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MEDICINAL PLANTS USE AS AN ANTI-INFLAMMATORY AGENT: A BRIEF REVIEW ON MOLECULAR PHARMACOLOGICAL APPROACH

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ABSTRACT
Inflammation is a vital therapeutic target for creating new methods for pharmacological interventions, aside from being a stage in the pathophysiology of many diseases, such as atherosclerosis and rheumatoid arthritis. Thus, molecular understanding of inflammation has led to new opportunities for drug creation and significant new implications for current clinical medicine. It has also revealed the biological targets and mechanisms of therapeutic action, opening up new opportunities to alter complex biological systems. Meanwhile, using medicinal plants to control inflammation has been recommended as an alternative to traditional therapeutic approaches for a variety of conditions, particularly when suppression of inflammation is anticipated. Several medicinal plant species have been demonstrated to have strong anti-inflammatory properties in contemporary research. The review article was discussed about the chemical constituents and biological properties of therapeutically active plants including curcumin from *Curcuma longa* and epigallocatechin-3-gallate from *Camellia sinensis*, including the molecular pharmacology of active constituents against inflammation.

INTRODUCTION

Inflammation is part of the body's defense mechanism and plays a role in the healing process. It is the response of body's immune system's as initial protective action against infection from outside invaders, such as bacteria and viruses, antigen. It engaged complex contacts between extracellular matrix molecules, resident cells, as well as invading cells and soluble mediators. Successful and well-managed inflammation is a beneficial process that aids in the removal of harmful stimuli and the restoration of regular physiology, which is managed by an intricate molecular cascade. The severity of the inflammatory reaction is vital as chronic inflammation, autoimmunity and

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excessive tissue damage result from acute inflammation which is incapable to manage pro-inflammatory stimuli [1, 2]. The chronic and persistent inflammation and the auto-immune response are associated to the progression of heart failure, Parkinson's disease, psoriasis, tumors, atherosclerosis, asthma, diabetes mellitus, myocardial infarction, Alzheimer's disease, osteoporosis, DNA damage, etc [3].

A number of illnesses have been treated with medicinal plants since the dawn of human civilization. Natural substances have been used for inflammatory purposes for a very long time. Identification, isolation and characterization, biological assay of a variety of naturally occurring bioactive constituents were confirmed by phyto-pharmacological evaluation. Molecular pharmacology was assured the potential anti-inflammatory activity of chemical constituents from different natural origin [4,5]. Therefore the study was carried out to explore the established molecular pharmacology of the naturally occurring anti-inflammatory agents.

Major signaling pathways, inflammatory receptors, and mediators

Histamine

Histamine (β-Imidazolylethylamine) is a powerful stimulator of vascular permeability, respiratory mucus, and gastric acid secretion as well as a vasodilator, smooth muscle constrictor, and smooth muscle constrictor. Numerous cell types, including smooth muscle cells, neurons, glandular (endocrine and exocrine) cells, blood cells and immune system cells are affected by it [6]. Histamine plays a role in immediate hypersensitivity reactions as well as H2-receptor-mediated anti-inflammatory activity, which includes suppressor T lymphocyte activation, inhibition of IgE-mediated histamine release from peripheral leukocytes, and inhibition of human neutrophil lysosomal enzyme release [7]. By decarboxylation of the amino acid histidine, histamine is produced in the Golgi apparatus of mast cells and basophils, where it is then deposited in secretory granules in complexes with heparin, protein, or both [8]. Histamine is released in sensitized people when some allergens attach to IgE antibodies on mast cells and basophils, starting a Ca^{++}-dependent degranulation process [9,10].

Recent research supports piecemeal degranulation, an alternative secretory pathway in humans in which mast cells release histamine while retaining empty granule containers within the cytoplasm [11]. Mast cells and basophils can release histamine through immunologic (IgE-mediated) and no immunologic (exercise-induced asthma) pathways, which can exacerbate allergy and anaphylactic symptoms [12]. Additionally, studies indicate that activated T lymphocytes may take part in the degranulation of mast cells by direct cell-to-cell contact [13].

Leukotrienes

The biologic mixture formerly known as the slow-reacting substance of anaphylaxis is made up of leukotriene (LT) C4 and its derivatives, LTD4 and LTE4. Most cell types involved in inflammatory reactions, such as mast cells, basophils, eosinophils, neutrophils, and monocytes, produce leukotrienes [14] function similarly to histamine in terms of biologic activity as chemical mediators of inflammation. The mechanism behind the effects of H1- receptor antagonists on leukotriene production may entail inhibiting the function of receptor-coupled G proteins, according to studies on the subject [15]. Arachidonic acid, which is produced from leukotrienes, is made accessible from phospholipids in cell membranes by the action of phospholipase A 212 or by the sequential action of phospholipase C and diacylglycerol lipase [16,17]. Arachidonic acid is transformed into 5S-hydroperoxy-6,8-trans-11,14-ciseicosatetraenoic acid by 5-lipoxygenase after being liberated from cell membranes by the action of phospholipase A2 [17]. The conversion of 5S-hydroperoxy-6,8-trans-11,14-cis-eicosatetraenoic acid to LT4 is carried out by the same 5-lipoxygenase pathway (LTA4). After that, LTA4 can either be transformed into LTB416 or LTC4 by being coupled with reduced glutathione [18,19] after being transported into the extracellular environment during the later stages of an allergic reaction, LTC4 can continue to be metabolized to form LTD4 and LTE4 [20,21].

Prostaglandins

Prostaglandins are a different class of chemicals generated from arachidonic acid that play a role in allergic reactions. PGD2 is the most prevalent form of cyclooxygenase produced by immunologic activation of human lung mast cells [22]. Human mast cells produce PGD2 after being stimulated by calcium ionophore or the IgE receptor [23]. Prostaglandins produced during mast cell-dependent reactions in tissues have a variety of biological consequences, such as modifying smooth muscle

contractility, vascular permeability, pruritus and pain sensations, and platelet aggregation and degranulation [24].

Cyclooxygenase, an enzyme connected to the endoplasmic reticulum of mast cells, produces prostaglandins. Cyclooxygenase like 5-lipoxygenase, catalysis the synthesis of the moderately unstable intermediates PG2 and PGH2 [25]. Specific isomerase/peroxidase or synthase enzymes can then transform these intermediates either no enzymatically or enzymatically to produce the primary prostaglandins PGD2, PGE2, and PGF [26].

Kinins

Strong peptide hormones called Kinins are created spontaneously during inflammation in bodily fluids and tissues. They are created by the proteolytic cleavage of two globulins (high and low molecular weight kininogens) by a number of enzymes, the most significant of which are plasma and tissue kallikreins [27]. Bradykinin, kallidin (lysbradykinin), and met-lys-bradykinin are three different kinins found in humans [28]. All kinins have the same fundamental pharmacologic features, such as inducing smooth muscle contractility, vasodilation, and enhanced capillary blood flow, despite some quantitative variances [29].

In the inflammatory response, kinins are produced by three different pathways: one that is dependent on plasma and another that is independent of plasma and tissue. The interaction of activated factor XII (Hageman factor) with prekallikrein [30] and high molecular weight kininogens is what starts the plasma pathway's kinin synthesis [31]. Prekallikrein is first converted to kallikreins by activated Hageman factor (factor XIIa), which then proceeds to convert factor XII to XIIa. High molecular weight kininogens enhances the ability of kallikreins to further convert factor XII to XIIa. This series of events results in the release of active kallikreins, which cleaves high molecular weight kininogens to produce bradykinin.

The tissue route for the production of bradykinin includes tissue kallikreins that differ from plasma kallikreins in terms of physio chemistry and immunology [31]. Low molecular weight kininogens make up around 70% of the overall pool of human kininogens, while tissue kallikreins release kinins from both high and low molecular weight kininogens. In the independent pathway, high and low molecular weight kininogens are split into bradykinin by the activity of kininogenases other than kallikreins [32]. As opposed to plasma kallikreins, tissue kallikreins have access to a broader pool of substrate due to their ability to react with both high and low molecular weight kininogens [33]. Tissue kallikreins are the only known enzymes to produce the bradykinin precursor kallidin, and once activated, they are less vulnerable to protease inhibitor suppression than plasma kallikreins. The cleavage of high and low molecular weight kininogens to produce bradykinin occurs via a separate route involving kininogenases other than kallikreins [34,35].

Cytokines and chemokines

A number of studies show that cytokines are crucial in late-phase inflammatory events linked to allergic rhinitis and asthma, and that the mast cell plays a key role in these processes. The source of several multifunctional cytokines is the cell [36]. IL-1, -2, -4, -5, -6, TNF-, and GMCSF are cytokines that affect how allergic inflammation develops by regulating inflammatory cells' activity such a T cells, B cells, eosinophils, and macrophages. IL-1 increases the growth and development of T-helper B cell expansion, whereas IL-2 promotes expansion of T cells and B lymphocyte activation [37]. IL-4 induces B lymphocytes to differentiate into IgE-secreting plasma cells and upregulates TNF- expression of high- and low-affinity IgE receptors on cells that deliver antigens.B lymphocytes become activated by IL-5, while eosinophils differentiate and live longer and for which IL-6, and B lymphocytes are generated and produced more immunoglobulins (IL-5) [38].

Medicinal plants with molecular pharmacology acts as an anti-inflammatory agent

1. Curcuma longa Linn.

Turmeric's pigmentation is brought on by curcumin, a diarylheptanoid that was isolated from the rhizomes of the *Curcuma longa* Linn plant, family Zingiberaceae. According to curcumin, it works to reduce inflammation by controlling a number of processes. Growing evidence from recent studies indicates that curcumin's anti-inflammatory effects are caused by modifying the JAKSTAT signaling system. Curcumin reduces inflammation in brain cells by blocking the JAK-STAT pathway [39].

It stopped the phosphorylation of STAT1 and STAT3, activation of pro-oncogenic inflammatory pathways such the Janus kinase (JAK) and nuclear factor-B (NF-B) and interleukin-6 (IL-6) pathways [40]. Curcumin prevents the MAPK pathway,

cytokine-mediated NF-B activation and pro-inflammatory gene expression by inhibitory factor I-kB kinase activity [41]. It is undeniable that increased levels of pro-inflammatory cytokines, such as TNF, IL-6, and IL-1, cause a progressive loss of dopaminergic neurons hence raising the possibility that increased inflammation may contribute to neurodegenerative illnesses. Curcumin also possesses anti-inflammatory qualities, which are an essential aspect of illnesses like malignancies or autoimmune diseases. Curcumin, a powerful anti-inflammatory, has notable effects on immunological regulation and may be used as an adjuvant immunosuppressant in organ transplants [42].

***2. Tripterygium wilfordii* Hook F**

The herb *Tripterygium wilfordii Hook F* (TWHF), (family: Celastraceae) is widely used as traditional medicine to treat a variety of autoimmune diseases. The majority of the biological action of this herb is attributed to three triterpenoids, specifically tripdiolide, triptonide, and tripdiolide. It is used in the therapy of immune-inflammatory conditions such psoriasis, asthma, systemic lupus erythematosus, and rheumatoid arthritis. Pentacyclic triterpene, a different component known as celastrol, is well-known for its wide range of biological effects, which include the treatment of cancer and inflammatory illnesses.

The isolated chemicals from *Tripterygium Wilfordii Hook F* exert their anti-inflammatory actions in a variety of ways. An extract or isolated chemical of According to recent research *Tripterygium wilfordii* used for the treatment of range of diseases like ankylosing spondylitis, rheumatoid arthritis, chronic nephritis, hepatitis, cancer, skin disorders [43].

3. Zingiber officinale

Ginger belongs to Zingiberaceae family. Ginger has been used as herbal remedies since thousands of years for catarrh and rheumatism any many more. Ginger produces medicinal properties due to contain of several numbers of chemical constituents gingerol, zingerone, yakuchinone A, diarylheptanoid, and 12-dehydrogingerdione (12-DHGD). Research in clinical studies established that ginger extract have number of pharmacological effects like anti-arthritic, anti-inflammatory, antidiabetic, antibacterial, antifungal, anticancer, allergic disorders, including acute respiratory distress syndrome and asthma. It have been shown that ginger reduce the inflammation by controlling the AA pathway, inhibiting PGE2 and COX-2 and inhibiting iNOS, mRNA. Also reduces inflammation by blocking the Nf-B pathway and reducing the production of IL-1, IL-6, and IL-12. [44].

4. Camellia sinensis

Tea made from the *Camellia sinensis* plant, which is a member of the Theaceae family, is popular worldwide. It has established numerous medical properties including as anti-inflammatory and antioxidant properties. Tea can also used to treat colitis, ulcer, atherosclerosis, pancreatitis etc. The chief constituent of leaves is catechin, found in different forms like epigallocatechin, epicatechin gallate, gallocatechin, epicatechin. Epigallocatechin gallate (EGCG) is initiate the inflammatory process by altering specific transducers of inflammation involving the NF-B pathway, JAK/STAT pathway, PI3K/Akt pathway and ameliorating the effects of COX-1, 5-LOX by affecting AA pathway [45].

5. Calea urticifolia

Calea urticifolia, a member of the Asteraceae family, is used extensively in traditional medicine as a treatment for gastric ulcers, infections, inflammation and also effective as antibacterial, anti-proliferative, cytotoxic, and antioxidant effects. Particularly flavonoid glycosides and derivatives of caffeoylquinic acid are bioactive ingredients linked to these characteristics. *Calea urticifolia* has anti-inflammatory properties are exhibited via decreasing the NF-B p65 and p50 subunits' ability to translocate to the nucleus, as well as by blocking the iNOS/NO pathway and COX-2 expression to some extent.These acts also prevent the significant inflammatory modulators from being released and the spread of inflammation from increasing. Due to its widespread use, the genus Calea is one of the most studied species. *Calea urticifolia* extract and extracted bioactive components are potential sources to treat inflammatory diseases, particularly those involving the gastrointestinal tract [46].

6. Angelica sinensis

The root of *Angelica sinensis* Diels, which is a member of the Apiaceae family, is called *Angelica sinensis*. Traditional medicine called *Angelica sinensis* Diels has been used to treat rheumatism, regulate the immune system, stop platelet aggregation, and lessen inflammation in a number of inflammatory illnesses. Plant contains polysaccharides, plant acids, ferulic acids, L ligustilide as bioactive compounds. These substances have the ability to reduce inflammation via blocking,

TNF- and IL-6 production and secretion are both prevented by blocking the NF-B pathway. They may be able to reduce inflammation by preventing NO emissions. Additionally, it would result in a decrease in local inflammation by preventing the release of macrophage inflammatory protein-2 (MIP-2) [47].

7. Solanum lycopersicum

Because it contains essential phytochemicals and bioactive compounds, *Solanum lycopersicum*, or tomato, family Solanaceae and is a great source of polyphenolic chemicals, like phenol. Generally speaking, acids and flavonoids exhibit modest toxicological action. These substances have suggested as therapeutic solutions for a variety of ailments it is popular. Used in conventional medicine to treat conditions such as asthma, lower cholesterol levels, and kidney and stomach ache. Biological processes like cytotoxic, antioxidant, and anti-inflammatory there have been reports of and antimicrobial for this species [48]. Numerous studies have demonstrated the anti-inflammatory properties of Solanum species in both acute and chronic conditions. Oxylipin and coumarin were among the numerous anti-inflammatory substances present in tomato extract fractions. Among these chemical compounds, daphnetin (7,8-dihydroxycoumarin) and 9-oxo-octadecadienoic acid (9-oxo-ODA) shown remarkable anti-inflammatory activity. [49]**.**

8. Belamcanda chinensis

Belamcanda chinensis is a member of the Iridaceae family. It is a traditional herbal medicine used as antibacterial, antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, antitumor drug. Plant extracts contain various classes of natural products including flavonoids, terpenoids, quinones, organic acids etc. [50]. The three main bioactive constituents were isolated from the rhizomes of *B. chinensis* were tectoridin, tectorigenin, and irigenin. The isolated chemicals from *B. chinensis* have anti-inflammatory properties via inhibiting the AA pathway, which lowers the activation of prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2) in inflammatory cells. The various chemicals put forth anti-inflammatory actions via reducing the generation of nitric oxide (NO) and inducible nitric oxide synthase (iNOS), as well as by regulating the NF-B pathway. [51].

9. Cornus Officinalis

Cornus officinalis (Cornaceae family) is widely obtainable in China and is commonly used in traditional Chinese medicine (TCM). Plant contains flavonoids, antioxidants and possesses anti-inflammatory properties, antibacterial, antifungal, and anticancer properties. The anti-inflammatory activity of extract of the plant is accomplished by down regulating COX-2 protein and mRNA expression and reducing inflammatory prostaglandins during the AA pathway, as well as by decreasing iNOS protein expression and preventing the production of inflammatory RNS and NF-B and p65 protein expression in the nuclear fraction reducing the production of IL-1, IL-6, and TNF. [52,53]

10. Cistanches herba

Cistanches herba (Family Orobanchaceae) is used in Traditional Chinese Medicine (TCM) has anti-inflammatory properties. It has remarkable effect on reducing muscle pain and inflammation. The biological basis for anti-inflammatory reactions is inhibition of the AA pathway at various stages through phospholipase A activation, COX-2 suppression, PGE2 inhibition, ROS production inhibition, and mast cell, neutrophil, and macrophage histamine release inhibition. However, it is also compatible with recent research that showed the analgesic, antioxidant, anti-fatigue actions and anti-inflammatory properties by the extract of the *Cistanches herba* [54].

CONCLUSION

Inflammation is a key player in the pathogenesis of many diseases and has emerged as a crucial therapeutic target for the development of cutting-edge pharmaceutical therapies. This review discusses some of the current research that has clarified the function of medicinal herbs by manage of several inflammatory modulators and pathways.

Several pharmacological targets have been revealed and are at presently employed therapeutically to control the degree of inflammation in the system following an injury. While classic interventional techniques can now be used to suppress inflammation, this has increased the positive response during inflammatory disorders and significantly decreased related problems and bad consequences.

In order to improve quality of life while minimizing associated negative effects during diseased states, medicinal plants are being developed as drugs. The current review has therefore provided an overview of both molecular mechanisms and approved targets for pharmacological intervention in inflammation.

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CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Dibyendu Shil conceptualized the idea and did the literature survey. Kishor Kumar Roy, Rasamalla Mounik drafted the manuscript and further revised it. Md Masud Reja, Subhasish Saha and Ranjan Kumar Maji contributed in conducting the literature survey and did the correction in the manuscript. All the authors contributed in correction of manuscript and final proof reading of the manuscript.

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