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Herbal Medicines As Natural Anti-Inflammatory Agents: A Comprehensive Review of Phytochemicals and Mechanisms of Action

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Abstract : *Inflammation is an adaptive biological reaction to noxious stimuli such as microbes, toxic chemicals and bodily injuries; however, continued activation of the inflammatory process leads to various diseases such as arthritis and heart ailments. Conventional anti-inflammatory medications, including steroids and non-steroidal anti-inflammatory drugs, work effectively, but their side effects preclude extended administration. This article explores the possibility of using natural plant-based chemicals as alternative treatments. The biological activity of natural molecules such as phenolic compounds, alkaloids and flavonoids helps to reduce inflammation by blocking the cyclooxygenase and lipoxygenase signaling pathways and by reducing the expression of pro-inflammatory factors such as interleukins and tumor necrosis factor-alpha. This review describes the major classes of phytochemicals, the biochemical mechanisms of inflammation, and the anti-inflammatory evidence for ginger, turmeric, neem, aloe vera, ashwagandha, tulsi and moringa. The advantages of herbal anti-inflammatory agents, namely multi-component action, fewer side effects and wide availability, are discussed together with their limitations, namely variable composition, non-standardized dosage and a lack of clinical data. Plant-derived compounds therefore appear to be promising candidates, but more extensive clinical studies are required to validate their medical potential.*

Keywords: Inflammation, Medicinal plants, Phytochemicals, Flavonoids, Herbal medicine, Natural products.

I. INTRODUCTION

Definition and causes

Inflammation can be described as the local reaction of the living tissue of mammals to injury by any means. It is a defense mechanism of the body aimed at eliminating or restricting the injurious agents and then disposing of the dead cells and tissues. The agents causing inflammation may be as follows:

1. Infectious agents, including microorganisms, their toxins and other organisms.
2. Immune agents, including cell-mediated and antigen-antibody reactions.
3. Physical agents, such as heat, cold, radiation and mechanical injury.
4. Chemical agents, including organic and inorganic poisons.
5. Inert substances, including foreign objects.

Inflammation is therefore distinct from infection; it is a protective mechanism in response to various causative agents. The four classical signs of inflammation were enumerated by the Roman writer Celsus: *rubor* (redness), *tumor* (swelling), *calor* (heat) and *dolor* (pain). A fifth sign, *functio laesa* (loss of function), was added later by Virchow. The word inflammation is derived from a Latin word meaning burning; this terminology was introduced in ancient times, but burning is now known to be only one of the signs of inflammation.[1]

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Inflammation is the body's defense mechanism against infection by microbes such as bacteria and viruses. It is categorized into two types: acute, the short-term and local response of the body, and chronic, the long-term response. The process of inflammation is mediated by cytokines such as interleukins (ILs) and tumor necrosis factor (TNF), and by non-cytokine mediators such as prostaglandin E2 (PGE2). Steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressant drugs are the common anti-inflammatory drugs, but their administration is always constrained by side effects.[2]

Recent research shows an increasing tendency to use natural anti-inflammatory agents instead of synthetic ones owing to their fewer side effects. Natural substances have effectiveness similar to that of NSAIDs but a safer profile. This literature review aims to examine the therapeutic value of natural substances, the differences between natural and synthetic agents, and the effectiveness of natural anti-inflammatory agents.[2]

Inflammation is an adaptive reaction of the body's immune system against damaging agents such as infection, cell injury, toxins or exposure to radiation. The key aim of inflammation is to remove the stimulus and facilitate recovery. While inflammation is essential for the healing process, if it is not controlled it may trigger chronic diseases such as rheumatoid arthritis, osteoarthritis, inflammatory bowel syndrome, psoriasis and atherosclerosis. Typical symptoms of inflammation are heat, swelling, pain, stiffness and loss of movement. Antiinflammatory medicines, including aspirin and NSAIDs, are prescribed to treat inflammation.

[3]

II. LITERATURE SURVEY

Devi et al.[1] described inflammation as a basic biological process in response to harmful factors such as pathogens, injured cells or irritants. Akhter et al.[2] reported that inflammation is a protective mechanism against tissue injury which, depending on its intensity, could cause different disease conditions. Krishna Reddy et al.[3] noted that inflammation is a major component of the response mechanisms of the body against any form of disruption or disease, and that many drugs have been developed from plant-derived products. Shin et al.[4] reported that phytochemicals show anti-inflammatory effects in various *in vitro* and *in vivo* models, including inflammation models, and described inflammation as the biological process by which the body fights exogenous factors such as infection and trauma.

Sethi and Bhadra[5] reviewed the holy basil tulsi (*Ocimum sanctum* L.), which is indigenous to India and greatly valued for its medicinal properties in the Ayurvedic and Siddha systems of medicine. Several *in vitro*, *in vivo* and clinical studies have supported its adaptogenic, antimicrobial, anti-inflammatory and cardioprotective effects. Lanka[6] reviewed *Aloe vera*, a succulent plant of dry and subtropical regions that is popular for its medicinal properties and is widely used in the Ayurvedic, homoeopathic and allopathic systems of medicine.

PHYTOCHEMICALS RESPONSIBLE FOR ANTI-INFLAMMATORY ACTIVITY

Inflammation acts as an important body defense system against disease-causing microbes, but chronic inflammation leads to various chronic diseases including cancer, autoimmune diseases, metabolic disorders and neurodegenerative diseases. The long-term administration of conventional anti-inflammatory medications is restricted by their side effects and expense. There is therefore increasing attention to natural substances derived from plants as more effective and economical substitutes. These plant-based chemicals show considerable antiinflammatory properties through different pathways.[4]

Major classes of phytochemicals

Plants contain diverse secondary metabolites, the vast majority of which do not appear to be involved in plant growth and development. According to their metabolic pathways, phytochemicals can be grouped into carotenoids, phenolics, alkaloids, nitrogen-containing compounds and organosulfur compounds (Fig. 1). One of the crucial classifications of phytochemicals was illustrated by Liu, who grouped almost all the phytochemicals found in the diet together with their major chemical constituents.[7] Although phytochemicals are known for their complex chemical structures and biosynthetic pathways, they were long considered to have little biological importance and did not attract much attention

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from plant biologists. Organic chemists, on the other hand, have studied these phytochemicals since the 1850s. Many scientific studies now show that phytochemicals help protect plants from various forms of illness and disease.[7]

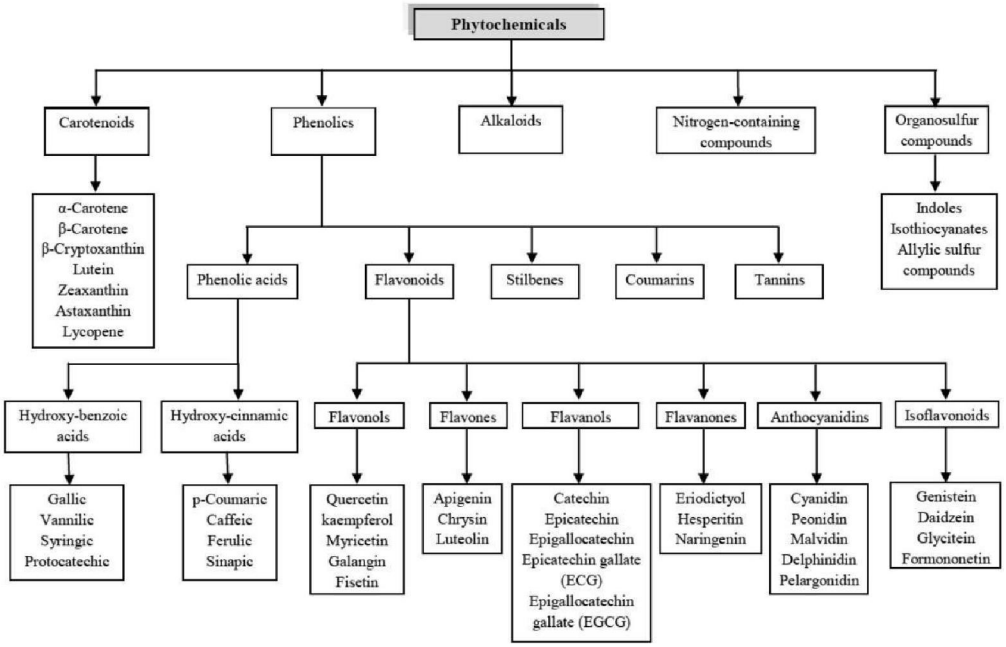


Fig. 1: classification of dietary phytochemicals

MECHANISM OF ACTION OF ANTI-INFLAMMATORY AGENTS

Multiple pathways for inflammation

Inflammation is a multi-step chemical response consisting of biochemical pathways such as prostaglandin production, interleukin activity, chemotoxins, the action of adhesion-protein receptors and platelet-activating factors. All of these contribute to inflammation because they act as chemotactic agonists and attract inflammatory cells to the injured site.

Initiation of inflammation

The process of inflammation starts when a stimulus acts on the cell membrane owing to stress, injury or any other external or internal factor. This stimulates enzymes and activates the inflammation cascade reaction.

Phospholipase A activation and arachidonic acid release

The stimulus activates phospholipase A enzymes, which catalytically split membrane phospholipids to produce arachidonic acid. This is important because arachidonic acid is an intermediate compound that gives rise to inflammatory mediators.

Formation of inflammatory mediators through the cyclooxygenase and lipoxygenase pathways

Arachidonic acid is converted into prostaglandins (PGE2, PGH2) and leukotrienes (LTB4, LTC4) through the actions of cyclooxygenase (COX) and lipoxygenase (LOX), respectively.

[1]

Action of cytokines in inflammation

Cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) serve as mediators of inflammation. They are produced by monocytes, macrophages, adipocytes and other cells, mediate the inflammatory response, and are mostly involved in immune responses against bacterial toxins such as lipopolysaccharides (LPS).

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Effects on gene expression and vasculature

IL-1, TNF-α and other cytokines (for example, interleukin-8) and growth factors increase the expression of certain genes and promote protein synthesis, thus enhancing inflammation. Other mediators, such as prostaglandins (PGE2, PGI2) and nitric oxide, cause vasodilation, increased blood flow and increased vascular permeability, enabling inflammatory mediators (histamine, bradykinin) to act effectively.

Leukocyte migration

Leukotriene B4 (LTB4) is a powerful chemo-attractant that recruits polymorphonuclear leukocytes (PMNs), eosinophils and monocytes. Its action results in their adherence to the endothelium, recruitment, degranulation and synthesis of reactive compounds.[3]

IMPORTANT HERBAL DRUGS WITH ANTI-INFLAMMATORY ACTIVITY

Ginger (*Zingiber officinale*, Zingiberaceae)

Ginger is usually employed for improving digestion (indigestion, constipation and ulcers) (Fig. 2). Shimoda et al. examined the anti-inflammatory effect of *Zingiber officinale* by preparing a 40% ethanolic extract from dried red ginger and testing it in acute and chronic inflammation models. The extract produced significant inhibition of both acute and chronic inflammation.[3]



Fig. 2: *Zingiber officinale* (ginger)

Turmeric (*Curcuma longa*)

For many years, turmeric (*Curcuma longa*) has been known as a medicinal plant (Fig. 3). It is a member of the ginger family and is usually used for coloring foods and in curry powders. Turmeric has historically been used to treat several disorders such as liver disorders, indigestion, dermatological problems and injuries. Its biological activity is generally associated with curcumin, the major active compound present in it.[8]



Fig. 3: turmeric (*Curcuma longa*)

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Neem (*Azadirachta indica*)

The anti-inflammatory effects of the carbon tetrachloride extract and of the constituent azadiradione isolated from the fruit skin of *Azadirachta indica* were evaluated at two doses (50 and 100 mg/kg body weight) in the carrageenan-induced paw edema model (Fig. 4). Animals receiving the 100 mg/kg dose of the extract and of azadiradione showed significant anti-inflammatory and antinociceptive effects. This investigation supports the traditional use of the plant by the tribal population for wounds, burns and injuries. Neem is also reported to have anti-arthritic, antipyretic, hypoglycemic, anti-gastric ulcer, antifungal, antibacterial and antitumor effects.



Fig. 4: neem (*Azadirachta indica*)

Aloe vera

The anti-inflammatory action of *Aloe vera* is achieved by inhibition of the cyclooxygenase pathway, resulting in reduced synthesis of prostaglandin E2 from arachidonic acid (Fig. 5). A new anti-inflammatory agent, C-glucosyl chromone, has recently been discovered in aloe gel extracts. Langmead et al. reported an anti-inflammatory effect of *Aloe vera* gel in human colorectal mucosa using an *in vitro* method. Reuter et al. described the anti-inflammatory effect of 97.5% *Aloe vera* gel using the ultraviolet erythema test, and Lee et al. studied the anti-inflammatory effect of *Aloe vera* adventitious root extracts, as summarized by Lanka.[6]



Fig. 5: *Aloe vera*

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***Ashwagandha* (Withania somnifera)**

Withania somnifera (L.) Dunal, belonging to the family Solanaceae, is commonly known as ashwagandha, a Sanskrit name owing to its extensive use in Indian folk medicine (Fig. 6). *W. somnifera* has earned an enviable place in Ayurvedic medicine as a Rasayana plant, that is, a plant whose rejuvenating qualities help maintain the well-being of the entire body system. It is also classed as a "plant adaptogen", meaning that it maintains the homeostasis of the entire body system not through a single pharmacological action but through multiple actions.[9]



Fig. 6: ashwagandha (*Withania somnifera*)

***Tulsi* (Ocimum sanctum)**

Tulsi (*Ocimum sanctum* L.), popularly called holy basil, is a highly revered medicinal and aromatic plant belonging to the family Lamiaceae and occurring naturally in the Indian subcontinent (Fig. 7). It is one of the most important medicinal plants in Ayurveda, in use for more than 3000 years, and is therefore known as the "Elixir of Life". Traditionally, tulsi has been employed to relieve conditions such as bronchitis and fever (pyrexia). Botanically, tulsi is an erect, aromatic shrub growing 30-60 cm tall, with hairy stems and aromatic green leaves. It is also of immense cultural and religious significance in Hinduism. Pharmacologically, tulsi possesses adaptogenic, antimicrobial, anti-inflammatory and respiratory properties.[5]



Fig. 7: tulsi (*Ocimum sanctum*)

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Moringa (*Moringa oleifera*)

Recent pharmacological studies on *Moringa oleifera* have shown strong anti-inflammatory and antinociceptive effects, mostly attributed to its high levels of antioxidants (Fig. 8). In various studies, extract preparations of different plant parts, especially leaves and roots, were effective in regulating the biological reaction to harmful insults such as pathogen invasion and cellular injury. This is achieved by inhibiting the production of inflammatory markers such as TNF-α and interleukin-6 (IL-6). As a result, pain, heat and swelling, the classic signs of acute inflammation, are prevented.[10] A systematic review of the pharmacological activities and safety of *Moringa oleifera* is also available.[11]



Fig. 8: moringa (*Moringa oleifera*)

III. ADVANTAGES AND LIMITATIONS OF HERBAL ANTI-INFLAMMATORY DRUGS

Advantages

1. Multi-component action: herbal drugs usually contain a mixture of components which act together to modulate several aspects of the inflammatory response.
2. Fewer side effects: as opposed to chemical drugs, herbal drugs usually have few side effects and can therefore be taken continuously.
3. Availability: herbal drugs are easily accessible and inexpensive in many regions.

Limitations

- Variable composition: the content of bioactive ingredients may differ between herbbased formulations depending on parameters such as the type of plant, cultivation practices and processing techniques, thus affecting their medicinal properties.
- Non-standardized dosage and quality control: most herbal supplements lack proper standardization of dosage, posing a risk to their quality and safety.
- Lack of clinical data: although several natural compounds have demonstrated promising results in preclinical tests, there is an urgent need for more extensive clinical studies to validate their medical potential.

IV. CONCLUSION

Inflammation is an important self-defense response in the body; however, when it persists or goes unchecked, it contributes to the emergence of several chronic illnesses. Even though existing pharmacologic anti-inflammatory medicines work well in controlling inflammatory disorders, their prolonged administration can be constrained by side effects. This article emphasizes the increasing significance of phytochemicals as a substitute choice owing to their anti-

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inflammatory properties. Plant-derived products such as ginger, turmeric, neem, aloe vera, ashwagandha, tulsi and moringa have potent anti-inflammatory properties through numerous modes of action.

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