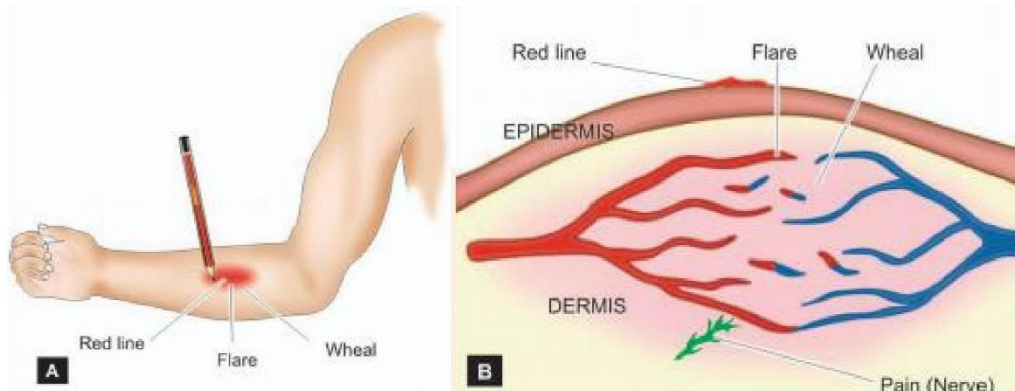


Figure 2 A) ‘Triple response’ elicited by firm stroking of skin of forearm with a pencil. **B)** Diagrammatic view of microscopic features of triple response of the skin.

2. Cellular Events: There are two processes that contribute to the cellular phase of inflammation: A. exudation of leucocytes; and B. phagocytosis.

i. Exudation of Leucocytes: On a cellular level one of the most important characteristic of inflammatory response is the movement of leucocytes from the lumen of microvasculature to the interstitial tissue. In acute inflammation, first line of defense are PMN’s or polymorphonuclear neutrophils, followed by macrophages and monocytes. The changes that lead to migration of leucocytes are as follows (Fig. 3):

a) Alteration in the formed constituents of blood: There is an increase in the rate of flow of blood due to vasodilatation in the affected area. But subsequently, there is stasis or slowing of the rate of flow of blood. Stasis or slowing affects normal axial flow of the stream of cells in blood. The normal axial flow in microcirculation comprised of RBCs, leucocytes and peripheral cell-free layer of plasma close to the wall of the vessel. The loss of plasma by exudation results in the peripheral plasma zone to become narrower while on the other hand the central stream of cells to become wider. This process is known as margination. Due to margination, neutrophils come nearer to the wall of vessel; this is known as pavementing.

b) Rolling and adhesion: Rolling Phase- In this phase neutrophils that were peripherally margined & pavemented slowly roll over the endothelial cells lining in the walls of vessel. Rolling phase is followed by Adhesion phase which involves formation of a transient bond between endothelial cells and white blood cells

or leucocytes. Rolling and adhesion phases are enabled by a number of cell adhesion molecules (CAMs) namely:

a.) Selectins b.) Cadherins c.) Integrins d.) Ig gene super family.

c) Emigration: The adhered neutrophils move along endothelial surface lining and find appropriate space and eject cytoplasmic pseudo pods. Afterwards, the neutrophils that was lodged between the endothelial cells and basement of the membrane damages the basement membrane locally with the secretion of collagenases and escapes into the extravascular space; this is known as emigration. The basement membrane which is damaged by neutrophils is repaired almost instantly. As previously stated, neutrophils are the dominant cells among all the cells that are secreted in acute inflammatory exudate in the first 24 hours. Macrophages and monocytes appear in the next 24- 48 hours. However, neutrophils are transitory while macrophages & monocytes survive much longer. The escape of erythrocytes (diapedesis) through gaps between the endothelial cells occurs simultaneous to emigration of leucocytes. Increased hydrostatic pressure as well as the defects in the endothelium after emigration are responsible for the passive process of diapedesis. Diapedesis thus gives hemorrhagic façade to the inflammatory exudate.

d) Chemotaxis: Chemotaxis is a chemo tactic factor-mediated process in which there is transmigration of leucocytes to the interstitial tissues after crossing several barriers (endothelium, basement membrane, perivascular myofibroblasts and matrix).

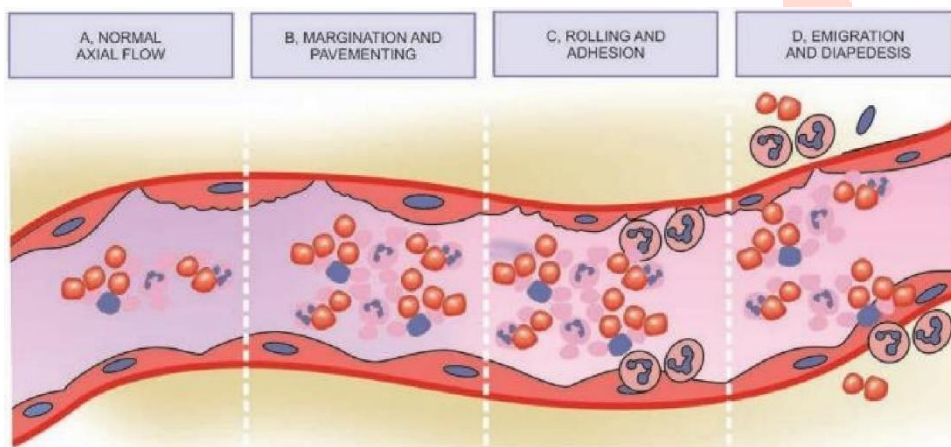


Figure 3: Sequence of changes in the exudation of leucocytes.

- A)** Normal axial flow of blood with central column of cells and peripheral zone of cell-free plasma. **B)** Margination and pavementing of neutrophils with narrow plasmatic zone. **C)** Adhesion of neutrophils to endothelial cells with pseudo pods in the intercellular junctions. **D)** Emigration of neutrophils and diapedesis with damaged basement membrane.

ii. Phagocytosis or cell eating: It is defined as the process of engulfment of a foreign particulate material by the cells (cell-eating). Phagocytes are the cells performing this function. There are two main types of phagocytic cells: i) Polymorphonuclear neutrophils (PMNs) which appear early in acute inflammatory response, sometimes called as microphages. ii) Circulating monocytes and fixed tissue mononuclear phagocytes, commonly called as macrophages [8].

B. CHRONIC INFLAMMATION: Chronic inflammation is the type of inflammation that occurs over a long course of time. It may happen if the causative agents are such that it produces chronic inflammation or when the causative agents or stimuli of acute inflammation persist over an extensive period. There is also chronic active in which there are acute exacerbations of inflammation throughout the course of disease. Presence of macrophages, plasma cells, lymphocytes, granulation tissue formation, and in unique circumstances as granulomatous inflammation are the major features of chronic inflammation. In addition, chronic inflammation can also lead to a number of diseases such as hay fever, cardiovascular diseases, pulmonary diseases, periodontitis, rheumatoid arthritis, arteriosclerosis, obesity, diabetes, neurologic diseases and cancer [9, 21].

MEDIATORS OF INFLAMMATION

The major endogenous chemical mediators of acute inflammation are: (Fig. 4).

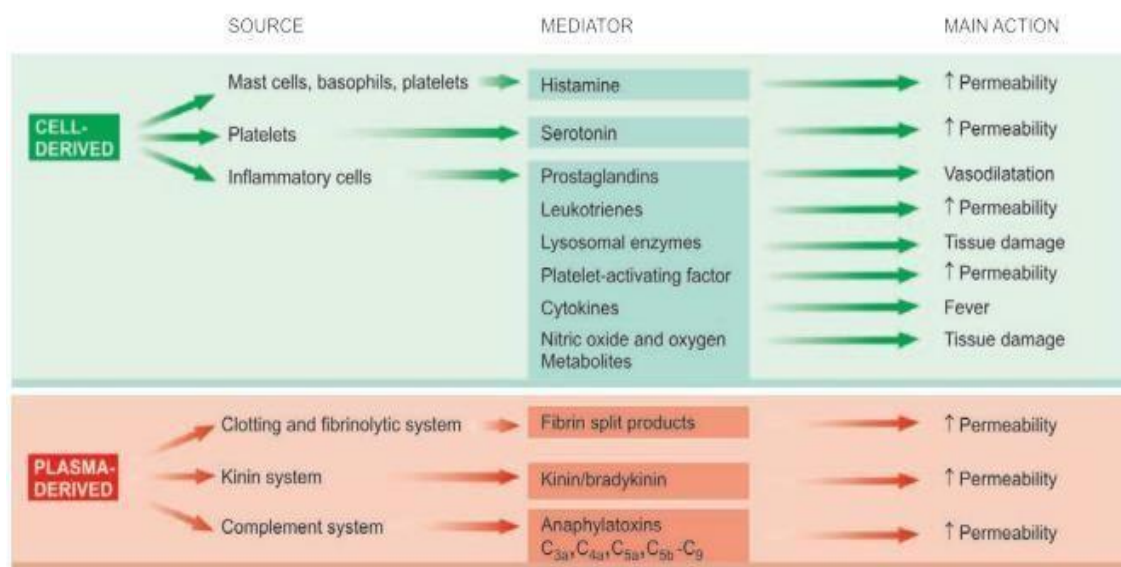


Figure 4: Chemical mediators of inflammation

1. Cell-Derived Mediators

1. Vasoactive amines (Histamine, 5-hydroxytryptamine (5-HT), neuropeptides)
2. Arachidonic acid metabolites (Eicosanoids)
 - a. Metabolites via cyclo-oxygenase (COX) pathway (PGs, thromboxane A₂, prostacyclin, resolvins)
 - b. Metabolites via lipo-oxygenase (LOX) pathway (5-HETE, leukotrienes, lipoxins)
3. Lysosomal components (from PMNs, macrophages)

4. Platelet activating factor
5. Cytokines (IL-1, TNF- α , TNF- β , IFN- γ , chemokines)
6. Free radicals (Oxygen metabolites, nitric oxide)

2. Plasma-Derived Mediators (Plasma Proteases)

1. The kinin system
2. The clotting system
3. The fibrinolytic system
4. The complement system

ANTI-INFLAMMATORY DRUG

There are a variety of drugs that are used for the resolution or treatment of acute as well as chronic inflammation. The drugs employed for the treatment of inflammation can be broadly classified as steroidal anti-inflammatory drugs and non-steroidal anti-inflammatory drugs (NSAIDs). Steroids are nothing but the hormones or the chemical compounds which are released by the adrenal cortex and have anti-inflammatory action by different mechanisms. Some steroidal hormones enhance gene expression of anti-inflammation, oxidative stress, phagocytosis, like glucocorticoids ^[10].

Another category of anti-inflammatory drugs is NSAIDs. NSAIDs show their effect by the inhibition of COX instead of phospholipase A2 and do not interfere with the actions of LOX ^[11]. NSAIDs inhibit both COX-1 and COX-2 hence hinder the production of prostaglandins. The major adverse effect is observed in the patients (about 1%) with chronic inflammatory ailment who take NSAIDs frequently is that they develop gastrointestinal (GI) complications such as mucosal damage and bleeding. ^[12]

The class of drugs that are classified as NSAIDs antipyretic, analgesic, and anti-inflammatory properties in varied measures. Narcotic drugs produce strong analgesia but depress the CNS and are abuse liable as well as may produce physical dependence. NSAIDs on the other hand does not do any of that and relatively produces weaker analgesia. Hence, they are also called non-narcotics, non-opioids or aspirin like analgesics. ^[13]

1. Nonselective COX inhibitors (traditional NSAIDs)

- ∑ **Salicylates:** Aspirin.
- ∑ **Propionic acid derivatives:** Ibuprofen
- ∑ **Fenamate:** Mephenamic acid
- ∑ **Enolic acid derivatives:** Piroxicam, tenoxicam.
- ∑ **Acetic acid derivatives:** Ketorolac, Indomethacine.
- ∑ **Pyrazolone derivatives:** Phenylbutazone, oxyphenbutazone

2. Preferential COX-2 inhibitors: Aceclofenac, Nimesulide, Meloxicam, Diclofenac

3. **Selective COX-2 inhibitors:** Celecoxib, Etoricoxib, parecoxib

4. **Analgesic-antipyretics with poor anti-inflammatory action**

∑ **Para aminophenol derivative:** Paracetamol

∑ **Pyrazolone derivatives:** Metamizol, Propiphenazone.

∑ **Benzoxazocine derivatives:** Nefopam

IMPORTANCE OF NATURAL DRUGS

There are a huge number of novel natural drugs that are gaining pharmacological recognition because of their wide range of effects in treatment of diseases like cancer. ^[14] Roughly 80% of the world's population especially in developing countries have a dependency on plant-derived medicines for their healthcare needs ^[15]. The scope of naturopathy & use of drugs from herbal resources is expanding in developed countries as the modern allopathic medicines are bound to have adverse effects. It is estimated that natural products make up approximately one fourth of the best-selling drugs worldwide ^[16]. In the current scenario almost 25% of all the prescribed drugs are derived or extracted from herbal resources and may be utilized as they are or with further modifications ^[17, 18] but then again innumerable pharmacologically active plant-derived compounds remain uncharted ^[19]. The anti-inflammatory activities of plants are due to the secondary metabolites. These bioactive compounds consist of steroids, polyphenols, alkaloids, terpenoids flavonoids, carotenoids, coumarins and curcumins ^[20].

Advantage of Herbal formulation

- ∑ Minimal cost
- ∑ Complete convenience
- ∑ Improved tolerance
- ∑ Additional protection
- ∑ Lesser adverse reactions
- ∑ Potency and efficiency are very high.

Disadvantages of Herbal formulation

- ∑ Not able to cure acute/rapid sickness and accidents
- ∑ Unsafe with self-dose regulation
- ∑ Standardization processes are complex

AYURVEDIC ANTI-INFLAMMATORY FORMULATION

Sandhi Guard: Sandhi Guard Cream and Sandhi Guard Oil are generally prescribed or taken in joints pain caused by inflammation. Sandhi Guard Cream /Oil act at COX-2 isoenzyme, it protects synovial fluid in the joints by inhibiting the oxidative depolymerization of hyaluronic acid and thus helps in effective anti-inflammatory and analgesic actions.



Ayusya Curcumin: Curcumin supplements contain majorly the phytoconstituents-curcuminoids; curcumin is majorly found in turmeric which is used as a spice and possesses innumerable benefits. It is known for its high antioxidant, anti-pyretic, analgesic as well as anti-inflammatory activity. The culmination of all these activities enable curcumin to benefit in joints well-being and mobility. Certain inflammation-modulating properties help relieve joint pain as well as is highly recommended for general wellness. Curcumin capsules are now even prescribed in alternative cancer treatments as an adjuvant therapy.



Nagarmotha Powder-Cyperus Rotundus: Nagarmotha powder is made from the roots of *Cyperus rotundus*. It is used as carminative, digestive, anti-inflammatory, hypolipidemic & also given in uterine health properties.



Shallaki Powder-Boswellia Serrata: Shallaki has been used for thousands of years to promote joint health. Shallaki powder is made from resin of *Boswellia serrata*. Anti-inflammatory properties The boswellic acids present in shallaki are responsible for the anti-inflammatory effects.



Haridra: Haridra or Haldi contains a pale yellow to orange-yellow volatile oil (6%) which is composed of a number of mono-terpenes and sesquiterpenes, including curcumin, zingiberene, and α - and β - turmerone, among others. The coloring principals (5%) are curcuminoids, 50–60% of which are a mixture of curcumin, mono-des-methoxy curcumin and bi-des-methoxy-curcumin. The curcuminoids contribute towards the anti-inflammatory, antioxidant, and cyto-protective properties of Haridra.



CONCLUSION

Acute inflammation is actually a good phenomenon as it prevents the microbial as well as foreign invading elements to enter the body but can be lethal in cases like an asthma attack. Inflammation is a contributor to a large number of chronic conditions like allergies, arthritis, pulmonary problems like COPD, autoimmune diseases like psoriasis, auto inflammatory diseases like Behcets disease. There is a growing market of drugs derived from natural resources in management of chronic inflammation as well as usage of these products along with NSAIDs in treatment of acute inflammation. One of the few major phytoconstituents that stand out

are polyphenolic pigments namely curcumin and gingerols. Their key features of the anti-inflammatory ayurvedic preparations is high tolerance & low toxicity.

There is wide prospective of ayurvedic preparations in the future- there is a huge scope in enhancing bioavailability of the drugs as well as novel dosage forms for these products. The goal of preparation should be such that it produces minimal adverse effects on GI while producing good anti-inflammatory and analgesic effect.

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