CHAPTER N0.

10

Pharmacology of Natural Anti-Inflammatory Agents: From Traditional Medicine to Modern Therapeutics

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ABSTRACT: Numerous significant health issues, including heart disease, metabolic abnormalities, brain degeneration, and immune system failure, are largely caused by persistent inflammation. Conventional anti-inflammatory medications frequently reduce symptoms but pose serious issues for long-term care, such as negative side effects and diminishing efficacy over time. Because they often have lower safety risks, natural chemicals have emerged as possible substitutes. This chapter sheds light on the pharmacological actions of the main classes of plant-based anti-inflammatory compounds. Curcumin and resveratrol are examples of polyphenolic compounds that alter important inflammatory signaling pathways, specifically nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and nuclear factor erythroid 2-related factor 2 (Nrf2), offering both anti-inflammatory and antioxidant protection. Flavonoids stabilize the oxidative equilibrium of cells while reducing the generation of pro-inflammatory cytokines and inhibiting enzymes such as lipoxygenase (LOX) and cyclooxygenase (COX). Terpenoids decrease immune cell tissue penetration and control the activity of inflammatory enzymes, whereas alkaloids limit not only the development of inflammasome complexes but also the release of inflammatory messengers. Early research has shown intriguing anti-inflammatory capabilities for coumarins, especially in sophisticated nanoparticle formulations. According to current research, problems include poor drug absorption and adverse pharmacokinetic properties that reduce the efficacy of treatment. Innovative distribution methods, enhanced formulations, and structural changes are some of the solutions. This chapter highlights the modern pharmacological significance of natural anti-inflammatory compounds and the need for ongoing development toward safe, effective, multi-targeted therapies. It does this by using experimental and clinical evidence to show how these compounds can be used as complementary treatment options for inflammatory diseases.
Keywords: Metabolic abnormalities, Conventional, Pro-inflammatory, Complementary

INTRODUCTION

Inflammation,A basic biological reaction, shields the body from a variety of damaging stimuli, such as chemical irritants, physical trauma, metabolic stress, and microbial invasion. It initiates tissue repair, restores homeostasis, and stops the spread of infection, making it a crucial part of innate immunity. The persistence or dysregulation of inflammatory processes results in chronic inflammation, a pathological state now acknowledged as a major contributor to many non-communicable diseases, whereas acute inflammation is typically transient and advantageous. Rheumatoid arthritis, atherosclerosis, type 2 diabetes, obesity-related metabolic dysfunction, cancer, neurodegenerative disorders, and inflammatory bowel diseases have all been linked to sustained inflammatory signaling (Medzhitov, 2021; Furman et al., 2019). Immune cells, soluble mediators, and intracellular signaling networks all work together in the inflammatory cascade. Nuclear factor-κB (NF-κB), mitogen-activated protein kinases (MAPKs), Janus kinase/signal transducers and activators of transcription (JAK/STAT), and enzymatic pathways like cyclooxygenases (COX-1/2) and lipoxygenases (LOX) are important molecular regulators. Activation of these pathways leads to the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines, reactive oxygen species (ROS), and eicosanoids, which together orchestrate the classical features of inflammation (Nathan and Ding, 2010; Chen et al., 2018).

Conventional pharmacotherapy for inflammatory disorders, most notably non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and COX-2 inhibitors, remains widely used because of their rapid symptom control. However, their long-term administration is restricted due to adverse outcomes such as gastrointestinal ulceration, renal impairment, hepatotoxicity, metabolic disturbances, and increased cardiovascular risk (Vonkeman and van de Laar, 2010; Rabinovitch et al., 2021). The adverse effects of NSAIDs, especially on prolonged usage, have intensified global interest in identifying safer, multi-target anti-inflammatory agents from natural origins.

Strong regulatory effects on inflammatory signaling are found in natural products, including flavonoids, alkaloids, terpenoids, phenolic acids, coumarins, and saponins. Several studies show that these phytochemicals reduce oxidative stress

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through Nrf2 activation, inhibit NF-κB translocation, suppress MAPK phosphorylation, and downregulate pro-inflammatory mediators such as TNF-α, IL-6, COX-2, and inducible nitric oxide synthase (iNOS) (Cruz et al., 2023; Tungmunnithum et al., 2018). These compounds are promising scaffolds for next-generation therapeutic development, as advances in molecular docking, network pharmacology, and SAR analyses have further elucidated how specific structural motifs contribute to their anti-inflammatory actions (Pan et al., 2020; Liu et al., 2022).

Natural anti-inflammatory medications have become useful substitutes or supplements to pharmaceuticals due to the increasing amount of scientific and clinical data, providing greater biological action with comparatively fewer side effects. This chapter integrates traditional medical knowledge with modern mechanistic insights to present a thorough overview of the main types of natural substances with anti-inflammatory potential. The debate highlights the importance of natural chemicals in developing safer and more effective anti-inflammatory therapies by emphasizing molecular pathways, therapeutic relevance, experimental findings, and translational possibilities.

TYPES AND SOURCES

Natural anti-inflammatory compounds come from a variety of biological sources, including fungi, plants, marine organisms, and animal products. The most extensively studied of these are secondary metabolites originating from plants, primarily because of their pharmacological effectiveness and structural diversity. Flavonoids, alkaloids, terpenoids, phenolic acids, and saponins are among the main classes of phytochemicals that comprise these bioactive natural compounds. Each of these classes has a distinct mechanism of anti-inflammatory action Sridharan et al., 2022).

Plant-Derived Anti-Inflammatory Agents

The main sources of therapeutic compounds have been medicinal plants used in traditional systems such as Ayurveda, Traditional Chinese Medicine, and Unani pharmacology. Phytochemicals have anti-inflammatory activity by modulating signaling pathways, scavenging free radicals, suppressing pro-inflammatory mediators, and enhancing endogenous antioxidant defenses (Salehi et al., 2021). About 50 medicinal plants have been documented to include phytochemicals from the class of flavonoids, terpenoids, polyphenols, saponins, tannins, alkaloids, anthraquinones, chemical components of essential oils, and some of their M/MONPs for the treatment of inflammatory illnesses. These plants' natural compounds showed encouraging anti-inflammatory properties to treat inflammatory conditions of the skin, liver, heart, joints, gastrointestinal tract, nervous system, and lungs. Numerous investigations into phytochemistry, M/MONPs, and the anti-inflammatory properties of phytochemicals from medicinal plants have produced new, safe, and less harmful substances. Phytochemicals, which are mainly responsible for the anti-inflammatory activities, were reported from the family of polyphenols, terpenoids, flavonoids, saponins, and tannins.

Polyphenols obtained from various plants in pure form, such as from *Curcuma pseudomontana*, or in the form of polyphenolic proteins, like from *Indigofera hirsute* (leaf), or sometimes as polyphenolic terpenoids as in the case of *Otostegia persica* (leaf) in the form of, and from *Trianthema portulacastrum* (leaves) in the form of polyphenolic flavonoids play their role as anti-inflammatory agents by helping the processs of nano formulation stabilization or they are reported for the inhibition of IL-8 production, which are inflammatory mediators (Gonfa et al., 2023). Flavonoids like quercetin, kaempferol, and luteolin inhibit the activation of NF-κB and suppress the expression of COX-2 and iNOS. Essential oils may also serve their role as anti-inflammatory phytochemicals because they complex mixture of various chemicals such as terpene fatty acid derivatives, benzene derivatives, amines, and phenylpropanoid constituents. And all these substances have a significant ability to produce an anti-inflammatory role. Terpenoids, including boswellic acids and curcuminoids, inhibit 5-LOX and MAPK pathways. Alkaloids such as berberine activate AMPK and decrease pro-inflammatory cytokine release. Antioxidant and immunomodulatory effects are exerted by the phenolic acids caffeic and ferulic acid. Several widely studied medicinal plants are given in Table 1.

Marine-Derived Anti-Inflammatory Agents

Marine organisms, including algae, corals, sponges, mollusks, cyanobacteria, and marine fungi, produce structurally unique bioactive compounds due to high ecological competition and extreme environmental conditions. These compounds often exhibit potent anti-inflammatory activity by modulating cytokine release, oxidative stress responses, and immune cell signaling pathways. Brown seaweeds such as *Fucus vesiculosus* and *Undaria pinnatifida* contain fucoidan, a sulfated polysaccharide known to downregulate TNF-α, IL-1β, and IL-6 production by inhibiting NF-κB and MAPK activation (Fitton et al., 2019; Park et al., 2020). Phlorotannins, another class of polyphenols from brown algae, reduce COX-2 and iNOS expression and exhibit

Table 1. Examples of common medicinal plants

Plant Name	Active Principle	Primary Mechanism	Traditional Use	References
Curcuma longa (Turmeric)	Curcumin	Inhibits NF-κB, COX-2, TNF-α	Arthritis, metabolic inflammation	Aggarwal and Harikumar, 2009; Hewlings and Kalman, 2017
Boswellia serrata	Boswellic acids	5-LOX inhibition	Chronic joint inflammation	Siddiqui, 2011; Kimmatkar et al., 2003
Zingiber officinale (Ginger)	Gingerols, shogaols	Inhibits prostaglandins and leukotrienes	Pain, swelling, digestive inflammation	Grzanna et al., 2005; Mashhadi et al., 2013
Camellia sinensis (Green tea)	EGCG	Antioxidant, inhibits MAPKs	Metabolic and vascular inflammation	Yang et al., 2016; Khan and Mukhtar, 2018

strong antioxidant activity by enhancing Nrf2/HO-1 signaling (Li et al., 2021). These marine polyphenols also mitigate metabolic inflammation, including obesity-induced insulin resistance.

Attention has been given to marine peptides from fish skin, mollusks, and marine microbes. For instance, peptides purified from anchovy, sardine, and oyster hydrolysates inhibit LPS-mediated macrophage activation through suppression of NO production and interruption of the JNK/p38 MAPK pathways. Conotoxins, from cone snails, have analgesic and anti-inflammatory action through modulation of voltage-gated calcium channels.

According to Jung et al. (2020), marine sterols like fucosterol (found in brown algae) have multi-target anti-inflammatory actions that include modulating PPAR-γ activity, reducing ROS, and suppressing pro-inflammatory cytokines. Many of the chemicals found in marine sponges, including manoalide, avarol, xestoquinone, and scalarane sesterterpenoids, are powerful inhibitors of the PLA2, NF-κB, and LOX pathways (Mayer et al., 2020). These substances show great promise for being developed into innovative anti-inflammatory medications. Phycocyanin, a biliprotein with proven anti-inflammatory and antioxidant qualities, is produced by marine cyanobacteria. It strengthens cellular defense mechanisms while suppressing COX-2, iNOS, and oxidative stress indicators. When taken as a whole, marine-derived chemicals constitute an important yet underutilized source of anti-inflammatory medicines with unique structures and processes, offering prospects for novel therapeutic advancements.

Fungal and Microbial Sources

Edible and medicinal mushrooms such as Ganoderma lucidum (Reishi) and Lentinula edodes (Shiitake) contain high concentrations of β-glucans, terpenoids, polysaccharides, and lectins that exert potent immunomodulatory and anti-inflammatory effects. By binding to dectin-1 and TLR-2/6 receptors, β-glucans control both innate and adaptive immune responses. This leads to the suppression of NF-κB, decreased secretion of TNF-α, IL-1β, and IL-6, and increased production of anti-inflammatory cytokines like IL-10 (Meng et al., 2021; Vetvicka and Vetvickova, 2019). Ganoderic acids, which are triterpenoids extracted from Ganoderma lucidum, lower oxidative stress and suppress the expression of COX-2 and iNOS, which helps to lessen chronic inflammatory diseases (Jong et al., 2020). Similarly, in autoimmune and metabolic illnesses, lentinan, a β-glucan derived from Lentinula edodes, improves immunological balance mediated by macrophages and reduces inflammatory mediators (Zhang et al., 2021).

A major source of anti-inflammatory secondary metabolites is soil microbes, which continue to be central to natural product-based drug discovery. Actinomycetes, particularly *Streptomyces* species, produce structurally diverse anti-inflammatory compounds such as rapamycin, tacrolimus (FK506), anisomycin, and resveratrol-like polyketides, many of which suppress mTOR, MAPK, or cytokine signaling pathways (Berdy, 2019). Soil-derived fungi, including *Aspergillus*, *Penicillium*, and *Trichoderma*, generate metabolites such as gliotoxin, pestacin, ergosterol derivatives, and cyclodepsipeptides, known to inhibit NF-κB activation, block ROS production, and suppress IL-1β and TNF-α. Bacterial-derived lipoxazolidinones, macrolides, and lipopeptides have also demonstrated inhibition of pro-inflammatory responses in macrophages and epithelial cells, highlighting the continuing value of soil ecosystems in discovering new anti-inflammatory agents.

Animal-Derived Anti-Inflammatory Substances

Certain bioactive compounds derived from animals also demonstrate significant anti-inflammatory potential. By suppressing NF-κB activation, lowering COX-2 expression, and lowering the generation of inflammatory cytokines like TNF-α and IL-1β, chondroitin sulfate, which is derived from animal cartilage (bovine, porcine, or marine sources), demonstrates anti-inflammatory potential. Because of its chondroprotective properties and ability to halt cartilage breakdown, it is frequently utilized in clinical settings for osteoarthritis. In chronic inflammatory disorders, chondroitin further lowers oxidative damage, stiffness, and joint swelling when coupled with glucosamine (Roman-Blas and Jimenez, 2020).

Omega-3 polyunsaturated fatty acids (PUFAs), specifically EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) generated from fish oils, are another important family of agents derived from animals. By displacing arachidonic acid in cell membranes, these PUFAs lessen inflammation by reducing the synthesis of pro-inflammatory eicosanoids such as PGE_2 and leukotrienes. Furthermore, EPA and DHA stimulate the production of specific pro-resolving mediators that actively reduce inflammation and promote tissue repair, including resolvins, protectins, and maresins (Calder, 2020; Serhan and Levy, 2018). Clinical advantages for rheumatoid arthritis, psoriasis, metabolic inflammation, cardiovascular disease, and inflammatory bowel disease have been demonstrated by omega-3 fatty acids. Hyaluronic acid (from rooster combs or microbial fermentation) is another notable animal-derived substance that improves cartilage lubrication and lowers joint inflammation by blocking the release of prostaglandin and bradykinin. By inhibiting IL-6, TNF-α, and LPS-induced oxidative stress, lactoferrin, a glycoprotein derived from bovine milk, exhibits dual antimicrobial and anti-inflammatory properties. It has emerging therapeutic applications in gut inflammation, arthritis, skin inflammation, and neuroinflammation. These naturally occurring substances from animals target several biochemical pathways to collectively help resolve the inflammation process, emphasizing their importance in evidence-based and integrative treatments of chronic inflammatory illnesses.

MOLECULAR MECHANISMS

Pharmacological activities of natural anti-inflammatory drugs are various biochemical processes related to the control of oxidative stress, immune cell responses, and inflammatory signalling (Fig. 1). Phytochemicals frequently affect multiple inflammatory mediators at once, which contributes to their

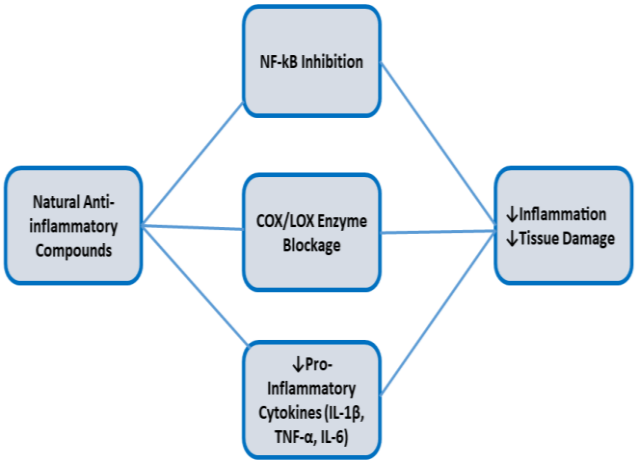

Fig. 1. Mechanistic approach of various natural anti-inflammatory compounds

wider therapeutic benefits with fewer side effects, in contrast to traditional synthetic medicines that usually operate via a single enzyme or receptor target (Rathee et al., 2009).

Inhibition of Pro-Inflammatory Enzymes

Overexpression of COX-2 and 5-LOX plays a critical role in chronic inflammatory conditions such as arthritis and inflammatory bowel disease (Ricciotti and FitzGerald, 2011). Curcumin inhibits COX-2 gene expression by blocking NF-κB activation. Boswellic acids selectively inhibit the activity of 5-LOX, leading to a decrease in the synthesis of leukotrienes. Gingerols inhibit both the COX and LOX enzymes, contributing to dual anti-inflammatory action (Table 2)

Suppression of the NF-κb Signaling Pathway

NF-κB is a transcription factor regulating the expression of cytokines (TNF-α, IL-1β, IL-6), adhesion molecules, and inflammatory enzymes. Continuous activation of NF-κB results in chronic inflammation. Several natural compounds inhibit NF-κB activation by preventing degradation of its regulatory protein IκBα (Liu et al., 2017).

Modulation of MAPK and JAK/STAT Signaling

The mitogen-activated protein kinase (MAPK) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways are central regulators of inflammation, controlling cytokine release, cell proliferation, and immune activation. MAPKs, including ERK1/2, JNK, and p38 MAPK, are activated in response to stress signals, LPS, cytokines, and oxidative damage. Their activation triggers transcription factors such as AP-1 and NF-κB, leading to the expression of pro-inflammatory mediators (IL-1β, IL-6, TNF-α). Similarly, the JAK/STAT signaling cascade, particularly JAK1/STAT1/STAT3, mediates cytokine-driven inflammatory responses and drives chronic inflammation when overactivated.

By focusing on these signaling axes, several natural substances have anti-inflammatory properties. It has been demonstrated that berberine, an isoquinoline alkaloid from the Berberis species, inhibits the phosphorylation of p38 MAPK and JNK, which reduces the production of TNF-α, IL-1β, IL-8, and MCP-1 in activated macrophages. Berberine reduces downstream transcription of inflammatory genes and inhibits oxidative stress-mediated signaling by blocking MAPK activation (Jeong et al., 2009; Deng et al., 2020). Berberine also reduces inflammatory responses synergistically by interfering with the interaction between the MAPK and NF-κB pathways.

Strong regulation of cytokine-mediated signaling is also demonstrated by flavonoids such as luteolin, which is present in celery, parsley, and chamomile. By preventing JAK1 and STAT3 phosphorylation, luteolin prevents IL-6-driven STAT3 activation, which is frequently increased in autoimmune and chronic inflammatory diseases. In order to restore immunological balance and stop prolonged inflammatory signaling, this inhibition lowers downstream expression of IL-6, IL-10, and other STAT3-dependent genes (Yoo et al., 2014; Seelinger et al., 2008). Additionally, luteolin inhibits MAPK pathways, specifically ERK and p38, which limits macrophage activation and lowers the synthesis of prostaglandin and nitric oxide.

Together, these results demonstrate that natural substances reduce inflammation by directly controlling important intracellular signaling networks that control the expression of inflammatory genes as well as by blocking surface receptors or enzymes.

Table 2. Mechanisms of Anti-Inflammatory Action of Key Natural Agents

Compound	Primary Molecular Target(s)	Effect on Cytokines / Enzymes	Outcome on Inflammation	References
Curcumin	NF-κB, COX-2, LOX, Nrf2	↓ TNF-α, IL-1β, IL-6	Reduces oxidative stress and inflammatory signaling	Gupta et al., 2013; Hewlings and Kalman, 2017
Boswellic acids	5-LOX enzyme inhibition	↓ leukotriene synthesis	Suppresses chronic inflammatory responses	Ammon, 2016; Sengupta et al., 2011
Resveratrol	SIRT1 activation, NF-κB inhibition	↓ IL-6, CRP, IL-8	Anti-proliferative and anti-inflammatory effects	Shakibaei et al., 2009; Poulsen et al., 2013
Quercetin	MAPK and JAK/STAT modulation	↓ IL-1β, IL-4, TNF-α	Stabilizes immune response and mast cell degranulation	Li et al., 2016; Mlcek et al., 2016
Gingerols	COX-2 and NF-κB modulation	↓ PGE2, IL-6	Reduces pain and inflammatory swelling	Grzanna et al., 2005; Daily et al., 2015
EGCG	Nrf2 activation, NF-κB downregulation	↓ ROS, ↓ IL-8	Antioxidant-mediated suppression of inflammation	Yang et al., 2016; Singh et al., 2011
Omega-3 (EPA/DHA)	Specialized pro-resolving mediator pathway	Forms resolvins and protectins	Promotes resolution of inflammation	Calder, 2020; Serhan, 2014

Antioxidant Activity and Reduction of Oxidative Stress

An important factor in the start and escalation of inflammation is oxidative stress, which is defined by an overabundance of reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS increase the production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), chemokines, and adhesion molecules by activating transcription factors like NF-κB and AP-1. This keeps the inflammatory response going. Furthermore, oxidative stress causes DNA damage, protein oxidation, and lipid peroxidation, all of which exacerbate tissue damage and persistent inflammation (Liguori et al., 2018).

As antioxidants, several natural substances reduce inflammation by either scavenging free radicals or strengthening the body's defenses. By donating hydrogen or electrons, phenolic acids, including ferulic acid, gallic acid, and caffeic acid, neutralize ROS and stop oxidative changes of proteins and lipids (Shahidi and Ambigaipalan, 2015). Quercetin, kaempferol, and luteolin are examples of flavonoids that chelate transition metals, block ROS-generating enzymes, and upregulate antioxidant enzymes to reduce inflammation caused by oxidative stress.

Silymarin, a polyphenolic flavonolignan from *Silybum marianum* (milk thistle), enhances hepatic antioxidant defense by increasing the activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while reducing lipid peroxidation markers such as malondialdehyde (MDA) (Surai, 2015). Similarly, vitamin E (α-tocopherol) and carotenoids (β-carotene, lycopene, astaxanthin) prevent ROS-mediated signaling cascades, stabilize mitochondrial function, and shield cellular membranes from lipid peroxidation, all of which help to reduce inflammation in neurodegenerative, hepatic, and cardiovascular diseases (Traber and Atkinson, 2007; Rao and Rao, 2007). Additionally, a number of polyphenols and carotenoids stimulate the Nrf2/ARE (antioxidant response element) pathway, which increases cytoprotective proteins, phase II detoxifying enzymes, and endogenous antioxidant enzymes, strengthening cellular resistance to oxidative stress (Kobayashi and Yamamoto, 2005). The interaction of anti-inflammatory and antioxidant properties emphasizes the dual protective function of natural substances in regulating inflammatory reactions and oxidative tissue damage.

Regulation of pro- and anti-inflammatory cytokines

One way that natural anti-inflammatory substances work is by adjusting the ratio of pro-inflammatory to anti-inflammatory cytokines. They inhibit the synthesis of important pro-inflammatory mediators that cause tissue damage, immunological overactivation, and chronic inflammation, such as TNF-α, IL-1β, and IL-6. Concurrently, these substances increase the production of anti-inflammatory cytokines, including TGF-β and IL-10, which support tissue repair, immunological homeostasis, and inflammation resolution (Gautam and Kaur, 2022; Liu et al., 2019). In autoimmune and chronic inflammatory conditions like metabolic syndrome, inflammatory bowel disease, and rheumatoid arthritis, where dysregulated cytokine networks prolong tissue damage, this dual immunomodulatory impact is especially beneficial. By restoring cytokine balance, phytochemicals and other natural agents reduce excessive immune activation while preserving host defense mechanisms.

CLINICALLY RELEVANT NATURAL ANTI-INFLAMMATORY AGENTS

Several natural compounds have progressed from traditional use to extensive experimental and clinical evaluation. Their significant pharmacological actions have been validated in a large number of inflammatory disorders, including arthritis, metabolic syndrome, neuroinflammation, and dermatological conditions. Below, key natural anti-inflammatory agents with proven pharmacological relevance are discussed in detail (Table 3).

Curcumin (Curcuma longa and Clematis viticella)

Curcumin, a polyphenolic compound derived from turmeric rhizome and also from aerial parts of *Clematis viticella*, exhibits broad anti-inflammatory effects. It inhibits NF-κB, COX-2, and the release of NOS, and downregulates pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Curcumin also enhances antioxidant responses through activation of Nrf2 signaling (Aggarwal et al., 2013). Clinical studies describe its effectiveness in rheumatoid arthritis, osteoarthritis, and ulcerative colitis. It usually gives relief of skin related inflammatory disorders (Gonfa et al., 2023).

Table 3. Natural Anti-Inflammatory agents with sources, mechanisms, and safety Profile

Compound	Source	Key Mechanism	Clinical Use Evidence	Safety Profile	References
Curcumin	Curcuma longa	Inhibits NF-κB, COX-2, enhances Nrf2	Arthritis, colitis	Generally safe; low absorption	Hewlings and Kalman, 2017; Gupta et al., 2013
Boswellic acids	Boswellia serrata	Inhibits 5-LOX	Osteoarthritis, asthma	Well-tolerated	Ammon, 2016; Sengupta et al., 2010
Gingerols	Zingiber officinale	Inhibits COX/LOX, TNF-α	Joint inflammation, dyspepsia	Safe at dietary doses	Daily et al., 2015; Grzanna et al., 2005
Resveratrol	Grapes, berries	Activates SIRT1, inhibits NF-κB	Metabolic and neurological disorders	Mild GI discomfort in high doses	Poulsen et al., 2013; Shakibaei et al., 2009
Quercetin	Fruits and vegetables	Blocks IKK, antioxidant	Allergy and inflammatory diseases	Safe up to 1 g/day	Li et al., 2016; Mlcek et al., 2016
Omega-3 fatty acids	Fish oil	Reduces pro-inflammatory eicosanoids	Arthritis and cardiovascular inflammation	Safe; high doses may affect bleeding time	Calder, 2020; Serhan, 2014

Boswellic acids (*Boswellia serrata*)

Boswellic acids are pentacyclic triterpenes that selectively inhibit 5-lipoxygenase, inhibiting leukotriene production. Boswellia extract has been demonstrated to be effective in managing pain in osteoarthritis and inflammatory bowel conditions and possesses a better gastrointestinal safety profile compared to NSAIDs.

Ginger constituents (*Zingiber officinale*)

Ginger contains gingerols and shogaols, which inhibit COX and LOX pathways and suppress pro-inflammatory cytokine release (Mashhadi et al., 2013). Clinical trials favours ginger containing formulations for osteoarthritis pain reduction and improved joint mobility.

Resveratrol

Resveratrol is a stilbene with antioxidant and anti-inflammatory activity. It reduces the synthesis, activation and release of NF-κB, which actually controls transcription of cytokine functions and proinflammatory mediators. Resveratrol also stimulates SIRT1, which is a protein involved in cellular resistance to stress and longevity (Gambini et al., 2015). It shows therapeutic promise for metabolic inflammation and neurodegenerative diseases.

Quercetin

Quercetin is a flavonoid extract that exerts anti-inflammatory effects through the inhibition of IKK-dependent NF-κB signaling and its free radical-scavenging effects. It also exerts membrane-stabilizing effects, reducing mast cell-driven inflammatory responses. Clinical studies by Li et al. (2016) have indicated its usefulness in allergic and autoimmune-mediated inflammatory states.

Omega-3 fatty acids (Fish oil)

Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), impede the formation of inflammatory eicosanoids from arachidonic acid and stimulate the synthesis of resolvins, compounds which actively resolve inflammation (Calder, 2020). The therapeutic uses of these essential fatty acids also include rheumatoid arthritis, atherosclerosis, and inflammatory bowel disease.

SAFETY, TOXICOLOGY AND LIMITATIONS

While generally considered to be safer than synthetic pharmaceuticals, there is certainly risk associated with the use of natural anti-inflammatory agents. Phytochemical safety is dependent on such variables as dose and duration of use, source purity, preparation method, and individual patient-specific variables including age, comorbidities, and drug interactions. Potential adverse effects, contraindications, and herb-drug interactions therefore warrant prudent consideration. In fact, many natural compounds exhibit therapeutic efficacy only within a certain dosage range. Higher concentrations of some phytochemicals exhibit cytotoxicity, hepatotoxicity, or nephrotoxicity (Nohynek et al., 2010). For example, excessive intake of curcumin hinders iron metabolism. High doses of quercetin administered in animal models have been associated with renal toxicity. Alkaloids, such as berberine, cause GI disturbances and hypotension if overdosed.

The mechanism of interaction between natural agents and medication includes the induction or inhibition of CYP450 enzymes, which eventually affects the metabolic pathway of a particular medication. Important interactions include such as; curcumin and Resveratrol may increase anticoagulant effects of warfarin. Ginger can increase bleeding risk when combined with antiplatelet drugs. St. John's Wort induces CYP3A4, thereby reducing the efficacy of many drugs. Therefore, co-administration should be monitored in clinical practice. The concentration of phytochemicals can differ from each other depending upon various reasons such as genetic variations, plant species, composition of the soil of different areas, environmental factors and harvesting and extraction methods. These deviations lead to varying therapeutic effects, making uniform extracts crucial for clinical use (Heinrich et al., 2021). For instance, compared to curcumin alone, 95% of curcuminoids have improved clinical result repeatability.

Commercial herbal products may contain a variety of contaminants that are harmful to human health, including as pesticide residue, synthetic drug contaminants, and heavy metals like lead and cadmium. Strict quality control and regulatory inspection are necessary since these pollutants might cause dangerous health issues. Despite their significant therapeutic potential, natural anti-inflammatory mediators have many drawbacks, including low absorption (curcumin, resveratrol, etc.), lack of extensive clinical trials data, and variations in formulations and dosage schedules. However, these restrictions can be overcome by employing phospholipid complexes, nanoformulations (liposomes, nanoparticles), and synergistic combination treatments.

CONCLUSION

Natural anti-inflammatory drugs continue to hold great therapeutic potential due to their diversified pharmacological actions and generally good safety profiles. Immune response controlled by cytokines can be modulated by these substances, and they may affect a number of key inflammatory pathways, including NF-κB, MAPKs, and COX/LOX enzymes. Due to the possibility of their multivalent action, they have a particular value for chronic inflammatory disorders during long-term treatment. Experimental and clinical data support the anti-inflammatory action of substances such as curcumin, boswellic acids, resveratrol, quercetin, components isolated from ginger, and omega-3 fatty acids. Application of its methods further rationalizes the scientific basis of many conventional medical approaches. There are many challenges that have to be overcome, such as the interaction of drugs with herbs and natural compounds, poor bioavailability, and variability in product quality. Future advances in formulation technologies, systematic clinical investigation, and improved regulatory guidelines will ensure enhanced therapeutic reliability. Innovations such as rational combination strategies and nanoparticle-based delivery hold promise for improved efficacy. In conclusion, natural anti-inflammatory drugs represent an important link between traditional medicine and

modern pharmacology. Ongoing studies will contribute to the design of safer multi-target-oriented anti-inflammatory therapies prepared from natural products and will help to elucidate their clinical applications and enhance their mechanisms.

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