

Inflammation in Health and Disease: Novel Therapeutic Approaches

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Abstract:- Inflammation, which is regarded as an innate immune mechanism, is a part of the intricate biological reactions of a tissue to injury that shield the organ by eliminating harmful stimuli and starting the healing process. The majority of non-steroidal anti-inflammatory medications on the market work well for inflammatory diseases. Several compounds that disrupt the inflammatory response have also been identified in Indian Medicinal Plants (IMP). The multitude of side effects associated with the anti-inflammatory medications now on the market has a negative impact on human well-being. Advent of novel anti-inflammatory therapies such as herbal preparations, recent developments in the use of bioactive ingredients from herbal remedies to treat osteoarthritis and in the application of synthetic COX-2 inhibitors, chitosan as a therapy for oral mucosal irritation, improvement in the medication used to treat acute pancreatitis, extracellular vesicles from mesenchymal cells for the therapy of inflammation, oral colonic drug delivery methods for treating inflammatory bowel disease and combined targeting therapy for inflammatory bowel management will not only effectively manage the inflammation and its associated disorders but also helps to significantly improve the quality of life. Hence the current review reveals the recent advances in the field of inflammation and anti-inflammatory activity in detail.

Keywords:- Inflammation, Anti-Inflammatory Activity, Recent Advances.

I. INTRODUCTION

The term "inflammation," which comes from the Latin word "inflammare," which means "to set fire," refers to our body's defensive reaction to harmful stimuli like allergens and/or tissue damage [1,2]. An internal or external infection, irritation, or damage can cause inflammation, which is a localized reaction characterized by redness, warmth, swelling, and pain [3]. The intricate biological reaction of vascular tissues to damaging stimuli such as pathogens, irritants, or damaged cells is known as inflammation. It is an attempt on behalf of the organism to both eliminate harmful stimuli and start the tissue's healing process [4].

Inflammation, a component of the immune response, is crucial for protecting the body from pathogens like bacteria, fungus, viruses, and other parasites [5]. However, an unchecked inflammatory response is the primary cause of a wide range of disorders, including cancer, autoimmune diseases, allergies, cardiovascular dysfunction, metabolic syndrome, and metabolic disorders, which have a significant financial impact on both the individual and the larger society [6]. Infections by bacteria, viruses, or fungi that enter the body, settle in specific tissues, or move through the bloodstream typically result in inflammation [7-9]. Inflammation is primarily caused by both the innate and adaptive immune responses. The primary defense system against cancer cells and invasive microbes is the innate immune system, which is composed of mast cells, dendritic cells, and macrophages. More specialized lymphocytes, such B and T cells, are involved in the adaptive immune system [7,10,11]. Numerous treatments are available for managing and repressing inflammatory crises; examples of these include immunosuppressants, steroids, and non-steroid anti-inflammatory pharmaceuticals. However, several of these medications have negative side effects. In actuality, though, we want to use the lowest possible effective dose while maintaining the greatest level of efficacy and minimizing side effects. In order to maximize pharmaceutical efficacy and minimize undesirable side effects, we must therefore incorporate natural anti-inflammatory components into medicine therapy [6,12]. Inflammation can be caused by a wide range of substances, but the most common ones are infections brought on by bacteria, viruses, or fungi; wounds, cuts, or scrapes; damage to the body from foreign objects, such as a splinter or thorn in the finger; and the effects of toxic compounds, chemicals, or radiation [13].

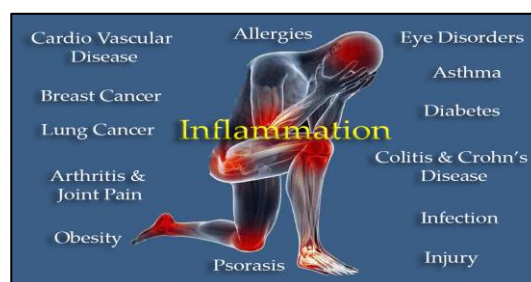


Fig 1: Inflammation

The two stages of the inflammatory process are acute and chronic, and both are recognized to be complex processes that are brought on by various chemical mediators, such as prostaglandins, leukotrienes, platelet activating factor, etc. [14]

A. Acute Inflammation:

It can manifest as redness, heat, or oedema, and it typically appears minutes or hours after tissue damage. It is a quick procedure. Fluids and plasma proteins exude from the wounded area, and leukocytes particularly neutrophils move in. The defensive mechanism that seeks to eradicate bacteria, viruses, and parasites benefits from this acute inflammatory response [15,16]. Acute inflammation goes away when the immune system successfully gets rid of harmful substances; if not, a chronic phase develops. Diseases including psoriasis, multiple sclerosis, rheumatoid arthritis, persistent asthma, and inflammatory bowel disease can all be brought on by cascades of inflammation [17].

B. Chronic Inflammation:

It is longer-lasting and associated with lymphocytes and macrophages present histologically, which causes fibrosis and necrosis of the tissue. Chronic inflammation promotes the development of degenerative illnesses, including multiple sclerosis, diabetes, aging, Alzheimer's, asthma, rheumatoid arthritis, atherosclerosis, heart disease, cancer, congestive heart failure, multiple sclerosis, gout, and other neurodegenerative CNS depressions. Additionally, aging-related muscle loss has been linked in part to chronic inflammation [18,19]. Vascular growth, fibrosis, tissue damage, and the presence of lymphocytes and macrophages are all linked to chronic inflammation. Chronic infections and inflammation have been found to be important risk factors for a number of cancer types in experimental and clinical research as well as epidemiological observations [17].

Monocytes/macrophages, neutrophils, platelets, and mast cells are among the cells that mediate them, along with plasma protein. A variety of receptors, including those involved in vascular muscle contraction, direct permeability, neutrophil chemotaxis, smooth enzymatic activity stimulation, induced pain, and mediated oxidative stress, are bound by chemical mediators, which are produced by viral or host proteins. When an inflammatory response occurs, a wide variety of inflammatory mediators are created and released. The pro- and anti-inflammatory groups of chemicals are typically used to categorize compounds that cause inflammation. Still, some mediators have both pro- and anti-inflammatory qualities, such as interleukin (IL)-12. Many inflammatory mediators and cellular pathways have been thoroughly investigated in relation to pathological diseases in humans. Two general categories of chemical mediators can be distinguished:

➤ *Mediators Generated from Cells:*

- Vasoactive amines (Histamine, neuropeptides, and 5-hydroxyhistamine)
- Arachidonic acid metabolites (Eicosanoids)
- ✓ Metabolite through cyclo-oxygenase pathway (Prostaglandins, thromboxane A2, Prostacyclin, resolvins)
- ✓ Metabolites metabolism through lipo-oxygenase pathway (5-HETE, leukotrienes, lipoxins)
- Lysosomal components (from PMNS, macrophages).
- Platelet activating factor
- Cytokines which include IL-1, TNF- α , TNF- β , TNF- γ , chemokines.
- Free radicals (oxygen metabolites, nitric oxide)

➤ *Mediators Derived from Plasma:*

- ✓ The Kinin system
- ✓ The Clotting system
- ✓ The Fibrinolytic system
- ✓ The Complement system [14]

II.RECENT ADVANCES IN THE FIELD OF INFLAMMATION AND ANTI-INFLAMMATORY ACTIVITY

❖ *Need for Development of New Anti-Inflammatory Agents*

The existing anti-inflammatory drugs reported to possess an array of side effects which adversely effects the quality of life of the mankind. Advent of new interventions for inflammation will not only effectively manage the inflammation and its associated disorders but also helps to significantly improve the quality of life. Recently attempts were being made to develop new avenues for controlling inflammation and finding new targets. Some of them were enlisted below:

A. Herbal Preparations:

In order to treat disease, maintain health, and reestablish the body's natural ability to defend, regulate, and repair itself, herbal therapy typically employs different plant components or botanical extract mixes [20] Several herbal anti-inflammatory remedies have been shown in a few

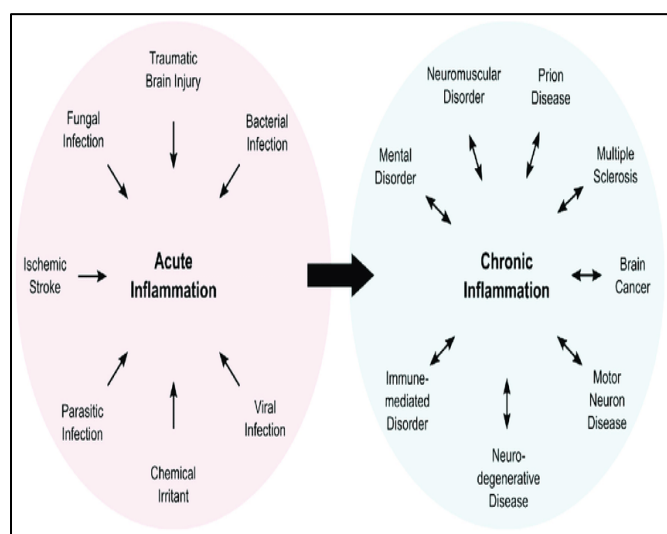


Fig 2: Acute and Chronic inflammation

Chemical mediators play a crucial part in the inflammatory process and are the substances that tend to steer it, which makes comprehending them comprehensive.

clinical investigations to be effective in treating inflammation with little adverse effects (see table 1). There are reports of major negative effects and interactions

between herbal medicines and synthetic preparations, as well as serious side effects from several of them [21].

Table 1: Clinical Trials on Selected Herbal Extract

S.no	Herbal formulation	Type of trial	Inference
1)	Ethyl acetate extract of purified (<i>gugulu commiphora mukul</i>)	Randomized and double-blind trial	No adverse effects during the analgesic and digestive phases
2)	Turmeric extract	Large, double-blind study	Osteoarthritis and rheumatoid arthritis
3)	Boswellia serrate extract	Randomized, double-blind, verum controlled, parallel group	Decreased inflammatory response when treating Crohn's illness
4)	White willow bark extract	A four-week crossover study that was double-blind and placebo-controlled	Treatment for acute episodes of persistent lower back pain in the short term.
5)	Ethanol extract of Devil's claw	Randomized, double-blind, parallel group study	Increased effectiveness in treating rheumatism, lower back pain, and knee and hip pain associated with osteoarthritis.

B. Recent Developments in The Use of Bioactive Ingredients From Herbal Remedies To Treat Osteoarthritis:

In recent research, 43 herbal substances with anti-OA properties were examined in relation to the treatment of osteoarthritis (OA). For the treatment of osteoarthritis (OA), articular cartilage, subchondral bone, synovial membrane, muscle, and circulatory system are the primary therapeutic sites of these molecules. There is potential for additional research and development as more than half of these compounds have good drug-like characteristics. Based on cheminformatics analysis, these constituents' pharmacokinetic behaviour still need refinement, which will help to improve their drug-like qualities. In the treatment of osteoarthritis, the use of herbal substances has advanced somewhat. Yet, the use of herbal remedies in OA is still

insufficient when compared to other types of arthritis, such as rheumatoid arthritis (RA). There are certain pathophysiological similarities between RA and OA, including oxidative stress, apoptosis, and inflammation. Thus, future studies will examine the possibility of anti-RA medications in the management of OA [22].

➤ *Heterocyclic compounds as anti-inflammatory agents*

Various families of heterocyclic compounds, including pyrazole, pyrimidine, benzimidazole, indole, and others, have been identified as heterocyclic anti-inflammatory drugs. These compounds can be classified as non-selective, COX-2 selective, LOX selective, or COX/LOX dual inhibitors. Table 2 lists the lead drugs with varying stages of clinical studies against inflammation [23].

Table-2: Clinical trials on novel compounds

S.no	Novel compound	Indications	Clinical trial reference
1	Bromfenac and Nepafenac	Extra (pulse) dose on the day of surgery for treatment of ocular inflammation associated with cataract surgery.	NCT0239465
2	Escitalopram	Analyse its impact on inflammation-causing depression	NCT02389465
3	Propofol	To assess how it affects the inflammatory process by regulating Apo A-1	NCT01115179
4	Captopril	Both alone and in conjunction with telmisartan to combat a patient's systemic inflammation while receiving hemodialysis	NCT01271478
5	Riluzole and Dexlansoprazole	Clinical advancements	NCT02074462 NCT01093755
6	Oral vitamin C	Evaluation in opposition to inflammation	NCT01356433

➤ *Developments in the Application of Synthetic COX-2 Inhibitors:*

The researchers found biological activity of synthetic COX-2, dual COX-2/lipoxygenase, and COX-2/soluble epoxide hydrolase hybrid inhibitors, which offer a number of benefits over NSAIDs like celecoxib, valdecoxib, and

rofecoxib such as anti-inflammatory activity, gastrointestinal protection, and a safer profile [24].

➤ *Chitosan as a Therapy for Oral Mucosal Irritation:*

Chitosan may lessen discomfort and promote better oral lesion healing in patients with oral mucositis (OM),

recurrent aphthous stomatitis (RAS), and denture stomatitis (DS). There is insufficient data to definitively support chitosan's superiority over other available treatments for oral mucositis, and their high risk of bias and poor quality exclude any suggestion about their therapeutic use [25].

➤ *New Lead Structures with Anti-Inflammatory Properties:*

Several alluring therapeutic targets, agents, and diagnostic indicators for the treatment of inflammatory disorders. The signalling pathway proteins, transcriptional factors (such as nuclear receptors), oncogenes, and lncRNA make up these biomarkers and targets. O-substituted tryptanthrin oxime derivatives are an example of a synthetic compound. Natural substances that are therapeutic agents include ginsenoside Rc and others. Along with defining complex gene-chemical connections, the researchers also outlined molecular pathways involved in the genesis of inflammatory illness. For the future management of inflammatory illnesses, our work may produce novel anti-inflammatory lead structures with established pharmacokinetics and efficacy in vivo. A more targeted and efficient approach to treating disease states would come from more research to determine which patients might benefit from a specific anti-inflammatory medication activity [26].

➤ *Improvements in the Medication Used to Treat Acute Pancreatitis:*

In order to validate their application in clinical practice, the discovered prospective therapeutics for acute pancreatitis (AP) are awaiting additional development and clinical evaluation from big trials. Future research efforts must center on these three critical areas of AP management: early diagnosis, risk stratification, and efficacious treatment strategies. These components are essential to changing the trajectory of the disease. In order to develop effective treatments for AP, therapeutic targets that influence illness severity and outcomes must be identified and assessed in the patient population through standardized clinical trials with well-defined objectives in the future [27].

➤ *Extracellular Vesicles from Mesenchymal Stromal Cells for the Therapy of Inflammation:*

Improved efficacy and robustness of EVs are vital, as is standardizing EV production and isolation procedures. MSC-derived extracellular vesicles (EVs) have been used as anti-inflammatory and pro-regenerative agents in a variety of inflammation-related conditions, including osteoarthritis, rheumatoid arthritis, Alzheimer's disease, cardiovascular disease, and preeclampsia. These EVs have regenerative effects on damaged or diseased tissues, especially when applied locally in large doses [28].

➤ *Oral Colonic Drug Delivery Methods for Treating Inflammatory Bowel Disease:*

The release of particular enzymes, reactive oxygen species (ROS), pH, or a combination of these causes an increase in the development of CDDS. With fewer side effects, these administration methods showed an improvement in therapy. In order to develop more targeted treatments, future approaches to treating this illness may

involve clarifying the molecular causes of IBD disorders and conducting additional in vivo tests to confirm the stability and specificity of the developed systems [29].

➤ *Combined Targeted Therapy for Inflammatory Bowel Disease Management:*

Treating IBD patients with combined biological or small-molecule medicines that target diverse sites creates a new therapeutic option. There is growing data on combination target therapy in two clinical scenarios: "double indication," with active EIMs, and "complex refractory IBD," when no mono therapeutic approach proved effective. For bio-naïve IBD patients, combination targeted therapy is not yet advised outside of clinical trials. It's uncertain if combination therapy should be used as maintenance therapy or just during the induction phase. Recent results from the VEGA trial suggested that golimumab and guselkumab, two innovative biologics, might be used together as a new kind of treatment for individuals with high-risk UC [30].

III. CONCLUSION

Established therapeutic anti-inflammatory drugs possess few adverse effects which slowly discriminating its use. Hence it is concluded that few recent advances in the therapy of inflammation might reduce the established side effects with more efficacy and long-term use. Further studies are required to provide a better mechanistic view.

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