REVIEW PAPER

Anti-Inflammatory Potential of Zingiber officinale and Nigella sativa: A Comprehensive Review

Kaushal Kumar[1], Dr. Garima Verma[2*], Dr. Arun Kumar[3]
[1]Ph. D Scholar (Pharmaceutical Science), Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Meerut
[2]Professor Department of Pharmaceutics, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Meerut
[3]Professor. Department of Pharmaceutics, Saraswati College of Pharmacy, Hapur
Corresponding Author:
Dr. Garima Verma
Professor Department of Pharmaceutics, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Meerut
Email:ID: garima.srivastava2111@gmail.com, Email:ID: pharmakaushal@rediffmail.com

ABSTRACT
Inflammation is a complex biological process which takes one of the leading roles in the pathogenesis of numerous acute and chronic pathologies. In spite of the fact that traditional anti-inflammatory options, including non-steroidal anti-inflammatory (NSAID) and corticosteroids, also prove to be effective, the long-term effects of these options often include adverse reactions and systemic toxicity, limiting their applicability in those cases. This has prompted a growing scientific curiosity as to phototherapeutic options that have a better safety profile. This review critically analyses the anti-inflammatory properties of Zingiber officinale (ginger) and Nigella sativa (black seed) as two herbal plants that have a traditional usage history in folk medicine. This article aims to shed some light on the pharmacological basis of these botanicals in terms of their investigation synthesis on evidence basis, in vivo and in vitro experimental studies, mechanistic understanding, and ethnomedicinal practices. The anti-inflammatory phenotype of ginger is exerting its effects by blocking the enzymatic activity of cyclooxygenase and lipoxygenase and impeding the activation of the NF-KB along with the synthesis of the pro-inflammatory cytokines. Similarly, Nigella sativa, primarily through thymoquinone, alters inflammatory signaling, suppressing NF-xB, suppressing NLRP3 inflammasome, suppressing oxidative stress, as well as simultaneously opposing immunoregulatory cytokine patterns. A comparative analysis reveals that ginger has a strong activity in the acute inflammatory condition, and Nigella sativa is a long-term therapeutic effect on chronic inflammatory diseases. The simultaneous or synergistic use of these botanicals leads to the creation of enhancement-based prospects of safer and multi-targeted anti-inflammatory interventions. Finally, this review identifies the therapeutic importance of ginger and Nigella sativa and the urgency of precisely planned clinical studies to support their inclusion in the management of inflammatory diseases today.

Keywords: Inflammation, Zingiber officinale, Nigella sativa, Gingerols, Phytotherapy, Cytokines; NF-κB; Oxidative stress, Herbal anti-inflammatory agents
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INTRODUCTION

Inflammation Concept

Inflammation serves as the body's innate immune defense mechanism against injury, infection, or irritants, involving immune cells, blood vessels, and molecular mediators to eliminate threats and promote repair(Punchard et al., 2004).Inflammation arises as a protective response to harmful stimuli like pathogens, damaged cells, or toxins, triggering vascular changes, leukocyte recruitment, and mediator release such as cytokines and prostaglandins. This process manifests through five cardinal si gns rubor (redness), calor (heat), tumor (swelling), dolor (pain), and functio laesa (loss of function) coined by Celsus and expanded by Galen(Schwager & Detmar, 2019). Biochemical cascades, including NF-κB activation and reactive oxygen species production, amplify the response while resolving via anti-inflammatory signals like resolvins(Nathan & Ding, 2010).

Relevance to Zingiber officinale and Nigella sativa

Zingiber officinale presents a powerful anti-inflammatory effect through the gingerol-mediated inhibition of cyclooxygenase and lipoxygenase enzymes, and suppression of proinflammatory cytokines and thus relieves arthritis and pain at low gastrointestinal morbidity. The central component of Nigela Sativa, thymoquinone, has antioxidant, antiviral and anti-inflammatory effects; in synergy with ginger, protects immunomodulation and decreases regulation of alpha-fetoprotein in clinical models.

**Author for Correspondence: Dr. Garima Verma*

These botanical agents meet the requirement of the low-toxicity therapeutics as supported by systematic reviews that recommend its replacement of synthetic drugs in favor of its use in the light of the increasing harm of NSAIDs (Abdel-Moneim et al., 2013).

Pathophysiology of Inflammation

Pathophysiology of inflammation involves a cascade of vascular, cellular, and molecular events triggered by harmful stimuli to protect tissues and initiate repair, progressing differently in acute and chronic phases

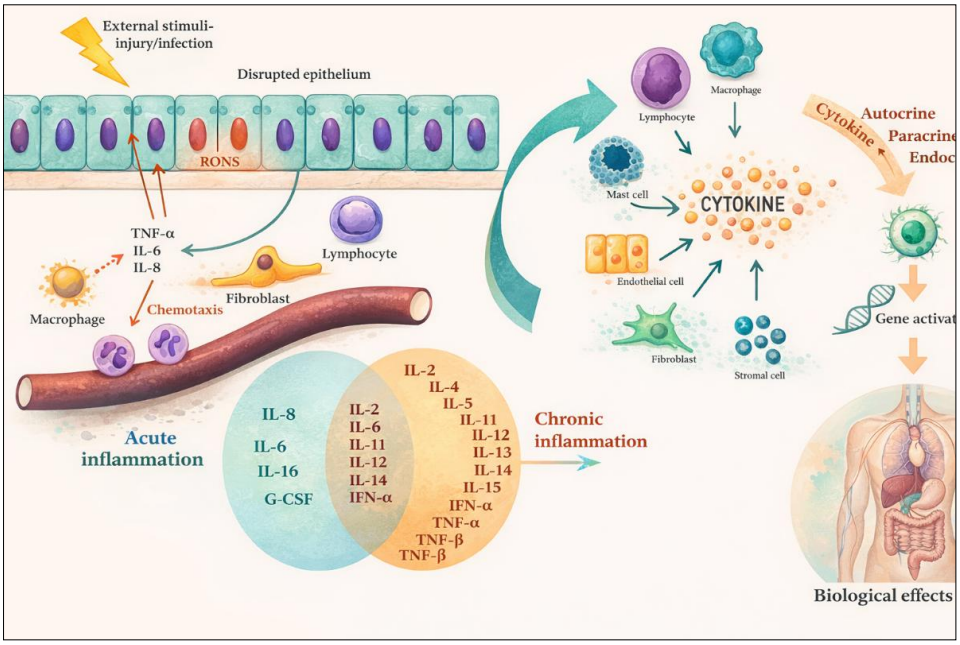

Figure 1. Molecular Pathways Involved in the Initiation and Progression of Inflammation

2.1 Acute and Chronic Inflammatory Responses

Acute inflammation begins rapidly (within minutes to hours) upon recognition of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors like Toll-like receptors (TLRs)(Hamidzadeh et al., 2017). This activates resident macrophages and mast cells to release mediators such as histamine, prostaglandins, and leukotrienes, causing vasodilation (increased blood flow, redness, heat) and increased vascular permeability (exudation of plasma proteins and fluid, leading to swelling)(Ptaschinski & Lukacs, 2018).

Neutrophils migrate via chemotaxis (driven by C5a, IL-8, LTB4), marginate, roll (selectins), adhere (integrins/ICAM-1), and transmigrate into tissues for phagocytosis of debris/pathogens, releasing reactive oxygen species (ROS), proteases, and NETs. Resolution occurs via apoptosis of neutrophils, efferocytosis by macrophages, and lipid mediators like resolvins/sphingosine-1-phosphate if stimuli are cleared; otherwise, it transitions to chronicity(Anderson & Jiang, 2017).

Key pathways include NF-κB activation (via IKK phosphorylation of IκB, freeing NF-κB for proinflammatory gene transcription like TNF-α, IL-1β, IL-6) and MAPK signaling, amplifying cytokine storms if dysregulated, as in sepsis.

Chronic Inflammatory Response

Chronic inflammation emerges from unresolved acute responses or persistent low-grade stimuli (autoantigens, metabolic stress), lasting weeks to years with mononuclear cell dominance (macrophages, lymphocytes). Macrophages polarize to M1 (proinflammatory, IFN-γ/LPS-induced, iNOS/IL-12 production) or M2 (resolving, IL-4/IL-13-induced, arginase/IL-10), but sustained M1 skewing drives tissue damage.

2.2 Inflammatory Mediators and Signaling Pathways

The complex molecular orchestra of inflammatory mediators and signaling pathways includes cell-derived and plasma-derived factors and transduction cascades that stimulate, maintain, or resolve inflammation in both acute and chronic settings. Cell-derived mediators initiate and propagate the response: vasoactive amines such as histamine (from mast cell degranulation via IgE cross-linking or C3a/C5a anaphylatoxins) and serotonin (from platelets) trigger immediate vasodilation of arterioles and increased endothelial gap formation, manifesting as the cardinal signs of redness, heat, and swelling within minutes; lipid mediators derived from arachidonic acid metabolism via phospholipase A2 activation bifurcate into cyclooxygenase pathways (COX-1 constitutively expressed for housekeeping, COX-2 inducible producing PGE2 for pain sensitization, fever via hypothalamic EP3 receptors, and PGI2 for vasodilation) and lipoxygenase pathways (5-LOX yielding LTB4 as a potent neutrophil chemoattractant binding BLT1 receptors, and LTC4/LTD4/E4 causing prolonged edema and bronchoconstriction); cytokines represent master regulators with TNF-α (from macrophages via TNFR1/2) inducing endothelial E-selectin/ICAM-1/VCAM-1 upregulation for leukocyte adhesion, apoptosis resistance, and systemic cachexia, IL-1β (similarly via IL-1R) driving fever and acute-phase responses like CRP/SAA synthesis in hepatocytes, and IL-6 (via gp130/JAK-STAT)

amplifying T/B cell responses and haematopoiesis chemokines such as CXCL8/IL-8 gradient-direct neutrophil trans endothelial migration, while growth factors like PDGF/VEGF promote angiogenesis in chronic phases. Plasma-derived mediators include C3a/C5a anaphylatoxins for mast cell activation and chemotaxis via C3aR/C5aR, kinins like bradykinin (cleaved from kininogens by kallikrein in the contact pathway) for pain and hypotension via B2 receptors, platelet-activating factor (PAF from leukocytes) for platelets and vascular leak, and fibrin degradation products for coagulation and inflammation. (Jamwal & Kumar, 2017)(Ajoolabady et al., 2024)(Cicala & Morello, 2023)(Chen et al., 2018).

2.3 Molecular Targets for Anti-Inflammatory Therapy

Anti-inflammatory therapy has molecular targets in key pathways of the inflammatory response, such as transcription factors, enzymes, cytokines, kinases and inflammasomes, that provide specific points of intervention to reduce pathological responses without compromising physiological defense. NF κB is a master regulator, which translocate to the nucleus in response to IKK degrading IikB to stimulate the transcription of TNF α, IL 6, cox2, and adhesion molecules; therapeutic interventions that stabilize IKK 2 using glucocorticoid-based therapy, or proteasomal inhibition such as BMS 345541 have shown effectiveness in preclinical models of colitis and arthritis. The celecoxib or rofecoxib selectively inhibit enzymes like COX-2 (inducible, generating pro-inflammatory PGE 2) but not cytosolic phospholipase A 2 (cPLA 2), whereas mPGES-1 selectively inhibit PGE 2 synthesis and iNOS selectively inhibit tissue damage by NO producer enzymes like inducible nitric oxide synthase (iNOS). Cytokines are biologically validated biologics: anti-tNF -alpha (infliximab, adalimumab) inhibit soluble/membrane-bound tissue to treat rheumatoid arthritis (RA) and Crohn disease by inhibiting TNFR1-mediated resistance to apoptosis and leukocytes transportation; IL-1 receptor antagonist anakinra or canakinumab antibody protects CAPS and gout by blocking TNFR1 reception; IL-6 blocker totilizumab Kinase targets, such as MAPKs p38 Alpha (SB203580 to reduce TNF in RA/COPD), JNK1/3 (SP600125 to prevent AP-1 in psoriasis/UC), ERK (tofacitinib to inhibit psoriasis/UC), and JAK1/2/3 (tofacitinib to block STAT phosphorylation in psoriasis/UC), are also provided with small-molecule opportunities, which have oral bioavailability. In cryopyrinopathies, atherosclerosis, and neurodegeneration, MCC950 (direct binding) or cryopyrin inhibitors target NLRP3 inflammasome assembly on K - efflux /ROS/PAMPs in order to stimulate caspase-1 to mature IL-1b/IL-18. An innate/adaptive interface (antagonized by BTK, ibrutinib to B-cell-based inflammation) and active termination (enhanced by resolution modulators, resolvins through ALX/FPR2 receptors) are targeted by emerging drugs (fostamatinib to RA), phytochemicals of *Zingiber officinale>gingerols (NF-kB/COX-2) and Nigella sativa thymoquinone (NLRP3/JAK-STAT) fit the multi-target profile of(Kaminska, 2005)(Krakauer, 2004).

3. Herbal Medicines in Inflammation Management

3.1 Role of Medicinal Plants in Traditional Systems

Medicinal plants have been of great importance in the treatment of inflammation in the various traditional medical practices. Using a host of bioactive phytochemicals, these botanicals are capable of reducing pains and swellings, fever, and various incurable disease cause in a multi-targeted manner, which has indeed been proven through millennia of use in India and China and beyond. In Ayurveda, e.g. Zingiber officinale (ginger, Shunthi) and Nigella sativa (black seed, Kalonji) are indispensable ingredients in anti-inflammatory preparations such as Trikatu, Panchakola and Sitopaladi churna. The Gingerols and shogaols in ginger have a potent effect on preventing COX-2 and LOX as well as inhibition of NF-kB-mediated cytokines, such as TNF-alpha, IL-1b and IL- 6, which is effective in alleviating the symptoms of both vata-kapha paradox and arthritis (amavata), gastrointestinal inflammation (grahan) and respiratory infections, like cough and asthma. Nigella sativa contains thymoquinone which provides antioxidant effects and immunomodulatory effects which reduces oxidative stress in the joint tissues. These ideas can be observed in Siddha practice with the use of ginger rhizome pastes (Arathai kashayam) as a topical agent in the treatment of rheumatic swellings, and the use of Nigella seed oils in the treatment of cutaneous swellings, which is in keeping with dosha harmony paradigms. Traditional Chinese Medicine (TCM) also brings in the use of Sheng Jiang (fresh ginger) to help stop wind-cold etiologies which generate acute phlegm-damp block; the Nigella sativa known as black cumin is said to strengthen spleen qi and empty heat and therefore keep meridians flowing and help to overcome stagnation.The Canon of Medicine by Ibn Sina is an example of the Greco Arab intellectual tradition which holds that Habbat al Sauda (Nigella sativa) should be used as a muharrik (warming) and munzij (resolvent) preparation. It is suggested in this treatise to be used in chronic inflammatory disease like bronchial asthma (zeeq-un-nafas), sciatica (irq-un-nisa), and hemorrhoidal disease and is commonly used in conjunction with honey or lipid carriers to increase its systemic absorption and efficacy. It is hypothesized that the synergistic effect of honey, a natural source of flavonoids and metabolic substrates, and the bioactive constituents of Nigella sativa will be greater on the inflammatory cascade as a result of empirical evidence of the integration of the two.The therapeutic range of plant resources can also be seen in ethnomedical systems in Africa and the Americas. The example of Lesotho is that over 90 per cent of flower flora catalogued are found to have a high anti-inflammatory activity in in-vitro bioassays, and sesquiterpenes and flavonoids represent most pharmacodynamic properties. These species serve the purpose of stabilizing edema, limiting infection and speeding up healing of wounds. The Native American analogies also take advantage of Salix alba (willow bark) as a source of salicin, the biochemical precursor to salicylic acid, and so create an antecedent of acetylsalicylic acid, and emphasizes the persistent potency of plant-derived analgesics. In all these international settings, the unification of empirical observations, low toxicity profiles and polypharmacy are in unison with the modern paradigms of phytotherapeutic methods, especially

in the face of increasing synthetic pharmaceutical resistance.(Oguntibeju, 2018)(Ghasemian et al., 2016b)(Nunes et al., 2020).

3.2 Advantages of Phototherapeutics over Synthetic Drugs

Phototherapeutic reagents provide visible benefits in comparison to traditional synthetic anti-inflammatory medications, and the growing number of peer-reviewed articles testifies to it. There is a significant reduction in their toxicity profiles that is likely attributed to the occurrence of varied phytochemicals that interact with different therapeutic targets in a synergistic manner. This multi-modal activity not only contributes to the efficacy but also provides the cost-effectiveness, which makes phototherapeutics especially applicable to be used in the context of the holistic approach to the healing process, in which the priority might be given to the minimization of the negative occurrences and to elimination of the factors that contributed to the development of the inflammatory processes (M. Gupta et al., 2021).Synthetic non-steroidal anti-inflammatories (NSAIDs), including ibuprofen or diclofenac, often cause gastrointestinal illness, renal dysfunction particularly in older years or dehydration, cardiovascular thrombotic effects (including myocardial infarction provoked by COX-2 selective drugs like rofecoxib), hepatotoxicity, and overreaction to withdrawal in response. Instead, herbal medicines are identified by a lower occurrence rate and less severe severity of adverse effects, which can be ascribed to their poly-phenol-enriched matrices, that offer natural antioxidant defense, mediate the buffering of acute pharmacologic activity of single bioactives, and stimulate self-regulatory response mechanisms without interfering with physiological homeostasis. It is the nature of the interaction between multiple constituents acting in concert to regulate key signalling cascades, such as NF -KB, COX/LOX, and cytokine networks, simultaneously that captures the idea of the entourage effect: the effect of many constituents acting as a single entity is significantly superior to single-target synthetics which frequently result in resistance, partial symptom suppression or disease progression in chronic conditions such as rheumatoid arthritis or inflammatory bowel disease. As an example, gingerol constituents of *Zingiber officinale* and thymoquinone of Nigella sativa are holistic inhibitors of pro-inflammatory inflammation and induce microbiome harmony and immune tolerance(Karimi et al., 2015)(Ghasemian et al., 2016a)

4. *Zingiber officinale* (Ginger)

4.1 Botanical Description and Ethnomedicinal Uses

Botanical Description

Ginger grows erect to 1-1.25 m tall as a slender, reed-like herb with unbranched pseudostems formed by overlapping leaf sheaths (pale green, often reddish at base, prominently veined, and covered in oblong scales 6 cm x 1 cm with scarious margins). The rhizome, the economic part, is thick (up to 2 cm diameter), horizontally branched primarily in the vertical plane, shallowly subterranean, with a thin, corky, pale yellow to reddish-brown epidermis bearing ring-like leaf scars and shallow cup-shaped stem remnants; internally, it features pale yellow, fibrous, juicy flesh rich in oleoresin (1-3% volatile oils like zingiberene, β-bisabolene, gingerols) exuding a spicy-citrus aroma(Kaufman, 2016)

Figure 2. Morphology of *Zingiber officinale* (Ginger)

Leaves are distichous, linear-lanceolate (20-30 cm long x 1.5-2 cm wide), acuminate, glabrous above with fine parallel veins, sparsely pilose below, and short bifid ligules (up to 5 mm, scarious). Inflorescences emerge directly from rhizomes on 10-30 cm scapes hidden by scales, forming ovoid to ellipsoidal spikes (4-7 cm x 3 cm) with imbricate, yellowish-green to reddish bracts (2-3 cm) each subtending a single flower; flowers are pale yellow with purple-streaked labellum (12-15 mm diameter, 3-lobed), tubular corolla (18-25 mm tube widening to ovate dorsal lobe 15-25 mm x 7-8 mm and oblong ventral lobes), versatile anther (7-9 mm, purple-beaked connective), filiform style, and globose 3-locular ovary topped by white nectaries(Singh et al., 2022).

Fruits are oblong, thin-walled, red, 3-valved capsules containing small, black, arillate seeds; cultivated plants rarely flower/fruit, propagated vegetatively via rhizome divisions(Zimazi et al., 2022).

Ethnomedicinal Uses

Zingiber officinale Roscoe (ginger) holds a prominent place in ethnomedicinal practices across diverse traditional systems, valued for its rhizome's pungent, warming

properties that address a wide spectrum of inflammatory, digestive, and respiratory ailments through empirical validation over millennia(SHAHRAJABIAN et al., 2019).

Ayurveda and Siddha

In Ayurveda, known as Shunthi (dried) or Adraka (fresh), ginger features in classical texts like Charaka Samhita and Sushruta Samhita as a deepana (appetizer), pachana (digestive), and vishaghna (antitoxic) agent, prescribed in formulations such as Trikatu churna (with black pepper and long pepper) for amavata (rheumatoid arthritis), grahani (IBS), and jwara (fever), where gingerols alleviate vata-kapha imbalances, reduce joint swelling, and combat ama (toxins); rhizome decoctions with jaggery treat cough, asthma, and postpartum recovery, while pastes address headaches and muscular pain. Siddha traditions employ Arathai (ginger) kashayam topically for rheumatic swellings, wounds, and skin inflammations, often combined with castor oil(Shahrajabian et al., 2019).

Traditional Chinese Medicine

Classified as a Yang-warming acrid herb (Xin Wen), Sheng Jiang (fresh ginger) dispels wind-cold invasions, harmonizes stomach qi for nausea/morning sickness, and resolves phlegm-dampness in respiratory disorders; it's integral to formulas like Jiang Ya Tang for hypertension and Xiao Qing Long Tang for cough with thin sputum, while Gan Jiang (dried) treats middle jiao cold; used for colic, atonic dyspepsia, and cardiovascular support per ancient(J. Gupta et al., 2025).

Unani Traditions

Unani medicine (Hindi Zanjabeel) views ginger as muharrik (stimulant) and munaffis (expectorant) for zeeq-un-nafas (asthma), irq-un-nisa (sciatica), and hemorrhoids, often with honey; Hippocratic and Galenic texts praise its purgative, antiemetic effects for digestive inflammations(Hongal et al., 2014).

Figure 3. Role of the Unani System of Medicine in the Management

Global Folklore

Iranian folk medicine uses ginger for anti-edema, migraines, gastric ulcers, and atherosclerosis; African healers apply rhizome pastes for sprains, infections, and bone injuries, with concoctions (most common form) for pre/postnatal care (labor induction, lactation); globally, it's a remedy for colds, sore throats, rheumatism, hypertension, dementia, and infectious diseases, also as a flavouring preservative("Traditional Uses of Ginger (Zingiber Officinale Roscoe) Based on Ethnomedicine Study in 254 Indonesia Ethnic Groups," 2024).

4.2 Major Phytochemical Constituents

Zingiber officinale Roscoe (ginger) rhizome is a treasure trove of bioactive phytochemicals, comprising volatile essential oils (1.2-3.5%), pungent non-volatile oleoresins (4-8%), and diverse secondary metabolites that underpin its pharmacological potency, with composition varying by cultivar, geography, age, and processing (fresh vs. dried) as detailed in comprehensive reviews. Volatile oils, extracted via steam distillation, are dominated by sesquiterpenes (65-85%) including α-zingiberene (15-35%, the signature bicyclic hydrocarbon imparting characteristic aroma), β-Sesquiphellandrene (10-20%), β-bisabolene (3-10%), ar-curcumene (2-8%), and zingiberenes, alongside monoterpenes like β-phellandrene (10-15%), camphene (7-18%), α-pinene (2-5%), β-pinene (1-17%), myrcene (2-4%), and oxygenated compounds such as citral (geranial + neral, 3-7%), eucalyptol (1-15%), linalool (trace), contributing antimicrobial, anti-inflammatory, and antioxidant activities; wild varieties elevate β-phellandrene (up to 73%) and isoeugenol, while domestic types favor zingiberene. Pungent principles, heat-labile vanilloid homologs, feature gingerols 6-gingerol (major, 0.5-3%, -gingerol or (S)--gingerol), 8-gingerol (0.2-1%), 10-gingerol

(0.1-0.5%) biotransforming to shogaols upon dehydration (6-shogaol 0.1-2%, more bioactive), paradols (6-paradol trace), zingerone (from shogaol hydration, sweet-spicy), and diarylheptanoids like gingerenones A-C, hexahydrocurcuminols, and dehydrogingerdiones, which potently inhibit NF-κB, COX-2, and 5-LOX while scavenging ROS. Additional constituents encompass flavonoids (quercetin, kaempferol, rutin glycosides), polysaccharides (gingerols, β-glucans for immunomodulation), phenolic acids (ferulic, caffeic), organic acids (citric 0.02%, malic), lipids (1-2%), raw fibers (4-8%), and minerals (K, Mg, P), with over 400 compounds identified via GC-MS/LC-MS, synergistically enhancing bioavailability and efficacy(Mao et al., 2019)(Abdullahi et al., 2020)(Liu et al., 2019)(Pop et al., 2020)(Raharjo et al., 2025)

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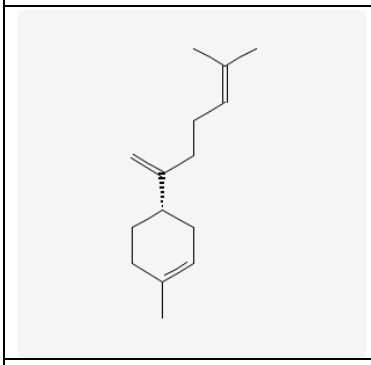
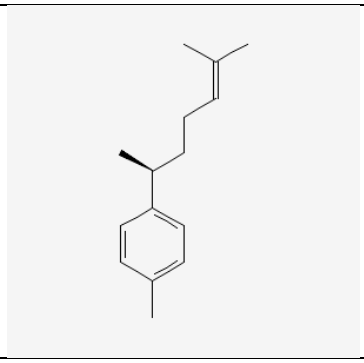
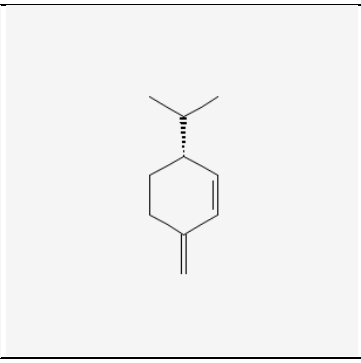
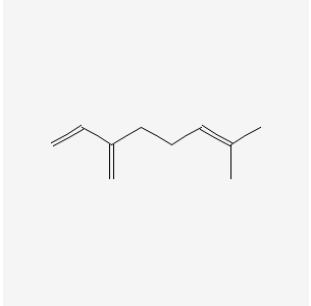
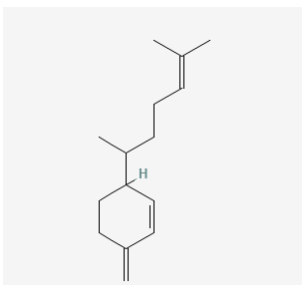
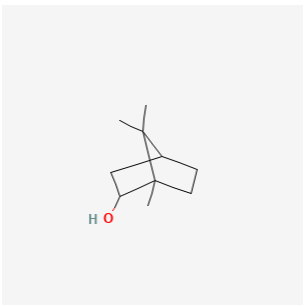
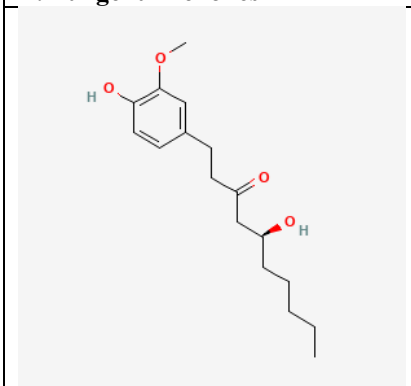
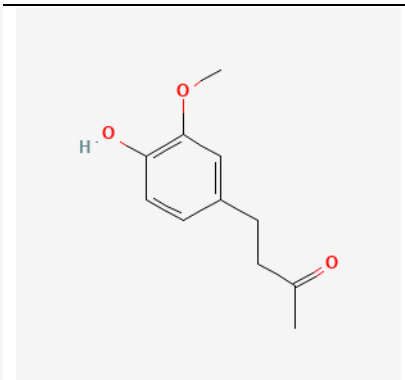
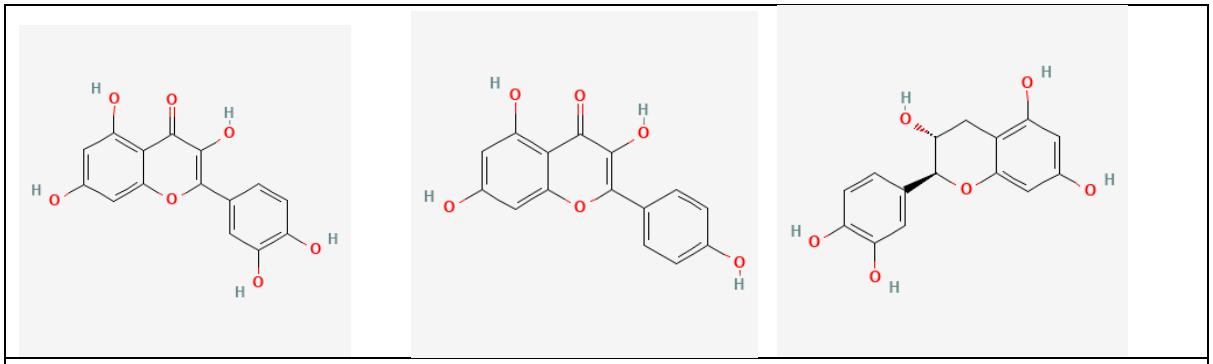
Table

A. Volatile Oil		
		
β-bisabolene	ar-curcumene	phellandrene
		
Myrcene	Sesquiphellandrene	Borneol
B. Pungent Phenolics		
		
Gingerols	Zingerone	
C.Flavonoids		



Quercetin	Kaempferol	Catechin

5.1Mechanisms of Anti-Inflammatory Action

Ginger (Zingiber officinale) manifests its anti-inflammatory action through multifaceted mechanisms orchestrated by bioactive pungent principles primarily 6-gingerol, 6-shogaol, 8-gingerol, zingerone, and diarylheptanoids that target critical nodes in the inflammatory cascade, including transcription factor suppression, enzyme inhibition, cytokine modulation, and oxidative stress mitigation, as evidenced across preclinical and clinical studies. At the molecular forefront, these compounds potently inhibit the NF-κB signaling pathway by preventing IKK-mediated phosphorylation and subsequent proteasomal degradation of IκBα, thereby blocking p65/p50 heterodimer nuclear translocation and transcription of proinflammatory genes encoding TNF-α (60-80% in LPS-stimulated RAW 264.7 macrophages), IL-1β, IL-6, IL-8/CXCL8, MCP-1, and COX-2/iNOS, with 6-shogaol demonstrating 2-5-fold greater efficacy than parent gingerol due to higher lipophilicity and stability; parallel suppression of MAPK cascades (phospho-p38, JNK, ERK1/2 reduced by 50-70%) and PI3K/Akt pathways curtails AP-1 activation and mTOR-driven survival signals in activated monocytes and synovial fibroblasts. Enzymatic targets include selective COX-2 (IC50 5-20 μM for 6-shogaol vs. ibuprofen), 5-LOX (reducing LTB4/C4 by 40-60%), and iNOS (NO production inhibited 70% in IFN-γ/LPS models), yielding decreased PGE2, thromboxane, and peroxynitrite without GI mucosal disruption; red ginger variants (var. rubrum) uniquely suppress PDE4 (elevating cAMP/PKA/CREB for IL-10 upregulation) and NETosis in neutrophils. Cytokine profiling reveals Th1/Th2 rebalancinlowered IFN-γ/IL-12 with elevated IL-10/TGF-β alongside NLRP3 inflammasome blockade (caspase-1/IL-1β cleavage inhibited), while antioxidant armory via Nrf2/HO-1 induction neutralizes ROS/RNS, preserves GPx/SOD, and prevents lipid peroxidation in arthritis/edema models; human meta-analyses corroborate serum reductions in CRP (SMD -0.45), hs-CRP (-1.2 mg/L), and TNF-α (-2.5 pg/mL) post 4-12 weeks supplementation (1-3 g/day). Synergistic entourage effects amplify bioavailability (e.g., piperine enhancement), positioning ginger as a safe COX-sparing alternative for chronic inflammation in osteoarthritis, IBD, and metabolic syndrome.(Ayustaningwarno et al., 2024a)(Ballester et al., 2022)(Pázmándi et al., 2024)(Morvaridzadeh et al., 2020)

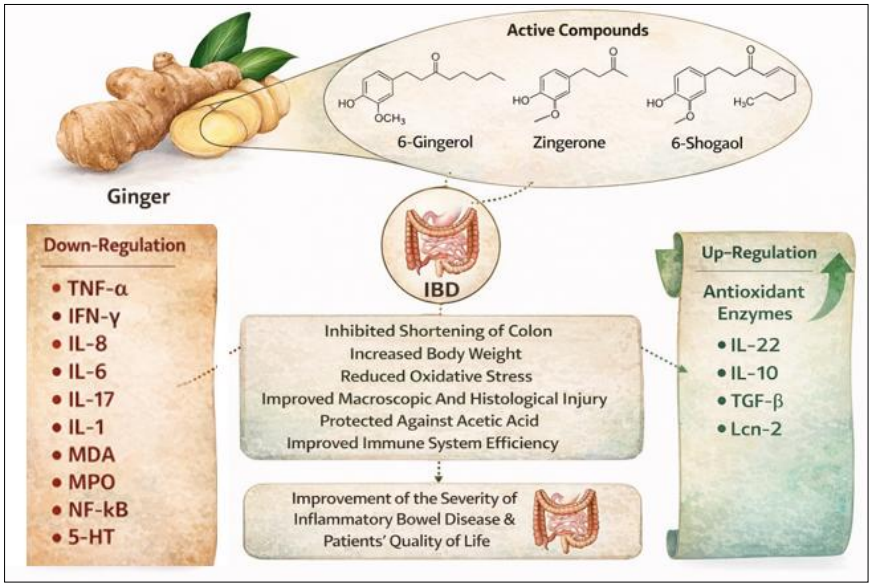


Figure 4. Mechanistic Role of Ginger and Its Bioactive Compounds in the Modulation of Inflammatory Bowel Disease

5.2 Evidence from In Vitro and In Vivo Studies

Zingiber officinale (ginger) demonstrates robust anti-inflammatory activity across diverse in vitro models

through its bioactive compounds primarily 6-gingerol, 6-shogaol, 8-shogaol, and zingerone that potently suppress proinflammatory cytokines, enzymes, eicosanoids, and signaling pathways in macrophages, synoviocytes, monocytes, and membrane stabilization assays, as evidenced by comprehensive studies. In LPS/IFN-γ-stimulated RAW 264.7 murine macrophages and primary peritoneal macrophages, supercritical CO2 ginger extracts (50-200 µg/mL), particularly liposome-encapsulated formulations, achieve 60-80% inhibition of NO production (baseline 102 µM reduced to 20-40 µM), 70% reduction in TNF-α secretion, and 65% suppression of IL-1β via blockade of iNOS/COX-2 induction, NF-κB p65 nuclear translocation, and IκBα phosphorylation, with liposomal delivery enhancing bioavailability 2-3 fold over DMSO-dispersed forms and 6-shogaol exhibiting IC50 values of 5-10 µM for PGE2/COX-2 inhibition. Human rheumatoid arthritis (RA) synoviocytes and 3D synovial organoid cultures treated with 8-shogaol (10-50 µM) show 50-75% downregulation of TNF-α/IL-1β/IL-17-induced IL-6, MMP-1/3/13, and CXCL8 alongside 75% inhibition of cell migration through dual NF-κB/p38 MAPK pathway suppression, preventing synovial hyperplasia in co-culture systems. Methanolic ginger extracts (50-1000 µg/mL) stabilize hypotonicity-induced human red blood cell (HRBC) membrane lysis by 86.34% (comparable to diclofenac sodium at 91.16%) and inhibit heat/NSAID-induced albumin/egg albumin denaturation by 60-80% (superior to indomethacin at low doses), indicating lysosomal stabilization and anti-edema potential. In J774.1A macrophages and activated monocytes, ginger essential oil and TiO2 nanoparticles biosynthesized with ginger extracts maximally suppress iNOS/NO (70% reduction), PGE2, and proinflammatory mediators, while 6-gingerol inhibits PDE4 to elevate cAMP/PKA/CREB signaling, upregulating anti-inflammatory IL-10; additional models confirm Nrf2/HO-1 induction for ROS scavenging and NLRP3 inflammasome blockade in THP-1 monocytes. These multi-target effects position ginger extracts as promising alternatives to synthetic NSAIDs, with synergistic low-dose combinations outperforming single agents in protein denaturation and cytokine assays(Justo et al., 2015)(Zammel et al., 2021)(Thakur et al., 2020)(Mutthuraj et al., 2020)

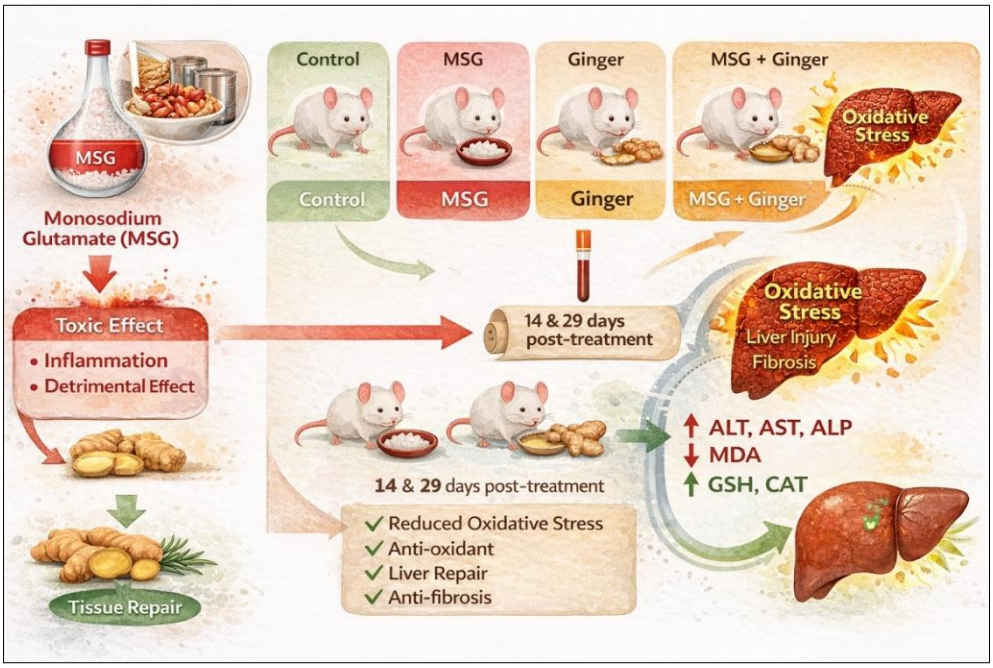


Figure 5. Protective Role of Ginger against Monosodium Glutamate–Induced Oxidative Stress and Liver Injury

6. *Nigella sativa* (Black Seed)

6.1 Botanical Description and Ethnomedicinal Importance

Botanical Description

Nigella sativa L., an annual herbaceous plant of the Ranunculaceae family native to the Mediterranean and Southwest Asia, exhibits distinctive morphological features that distinguish it within the genus, growing erect to 20-90 cm tall on slender, branching, glabrous to pubescent, green-striate stems that bear alternate, sessile to subsessile leaves arranged in a loose spiral. The leaves are 2-3-pinnately compound, finely dissected into linear-filiform segments (0.5-2 mm wide, 1-3 cm long), glaucous green with entire margins, lacking stipules, and presenting a feathery, thread-like appearance typical of the genus. Flowers emerge solitary and terminal or axillary on peduncles measuring 2-5 cm, displaying actinomorphic symmetry with 5 petaloid sepals (oblong, 1-1.5 cm) and 5-10 true petals (delicate, 1-2 cm long) in shades of pale blue, white, yellow, pink, or pale purple, surrounding numerous (13+) stamens with pale yellow anthers and a superior, 5-10 carpellate ovary topped by white nectaries; the corolla tube is short, and styles are filiform. The fruit forms a characteristic large (2-3 cm), inflated, ovoid-oblong capsule composed of 3-7 united follicles that dehisce apically at maturity, each follicle housing 30-50 small, trigonal-angular seeds (2-3.5 mm × 1-2 mm) with a black, regulose-tubercular exocarp, white interior, slightly aromatic odor, and bitter taste; microscopically, seeds reveal a single-layered epidermis of

elliptical thick-walled cells with papillose cuticle and dark brown contents rich in fixed oil.(Ahmad et al., 2013)(Alberts et al., 2024)(Salehi et al., 2021)

Figure 6. morphology of *Nigella sativa* (Black Seed)

Plant Feature

Feature	Description
Height	20-90 cm, branching stem
Leaves	2-3-pinnate, linear segments
Flowers	Pale blue/white, 5-10 petals
Fruit	Inflated capsule, 3-7 follicles
Seeds	Black, trigonal, 2-3.5 mm

Ethnomedicinal Importance

Revered as "the cure for all diseases except death" in Hadith literature, Nigella sativa seeds and oil hold central roles across traditional systems: in Unani-Tibb (Habbat al-Sauda), prescribed for respiratory ailments (asthma, cough), digestive disorders, rheumatism, and skin conditions per Ibn Sina's Canon; Ayurveda/Siddha employs it as Kalonji for antidiabetic, anthelmintic, and anti-inflammatory uses in formulations like Panchakola; TCM analogs treat "cold-bi" syndromes; Middle Eastern/North African traditions use seed pastes for wounds, swellings, and infections, while Ethiopian/Yemeni folklore addresses hypertension, diabetes, and postpartum recovery. Globally valued for immunomodulatory, antioxidant, and anti-inflammatory properties in teas, oils, and confections(Ahmad et al., 2013)(Tariq, 2008)

6.3 Bioactive Constituents

Nigella sativa L. seeds contain a diverse array of phytochemical constituents, with fixed oil (32-40%) comprising over 58% thymoquinone (TQ, 1.5-4.85%, the signature bioactive quinone), alongside essential volatile oil (0.4-2.5%) rich in p-cymene (14-21%), trans-thymoquinone, α-thujene, α-pinene, β-pinene, carvacrol, longifolene, and trans-anethole, as identified via GC-MS profiling across studies. Non-volatile components include flavonoids (quercetin, kaempferol, rutin glycosides like nicotiflorin/kaempferol-3-O-rutinoside, nigelflavonoside G), phenolic acids (sinapic, ferulic, p-coumaric), tannins, saponins, alkaloids (nigellimine, nigellicine), sterols (β-sitosterol, daucosterol), triterpenes, and polysaccharides; hexane extracts yield toluene, m-cymene, decane, allopurinol, while methanol extracts feature ethylenimine, ethylbenzene, o-xylene, contributing antimicrobial/antioxidant synergy. TQ derivatives (dithymoquinone DTQ, thymohydroquinone THQ) dominate bioactivity, with nutritional elements (proteins 21%, carbs 34%, fibers 10%, minerals K/Ca/Fe) enhancing therapeutic value(Akram Khan & Afzal, 2016)

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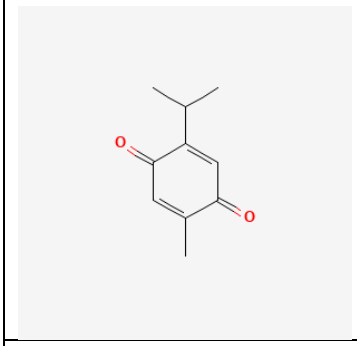
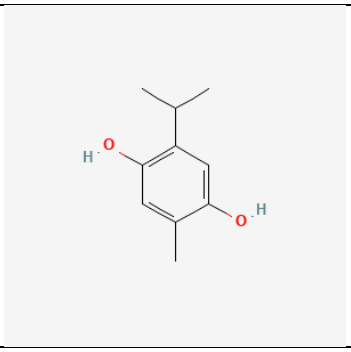
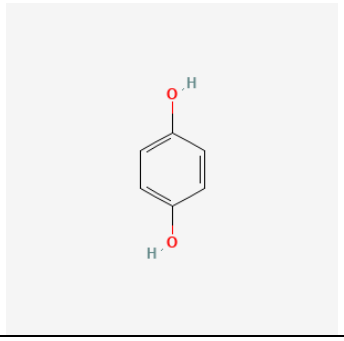
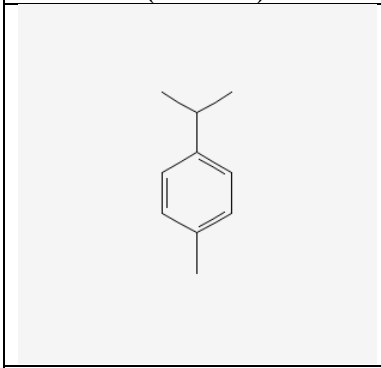
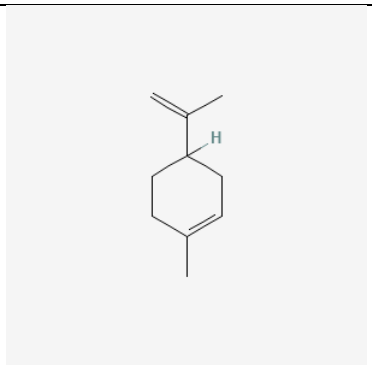
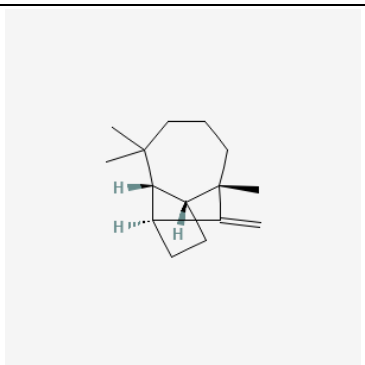
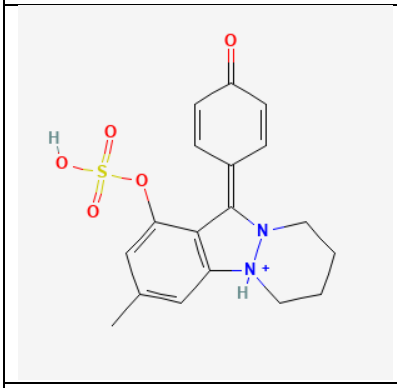
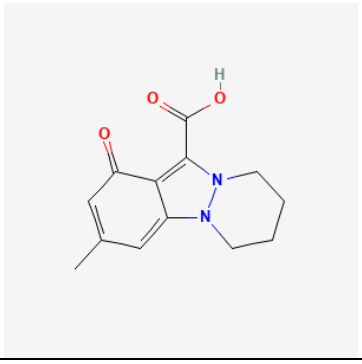
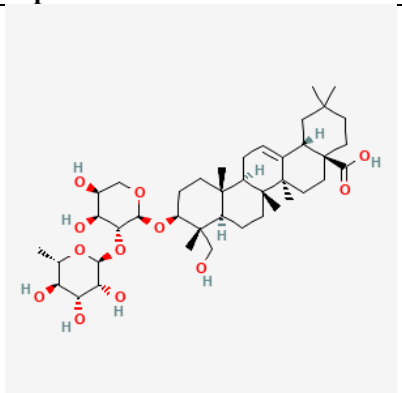
A. Quinones (Major Bioactive Markers)

		
Thymoquinone	Thymohydroquinone	Hydroquinone
B. Volatile (Essential) Oil Constituents		
		
P-CYMENE	Limonene	Longifolene
C. Alkaloids		
		
Nigellidine	Nigellicine	
D. Saponins		
		
α-Hederin		

6.4 Anti-Inflammatory and Immunomodulatory Mechanisms

Nigella sativa L. (black seed) manifests its anti-inflammatory and immunomodulatory effects through multifaceted mechanisms orchestrated primarily by

thymoquinone (TQ, 1.5-4.85%), its dimeric form dithymoquinone (DTQ), thymohydroquinone (THQ), and synergistic seed matrix components that intercept key inflammatory cascades, cytokine networks, and immune cell polarization while promoting resolution pathways, as comprehensively reviewed in pharmacological literature. At the molecular core, TQ potently suppresses NF-κB signaling by inhibiting IKKα/β phosphorylation of IκBα at Ser32/36 (IC50 5-15 μM), preventing p65/p50 heterodimer nuclear translocation and κB-site binding to silence transcription of proinflammatory mediators including TNF-α (60-80% in LPS/IFN-γ-stimulated RAW 264.7 macrophages), IL-1β, IL-6, COX-2, iNOS, and adhesion molecules (ICAM-1/VCAM-1), thereby curtailing endothelial activation, leukocyte extravasation, and systemic acute-phase responses like CRP/SAA synthesis; concurrent blockade of MAPK modules phospho-p38 (↓50-70% via MKK3/6 inhibition), JNK (AP-1/c-Jun suppression), and ERK1/2 interrupts downstream AP-1 synergy and stress kinase amplification of cytokine loops. Enzymatic targets encompass selective COX-2/PGE2 downregulation (comparable to celecoxib without CV risks), 5-LOX pathway inhibition yielding reduced LTB4/C4-mediated chemotaxis and bronchospasm, and phospholipase A2 blockade to limit arachidonic acid mobilization; TQ further attenuates NLRP3 inflammasome oligomerization(Jain et al., 2025) (via K+ efflux/ROS/P2X7R sensing) by suppressing ASC/caspase-1 assembly and pro-IL-1β/IL-18 cleavage, critical in gout, cryopyrinopathies, and metabolic inflammation. Immunomodulation features Th1/Th2 rebalancing with diminished IFN-γ/IL-12/IL-17 (Th17 inhibition via RORγt suppression) alongside elevated IL-4/IL-10/TGF-β from Tregs, enhanced NK cell cytotoxicity (against K562 tumors), B-cell proliferation with IgG isotype switching, and mast cell stabilization (↓histamine/β-hexosaminidase from RBL-2H3 via c-kit/Syk blockade); antioxidant armory via Nrf2 nuclear translocation induces HO-1/NQO1/GPx to neutralize ROS/RNS, inhibit lipid peroxidation (↓MDA), and preserve mitochondrial integrity. These pleiotropic actions position Nigella sativa as a natural multi-target immunomodulator for chronic inflammatory conditions like RA, asthma, IBD, and neuroinflammation, synergizing with synthetic therapies while exhibiting superior safety profiles..(Ayustaningwarno et al., 2024b)(Majdalawieh & Fayyad, 2015)(Kohandel et al., 2021)(Fatima Shad et al., 2021)

6.5 In Vitro Studies

Nigella sativa L. (black seed) exhibits potent anti-inflammatory effects validated through extensive in vitro studies primarily mediated by thymoquinone (TQ, 5-20 μM) and seed extracts (10-100 μg/mL) that suppress proinflammatory mediators and signaling pathways across diverse cellular models of inflammation. In lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophages, black cumin seed extract (BCS) dose-dependently inhibits production of prostaglandin E2 (PGE2), nitric oxide (NO), tumor necrosis factor-α (TNF-α), interleukin(Jain et al., 2024)-1β (IL-1β), IL-6, and monocyte chemoattractant protein-1 (MCP-1) by 50-80%, alongside significant downregulation of COX-2/iNOS mRNA expression and phosphorylation of NF-κB p65 subunit, IκBα degradation, p38 MAPK, and JNK pathways, demonstrating robust IC50 values (~32.8 μg/mL for DPPH radical scavenging activity); TQ specifically blocks β-hexosaminidase and histamine degranulation in RBL-2H3 rat basophilic leukemia cells (anti-allergic mechanism) while suppressing TNF-α secretion in J774.1A macrophages via c-kit/Syk signaling inhibition. In Simpson-Golabi-Behmel syndrome (SGBS) pre-adipocytes modeling chronic low-grade metabolic inflammation, fresh Nigella sativa essential oil (FEO, containing 33% higher TQ than stored oil) significantly reduces TNF-α-induced IL-1α elevation, enhances cellular viability under inflammatory stress, and outperforms aged extracts, highlighting lipid peroxidation protection. Ethanol seed extracts mediated biogenic silver nanoparticles exhibit dose-dependent inhibition of heat/trypsin-induced albumin denaturation (comparable to diclofenac sodium 100 μg/mL), proteinase inhibitory activity, and HRBC membrane stabilization, indicating lysosomal protection relevant to rheumatoid arthritis and edema. In 3T3-L1 preadipocytes, BCS attenuates LPS-induced adipogenesis and inflammation by downregulating peroxisome proliferator-activated receptor γ (PPARγ), CCAAT/enhancer-binding protein α (C/EBPα), adipocyte protein 2 (aP2), lipoprotein lipase (LPL), fatty acid synthase (FAS), and sterol regulatory element-binding protein-1c (SREBP-1c) by 50-65%, limiting lipid droplet accumulation and cytokine secretion. Additional THP-1 monocyte models confirm TQ's suppression of NLRP3 inflammasome activation (↓caspase-1/IL-1β), ROS production, and endothelial adhesion molecule expression, positioning Nigella sativa extracts as multi-target alternatives to synthetic NSAIDs.(Bashir et al., 2023)(Shaheen et al., 2021)(Shehensha & Jyothi, 2020)

7. Comparative Anti-Inflammatory Potential

7.1 Comparison of Phytochemicals and Mechanisms

Zingiber officinale (ginger) and Nigella sativa L. (black seed) demonstrate complementary anti-inflammatory potential through distinct yet overlapping phytochemical profiles and mechanistic signatures, with ginger's pungent vanilloids (6-gingerol 1-3%, 6-shogaol post-dehydration) and sesquiterpenes (α-zingiberene 15-30%) targeting eicosanoid biosynthesis via potent COX-2/5-LOX inhibition (IC50 5-20 μM) and NF-κB/p38 MAPK blockade to rapidly suppress acute PGE2/LTB4/TNF-α/IL-6 cascades, while Nigella's quinone-rich fixed oil (thymoquinone/TQ 1.5-4.85%, p-cymene 14-21%) excels in sustained NLRP3 inflammasome suppression (caspase-1/IL-1β ↓60%), STAT3 inhibition, and Th1/Th2 immunomodulation (↑IL-10/Tregs, ↓IFN-γ/IL-17) alongside iNOS/NO reduction, as evidenced by comparative paw edema models where ginger provides faster onset but Nigella sustains prolonged resolution. Ginger uniquely elevates cAMP via PDE4 blockade for M2 macrophage polarization and Nrf2/HO-1-mediated ROS quenching (↑SOD/GPx, ↓MDA), mitigating NETosis and lipid peroxidation in synovial models, whereas Nigella enhances NK cytotoxicity, mast cell stabilization

(↓histamine via c-kit/Syk), and humoral IgG switching while curbing IgE-driven allergy; both converge on IκBα stabilization to silence NF-κB p65 nuclear translocation (↓proinflammatory gene transcription 50-80%) and MAPK phosphorylation (p38/JNK/ERK ↓50-70%), yielding synergistic polypharmacy potential ginger for acute flare-ups (arthritis, gastroenteritis) and Nigella for chronic low-grade inflammation (metabolic syndrome, asthma) with entourage effects amplifying bioavailability when combined, positioning them as safer NSAID alternatives devoid of GI/CV toxicities.(Ayustaningwarno et al., 2024a)(Majdalawieh & Fayyad, 2015)

7.2 Synergistic and Complementary Effects

Zingiber officinale (ginger) and Nigella sativa L. (black seed) exhibit synergistic and complementary anti-inflammatory effects through their distinct phytochemical profiles that target overlapping yet divergent inflammatory pathways, enhancing therapeutic efficacy when combined as supported by preclinical evidence. Ginger's pungent gingerols (6-gingerol) and shogaols provide rapid COX-2/5-LOX inhibition (↓PGE2/LTB4 by 60-80%) and NF-κB/p38 MAPK suppression for acute flare-ups, while Nigella's thymoquinone (TQ) delivers sustained NLRP3 inflammasome blockade (↓caspase-1/IL-1β), STAT3 inhibition, and Th2/Treg promotion (↑IL-10/IL-4), creating polypharmacy synergy where ginger accelerates onset and Nigella prolongs resolution; comparative paw edema models demonstrate combination superiority over individual extracts. Mechanistic complementarity amplifies Nrf2/HO-1 antioxidant induction (ginger ↑SOD/GPx, Nigella ↓ROS/MDA), cAMP elevation via dual PDE4 blockade, and cytokine rebalancing (↓Th1/Th17 cytokines, ↑regulatory mediators), with entourage effects enhancing bioavailability piperine analogs in ginger boosting TQ absorption; clinical formulations combining both reduce CRP/TNF-α more effectively than monotherapy in metabolic inflammation(Zhou et al., 2022)

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CONCLUSION

The collective evidence presented in this review clearly demonstrates that *Zingiber officinale* and *Nigella sativa* possess significant anti-inflammatory potential mediated through diverse and complementary molecular mechanisms. Both plants target key inflammatory mediators, including cytokines, transcription factors, and oxidative stress pathways, while maintaining favorable safety profiles compared to synthetic anti-inflammatory drugs. Ginger predominantly acts through rapid suppression of pro-inflammatory enzymes and cytokines, making it particularly effective in acute inflammatory conditions. In contrast, *Nigella sativa*, with thymoquinone as its principal bioactive constituent, exhibits strong immunomodulatory and antioxidant actions that are more suited to chronic and systemic inflammatory disorders. Importantly, the multi-target nature of these phytochemicals allows modulation of inflammation without complete immune suppression, an advantage over single-target pharmacological agents. Despite substantial preclinical evidence, clinical validation remains limited and often heterogeneous in study design. Therefore, future research should focus on standardized extracts, optimized dosing regimens, pharmacokinetic profiling, and large-scale clinical trials. Overall, *Zingiber officinale* and *Nigella sativa* represent valuable natural resources with strong potential to complement or reduce reliance on conventional anti-inflammatory therapies

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SUMMARY

This comprehensive review explores inflammation as a biological process and evaluates the therapeutic potential of *Zingiber officinale* and *Nigella sativa* as natural anti-inflammatory agents. The paper outlines the pathophysiology of acute and chronic inflammation, highlights key inflammatory mediators and signalling pathways, and discusses molecular targets relevant to therapy. Detailed sections on ginger and black seed cover their botanical features, traditional uses, phytochemical profiles, and experimentally validated anti-inflammatory mechanisms. Comparative analysis reveals distinct yet complementary actions of the two plants, supporting their possible synergistic use. Overall, the review emphasizes the relevance of these medicinal plants as safer, multi-targeted alternatives for inflammation management and identifies future research directions to facilitate their clinical translation.

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ABBREVIATIONS

OX (Cyclooxygenase), LOX (Lipoxygenase), NF-κB (Nuclear Factor Kappa B), NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), TQ (Thymoquinone), MAPK (Mitogen-Activated Protein Kinase), ROS (Reactive Oxygen Species), RNS (Reactive Nitrogen Species), IL (Interleukin), TNF-α (Tumor Necrosis Factor Alpha), iNOS (Inducible Nitric Oxide Synthase), PGE2 (Prostaglandin E2), NLRP3 (NOD-, LRR-, and Pyrin Domain-Containing Protein 3), JNK (c-Jun N-terminal Kinase), ERK (Extracellular Signal-Regulated Kinase), CRP (C-Reactive Protein), TLRs (Toll-Like Receptors), DAMPs (Damage-Associated Molecular Patterns), PAMPs (Pathogen-Associated Molecular Patterns), Tregs (Regulatory T Cells), COX-2 (Cyclooxygenase-2), and HRBC (Human Red Blood Cells)

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