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A REVIEW ON ANTI-INFLAMMATORY ACTIVITY OF NATURAL PRODUCTS: CURRENT TRENDS AND FUTURE PERSPECTIVES

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ABSTRACT: Inflammation is an essential component of the innate immune response and serves as a protective mechanism against harmful stimuli such as physical injury, infectious agents, toxic chemicals, and allergens. Although beneficial in acute phases, uncontrolled or chronic inflammation is associated with the development of numerous diseases, including rheumatoid arthritis, cardiovascular disorders, obesity, and cancer. During inflammatory responses, mediators such as interleukins, interferons, and tumor necrosis factor-α (TNF-α) are released, producing the characteristic signs of redness, pain, heat, swelling, and loss of function. Natural products have long played a significant role in managing inflammatory conditions, even with the availability of synthetic agents such as NSAIDs. Many medicinal plants contain bioactive secondary metabolites capable of modulating key steps in the inflammatory cascade by targeting pathways including COX, LOX, NF-κB, and oxidative stress. Numerous studies continue to highlight the anti-inflammatory potential of plant extracts, essential oils, and isolated phytochemicals. This review compiles recent findings on these natural agents, emphasizing their mechanisms of action and relevance in inflammation-associated metabolic disorders. It also provides updated insights on traditionally used plants that have only recently been scientifically evaluated for their anti-inflammatory properties.

INTRODUCTION: The term inflammation, originating from the Latin word inflammare meaning to set on fire, refers to a highly coordinated biological response triggered when vascular tissues encounter harmful stimuli such as pathogens, irritants, allergens, or injured cells. This complex process involves numerous chemical mediators and plays a vital protective role by eliminating the harmful agent and initiating tissue repair. For thousands of years, medicinal plants and herbal formulations have remained an integral part of traditional healthcare systems across the world.

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According to the World Health Organization, nearly 80% of the global population still depends on traditional medicine including herbal preparations for primary healthcare. Modern research continues to validate these practices by identifying plant-derived bioactive molecules capable of influencing a variety of physiological pathways. Although only a small proportion of the estimated 500,000 plant species on Earth has been scientifically explored, many already show significant anti-inflammatory properties.

Plants naturally produce a diverse array of secondary metabolites such as flavonoids, alkaloids, terpenoids, and phenolic compounds as a defence against environmental stress and microbial attack. These phytochemicals exhibit multiple biological effects, with anti-inflammatory activity being particularly noteworthy. While inflammation is essential for host defence, persistent or chronic

inflammation contributes to the progression of several disorders, including metabolic diseases, diabetes, cardiovascular conditions, and cancer.

Due to the limitations, adverse reactions, and long-term risks associated with conventional synthetic anti-inflammatory drugs, interest in plant-based therapeutic alternatives has grown substantially. Recent scientific evidence also highlights the role of the gut microbiota in transforming plant metabolites into smaller, more active compounds, which may enhance their therapeutic potential. This emerging insight offers promising avenues for the discovery and development of safer, naturally derived anti-inflammatory agents.

The long-term use of synthetic anti-inflammatory medications is often limited by adverse effects, driving increasing interest in plant-based therapeutic alternatives. Recent studies indicate that metabolites derived from medicinal plants may also interact with the gut microbiota, resulting in the formation of smaller, biologically active compounds that can amplify therapeutic benefits. This relationship between phytochemicals and gut microorganisms opens new avenues for identifying naturally derived anti-inflammatory agents.

For centuries, plants have been integral to human healthcare. As part of their defense mechanisms against pathogens and environmental stresses, plants synthesize a wide range of secondary metabolites with diverse biological activities. Many of these compounds exhibit significant anti-inflammatory properties. Inflammation itself is a highly conserved protective response essential for survival. It consists of a series of coordinated events aimed at removing harmful stimuli whether infectious agents, toxins, physical injuries such as burns or radiation, or chemical irritants and initiating tissue repair. The classical signs of inflammation include redness, swelling, heat, pain, and functional impairment.

Under normal conditions, these processes restore tissue homeostasis. However, when inflammatory mediators continue to be produced excessively or when harmful signaling pathways remain activated, inflammation becomes chronic. Persistent, low-grade inflammation is associated with numerous long-term health conditions, including metabolic disorders such as obesity and diabetes, as well as cancer and cardiovascular diseases. Given these challenges, the development of next-generation therapeutic agents that effectively support the resolution of inflammation is of great importance. Medicinal plants, rich in bioactive secondary metabolites, represent a promising source for such drug discovery efforts.

Another emerging area of interest involves the interaction between plant-derived compounds and the gut microbiota. Certain microbial species are capable of metabolizing complex phytochemicals such as tannins and anthocyanins into smaller, more bioavailable molecules with enhanced biological activity. These microbial metabolites may also help regulate gut microbial balance, offering additional benefits in the prevention of metabolic disorders.

Anti-Inflammatory Drugs: Anti-inflammatory drugs can interfere in the pathophysiology of inflammation, seeking to minimize tissue damage and provide greater patient comfort. The major classes of anti-inflammatory agents are the glucocorticoids and non steroidal anti-inflammatory drugs (NSAIDs). Fundamentally these differ in their mode of action. In short, glucocorticoids act by inhibiting prostaglandins and proteins involved in inflammatory processes, such as corticosteroids, which among other indications are used in treatment for asthma and autoimmune inflammatory response. Non-steroidal drugs, on the other hand, have an inhibitory action through the enzyme cyclooxygenase and are indicated for moderate and mild pain and body temperature control. An example of a non-steroidal drug is acetylsalicylic acid

NSAIDs are the most commonly used drugs worldwide, utilized to treat acute and chronic pain resulting from an inflammatory process. NSAIDs encompass a range of agents and, in general, all their effects are related to the inhibition of COX action in the production of prostaglandins and thromboxanes. The main mechanism of action of NSAIDs is the inhibition of COX, both central and peripheral, interfering in the conversion of arachidonic acid to prostaglandins E2, prostacyclins, and thromboxanes.

Enzymes related to the action of NSAIDs can be divided into COX-1 and COX-2, acting in different regions. COX-1 appears in most cells, even fetal and amniotic fluid, and participates in physiological effects, such as regulatory and protective effects. On the other hand, COX-2 is activated by inflammation and proinflammatory cytokines.

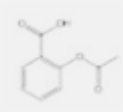
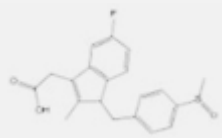
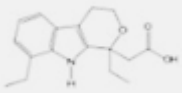
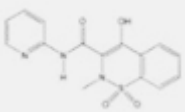
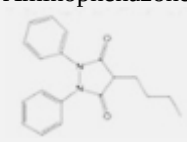
There are several ways to classify NSAIDs; according to COX-2 inhibitory potency over COX-1, concentration to achieve clinical effects, among others. NSAIDs can be classified into non-selectiveNSAIDs (ketoprofen, aspirin, naproxen, flunixin, meglumine, and others), preferential COX-2 inhibitors (meloxican, etodolac, nimesulide), and highly selective COX-2 inhibitors (coxib). Most of the side effects are related to the inhibition of COX-1 due to its performance in several systems related to cell cleansing. Besides, NSAIDs can also be classified according to their chemical structure.

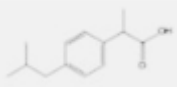
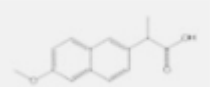
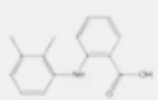
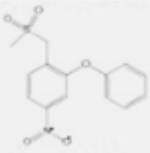
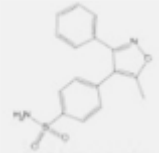
Structurally, COX-2 selective drugs contain sulfonamide groups or sulfones, responsible for the selectivity of the enzyme and do not have a carboxylic group and, therefore, they can selectively target the COX-2 enzyme. They have little water solubility, which hinders parenteral administration.

Acetylsalicylic acid (ASA) is one of the most widely used drugs in the world. It is used as an analgesic, antipyretic, and anti-inflammatory. This drug also has antiplatelet or anticoagulant effects and is used to prevent heart attacks, strokes, and blood clots. However, its use can also lead to exacerbated respiratory tract disease and cancer historically; non-steroidal anti-inflammatory drugs, such as acetylsalicylic acid (Aspirin®), indomethacin, ibuprofen, and piroxicam have been used clinically for the treatment of inflammation due to their suppression of the effects of COX activity.

However, these traditional NSAIDs act in a non-selective manner inhibiting both forms of COX and have also demonstrated side effects. Specific modalities of anti-inflammatory effects and side effects are associated with the existence of two COX isoforms.

TABLE 1: CLASSIFICATION OF NSAID'S

Salicylates	Indoleacetic acid derivatives	Aryl acetic derivatives	Enolic Acids	
Acetylsalicylic acid	Acemethacin	Aceclofenac		Pyrazolones:
Lysine clonixinate	Glucamethacin	Diclofenac	Oxicans	Phenylbutazone
Benorilate	Indomethacin	Etodolac	Droxicam	Mofebutazone
Diflunisal	Proglumethacin	Fentiazac	Meloxicam	Oxyphenbutazone
Salicylamide	Oxamethacin	Ketorolac	Pirooxicam	Kebuzone
Etersalate	Sulindac	Bufexamac	Tenoxicam	Metamizole (Dipyrone)
Salsalate or salicylic acid	Tolmetin	Lonazolac	Oxaprozin	Feprazone
	Difenpiramide	Alclofenac	Lomoxicam	Nifenazone
		Zomepirac		Suxibuzone
				Aminophenazone
				
Arylpropionic Derivatives		Phenemates	Others	
Butibufen	Ketoprofen		Nabumetone	
Phenoprofen	Dexetoprofen		Glucosamine	
Phenobufen	Pyprophene		Diacerhein	Coxibs
Flurbiprofen	Indoprofen	Meclofenamic acid	Nimesulide	Celecoxib
Benoxaprofen	Naproxen	Mefenamic acid	Proquazone	Rofecoxib
Suprofen	Oxaprozin	Flufenamic acid	Azapropazone	Parecoxib
	Tiaprofen	Tolipanic acid	Benzidamine	Valdecoxib
		Niflumic acid		

Ibuprofen Ibuproxam	Dexibuprofen Phenoprofen Flunoxaprofen Alminoprofen	Etofenamate	Orgotein Feprazone Morniflumato Tenidap Glucosaminoglycan	Etoricoxib 4-Aminophenol Paracetamol (Acetaminophen
				
(S)-Ibuprofen	Naproxen	Mefenamic acid	Nimesulide	Valdecoxib

Miscellaneous Anti-Inflammatory Agents:

Algae: *Spirulina fusiformis* (Oscillateriaceae), known as "blue green algae", are important due to their AIA and allied therapeutic uses like analgesic and antiarthritic actions. When studied for its AIA in rats by measuring the paw volumes, body weights as measures of inflammation showed promising results in terms of reduction in body weight as compared to adjuvants.

Methanolic extract of *Cheilanthes farinosa* (Adianthaceae), a fern grown indigenously in southeast Africa, showed stronger value of AIAs due to the presence of rutin, cinnamic acids, caffeic acid and its quinic acid derivative, chlorogenic acid.

Research work in the recent years has led to the discovery of "marine red algae" obtained from Neorhodomela aculeate. When investigated for their anti-inflammatory and antioxidant properties, they showed promising value with neuronal and microglial cells. Similarly, other actions of the extract include potent neuroprotective effect elicited by glutamate-induced Neurotoxicity and inhibition of ROS expression in murine Hippocampal HT22 cell line, and inhibition of H_2O_2-induced lipid peroxidation in rat brain homogenates.

Marine Plants: Pseudopterosins are newer class of natural products isolated from *Pseudopterogorgia elisabe*, which have been characterized as diterpene pentose glycosides. The pseudopterosins possess considerable analgesic activity and AIA.

In search for new biologically active natural products, a number of isolates derived from algae and sponges were evaluated. Of these, palisol and dictyol C demonstrated the most potent Inhibition of COX2.

Methanolic extract of the sea grass *Zostera japonica* has shown AIA. Its hexane, dichloromethane, acetate and water extracts showed the highest capacity to inhibit expression in LPS stimulated J774A cell line due to the presence of palmitic acid, Palmitic acid methyl ester, linoleic acid methyl ester, oleic acid methyl ester and linoleic acid.

Kang *et al,* showed that dichloromethane and ethanol extracts of the brown seaweeds, *Sargassum fulvellum* and *Sargassum thunbergii*, when examined for analgesic, anti-inflammatory and other allied activities showed reduced signs of inflammation in mice.

Natural Products that shows Anti-Inflammation Activity:

FIG. 1: TURMERIC (*CURCUMA LONGA*)

- Turmeric (*Curcuma longa*)
- Active compound: Curcumin
- Mechanism:
- Inhibits COX-2, LOX, TNF-α, IL-1β, NF-κB
- Use: Arthritis, skin inflammation, digestive inflammation.

FIG. 2: GINGER (*ZINGIBER OFFICINALE*)

- Active compounds: Gingerols, Shogaols
- Mechanism:
- Inhibits prostaglandin and leukotriene synthesis
- Use: Musculoskeletal pain, nausea-related inflammation.

The Anti-Inflammation Activity of Plant Products:

FIG. 3: *PORTULACA OLERACEA*:

- Family: Portulacaceae.
- Major Method of Testing: Hot-plate method for assessing Analgesia activity; carrageenan-Induced paw edema.
- Main Effects on Inflammation: A significant reduction in paw edema and an Analgesic effect, similar to that of diclofenac.

FIG. 4: *SALVIA OFFICINALIS*

- Family: Lamiaceae.
- Major Method of Testing: Croton oil-induced ear edema in Mice.
- Main Effects on Inflammation: n-Hexane and CHCl3 extracts prominently decreased ear edema; MeOH extract had a weak effect while the essential oil was ineffective; the significant effect of ursolic Acid was 2-fold stronger in reducing the edema than indomethacin.

FIG. 5: *CORCHORUS OLITORIUS*

- Family: Malvaceae.
- Major Method of Testing: Yeast-induced pyrexia and Carrageenan-induced paw edema and in rats.
- Main Effects on Inflammation: A significant reduction in paw edema which was stronger than that of aspirin; attenuation of hyperthermia (fever).

CONCLUSION: Inflammation is a complex physiological process essential for host defense, yet its dysregulation contributes to the development of numerous chronic disorders, including arthritis, diabetes, cardiovascular diseases, and metabolic syndromes. Although synthetic anti-inflammatory drugs such as NSAIDs and corticosteroids remain widely used, their long-term use is frequently associated with significant adverse effects. This has intensified scientific interest in natural products as safer and more sustainable therapeutic alternatives.

The evidence reviewed in this paper highlights the remarkable anti-inflammatory potential of medicinal plants, marine organisms, algae, and isolated phytoconstituents. These natural agents exert their effects through multiple mechanisms,

including inhibition of COX and LOX enzymes, suppression of pro-inflammatory cytokines (TNF-α, IL-1β), modulation of NF-κB and MAPK signaling, and potent antioxidant activity. Plants such as **Curcuma longa**, **Zingiber officinale**, **Portulaca oleracea**, **Salvia officinalis**, and marine-derived compounds demonstrate significant activity comparable to standard anti-inflammatory drugs in various experimental models.

Despite the promising findings, many natural products remain insufficiently explored, especially regarding their molecular mechanisms, bioavailability, and clinical efficacy. Future research should focus on advanced analytical methods, in vivo studies, and well-designed clinical trials to validate their therapeutic potential. Additionally, the interaction between natural compounds and gut microbiota presents an emerging field that may further enhance the discovery of novel anti-inflammatory agents.

In conclusion, natural products represent a vast, diverse, and largely untapped reservoir of bioactive compounds with significant anti-inflammatory properties. With continued scientific exploration and appropriate standardization, these natural agents may contribute to the development of safer, more effective, and more holistic strategies for managing inflammation-related diseases.

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CONFLICT OF INTEREST: Nil

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