Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.69980/b8sdy555

LEMONGRASS BIOACTIVE COMPOUNDS IN MODULATING NF-κB AND MAPK INFLAMMATORY SIGNALING PATHWAYS: MOLECULAR MECHANISMS, EXPERIMENTAL EVIDENCE, AND THERAPEUTIC PERSPECTIVES

Siddhartha Mehrotra[1], Dr. Gauri Saxena[2]
[1]Research Scholar, Department of Botany, University of Lucknow, siddharthamehrotra10@gmail.com, 0009-0009-1514-4495
[2]Professor, Department of Botany, University of Lucknow, gaurigupta72@yahoo.com, 0000-0003-2235-2755

Abstract

Inflammation is a tightly regulated biological defense mechanism that protects the body against microbial invasion, physical injury, and other harmful stimuli while promoting tissue repair and restoration of homeostasis. Although this response is essential for maintaining physiological balance, prolonged or dysregulated inflammation contributes to the onset and progression of numerous chronic disorders. Among the key molecular regulators of inflammatory responses, the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways play central roles by controlling the expression of genes encoding pro-inflammatory mediators. Consequently, these pathways have become important therapeutic targets for the development of safer and more effective anti-inflammatory interventions.

Cymbopogon citratus (lemongrass) is a widely used medicinal and aromatic plant recognized for its rich phytochemical composition and diverse pharmacological properties. This review comprehensively examines the phytochemistry of C. citratus and discusses the molecular mechanisms through which its bioactive constituents regulate inflammatory signaling pathways. Particular attention is given to major phytochemicals, including citral, chlorogenic acid, flavonoids, and geraniol, which have demonstrated significant anti-inflammatory activity through modulation of NF-κB and MAPK signaling.

Evidence obtained from phytochemical investigations, cell-based experiments, and animal studies indicates that lemongrass-derived bioactive compounds suppress inflammatory responses by reducing the production of pro-inflammatory mediators, limiting oxidative stress, and regulating multiple intracellular signaling pathways. The available findings further suggest that these compounds exert complementary and multitarget actions, thereby enhancing their overall therapeutic potential against inflammation-associated diseases.

Despite encouraging experimental evidence, several challenges remain before the clinical application of lemongrass-derived therapeutics can be fully realized. These include the need for standardized phytochemical preparations, improved understanding of pharmacokinetic behavior, optimization of dosage, and well-designed clinical trials to validate efficacy and safety in humans.

Addressing these limitations will strengthen the scientific basis for the development of lemongrass-based anti-inflammatory agents and support their future therapeutic application.

Keywords: Cymbopogon citratus; Lemongrass; Bioactive compounds; Inflammation; NF-κB; MAPK; Citral; Phytochemicals; Oxidative stress; Anti-inflammatory activity.

1. Introduction

Inflammation is an essential biological defense mechanism that safeguards the body against microbial invasion, chemical injury, and tissue damage while preserving physiological homeostasis. This highly regulated process involves coordinated interactions among immune cells, inflammatory mediators, signaling molecules, and vascular components that collectively eliminate harmful stimuli and promote tissue repair. Under normal physiological conditions, inflammation is acute, localized, and self-limiting. However, persistent activation of inflammatory signaling pathways can result in chronic inflammation, which is now recognized as a fundamental contributor to the development of cardiovascular diseases, diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, neurodegenerative disorders, obesity, and various forms of cancer (Medzhitov, 2008; Lawrence, 2009).

The inflammatory response begins when pattern-recognition receptors (PRRs), particularly Toll-like receptors (TLRs), detect pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Recognition of these molecular signals initiates intracellular signaling cascades that activate transcription factors responsible for the synthesis of pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes. Among these signaling networks, the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways function as the principal regulators of inflammatory gene expression. Activation of these pathways promotes the production of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), nitric oxide (NO), and prostaglandin E_2 (PGE_2), thereby amplifying inflammatory responses and contributing to progressive tissue injury when activation becomes sustained (Tak & Firestein, 2001; Arthur & Ley, 2013).

Conventional anti-inflammatory therapies, including non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, remain effective for controlling inflammation but are frequently associated with adverse effects such as gastrointestinal ulceration, renal impairment, hepatotoxicity, cardiovascular complications, and immunosuppression following long-term use. Consequently, increasing attention has been directed toward identifying naturally occurring bioactive compounds capable of modulating multiple inflammatory targets while exhibiting improved safety profiles. Plant-derived phytochemicals are particularly attractive because they often regulate several interconnected signaling pathways simultaneously rather than acting on a single molecular target (Pan et al., 2014; Shin et al., 2020).

Among medicinal and aromatic plants, Cymbopogon citratus (DC.) Stapf, commonly known as lemongrass, has gained considerable scientific interest owing to its diverse phytochemical composition and broad spectrum of pharmacological activities. Traditionally, lemongrass has been utilized throughout Asia, Africa, and South America for the management of fever, infections, gastrointestinal disorders, pain, and inflammatory conditions. Phytochemical investigations have identified numerous biologically active constituents, including citral (geranial and neral), geraniol, myrcene, flavonoids, phenolic acids, chlorogenic acid, and tannins. Collectively, these compounds exhibit antioxidant, antimicrobial, anticancer, antidiabetic, and anti-inflammatory activities, making lemongrass one of the most extensively investigated medicinal grasses (Bachiega & Sforcin, 2011; Francisco et al., 2011; Francisco et al., 2013).

Experimental studies demonstrate that lemongrass-derived bioactive compounds suppress inflammatory responses through multiple complementary molecular mechanisms. These phytochemicals inhibit NF-κB activation by preventing degradation of inhibitor κB (IκB), suppress phosphorylation of MAPK proteins including ERK, JNK, and p38, and consequently reduce the production of inflammatory cytokines and enzymes. In addition, their antioxidant properties attenuate oxidative stress, thereby limiting redox-sensitive inflammatory signaling. Because these mechanisms simultaneously target multiple stages of the inflammatory cascade, lemongrass has emerged as a promising source of multifunctional anti-inflammatory agents (Francisco et al., 2011; Francisco et al., 2013; Han & Parker, 2017).

Although numerous investigations have explored the anti-inflammatory properties of C. citratus, the available evidence remains dispersed across phytochemical, pharmacological, and molecular biology studies. An integrated synthesis linking phytochemical composition with the molecular regulation of NF-κB and MAPK signaling is therefore warranted. Accordingly, this review critically examines the major bioactive compounds present in lemongrass, summarizes current evidence regarding their regulation of inflammatory signaling pathways, discusses their downstream effects on inflammatory mediators, and highlights their therapeutic potential together with future research directions for the management of inflammation-associated diseases.

Figure 1. Overall Scope of the Review

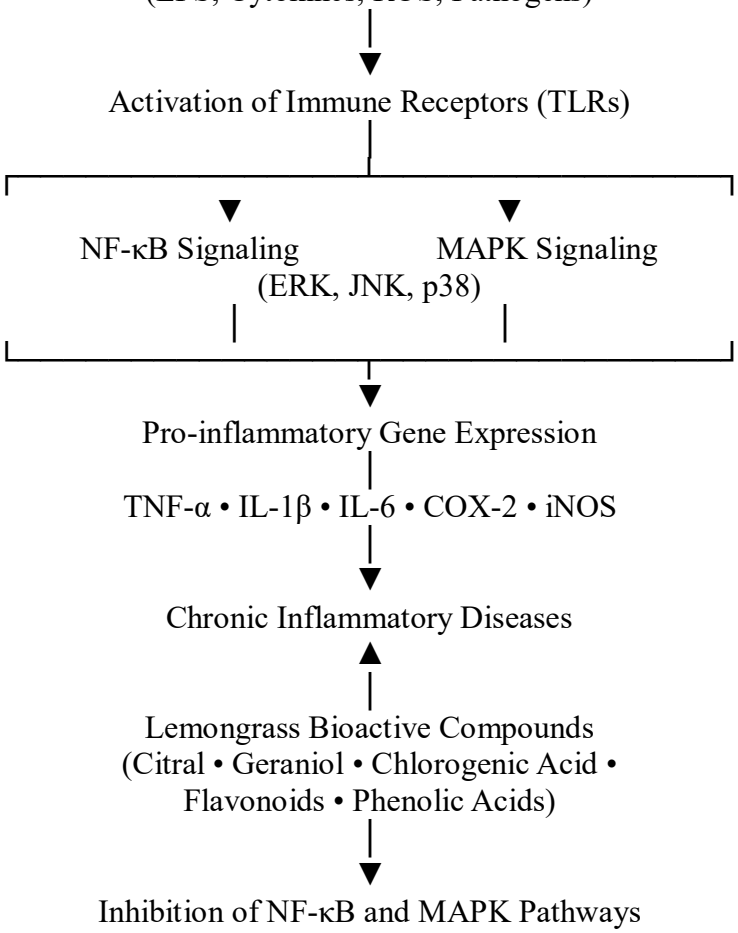


Figure 1. Conceptual framework illustrating the overall scope of the review. Lemongrass-derived bioactive compounds target key inflammatory signaling pathways, particularly NF-κB

and MAPK, thereby suppressing inflammatory mediator production and reducing the progression of chronic inflammatory diseases.

Table 1. Scope and Organization of the Review

Section	Major Focus	Expected Outcome
Introduction	Background and rationale	Establishes the importance of inflammation and lemongrass
Biology of Inflammation	Cellular and molecular mechanisms	Explains inflammatory mediators and immune regulation
NF-κB and MAPK Signaling	Molecular pathways	Identifies major therapeutic targets
Phytochemistry	Bioactive compounds	Describes chemical constituents responsible for biological activity
Molecular Mechanisms	Regulation of inflammatory signaling	Explains how lemongrass compounds inhibit inflammation
Experimental Evidence	In vitro and in vivo studies	Summarizes pharmacological evidence
Therapeutic Applications	Disease-specific benefits	Highlights translational potential
Future Perspectives	Research gaps and opportunities	Guides future investigations

2. Biology Of Inflammation And Molecular Basis Of Nf-Kb/Mapk Activation

2.1 Overview of the Inflammatory Response

Inflammation represents a highly regulated physiological defense response that protects tissues from invading pathogens, harmful chemicals, toxins, and physical injury while facilitating tissue repair and maintaining homeostasis. The inflammatory process is initiated when cells of the innate immune system recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) through pattern-recognition receptors (PRRs), particularly Toll-like receptors (TLRs). Activation of these receptors triggers a cascade of intracellular signaling events that promote immune cell recruitment, cytokine secretion, and the production of inflammatory mediators. Under normal conditions, these responses are tightly controlled and resolve once the harmful stimulus has been eliminated. In contrast, persistent or dysregulated activation of inflammatory pathways results in chronic inflammation, which contributes to the pathogenesis of numerous disorders, including rheumatoid arthritis, inflammatory bowel disease, cardiovascular diseases, diabetes mellitus, neurodegenerative disorders, and cancer (Medzhitov, 2008; Nathan & Ding, 2010).

Acute inflammation is characterized by rapid vasodilation, increased vascular permeability, infiltration of neutrophils, and activation of resident macrophages at the site of injury or infection. During the resolution phase, macrophages clear apoptotic neutrophils and cellular debris while releasing anti-inflammatory mediators that promote tissue regeneration and restoration of normal tissue architecture. Failure to complete this resolution process results in chronic inflammation, where macrophages, lymphocytes, and plasma cells remain within the affected tissues and continuously produce inflammatory cytokines, reactive oxygen species (ROS), nitric oxide (NO), and proteolytic enzymes, thereby sustaining tissue injury and disease progression (Lawrence, 2009).

2.2 Cellular Components Involved in Inflammation

Macrophages are regarded as the principal regulators of inflammatory responses because they integrate signals derived from invading pathogens, damaged tissues, and inflammatory mediators. Following activation, these cells release a wide range of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, nitric oxide (NO), prostaglandin E_2 (PGE_2), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). These mediators recruit additional immune cells to the site of inflammation and amplify inflammatory signaling through positive feedback mechanisms (Tak & Firestein, 2001).

Neutrophils are the earliest leukocytes recruited during acute inflammation and contribute to host defense through phagocytosis, degranulation, and oxidative burst. Dendritic cells function as professional antigen-presenting cells that bridge innate and adaptive immunity, whereas T lymphocytes regulate chronic inflammatory responses through cytokine secretion and immune modulation. Together, these immune cell populations coordinate the initiation, progression, and resolution of inflammatory responses (Nathan & Ding, 2010).

Figure 2. Cellular Events During the Inflammatory Response

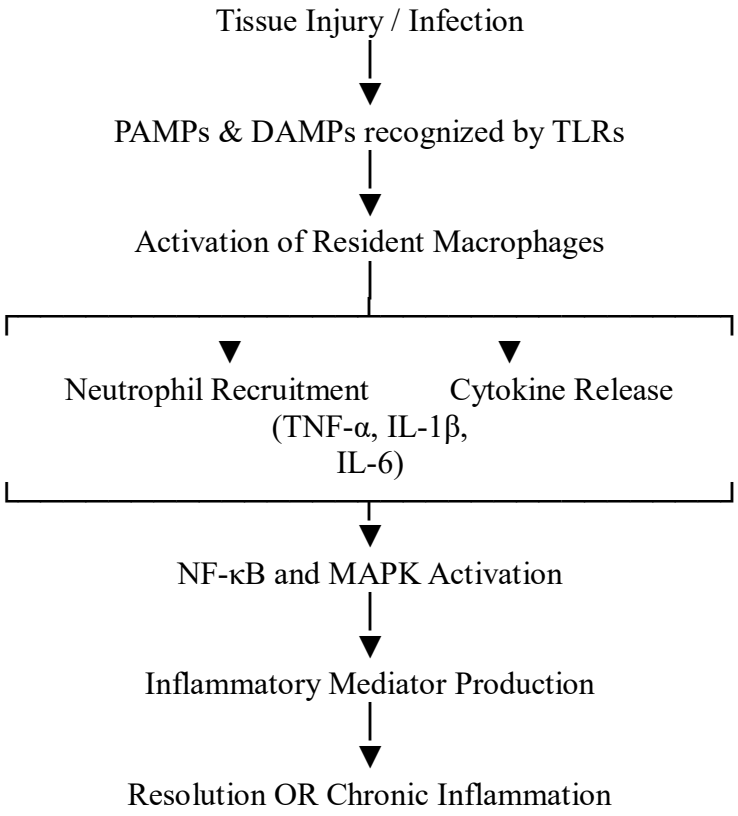


Figure 2. Simplified overview of the cellular events occurring during the inflammatory response. Recognition of pathogenic or endogenous danger signals activates macrophages and downstream inflammatory signaling pathways that determine whether inflammation resolves or progresses to chronic disease.

2.3 Major Inflammatory Mediators

The progression of inflammation is governed by a coordinated network of cytokines, chemokines, enzymes, and lipid mediators that regulate immune cell recruitment and tissue responses. Among these, TNF-α, IL-1β, and IL-6 are recognized as the principal pro-inflammatory cytokines because they activate endothelial cells, promote leukocyte migration, stimulate acute-phase protein synthesis, and enhance both NF-κB and MAPK signaling. In addition, inducible nitric oxide synthase (iNOS) catalyzes excessive nitric oxide production, whereas cyclooxygenase-2 (COX-2) generates prostaglandin E_2 (PGE_2). Together, these mediators contribute to pain, edema, vascular permeability, oxidative stress, and tissue injury (Tak & Firestein, 2001; Cho et al., 2003)

Reactive oxygen species (ROS) also play a dual role during inflammation. At physiological concentrations, ROS contribute to pathogen elimination and cellular signaling. However, excessive ROS production activates redox-sensitive transcription factors, particularly NF-κB and MAPKs, thereby perpetuating inflammatory signaling and tissue damage. This close interaction between oxidative stress and inflammatory pathways provides a mechanistic explanation for the potent anti-inflammatory effects frequently observed with antioxidant phytochemicals (Reuter et al., 2010).

Table 2. Major Inflammatory Mediators and Their Biological Functions

Mediator	Primary Source	Major Biological Function	Role in Chronic Inflammation
TNF-α	Macrophages	Cytokine amplification and leukocyte recruitment	Promotes persistent inflammation
IL-1β	Macrophages	Fever, endothelial activation, cytokine production	Tissue destruction
IL-6	Macrophages, T cells	Acute-phase response and immune regulation	Chronic inflammatory disorders
COX-2	Activated macrophages	Prostaglandin synthesis	Pain and edema
iNOS	Macrophages	Nitric oxide production	Oxidative tissue damage
NO	Macrophages	Antimicrobial defense	Cellular injury when excessive
PGE_2	COX-2 pathway	Vasodilation and pain sensitization	Chronic inflammation
ROS	Neutrophils, macrophages	Microbial killing and signaling	Oxidative stress and NF-κB activation

2.4 NF-κB and MAPK as Master Regulators of Inflammation

Among the numerous signaling pathways involved in inflammation, NF-κB and MAPKs are widely recognized as the principal molecular regulators coordinating inflammatory gene expression. These signaling pathways integrate extracellular signals generated by cytokines, microbial products, oxidative stress, and tissue injury to regulate the transcription of genes involved in inflammatory responses. Because activation of NF-κB and MAPKs precedes the production of many inflammatory mediators, inhibition of these pathways has become an important therapeutic strategy for controlling excessive inflammation (Arthur & Ley, 2013; Shin et al., 2020).

The anti-inflammatory activity of Cymbopogon citratus is largely attributed to its ability to interfere with these signaling networks through multiple complementary mechanisms. Consequently, understanding the molecular organization and regulation of NF-κB and MAPK pathways provides the foundation for explaining the pharmacological actions of lemongrass-derived bioactive compounds. The following sections examine these signaling pathways in greater detail before discussing how individual phytochemicals regulate their activity.

3. Phytochemical Profile Of Cymbopogon Citratus

3.1 Overview of Lemongrass Phytochemistry

Cymbopogon citratus (DC.) Stapf is among the most extensively studied aromatic medicinal plants because of its diverse repertoire of biologically active secondary metabolites. These phytochemicals are synthesized through specialized metabolic pathways and play an essential role in protecting the plant against environmental stress, microbial pathogens, and herbivores. Beyond their ecological functions, these compounds possess a wide range of pharmacological properties, including antioxidant, antimicrobial, anticancer, antidiabetic, immunomodulatory, and anti-inflammatory activities (Negrelle & Gomes, 2007; Avoseh et al., 2015).

The phytochemical composition of C. citratus is influenced by several factors, including cultivar, geographical origin, climatic conditions, soil characteristics, harvesting stage, plant part, and extraction technique. In general, the leaves represent the richest source of essential oils and phenolic compounds, whereas the volatile oil fraction is predominantly composed of oxygenated monoterpenes. Comprehensive phytochemical investigations have identified terpenoids, flavonoids, phenolic acids, tannins, alkaloids, saponins, and glycosides as the principal classes of bioactive constituents responsible for the medicinal value of lemongrass (Shah et al., 2011; Figueirinha et al., 2008).

Among these metabolites, citral remains the predominant bioactive constituent and generally accounts for approximately 65–85% of the total essential oil, depending on the chemotype. Citral consists of two geometric isomers, geranial (trans-citral) and neral (cis-citral), which together are responsible for the characteristic lemon aroma and a substantial proportion of the plant's biological activities. In addition to citral, other terpenoid constituents such as geraniol, limonene, β-myrcene, citronellal, linalool, and β-caryophyllene have been identified and contribute to the therapeutic properties of the essential oil (Naik et al., 2010; Bachiega & Sforcin, 2011).

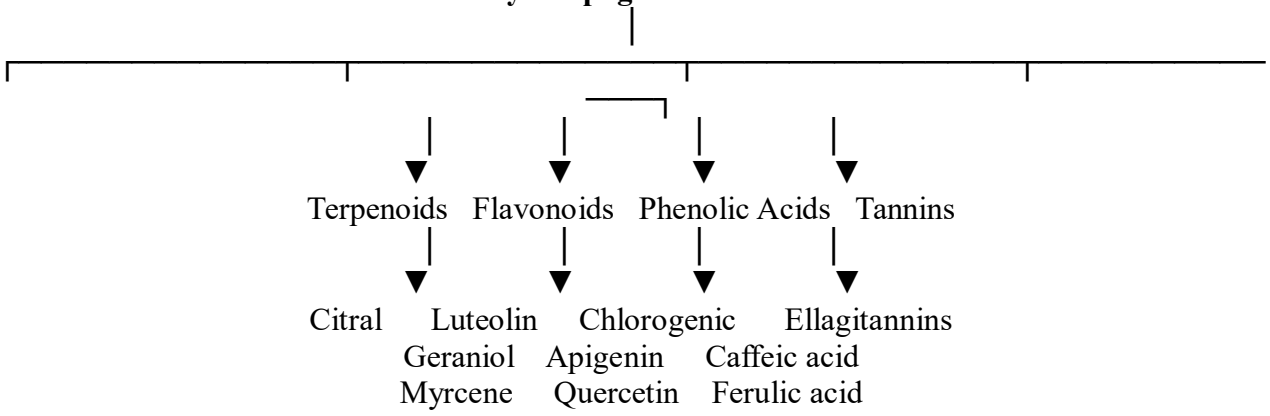
Besides volatile constituents, lemongrass is also rich in non-volatile phenolic compounds. Chlorogenic acid, caffeic acid, ferulic acid, p-coumaric acid, luteolin, apigenin, quercetin derivatives, and various C-glycosyl flavones have been reported in aqueous and hydroalcoholic extracts. Owing to their hydroxyl-rich chemical structures, these phenolic compounds exhibit remarkable antioxidant capacity by scavenging reactive oxygen species, chelating transition metals, and modulating multiple inflammatory signaling pathways (Figueirinha et al., 2008; Francisco et al., 2013).

Current evidence indicates that the pharmacological efficacy of C. citratus cannot be attributed to a single phytochemical. Instead, its biological activities arise from synergistic interactions among numerous bioactive constituents. Essential oil components primarily influence membrane-associated signaling events, whereas phenolic acids and flavonoids predominantly regulate intracellular signaling pathways and transcription factors associated with inflammation. This complementary mode of action is believed to underlie the broad spectrum of pharmacological activities reported for lemongrass extracts (Avoseh et al., 2015; Francisco et al., 2011).

Table 3. Major Classes of Bioactive Compounds in Cymbopogon citratus

Phytochemical Class	Major Compounds	Major Biological Activities
Monoterpenes	Citral (Geranial, Neral), Geraniol, Myrcene, Limonene	Anti-inflammatory, antimicrobial, antioxidant
Sesquiterpenes	β-Caryophyllene	Anti-inflammatory, antioxidant
Phenolic acids	Chlorogenic acid, Caffeic acid, Ferulic acid, p-Coumaric acid	Antioxidant, anti-inflammatory
Flavonoids	Luteolin, Apigenin, Quercetin derivatives, C-glycosyl flavones	Antioxidant, immunomodulatory, anti-inflammatory
Tannins	Condensed tannins	Free radical scavenging, anti-inflammatory
Saponins	Various saponins	Immunomodulatory
Alkaloids	Trace alkaloids	Antimicrobial
Glycosides	Various glycosides	Antioxidant activity

Figure 3. Major Bioactive Compound Classes in Lemongrass Cymbopogon citratus



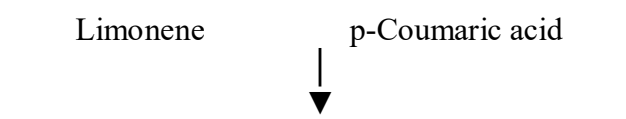


Figure 3. Classification of the principal phytochemical groups identified in Cymbopogon citratus and their major representative compounds.

3.2 Essential Oil Composition

The essential oil is the best-characterized phytochemical fraction of Cymbopogon citratus and is largely responsible for its distinctive lemon fragrance as well as many of its pharmacological properties. This volatile oil is stored in specialized secretory tissues within the leaves and is commonly obtained by steam distillation or hydrodistillation. Both the yield and chemical composition of the oil are influenced by geographical origin, climatic conditions, harvesting season, plant maturity, genotype, cultivation practices, and extraction methods (Negrelle & Gomes, 2007; Shah et al., 2011).

Oxygenated monoterpenes constitute the dominant components of C. citratus essential oil, with citral representing the principal constituent. Citral comprises two geometric isomers—geranial (trans-citral) and neral (cis-citral)—which together generally account for approximately 65–85% of the total oil. Geranial is usually present in greater abundance than neral and contributes significantly to both the characteristic citrus aroma and the biological activity of lemongrass. Consequently, C. citratus has become one of the most commercially valuable natural sources of citral for applications in the food, cosmetic, fragrance, and pharmaceutical industries (Naik et al., 2010; Bachiega & Sforcin, 2011).

In addition to citral, lemongrass essential oil contains numerous minor constituents, including myrcene, geraniol, limonene, citronellal, linalool, citronellol, β-caryophyllene, α-pinene, β-pinene, and geranyl acetate. Although these compounds occur at relatively lower concentrations, they contribute collectively to the antioxidant, antimicrobial, and anti-inflammatory properties of the essential oil through additive and synergistic interactions (Negrelle & Gomes, 2007; Avoseh et al., 2015).

Gas chromatography coupled with mass spectrometry (GC–MS) is widely employed for the qualitative and quantitative characterization of essential oil constituents. Numerous investigations have demonstrated considerable chemotypic variation among lemongrass populations grown under different environmental conditions. Therefore, standardization of cultivation practices and extraction procedures is essential for achieving reproducible phytochemical profiles and consistent biological activity (Shah et al., 2011).

Emerging evidence further indicates that the anti-inflammatory efficacy of lemongrass essential oil results from the combined action of multiple terpenoid constituents rather than citral alone. Synergistic interactions among major and minor compounds may enhance membrane permeability, regulate diverse intracellular signaling pathways, and broaden the spectrum of pharmacological activity. This multicomponent nature distinguishes botanical extracts from isolated compounds and contributes to the therapeutic versatility of C. citratus essential oil (Bachiega & Sforcin, 2011).

Table 4. Major Constituents of Cymbopogon citratus Essential Oil and Their Biological Activities

Essential Oil Constituent	Chemical Class	Approximate Contribution/Occurrence	Major Biological Activities	Relevance to Anti-inflammatory Activity
Citral (Geranial + Neral)	Oxygenated monoterpene aldehyde	Major constituent (approximately 65–85% of essential oil)	Anti-inflammatory, antioxidant, antimicrobial	Principal contributor to suppression of inflammatory signaling and mediator production
Geraniol	Oxygenated monoterpene alcohol	Minor to moderate constituent	Antioxidant, antimicrobial, anti-inflammatory	Provides complementary regulation of inflammatory responses
Myrcene	Monoterpene hydrocarbon	Minor constituent	Analgesic, antioxidant, anti-inflammatory	Supports overall pharmacological activity of essential oil
Limonene	Monoterpene	Minor constituent	Antioxidant,	Contributes to

	hydrocarbon		antimicrobial, anti-inflammatory	synergistic biological effects
Citronellal	Monoterpene aldehyde	Minor constituent	Antioxidant, antimicrobial	Enhances biological activity of volatile fraction
Linalool	Oxygenated monoterpene	Minor constituent	Antioxidant, antimicrobial, immunomodulatory	May contribute to regulation of inflammatory processes
β-Caryophyllene	Sesquiterpene	Trace constituent	Anti-inflammatory, antioxidant	Provides additional modulatory effects on inflammatory pathways
Geranyl acetate	Ester derivative	Minor constituent	Antimicrobial, antioxidant	Supports combined activity of essential oil components

Figure 4. Major Constituents of Lemongrass Essential Oil

Lemongrass Essential Oil

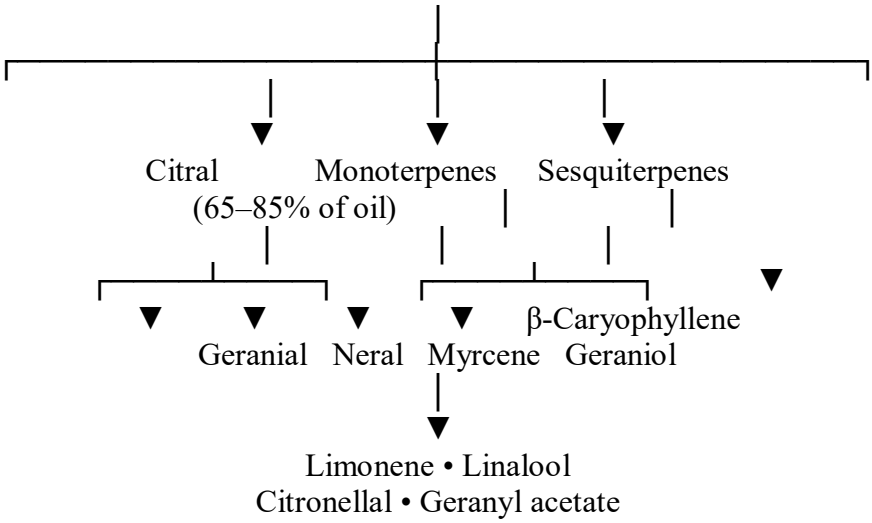


Figure 4. Schematic representation of the major volatile constituents of Cymbopogon citratus essential oil. Citral (geranial and neral) is the dominant component, while several minor monoterpenes and sesquiterpenes contribute to the overall biological activity.

3.3 Major Anti-inflammatory Bioactive Compounds of Cymbopogon citratus

The anti-inflammatory activity of Cymbopogon citratus is attributed to a diverse spectrum of volatile and non-volatile phytochemicals that collectively regulate oxidative stress, inflammatory signaling pathways, and cytokine production. Rather than depending on a single active constituent, the therapeutic efficacy of lemongrass arises from the synergistic and complementary interactions among its major secondary metabolites. Among the compounds identified to date, citral, chlorogenic acid, flavonoids, geraniol, myrcene, and several minor terpenoids have attracted considerable scientific interest because of their ability to regulate inflammatory mediators and intracellular signaling pathways (Negrelle & Gomes, 2007; Avoseh et al., 2015).

Citral is recognized as the predominant bioactive constituent of lemongrass essential oil and is considered the primary contributor to its anti-inflammatory activity. Structurally, citral is composed of two geometric isomers, geranial and neral, which together constitute the major proportion of the essential oil fraction. Experimental investigations have demonstrated that citral suppresses the production of inflammatory cytokines, inhibits nitric oxide synthesis, and attenuates inflammatory responses in activated macrophages. These findings highlight citral as one of the most promising naturally occurring monoterpenes for the management of inflammatory disorders (Bachiega & Sforcin, 2011).

Apart from volatile terpenoids, lemongrass contains substantial quantities of phenolic acids, including chlorogenic acid, caffeic acid, ferulic acid, and p-coumaric acid. These compounds exhibit strong antioxidant activity owing to the presence of multiple hydroxyl groups, enabling them to neutralize reactive oxygen species and interrupt oxidative stress-mediated inflammatory signaling. Among them, chlorogenic acid has received particular attention because of its ability to regulate inflammatory gene expression while simultaneously reducing oxidative damage and preserving cellular homeostasis (Figueirinha et al., 2008; Francisco et al., 2013).

Flavonoids constitute another important class of anti-inflammatory phytochemicals present in C. citratus. Major flavonoids identified in lemongrass include luteolin, apigenin, quercetin derivatives, and C-glycosyl flavones, which are abundant in aqueous and hydroalcoholic leaf extracts. These

compounds possess potent antioxidant properties through free radical scavenging, metal ion chelation, and maintenance of intracellular redox balance. Furthermore, flavonoids regulate multiple signaling pathways associated with inflammation, thereby contributing significantly to the overall pharmacological efficacy of lemongrass extracts (Figueirinha et al., 2008; Avoseh et al., 2015).

Geraniol is another biologically active oxygenated monoterpene detected in lemongrass essential oil. Although its concentration is considerably lower than that of citral, geraniol contributes to both the antioxidant and anti-inflammatory activities of the plant and may interact synergistically with other terpenoids to enhance biological efficacy. Similarly, myrcene and limonene provide additional antioxidant and antimicrobial effects that complement the pharmacological profile of lemongrass (Naik et al., 2010).

Overall, the biological activity of C. citratus should be regarded as the cumulative outcome of coordinated interactions among multiple phytochemicals rather than the effect of a single bioactive constituent. Such phytochemical synergy is a characteristic feature of medicinal plants and frequently results in broader pharmacological efficacy than isolated compounds. Consequently, understanding the distribution, abundance, and biological functions of individual bioactive constituents provides the molecular basis for interpreting the anti-inflammatory mechanisms discussed in the subsequent sections.

Table 5. Major Anti-inflammatory Bioactive Compounds of Cymbopogon citratus

Compound	Chemical Class	Major Biological Activities	Major Anti-inflammatory Relevance
Citral (Geranial + Neral)	Oxygenated monoterpene	Antioxidant, antimicrobial	Principal anti-inflammatory constituent
Chlorogenic acid	Phenolic acid	Antioxidant	Regulates inflammatory signaling
Luteolin	Flavonoid	Antioxidant	Modulates inflammatory mediator production
Apigenin	Flavonoid	Antioxidant	Immunomodulatory activity
Quercetin derivatives	Flavonoids	Free radical scavenging	Supports anti-inflammatory effects
Geraniol	Monoterpene alcohol	Antioxidant	Complementary anti-inflammatory activity
Myrcene	Monoterpene hydrocarbon	Analgesic, antioxidant	Supports inflammation control
Limonene	Monoterpene hydrocarbon	Antioxidant	Contributes to overall pharmacological activity

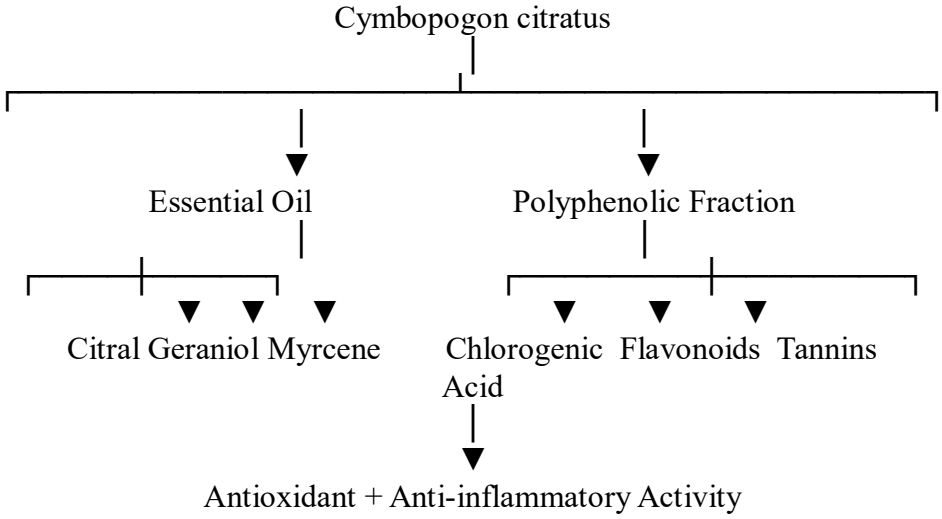


Figure 5. Major Anti-inflammatory Bioactive Compounds in Cymbopogon citratus

3.4 Comparative Anti-inflammatory Potential of Major Lemongrass Bioactive Compounds

The anti-inflammatory efficacy of Cymbopogon citratus arises from the collective actions of multiple phytochemicals rather than the dominance of a single constituent. Although citral represents the principal component of the essential oil, growing evidence indicates that phenolic acids, flavonoids, and minor terpenoids also make substantial contributions to the overall pharmacological activity. These compounds differ in their chemical structures, physicochemical characteristics, molecular targets, and biological functions, yet they converge in suppressing inflammatory responses through complementary mechanisms (Bachiega & Sforcin, 2011; Francisco et al., 2013).

Citral has received the greatest scientific attention because of its high abundance and pronounced biological activity. It primarily exerts its anti-inflammatory effects by reducing the production of inflammatory cytokines and other pro-inflammatory mediators in activated macrophages. In comparison, chlorogenic acid displays superior antioxidant activity and contributes to inflammation control by limiting oxidative stress while simultaneously regulating inflammatory signaling pathways. Flavonoids, including luteolin, apigenin, and quercetin derivatives, possess broad-spectrum antioxidant and immunomodulatory properties, enabling them to influence multiple intracellular signaling cascades associated with inflammatory responses (Figueirinha et al., 2008; Francisco et al., 2013).

Minor terpenoids such as geraniol, myrcene, limonene, and β-caryophyllene, although present at relatively lower concentrations, further enhance the biological activity of lemongrass extracts through synergistic interactions. These constituents provide complementary antioxidant, antimicrobial, and membrane-stabilizing activities that reinforce the actions of major bioactive compounds. Such synergistic effects are characteristic of botanical extracts and may explain why whole-plant preparations frequently exhibit broader pharmacological efficacy than isolated phytochemicals (Naik et al., 2010; Avoseh et al., 2015).

The remarkable diversity of phytochemicals present in C. citratus enables simultaneous regulation of multiple biological processes involved in inflammation. Consequently, lemongrass should be regarded as a multicomponent and multitarget phytotherapeutic system in which individual compounds contribute cooperatively to the overall anti-inflammatory response. Understanding these complementary roles provides the mechanistic foundation for explaining how lemongrass regulates intracellular inflammatory signaling pathways discussed in the following sections.

Table 6. Comparative Characteristics of Major Anti-inflammatory Bioactive Compounds in Cymbopogon citratus

Compound	Major Source	Relative Abundance	Principal Biological Activities	Importance in This Review
Citral (Geranial + Neral)	Essential oil	Very High	Anti-inflammatory, antimicrobial, antioxidant	Principal regulator of inflammatory signaling
Chlorogenic acid	Polyphenolic fraction	Moderate	Antioxidant, anti-inflammatory	Important phenolic modulator
Luteolin	Flavonoid fraction	Low	Antioxidant, immunomodulatory	Supports inflammatory regulation
Apigenin	Flavonoid fraction	Low	Antioxidant	Auxiliary anti-inflammatory compound
Quercetin derivatives	Flavonoid fraction	Low	Free radical scavenging	Contribute to antioxidant defense
Geraniol	Essential oil	Low	Antioxidant, antimicrobial	Complementary terpenoid
Myrcene	Essential oil	Low	Analgesic, antioxidant	Synergistic activity
β-Caryophyllene	Essential oil	Trace	Anti-inflammatory	Minor supportive constituent

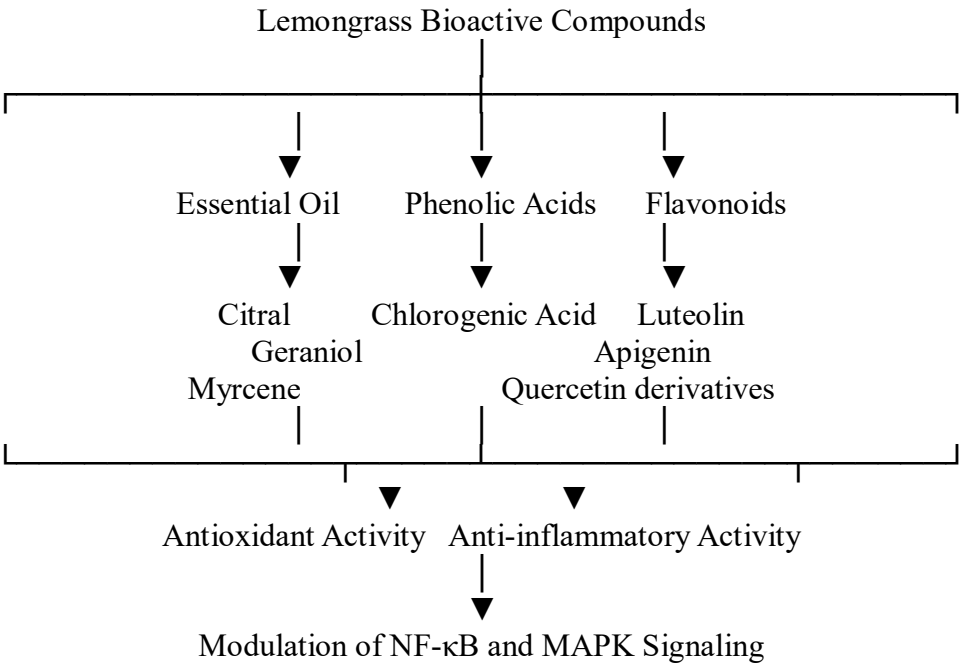


Figure 6. Relative Contribution of Major Bioactive Compounds to the Anti-inflammatory Activity of Lemongrass

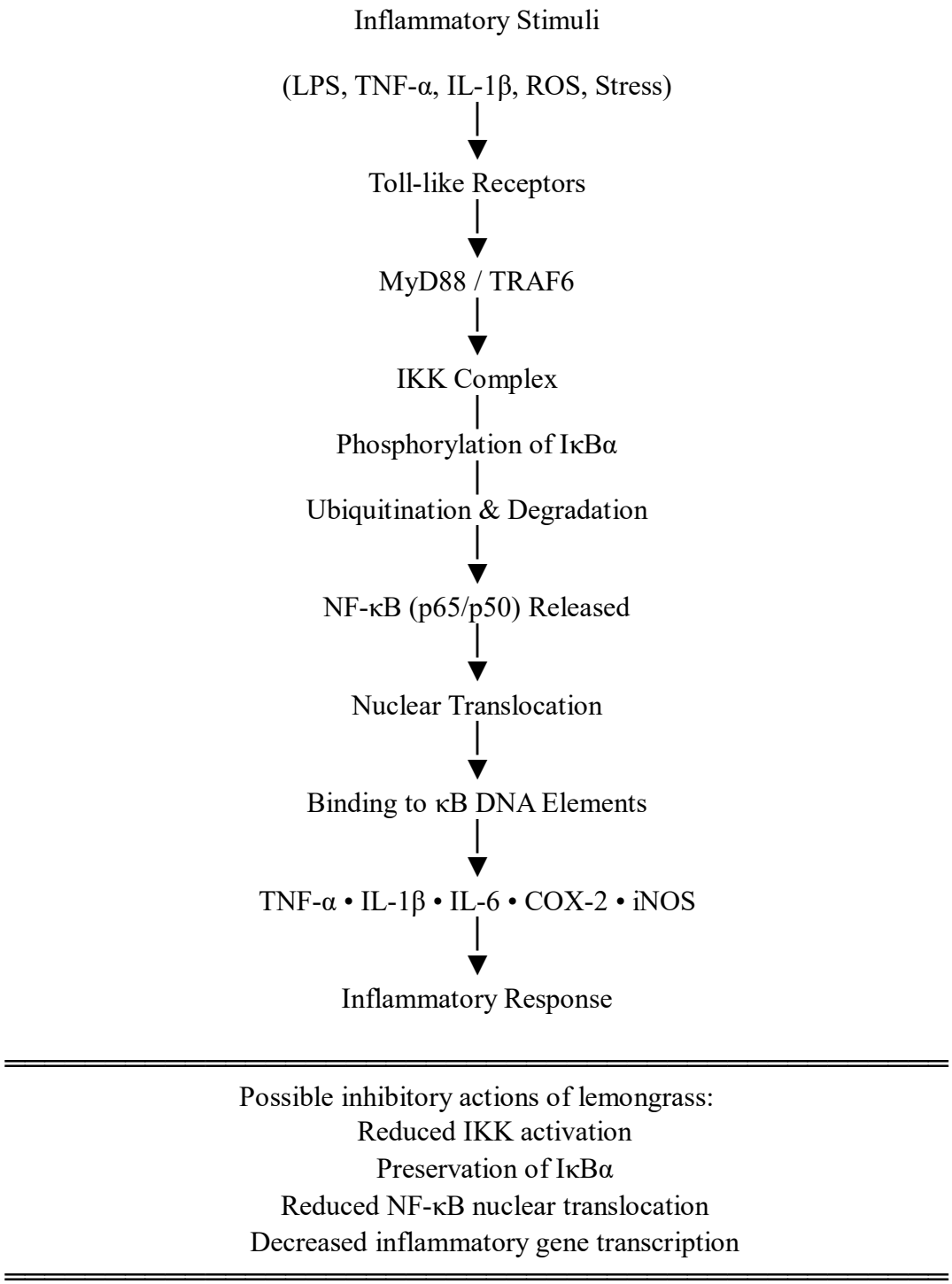
4. Modulation Of Nf-Kb Signaling Pathway By Lemongrass Bioactive Compounds

4.1 Canonical NF-κB Signaling Pathway

The nuclear factor-kappa B (NF-κB) signaling pathway is one of the most important molecular regulators of inflammation and innate immune responses. Under physiological conditions, NF-κB remains in an inactive state within the cytoplasm through its association with inhibitor of κB (IκB) proteins, particularly IκBα. This interaction prevents NF-κB from entering the nucleus and thereby maintains basal inflammatory activity. Exposure to inflammatory stimuli, including lipopolysaccharide (LPS), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), reactive oxygen species (ROS), and microbial components, activates Toll-like receptors (TLRs) and initiates intracellular signaling through adaptor proteins such as MyD88 and TRAF6. These events subsequently activate the IκB kinase (IKK) complex (Tak & Firestein, 2001; Lawrence, 2009).

Activated IKK phosphorylates IκBα, promoting its ubiquitination and subsequent degradation by the proteasome. The degradation of IκBα releases the NF-κB p65/p50 heterodimer, allowing its translocation into the nucleus, where it binds κB-responsive DNA elements and initiates transcription of numerous inflammatory genes. Consequently, activation of NF-κB stimulates the expression of TNF-α, IL-1β, IL-6, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), chemokines, adhesion molecules, and several enzymes involved in inflammatory amplification. Sustained activation of this pathway has therefore been closely associated with chronic inflammatory disorders, autoimmune diseases, metabolic syndrome, cardiovascular diseases, and cancer (Tak & Firestein, 2001; Lawrence, 2009).

Figure 7. Canonical NF-κB Signaling Pathway and Potential Targets of Lemongrass Bioactive Compounds



4.2 Molecular Targets of Lemongrass within the NF-κB Pathway

Available experimental evidence suggests that the anti-inflammatory effects of Cymbopogon citratus arise from the simultaneous regulation of multiple molecular events within the NF-κB signaling cascade rather than inhibition of a single downstream target. Bioactive constituents of lemongrass interfere with upstream kinase activation, preserve IκBα stability, reduce nuclear translocation of NF-κB, and suppress the transcription of inflammatory genes. Through these

coordinated actions, lemongrass produces broad-spectrum suppression of inflammatory responses and differs from many conventional synthetic agents that act on a single molecular target (Francisco et al., 2011; Francisco et al., 2013).

Although several phytochemicals contribute to these biological effects, citral is regarded as the principal constituent responsible for suppressing inflammatory signaling. In addition, chlorogenic acid and flavonoids enhance this activity by reducing oxidative stress and limiting redox-sensitive activation of NF-κB. Consequently, the anti-inflammatory efficacy of lemongrass reflects the combined actions of volatile terpenoids and non-volatile phenolic compounds rather than the activity of any single constituent (Bachiega & Sforcin, 2011; Francisco et al., 2013).

Table 7. Principal Molecular Events in the NF-κB Pathway and Proposed Effects of Lemongrass Bioactive Compounds

NF-κB Signaling Event	Physiological Function	Proposed Effect of Lemongrass Bioactive Compounds
TLR activation	Recognition of inflammatory stimuli	Attenuation of upstream inflammatory signaling
IKK activation	Phosphorylates IκBα	Reduced kinase activation
IκBα degradation	Releases NF-κB	Preservation of IκBα stability
NF-κB nuclear translocation	Activates inflammatory genes	Reduced nuclear accumulation
DNA binding	Transcription of inflammatory genes	Suppressed transcriptional activity
Cytokine production	TNF-α, IL-1β, IL-6 synthesis	Reduced cytokine expression
COX-2 and iNOS expression	Production of PGE_2 and NO	Downregulated inflammatory enzymes

4.3 Relationship Between NF-κB Inhibition and Anti-inflammatory Activity

Because NF-κB regulates the expression of numerous inflammatory mediators simultaneously, inhibition of this pathway results in broad anti-inflammatory effects that extend beyond suppression of individual cytokines. Reduced NF-κB activation decreases the expression of TNF-α, IL-1β, IL-6, COX-2, and iNOS, thereby limiting leukocyte recruitment, oxidative stress, vascular permeability, and tissue injury. This extensive regulatory role has established NF-κB as one of the most attractive molecular targets for plant-derived anti-inflammatory compounds (Lawrence, 2009).

Current evidence indicates that lemongrass-derived bioactive compounds influence multiple stages of NF-κB activation rather than acting exclusively on terminal inflammatory mediators. Such a multitarget mechanism may improve therapeutic efficacy while reducing the possibility of compensatory activation of alternative inflammatory pathways. Nevertheless, the precise molecular interactions between individual phytochemicals and specific components of the NF-κB signaling cascade remain incompletely understood. Additional mechanistic investigations employing purified compounds, molecular docking analyses, and translational studies are therefore required to clarify these interactions.

Table 8. Experimental Evidence Supporting the Modulation of NF-κB Signaling by Major Lemongrass Bioactive Compounds

Bioactive Compound	Experimental Model	Molecular Target(s)	Observed Anti-inflammatory Effects	Potential Mechanism	Reference
Citral	LPS-stimulated macrophages	NF-κB, IκBα	Reduced TNF-α, IL-1β, IL-6 production	Inhibition of NF-κB activation and preservation of IκBα	Bachiega & Sforcin, 2011
Citral	Murine inflammatory model	NF-κB	Reduced inflammatory cell infiltration	Suppression of inflammatory gene expression	Francisco et al., 2011
Citral-rich essential oil	Macrophage model	NF-κB, COX-2, iNOS	Decreased NO and PGE_2 production	Downregulation of inflammatory enzymes	Francisco et al., 2013
Chlorogenic acid	Cell-based inflammatory model	NF-κB	Reduced oxidative stress and cytokine production	Antioxidant-mediated suppression of inflammatory signaling	Figueirinha et al., 2008
Flavonoid-rich extract	Macrophage model	NF-κB	Lower cytokine secretion	Reduced transcription of inflammatory mediators	Avoseh et al., 2015
Lemongrass extract	Experimental inflammation model	NF-κB	Reduced inflammatory response	Synergistic action	Shah et al., 2011

				of multiple phytochemicals	

Abbreviations: COX-2, cyclooxygenase-2; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NF-κB, nuclear factor-kappa B; NO, nitric oxide; PGE_2, prostaglandin E_2; TNF-α, tumor necrosis factor-alpha.

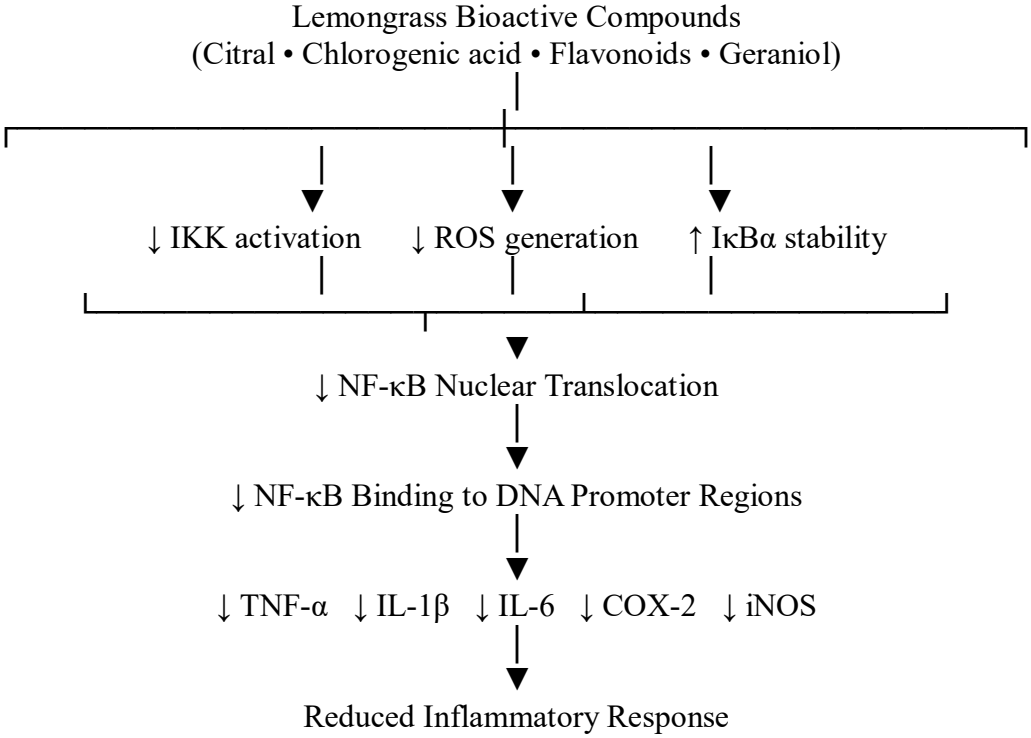


Figure 8. Proposed Mechanisms Through Which Lemongrass Bioactive Compounds Suppress NF-κB Signaling

4.4 Key Insights

Collectively, the available evidence demonstrates that lemongrass bioactive compounds regulate multiple components of the NF-κB signaling pathway rather than targeting a single molecular event. Citral appears to be the dominant contributor because of its high abundance in the essential oil and its consistently reported anti-inflammatory activity across experimental models. Nevertheless, chlorogenic acid, flavonoids, and several minor phytochemicals further strengthen these effects through complementary antioxidant and immunomodulatory mechanisms. The combined activity of these constituents results in broad suppression of inflammatory mediator production, supporting the concept that Cymbopogon citratus functions as a multicomponent and multitarget phytotherapeutic agent for the regulation of inflammatory responses (Francisco et al., 2011; Francisco et al., 2013).

5. Modulation Of Mapk Signaling Pathway By Lemongrass Bioactive Compounds

5.1 Overview of MAPK Signaling

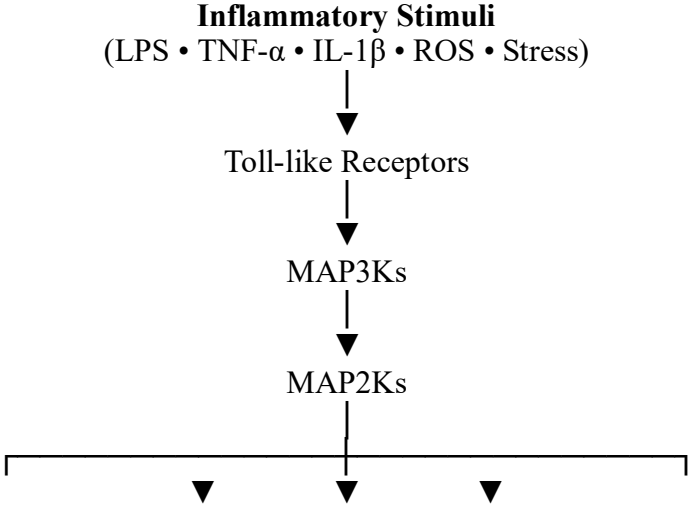
Mitogen-activated protein kinase (MAPK) signaling is one of the principal intracellular signaling networks involved in regulating inflammatory responses, cell proliferation, differentiation, apoptosis, and immune function. Similar to the NF-κB pathway, MAPK signaling is rapidly activated following exposure to inflammatory stimuli such as lipopolysaccharide (LPS), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), reactive oxygen species (ROS), ultraviolet radiation, and various forms of environmental stress. Activation of this signaling cascade ultimately regulates transcription factors responsible for inflammatory gene expression, making MAPKs attractive molecular targets for controlling excessive inflammation (Kim & Choi, 2010; Arthur & Ley, 2013).

The MAPK signaling cascade comprises three major kinase families: extracellular signal-regulated kinase (ERK1/2), c-Jun N-terminal kinase (JNK), and p38 MAPK. These kinases are activated sequentially through phosphorylation events involving MAP kinase kinase kinases (MAP3Ks), MAP kinase kinases (MAP2Ks), and the terminal MAPKs. Although these signaling branches share a common activation framework, each pathway performs distinct biological functions and responds differently to inflammatory stimuli (Kim & Choi, 2010).

ERK signaling primarily regulates cell proliferation, differentiation, and survival, but it also contributes to cytokine production during inflammatory responses. In contrast, JNK and p38 MAPK are preferentially activated under conditions of cellular stress and inflammation, where they regulate apoptosis, cytokine synthesis, oxidative stress responses, and inflammatory gene expression. Collectively, these kinases coordinate the transcription of genes encoding TNF-α, IL-1β, IL-6, COX-2, iNOS, and numerous chemokines that sustain inflammatory responses (Arthur & Ley, 2013).

Because MAPK activation occurs upstream of numerous inflammatory mediators, inhibition of ERK, JNK, and p38 phosphorylation has become an important therapeutic strategy for suppressing chronic inflammation. Increasing evidence indicates that many plant-derived phytochemicals interfere with one or more branches of the MAPK cascade, thereby reducing inflammatory mediator production and minimizing tissue injury (Pan et al., 2014).

Figure 9. MAPK Signaling Pathway During Inflammation



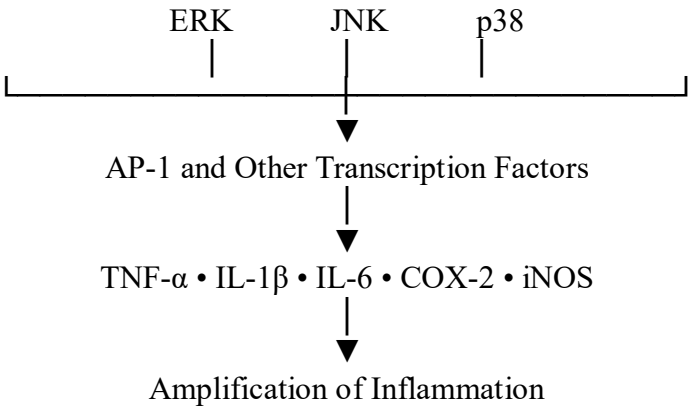


Table 9. Biological Functions of the Major MAPK Pathways

MAPK Family	Major Activating Stimuli	Primary Biological Functions	Role in Inflammation
ERK1/2	Growth factors, cytokines, LPS	Cell proliferation, differentiation, survival	Regulates cytokine production
JNK	Oxidative stress, cytokines, UV radiation	Stress response, apoptosis	Promotes inflammatory gene expression
p38 MAPK	LPS, TNF-α, IL-1β, ROS	Cytokine synthesis, immune regulation	Controls inflammatory mediator production

5.2 ERK Signaling and Lemongrass Bioactive Compounds

Among the MAPK family members, ERK1/2 is primarily associated with regulating cell growth, differentiation, and survival. Nevertheless, accumulating evidence indicates that ERK also participates in inflammatory cytokine production following activation of macrophages and other immune cells. Phosphorylation of ERK activates transcription factors that promote the expression of inflammatory mediators, thereby contributing to the amplification of inflammatory responses (Kim & Choi, 2010).

Experimental investigations involving Cymbopogon citratus suggest that its bioactive constituents are capable of suppressing ERK phosphorylation, thereby limiting the expression of inflammatory genes. Citral, chlorogenic acid, and flavonoids are believed to interfere with ERK activation directly or indirectly by reducing oxidative stress and regulating upstream signaling events. Consequently,

inhibition of ERK signaling contributes to the overall anti-inflammatory activity of lemongrass and reduces the production of inflammatory mediators (Francisco et al., 2013; Han & Parker, 2017).

5.3 JNK and p38 MAPK Regulation by Lemongrass

The JNK and p38 MAPK pathways are predominantly activated in response to inflammatory cytokines, oxidative stress, and other cellular stress signals. Activation of these kinases stimulates transcription factors, including activator protein-1 (AP-1), leading to enhanced expression of inflammatory cytokines, chemokines, and enzymes involved in inflammatory amplification. Persistent activation of JNK and p38 MAPK has been implicated in the progression of chronic inflammatory diseases, autoimmune disorders, metabolic abnormalities, and neurodegenerative conditions (Arthur & Ley, 2013).

Available evidence indicates that lemongrass-derived phytochemicals suppress phosphorylation of both JNK and p38 MAPK, thereby attenuating downstream inflammatory signaling. Citral has been identified as the principal contributor to this inhibitory activity, while chlorogenic acid and flavonoids further enhance these effects through their antioxidant properties and regulation of redox-sensitive signaling mechanisms. Through simultaneous modulation of multiple MAPK branches, lemongrass effectively reduces inflammatory mediator production and limits tissue injury (Francisco et al., 2011; Francisco et al., 2013).

5.4 MAPK Inhibition and Anti-inflammatory Mechanisms

The anti-inflammatory activity of Cymbopogon citratus is closely associated with its ability to suppress MAPK-mediated signaling events. By reducing phosphorylation of ERK, JNK, and p38 MAPK, lemongrass bioactive compounds decrease activation of downstream transcription factors responsible for inflammatory gene expression. This ultimately results in reduced synthesis of TNF-α, IL-1β, IL-6, COX-2, iNOS, and other inflammatory mediators that contribute to tissue injury and disease progression.

The simultaneous regulation of multiple MAPK components provides an important therapeutic advantage because it enables broad suppression of inflammatory signaling rather than selective inhibition of a single molecular target. Such multitarget regulation is characteristic of botanical medicines and may explain the broad pharmacological activities consistently reported for lemongrass extracts. Nevertheless, additional mechanistic studies are required to clarify the direct molecular interactions between individual phytochemicals and specific MAPK components.

5.5 Key Insights

Current evidence indicates that the anti-inflammatory activity of Cymbopogon citratus is closely associated with its capacity to regulate multiple components of the MAPK signaling cascade rather than a single molecular target. The coordinated inhibition of ERK, JNK, and p38 MAPK by lemongrass-derived bioactive compounds contributes to reduced activation of downstream transcription factors and subsequent suppression of inflammatory gene expression. Consequently, the production of key inflammatory mediators, including TNF-α, IL-1β, IL-6, COX-2, and iNOS, is markedly diminished, thereby attenuating inflammatory responses.

Among the identified phytochemicals, citral appears to play a predominant role because of its high abundance in the essential oil and its consistently reported anti-inflammatory activity across experimental studies. Nevertheless, chlorogenic acid, flavonoids, geraniol, and other minor

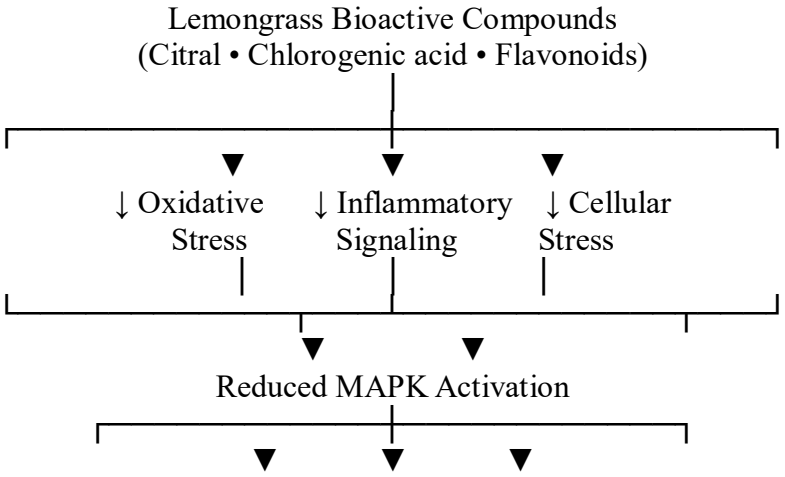
constituents also contribute substantially through complementary antioxidant and immunomodulatory mechanisms. The collective activity of these compounds provides broader regulation of inflammatory signaling than would be expected from any individual constituent alone.

The multitarget nature of lemongrass distinguishes it from conventional anti-inflammatory agents that frequently act on a single enzyme or receptor. By simultaneously modulating MAPK signaling, reducing oxidative stress, and limiting inflammatory mediator production, C. citratus demonstrates considerable promise as a multifunctional phytotherapeutic agent for the management of inflammation-associated disorders. Although the available experimental evidence is encouraging, additional mechanistic investigations, standardized phytochemical analyses, and clinical studies are required to validate these findings and facilitate their translation into therapeutic applications.

Table 10. Comparative Characteristics of the Three Major MAPK Signaling Pathways

MAPK Component	**Major Activating Stimuli**	**Primary Biological Function**	**Contribution to Inflammation**	**Potential Influence of Lemongrass Bioactive Compounds***
ERK1/2	Growth factors, cytokines	Cell proliferation and survival	Supports cytokine production	May reduce upstream inflammatory signaling
JNK	ROS, inflammatory cytokines, stress	Stress response and apoptosis	Promotes AP-1 activation and cytokine synthesis	Antioxidant activity may reduce stress-induced activation
p38 MAPK	LPS, TNF-α, IL-1β, ROS	Cytokine production and immune regulation	Regulates COX-2, iNOS and inflammatory mediators	Antioxidant phytochemicals may attenuate activation

*Based on evidence available in studies published up to 2020. Direct molecular evidence varies among individual compounds.



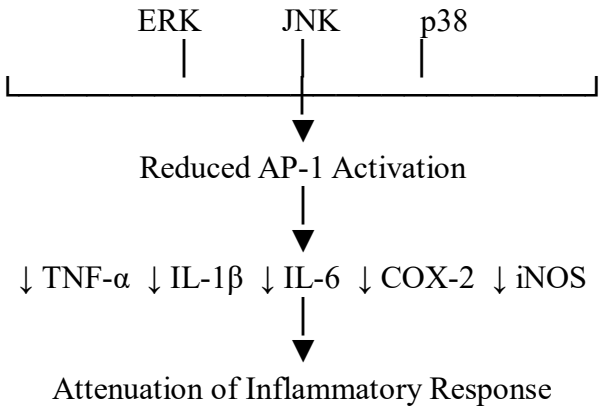


Figure 10. Proposed Regulation of MAPK Components by Lemongrass Bioactive Compounds

6. Crosstalk Between Nf-Kb And Mapk Signaling Pathways: Integrated Regulation By Lemongrass Bioactive Compounds

6.1 Functional Interactions Between NF-κB and MAPK Signaling

Inflammatory responses are orchestrated through a complex network of interconnected signaling pathways rather than isolated molecular mechanisms. Among these, the NF-κB and MAPK pathways exhibit extensive functional crosstalk that enables cells to coordinate immune and inflammatory responses following exposure to pathogens, inflammatory cytokines, oxidative stress, or tissue injury. Activation of Toll-like receptors (TLRs) initiates signaling through common adaptor proteins, including MyD88 and TRAF6, leading to simultaneous activation of both NF-κB and MAPK cascades. As a result, these pathways regulate overlapping sets of inflammatory genes and collectively amplify cytokine production during the inflammatory response (Tak & Firestein, 2001; Arthur & Ley, 2013).

Although NF-κB primarily governs the transcription of inflammatory cytokines and enzymes, the MAPK pathway regulates transcription factors such as activator protein-1 (AP-1), which acts cooperatively with NF-κB to maximize inflammatory gene expression. Consequently, concurrent activation of both signaling pathways produces a substantially greater inflammatory response than activation of either pathway alone. Persistent stimulation of these interconnected signaling networks has therefore been implicated in the progression of numerous chronic inflammatory diseases (Lawrence, 2009).

Reactive oxygen species (ROS) further strengthen this molecular interaction by serving as intracellular secondary messengers capable of activating both NF-κB and MAPK signaling. Elevated oxidative stress establishes a self-perpetuating cycle in which ROS stimulate inflammatory signaling, while inflammatory mediators promote additional ROS generation. This reciprocal relationship contributes to sustained inflammation, progressive tissue injury, and disease development (Reuter et al., 2010).

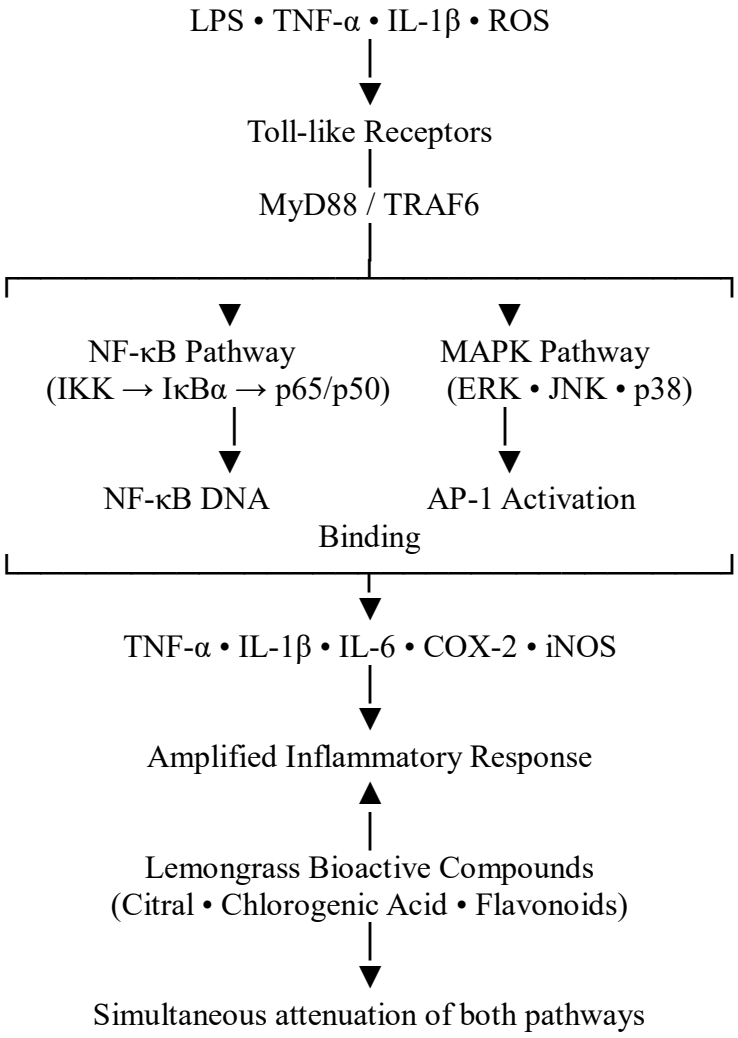


Figure 11. Crosstalk Between NF-κB and MAPK Signaling During Inflammation

6.2 Coordinated Regulation of NF-κB and MAPK Signaling by Lemongrass Bioactive Compounds

Emerging evidence indicates that the anti-inflammatory activity of Cymbopogon citratus extends beyond the modulation of individual signaling pathways. Instead, its bioactive constituents appear to regulate both NF-κB and MAPK signaling simultaneously, thereby providing broader suppression of inflammatory responses. Citral, chlorogenic acid, flavonoids, and related phytochemicals reduce oxidative stress while attenuating multiple intracellular signaling events that contribute to inflammation. This coordinated modulation may explain the consistent anti-inflammatory effects observed across diverse experimental models using lemongrass extracts (Francisco et al., 2013; Avoseh et al., 2015).

The antioxidant properties of lemongrass phytochemicals provide an additional mechanism for interrupting communication between these signaling pathways. Because oxidative stress functions as a common upstream activator of both NF-κB and MAPK, reducing intracellular ROS levels limits activation of each pathway simultaneously. This interruption weakens the positive feedback mechanisms responsible for sustaining inflammatory signaling and ultimately contributes to the attenuation of chronic inflammation. Nevertheless, additional mechanistic investigations are required to define the precise molecular interactions responsible for this coordinated regulation.

Table 11. Comparative Roles of NF-κB and MAPK Signaling in Inflammation and Proposed Regulatory Effects of Lemongrass Bioactive Compounds

Parameter	NF-κB Pathway	MAPK Pathway	Proposed Influence of Lemongrass
Primary function	Transcription of inflammatory genes	Regulation of stress-responsive kinases	Simultaneous modulation of both pathways
Major activators	LPS, TNF-α, IL-1β, ROS	LPS, ROS, cytokines, stress	Reduction of upstream inflammatory stimuli
Key signaling proteins	IKK, IκBα, p65/p50	ERK, JNK, p38	Potential attenuation of pathway activation
Major transcription factors	NF-κB	AP-1	Reduced transcriptional activity
Downstream mediators	TNF-α, IL-1β, IL-6, COX-2, iNOS	TNF-α, IL-1β, IL-6, COX-2, iNOS	Reduced inflammatory mediator production
Overall outcome	Amplification of inflammation	Amplification of inflammation	Attenuation of inflammatory response

6.3 Experimental Evidence Supporting the Crosstalk Between NF-κB and MAPK Pathways

Accumulating experimental evidence demonstrates that NF-κB and MAPK signaling pathways operate as interconnected regulatory networks rather than independent molecular systems. A wide range of in vitro and in vivo studies has shown that inflammatory stimuli simultaneously activate both pathways, resulting in coordinated upregulation of pro-inflammatory cytokines, chemokines, and inflammatory enzymes. This functional interaction enables inflammatory signals to be amplified efficiently, while inhibition of one pathway frequently influences the activity of the other, emphasizing the extensive molecular crosstalk between these signaling cascades (Tak & Firestein, 2001; Arthur & Ley, 2013).

Experimental studies further suggest that bioactive constituents of Cymbopogon citratus regulate both NF-κB and MAPK signaling pathways simultaneously. Phytochemicals such as citral, chlorogenic acid, and flavonoids have been reported to suppress oxidative stress while attenuating intracellular inflammatory signaling, leading to reduced activation of both pathways. This coordinated modulation provides a plausible explanation for the broad-spectrum anti-inflammatory effects consistently observed in experimental models using lemongrass extracts (Francisco et al., 2013; Avoseh et al., 2015).

The antioxidant properties of lemongrass bioactive compounds provide an additional mechanism for regulating pathway crosstalk. Since oxidative stress functions as a common upstream activator of both NF-κB and MAPK, reduction of intracellular ROS levels interrupts the positive feedback loops that sustain inflammatory signaling. Consequently, simultaneous suppression of oxidative stress and

inflammatory signaling contributes to attenuation of chronic inflammation and limits excessive production of inflammatory mediators. Nevertheless, further pathway-specific molecular investigations are required to clarify the precise interactions between individual phytochemicals and the regulatory components governing NF-κB–MAPK crosstalk.

Table 12. Experimental Evidence Demonstrating Coordinated Regulation of NF-κB and MAPK Signaling

Experimental Observation	NF-κB Response	MAPK Response	Overall Biological Outcome
Inflammatory stimulation	Activation	Activation	Increased cytokine production
Increased oxidative stress	Enhanced NF-κB activation	Enhanced MAPK activation	Amplified inflammatory response
Antioxidant phytochemicals	Reduced activation	Reduced activation	Suppression of inflammatory mediators
Lemongrass bioactive compounds	Decreased inflammatory signaling	Reduced kinase activation	Attenuation of inflammation
Combined pathway modulation	Lower cytokine production	Reduced inflammatory enzyme expression	Improved anti-inflammatory activity

Abbreviations: MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B.

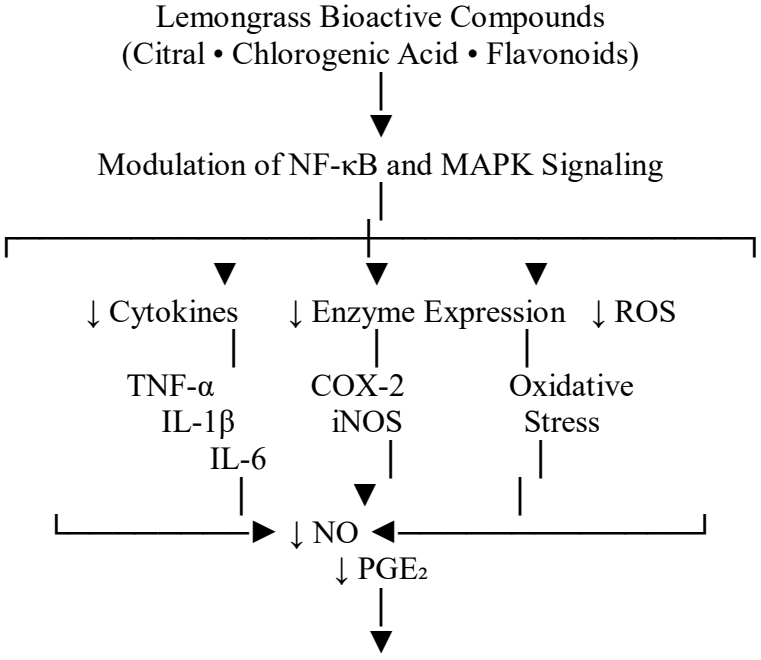


Figure 12. Downstream Inflammatory Mediators Regulated by Lemongrass Bioactive Compounds

6.4 Key Insights

Current evidence indicates that the anti-inflammatory activity of Cymbopogon citratus is mediated through coordinated regulation of interconnected inflammatory signaling pathways rather than selective inhibition of a single molecular target. Simultaneous modulation of NF-κB and MAPK signaling, together with potent antioxidant activity, enables lemongrass-derived phytochemicals to reduce cytokine production, suppress inflammatory enzyme expression, and alleviate oxidative stress through complementary mechanisms. This multitarget mode of action distinguishes lemongrass from many conventional anti-inflammatory agents that primarily act on individual enzymes or receptors (Francisco et al., 2013; Avoseh et al., 2015).

Although current experimental findings strongly support the coordinated regulation of inflammatory signaling by lemongrass bioactive compounds, additional investigations employing standardized phytochemical preparations, pathway-specific molecular analyses, pharmacokinetic evaluation, and well-designed translational studies are required. Such studies will provide a more comprehensive understanding of the molecular basis of NF-κB–MAPK crosstalk and strengthen the evidence supporting the therapeutic application of Cymbopogon citratus in chronic inflammatory diseases.

7. Regulation Of Downstream Inflammatory Mediators By Cymbopogon Citratus Bioactive Compounds

7.1 Overview of Downstream Inflammatory Mediators

Activation of the NF-κB and MAPK signaling pathways culminates in the transcription, synthesis, and release of numerous inflammatory mediators that regulate both innate and adaptive immune responses. These downstream mediators include pro-inflammatory cytokines, inflammatory enzymes, reactive nitrogen species, chemokines, lipid-derived mediators, and reactive oxygen species, all of which coordinate host defense mechanisms and tissue repair. While these molecules are indispensable for normal immune function, excessive or persistent production contributes to chronic inflammation, oxidative stress, immune dysregulation, and progressive tissue injury. Consequently, suppression of these downstream inflammatory mediators represents one of the principal mechanisms through which anti-inflammatory therapies exert their beneficial effects (Tak & Firestein, 2001; Lawrence, 2009).

Experimental studies have demonstrated that extracts and bioactive compounds derived from Cymbopogon citratus reduce the production of multiple inflammatory mediators through coordinated modulation of intracellular signaling pathways. Rather than selectively targeting a single cytokine or inflammatory enzyme, lemongrass phytochemicals simultaneously regulate several downstream mediators, resulting in a broader and more integrated anti-inflammatory response. This multitarget mechanism is consistent with the chemically diverse phytochemical composition of the plant and provides a molecular explanation for its long-standing use in traditional medicine for inflammatory disorders (Francisco et al., 2011; Francisco et al., 2013).

7.2 Major Inflammatory Mediators Regulated by Lemongrass

Among the pro-inflammatory cytokines, TNF-α, IL-1β, and IL-6 are considered the principal mediators responsible for initiating and amplifying inflammatory responses. These cytokines stimulate leukocyte recruitment, endothelial activation, vascular permeability, and the synthesis of additional inflammatory mediators, thereby establishing a positive feedback loop that perpetuates inflammation. Persistent overproduction of these cytokines has been implicated in the pathogenesis of rheumatoid arthritis, inflammatory bowel disease, metabolic disorders, cardiovascular diseases, and several neurodegenerative conditions (Tak & Firestein, 2001; Lawrence, 2009).

Inflammatory enzyme expression also plays a pivotal role in sustaining chronic inflammatory responses. Cyclooxygenase-2 (COX-2) catalyzes the synthesis of prostaglandin E_2 (PGE_2), a lipid mediator responsible for pain sensitization, vasodilation, and edema. Similarly, inducible nitric oxide synthase (iNOS) produces large amounts of nitric oxide (NO), which contributes to host defense under physiological conditions but promotes oxidative tissue damage when generated excessively. Together, these enzymes amplify inflammatory signaling and accelerate tissue injury during chronic inflammation (Cho et al., 2003).

In addition to cytokines and inflammatory enzymes, excessive production of reactive oxygen species (ROS) further intensifies inflammation by activating redox-sensitive signaling pathways and stimulating additional cytokine release. Because oxidative stress and inflammatory signaling reinforce one another through reciprocal positive feedback mechanisms, phytochemicals possessing both antioxidant and anti-inflammatory properties are expected to provide greater therapeutic benefits than agents acting on a single inflammatory mediator (Reuter et al., 2010).

Table 13. Major Downstream Inflammatory Mediators Regulated by Cymbopogon citratus

Inflammatory Mediator	Primary Biological Function	Role in Chronic Inflammation	Proposed Effect of C. citratus
TNF-α	Initiates inflammatory signaling and recruits immune cells	Sustains inflammatory responses and tissue injury	Reduced production
IL-1β	Promotes fever, endothelial activation, and leukocyte migration	Amplifies inflammatory cascades	Reduced production
IL-6	Regulates acute-phase responses and immune activation	Associated with chronic inflammatory diseases	Reduced production
COX-2	Catalyzes prostaglandin synthesis	Promotes pain, edema, and inflammation	Reduced expression
iNOS	Produces nitric oxide during inflammation	Excessive NO contributes to oxidative tissue injury	Reduced expression
NO	Mediates antimicrobial defense and cellular signaling	Excess accumulation promotes cellular damage	Reduced production
PGE_2	Regulates vasodilation, pain, and vascular	Contributes to persistent inflammation	Reduced productio

	permeability		n
ROS	Functions in microbial killing and intracellular signaling	Promotes oxidative stress and inflammatory amplification	Reduced accumulation

Abbreviations: COX-2, cyclooxygenase-2; IL, interleukin; iNOS, inducible nitric oxide synthase; NO, nitric oxide; PGE_2, prostaglandin E_2; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

7.3 Biological Significance

The coordinated regulation of cytokines, inflammatory enzymes, and oxidative mediators provides a mechanistic basis for the broad-spectrum anti-inflammatory activity of Cymbopogon citratus. Unlike therapeutic agents that selectively inhibit a single inflammatory target, the phytochemical constituents of lemongrass appear to influence multiple downstream mediators simultaneously, thereby disrupting several stages of the inflammatory cascade. This integrated pharmacological profile may explain the diverse anti-inflammatory effects reported across experimental studies and supports the potential application of lemongrass as a multitarget therapeutic agent for inflammatory disorders (Bachiega & Sforcin, 2011; Francisco et al., 2013).

The combined suppression of TNF-α, IL-1β, IL-6, COX-2, iNOS, NO, PGE_2, and ROS suggests that lemongrass bioactive compounds act at multiple regulatory levels within the inflammatory response. Such simultaneous modulation not only limits the amplification of inflammatory signaling but also reduces oxidative damage and preserves cellular homeostasis. Consequently, the pharmacological effects of C. citratus extend beyond simple cytokine inhibition and encompass comprehensive regulation of the molecular networks responsible for inflammation.

The multitarget nature of lemongrass is particularly important because chronic inflammatory diseases are driven by interconnected signaling pathways rather than isolated molecular abnormalities. Therefore, botanical preparations containing chemically diverse phytochemicals may offer greater therapeutic flexibility than single-target agents by simultaneously regulating multiple inflammatory processes. Nevertheless, further experimental investigations are required to determine the relative contribution of individual bioactive compounds, establish standardized formulations, and validate these mechanisms through well-designed preclinical and clinical studies.

8. Experimental Evidence Supporting The Anti-Inflammatory Activity Of Cymbopogon Citratus

8.1 Overview Of Experimental Evidence

Over the past two decades, a substantial body of experimental research has expanded our understanding of the anti-inflammatory properties of Cymbopogon citratus. Investigations have employed diverse experimental platforms, including phytochemical analyses, cell culture systems, animal models, and mechanistic studies, to evaluate the biological activity of lemongrass and its major phytochemical constituents. Collectively, these studies indicate that C. citratus attenuates inflammatory responses through modulation of intracellular signaling pathways, suppression of oxidative stress, and reduction of pro-inflammatory mediator production. Despite these encouraging findings, considerable heterogeneity exists in extraction procedures, phytochemical composition,

experimental models, dosage regimens, treatment duration, and analytical methods, making direct comparison among studies challenging (Negrelle & Gomes, 2007; Avoseh et al., 2015).

Most published investigations have focused on in vitro macrophage-based models and in vivo rodent models of acute inflammation. Across these experimental systems, treatment with lemongrass extracts or isolated bioactive compounds consistently reduced inflammatory cytokine production, nitric oxide synthesis, oxidative stress, and inflammatory enzyme expression. However, relatively few studies have simultaneously examined multiple signaling pathways, including both NF-κB and MAPK, highlighting the need for more comprehensive mechanistic investigations that integrate these interconnected molecular networks.

Table 14. Representative In Vivo Studies Evaluating the Anti-inflammatory Activity of Cymbopogon citratus

Study	Experimental Animal Model	Intervention	Primary Outcome Assessed	Major Findings	Study Limitation
Bachiega & Sforcin (2011)	Experimental inflammation model	Citral	Inflammatory response	Citral markedly reduced inflammatory responses in the experimental model	Detailed molecular mechanisms were not comprehensively investigated
Francisco et al. (2011)	Animal model of inflammation	Cymbopogon citratus extract	Tissue inflammatory response	Lemongrass extract exhibited significant anti-inflammatory efficacy	Further dose optimization and pharmacodynamic evaluation are required
Naik et al. (2010)	Pharmacological animal evaluation	Essential oil	Overall anti-inflammatory activity	Essential oil demonstrated promising pharmacological effectiveness against inflammation	Limited assessment of molecular signaling pathways

Avoseh et al. (2015)	Literature-based evidence synthesis	Whole plant	Pharmacological evidence	Comprehensive review highlighted the anti-inflammatory potential of C. citratus	Findings were based on previously published studies rather than new experimental investigations

Abbreviations: C. citratus, Cymbopogon citratus.

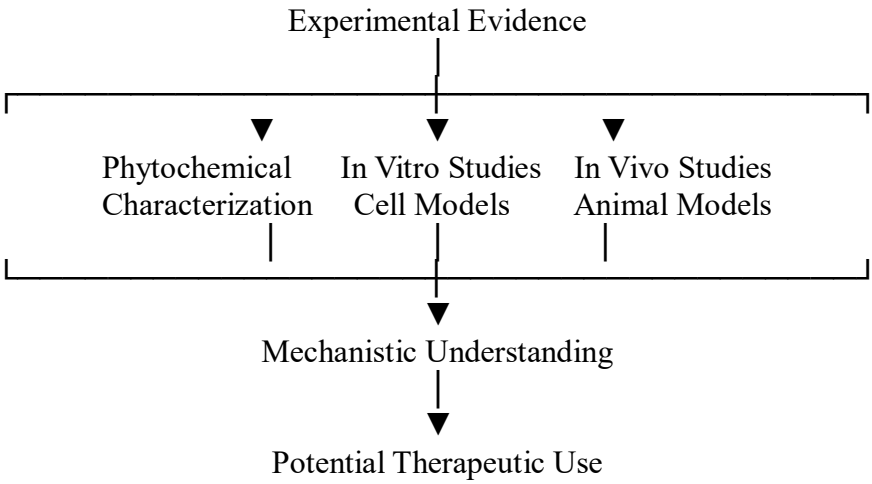


Figure 13. Hierarchy of Experimental Evidence Supporting the Anti-inflammatory Activity of Cymbopogon citratus

8.2 Strengths and Limitations of Current Experimental Evidence

The current body of literature provides convincing experimental support for the anti-inflammatory potential of Cymbopogon citratus. Evidence generated from phytochemical investigations, cell-based experiments, and animal studies consistently demonstrates reductions in pro-inflammatory cytokine production, oxidative stress, inflammatory enzyme expression, and tissue inflammation following treatment with lemongrass extracts or their bioactive constituents. Collectively, these findings provide a strong scientific rationale for the traditional medicinal use of lemongrass and support its continued investigation as a source of novel anti-inflammatory phytochemicals.

Despite these encouraging findings, several important limitations continue to restrict the interpretation and clinical translation of the available evidence. Considerable variability exists among studies with respect to extraction procedures, phytochemical composition, experimental models, dosage regimens, treatment duration, and analytical methodologies. Such heterogeneity reduces comparability between investigations and complicates the identification of optimal

experimental conditions. Moreover, numerous studies have evaluated crude plant extracts without comprehensive phytochemical characterization, making it difficult to determine the specific contribution of individual bioactive compounds to the observed biological effects.

Another major limitation is the scarcity of well-designed human clinical studies. Most currently available evidence originates from in vitro experiments and in vivo animal models, whereas clinical validation remains limited. Consequently, important aspects such as pharmacokinetics, bioavailability, standardized formulations, long-term safety, and therapeutic efficacy in human populations remain insufficiently investigated. Addressing these gaps through standardized phytochemical analyses, integrated molecular investigations, and rigorously designed clinical trials will be essential for translating experimental findings into evidence-based therapeutic applications.

Figure 14. Strengths and Limitations of Current Evidence

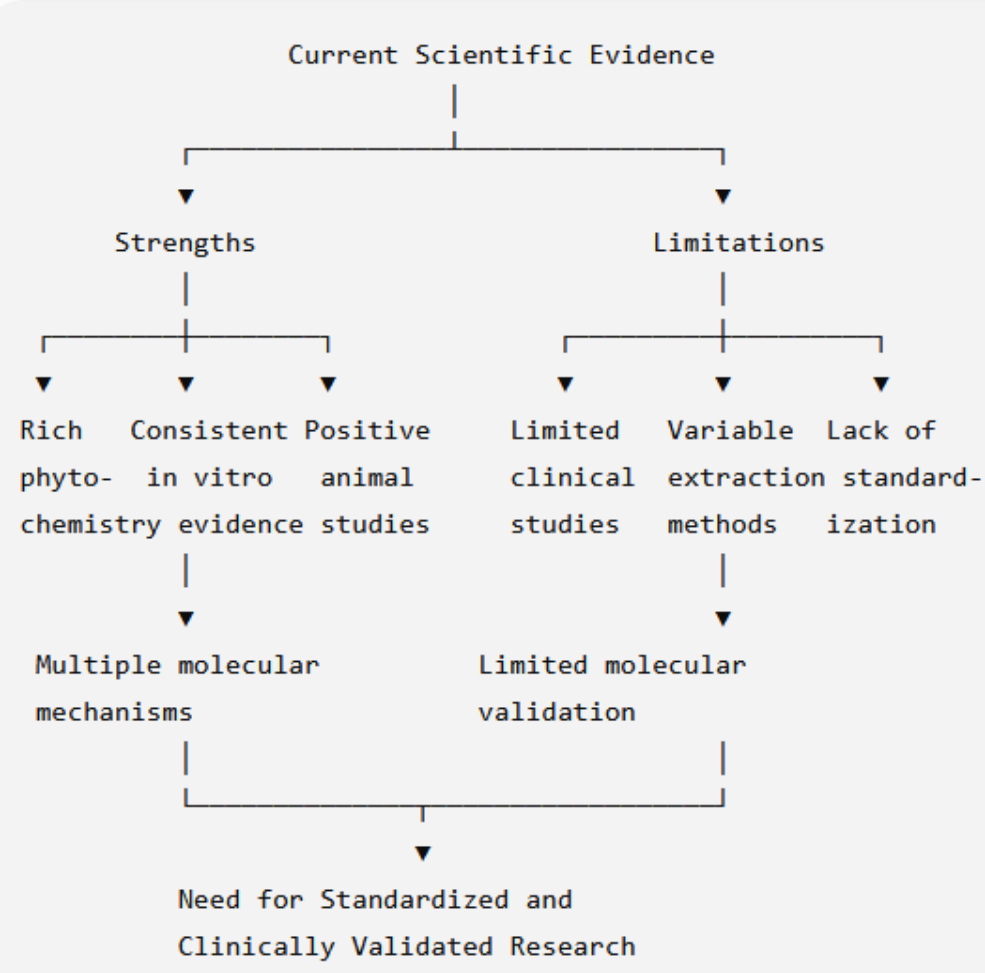


Figure 14. Strengths and limitations of current scientific evidence supporting the anti-inflammatory activity of Cymbopogon citratus. The available literature demonstrates strong phytochemical diversity, consistent experimental findings, positive animal studies, and multiple proposed mechanisms. However, limitations including limited clinical validation, variability in extraction procedures, lack of standardization, and insufficient molecular characterization remain major challenges for therapeutic translation.

9. Therapeutic Applications Of Cymbopogon Citratus Bioactive Compounds In Inflammation-Associated Diseases

9.1 Overview

Chronic inflammation represents a common pathogenic mechanism underlying numerous non-communicable diseases. Sustained activation of inflammatory signaling pathways, particularly NF-κB and MAPK, promotes continuous production of pro-inflammatory cytokines, inflammatory enzymes, oxidative mediators, and chemokines, ultimately leading to progressive tissue injury and functional impairment of affected organs. Consequently, modulation of these signaling pathways has emerged as an important therapeutic strategy for preventing or slowing the progression of inflammation-associated diseases. Experimental evidence indicates that Cymbopogon citratus possesses considerable therapeutic potential because its bioactive constituents simultaneously regulate multiple components of the inflammatory cascade. Unlike conventional pharmacological agents that frequently target a single enzyme or receptor, lemongrass-derived phytochemicals exert coordinated effects on intracellular signaling pathways, oxidative stress, inflammatory cytokines, and inflammatory enzymes. This multitarget mode of action provides a mechanistic basis for their potential application across a broad spectrum of chronic inflammatory disorders. The following sections summarize the current experimental evidence supporting the potential application of C. citratus in selected inflammation-associated diseases while emphasizing that most available findings originate from in vitro investigations and animal studies. Therefore, although the experimental evidence is encouraging, further clinical validation is required before routine therapeutic application can be recommended.

9.2 Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune disorder characterized by persistent synovial inflammation, progressive cartilage destruction, and bone erosion. Excessive activation of NF-κB and MAPK signaling pathways promotes continuous production of TNF-α, IL-1β, IL-6, COX-2, and other inflammatory mediators that sustain joint inflammation and accelerate disease progression. Available experimental evidence suggests that lemongrass bioactive compounds may attenuate inflammatory responses associated with rheumatoid arthritis by suppressing cytokine production, reducing oxidative stress, and modulating intracellular inflammatory signaling pathways. Although these findings demonstrate promising pharmacological potential, additional preclinical investigations and well-designed clinical studies are required to establish their therapeutic efficacy in patients with rheumatoid arthritis.

9.3 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) encompasses chronic inflammatory disorders of the gastrointestinal tract that arise from dysregulated immune responses and persistent intestinal inflammation. Activation of NF-κB signaling contributes significantly to intestinal cytokine production, epithelial barrier dysfunction, and recruitment of inflammatory cells, thereby perpetuating disease progression.

9.4 Cardiovascular Diseases

Experimental investigations indicate that antioxidant and anti-inflammatory phytochemicals present in Cymbopogon citratus may reduce intestinal inflammatory responses by regulating inflammatory signaling pathways and limiting oxidative stress. Although these observations support the potential application of lemongrass in intestinal inflammatory disorders, the current evidence remains largely experimental, and clinical confirmation is still lacking.

Chronic vascular inflammation plays a fundamental role in the initiation and progression of atherosclerosis and other cardiovascular disorders. Persistent activation of inflammatory signaling pathways promotes endothelial dysfunction, oxidative stress, and cytokine production, thereby accelerating vascular injury and disease progression.

The antioxidant properties of lemongrass phytochemicals, together with their ability to regulate inflammatory signaling, suggest a potential supportive role in reducing vascular inflammation. By attenuating oxidative stress and modulating inflammatory mediators, C. citratus may contribute to cardiovascular protection. However, confirmation of these effects requires further mechanistic investigations and well-controlled clinical studies.

9.5 Diabetes Mellitus

Persistent low-grade inflammation is a major contributor to the development and progression of type 2 diabetes mellitus. Continuous activation of inflammatory signaling pathways interferes with insulin signaling, enhances oxidative stress, and promotes the release of pro-inflammatory cytokines, thereby accelerating metabolic dysfunction and insulin resistance. Increasing evidence indicates that modulation of inflammatory pathways may represent an effective strategy for improving metabolic homeostasis and reducing diabetes-associated complications.

The antioxidant and anti-inflammatory properties of Cymbopogon citratus suggest its potential utility in mitigating inflammation associated with metabolic disorders. Experimental studies indicate that lemongrass-derived phytochemicals may attenuate oxidative stress and inflammatory signaling, thereby reducing inflammatory burden during the progression of diabetes mellitus. Nevertheless, the precise molecular mechanisms through which these bioactive compounds influence insulin resistance and metabolic inflammation remain insufficiently understood. Additional mechanistic investigations and well-controlled experimental studies are therefore required to establish their therapeutic relevance in diabetes management (Pan et al., 2014).

9.6 Neuroinflammatory Disorders

Neuroinflammation is increasingly recognized as a central pathological feature of numerous neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and related neurological conditions. Sustained activation of microglial cells promotes excessive production of inflammatory cytokines, nitric oxide, and reactive oxygen species, resulting in neuronal dysfunction and progressive neurodegeneration. Since NF-κB and MAPK signaling pathways are key regulators of microglial activation, their modulation has emerged as an important therapeutic approach for limiting neuroinflammatory injury. The phytochemical profile of Cymbopogon citratus, particularly its antioxidant and anti-inflammatory constituents, provides a scientific basis for exploring its neuroprotective potential. By reducing oxidative stress and regulating inflammatory signaling pathways, lemongrass bioactive compounds may contribute to the attenuation of neuroinflammatory processes. However, direct experimental evidence supporting these effects remains limited, and additional preclinical and clinical investigations are necessary to clarify their efficacy, underlying molecular mechanisms, and potential therapeutic applications in neurodegenerative diseases.

9.7 General Perspective on Therapeutic Applications

The collective experimental evidence indicates that Cymbopogon citratus possesses broad therapeutic potential across a wide range of inflammation-associated disorders. Rather than targeting a disease-specific pathway, lemongrass bioactive compounds regulate fundamental inflammatory mechanisms that are shared among multiple chronic diseases. Through coordinated modulation of NF-κB and MAPK signaling pathways, suppression of pro-inflammatory cytokine production, reduction of oxidative stress, and inhibition of inflammatory enzyme expression, these phytochemicals exert multitarget anti-inflammatory effects that may be beneficial in diverse pathological conditions. Although the available findings strongly support the pharmacological potential of lemongrass, most evidence has been generated from phytochemical analyses, in vitro studies, and experimental animal models. Consequently, translation of these observations into clinical practice requires standardized phytochemical preparations, comprehensive pharmacokinetic evaluation, optimization of dosage regimens, and rigorously designed randomized clinical trials. Addressing these challenges will strengthen the evidence base and facilitate the development of Cymbopogon citratus-derived therapeutics for the management of chronic inflammatory diseases.

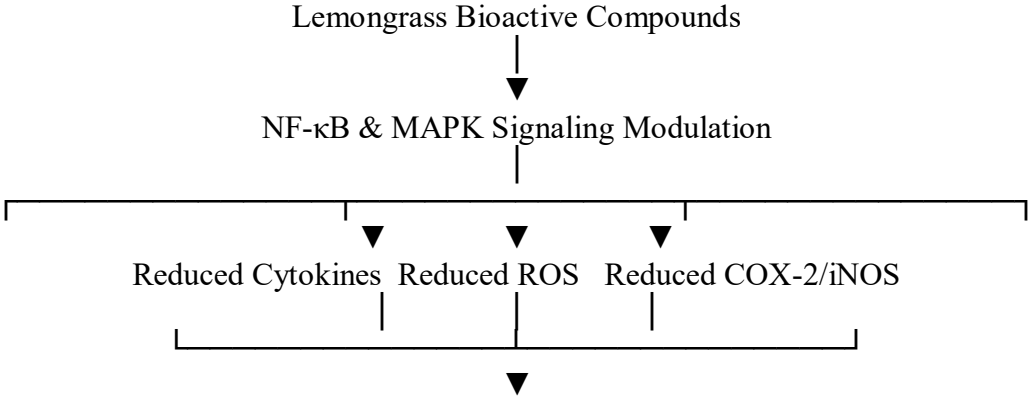
Table 15. Potential Therapeutic Applications of Cymbopogon citratus Based on Current Experimental Evidence

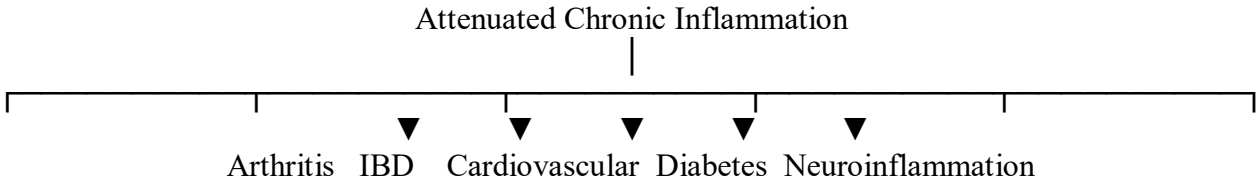
Disease/Condition	Major Inflammatory Mechanism	Key Signaling Pathways	Potential Therapeutic Role of C. citratus	Current Evidence

Rheumatoid arthritis	Chronic synovial inflammation	NF-κB, MAPK	May suppress cytokine production and oxidative stress	Experimental
Inflammatory bowel disease	Intestinal immune dysregulation	NF-κB	Potential to alleviate intestinal inflammation	Limited experimental
Cardiovascular diseases	Vascular inflammation and oxidative stress	NF-κB, MAPK	Antioxidant and anti-inflammatory activity	Experimental
Type 2 diabetes mellitus	Chronic metabolic inflammation	NF-κB	May reduce inflammatory stress and metabolic dysfunction	Experimental
Neurodegenerative disorders	Microglial activation and neuroinflammation	NF-κB, MAPK	Potential neuroprotective and anti-inflammatory effects	Limited experimental
General inflammatory conditions	Excessive cytokine production	NF-κB, MAPK	Broad-spectrum anti-inflammatory activity	Strong experimental

Abbreviations: MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B.

Figure 15. Therapeutic Potential of Lemongrass Through Modulation of NF-κB and MAPK Signaling





10. Challenges, Research Gaps, And Future Perspectives

10.1 Current Challenges In Translating Cymbopogon Citratus Bioactive Compounds Into Therapeutic Applications

Although considerable progress has been made in elucidating the anti-inflammatory properties of Cymbopogon citratus, several scientific and technological challenges continue to impede its translation into evidence-based therapeutic applications. The majority of published studies have been conducted using in vitro cell culture systems or experimental animal models, whereas rigorously designed human clinical investigations remain limited. Consequently, despite substantial experimental support for the biological activity of lemongrass and its phytochemicals, important aspects such as clinical efficacy, optimal dosage, pharmacokinetic behavior, and long-term safety have yet to be fully established.

Another significant challenge is the considerable variability in the phytochemical composition of C. citratus. Factors including geographical origin, genotype, environmental conditions, cultivation practices, harvesting stage, plant part, and post-harvest processing substantially influence the concentration of major bioactive constituents, particularly citral and phenolic compounds. This phytochemical variability complicates comparison among published studies and limits reproducibility across independent investigations.

Variations in extraction methodologies represent an additional source of inconsistency. Hydrodistillation, steam distillation, aqueous extraction, ethanolic extraction, methanolic extraction, and hydroalcoholic extraction frequently produce extracts with distinct phytochemical profiles. Since pharmacological activity is directly related to chemical composition, differences in extraction procedures may significantly influence biological outcomes and contribute to discrepancies among experimental findings.

A further limitation involves incomplete mechanistic characterization. While numerous studies demonstrate suppression of inflammatory cytokines and oxidative stress, comparatively few have comprehensively investigated the molecular interactions through which lemongrass phytochemicals regulate NF-κB, MAPK, and related signaling pathways. Consequently, several proposed mechanisms remain only partially validated and require additional experimental confirmation.

10.2 Major Research Gaps

Despite substantial advances in phytochemical and pharmacological research, several important knowledge gaps remain. Addressing these limitations will improve mechanistic understanding and accelerate the clinical development of lemongrass-derived anti-inflammatory therapeutics.

First, most available studies have evaluated crude extracts rather than purified phytochemicals or chemically standardized formulations. As a result, the relative contribution of individual bioactive compounds to the overall anti-inflammatory activity of C. citratus remains incompletely defined.

Second, direct comparative investigations examining essential oils, aqueous extracts, hydroalcoholic extracts, and purified compounds under identical experimental conditions are scarce. Such studies are necessary to identify the most effective phytochemical fraction for modulating inflammatory signaling pathways and to establish standardized therapeutic preparations.

Third, integrated molecular studies simultaneously evaluating NF-κB and MAPK signaling remain uncommon. Most published investigations focus on individual signaling pathways or a limited number of inflammatory biomarkers, thereby restricting comprehensive understanding of pathway crosstalk and coordinated intracellular regulation.

Finally, translational research remains insufficient. Relatively few studies have examined pharmacokinetics, bioavailability, formulation strategies, or long-term safety, all of which are essential prerequisites for the development of scientifically validated phytopharmaceutical products suitable for clinical application.

Table 16. Current Challenges and Future Research Priorities

Challenge	Current Status	Impact on Research	Future Priority
Limited clinical studies	Very limited	Restricts clinical translation	Conduct well-designed randomized clinical trials
Phytochemical variability	High	Reduces reproducibility among studies	Standardize cultivation, harvesting, and post-harvest processing
Extraction variability	High	Produces inconsistent phytochemical profiles	Develop standardized extraction protocols
Limited pathway integration	Moderate	Incomplete mechanistic understanding	Simultaneously evaluate NF-κB and MAPK signaling pathways
Lack of standardized formulations	Common	Variable biological activity	Develop chemically standardized extracts and formulations
Limited bioavailability data	Limited	Uncertain therapeutic exposure	Conduct comprehensive pharmacokinetic studies
Insufficient long-term safety evaluation	Limited	Limits clinical confidence	Perform chronic toxicity and safety assessments

Comparative phytochemical studies	Limited	Difficult to identify principal active constituents	Conduct systematic comparative phytochemical analyses

Figure 16. Future Research Roadmap for Cymbopogon citratus Anti-inflammatory Research

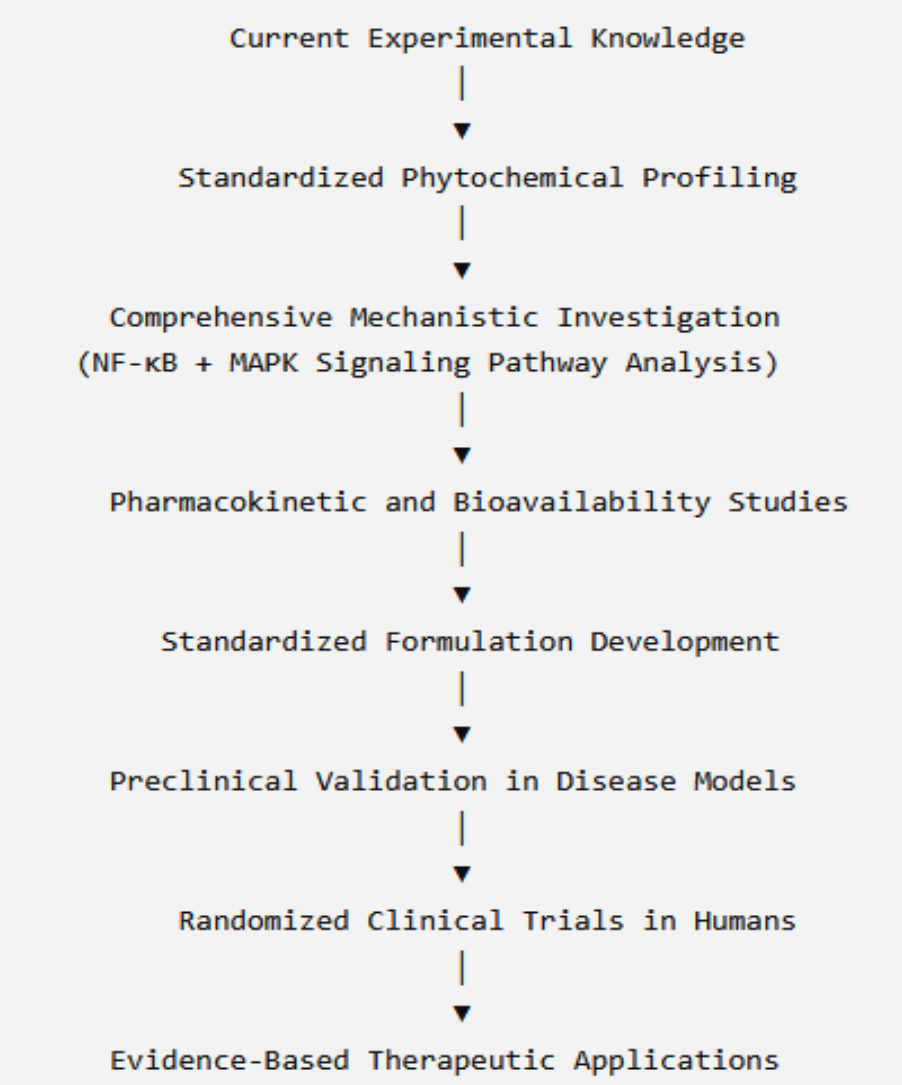


Figure 16. Future research roadmap for advancing the anti-inflammatory potential of Cymbopogon citratus. The proposed framework highlights the sequential progression from standardized phytochemical characterization and molecular mechanism validation to pharmacokinetic evaluation, formulation development, preclinical assessment, clinical validation, and evidence-based therapeutic applications.

10.3 Future Perspectives

Future research should emphasize the integration of phytochemical standardization, mechanistic validation, and clinical translation to maximize the therapeutic potential of Cymbopogon citratus. Establishing standardized cultivation practices, harvesting conditions, and extraction procedures will be essential for producing reproducible phytochemical profiles and ensuring consistent biological activity across experimental and clinical investigations. Such standardization will improve the comparability of published studies and facilitate the development of reliable lemongrass-based therapeutic formulations.

Future mechanistic investigations should adopt comprehensive molecular approaches that simultaneously evaluate NF-κB, MAPK, oxidative stress biomarkers, inflammatory cytokines, and downstream inflammatory mediators. Integrating these interconnected signaling networks within a single experimental framework will provide a more complete understanding of the molecular mechanisms underlying the anti-inflammatory activity of C. citratus. Furthermore, pathway-specific studies employing purified phytochemicals and standardized extracts will help identify the relative contribution of individual bioactive constituents and clarify their molecular targets.

Advances in pharmacokinetic research and formulation science are also essential for successful clinical translation. Future studies should investigate the absorption, distribution, metabolism, excretion, bioavailability, and long-term safety of lemongrass-derived bioactive compounds. In parallel, the development of optimized delivery systems and standardized phytopharmaceutical formulations may enhance therapeutic efficacy, improve chemical stability, and increase clinical applicability. Well-designed randomized clinical trials will ultimately be required to establish the efficacy and safety of these formulations in patients with inflammation-associated diseases.

Emerging multidisciplinary technologies offer additional opportunities to accelerate research on Cymbopogon citratus. Approaches including metabolomics, transcriptomics, proteomics, molecular docking, network pharmacology, systems biology, and artificial intelligence-assisted drug discovery can provide deeper insight into the complex interactions between lemongrass phytochemicals and inflammatory signaling pathways. The integration of these advanced technologies may facilitate the identification of novel molecular targets, improve phytopharmaceutical development, and strengthen the evidence base supporting lemongrass-derived anti-inflammatory therapeutics.

Overall, addressing the current limitations through standardized methodologies, comprehensive mechanistic investigations, and rigorous clinical validation will strengthen the scientific foundation for the therapeutic application of Cymbopogon citratus. These efforts will support the development of safe, standardized, and evidence-based phytopharmaceutical products capable of contributing to the management of chronic inflammatory diseases.

11. Conclusion

The available scientific evidence identifies Cymbopogon citratus as a valuable medicinal plant with considerable potential for the management of inflammatory disorders. Its rich phytochemical composition, particularly citral, chlorogenic acid, flavonoids, geraniol, and other phenolic constituents, contributes to a wide range of biological activities, including antioxidant and anti-inflammatory effects. Current experimental findings demonstrate that these bioactive compounds regulate major inflammatory signaling pathways, especially NF-κB and MAPK, resulting in reduced production of pro-inflammatory cytokines, inflammatory enzymes, and oxidative mediators.

Collectively, these molecular actions provide a mechanistic basis for the diverse pharmacological activities reported for lemongrass in experimental investigations.

Evidence obtained from phytochemical characterization, in vitro studies, and in vivo experimental models consistently supports the anti-inflammatory efficacy of C. citratus. However, despite these encouraging findings, the current knowledge base remains largely preclinical. Important challenges, including phytochemical variability, lack of standardized formulations, limited pharmacokinetic information, and the scarcity of well-designed human clinical trials, continue to restrict the translation of experimental findings into evidence-based therapeutic applications. Addressing these limitations should therefore be considered a priority for future research.

In conclusion, Cymbopogon citratus represents a promising source of multitarget anti-inflammatory phytochemicals with significant potential for future pharmaceutical development. Continued multidisciplinary investigations integrating phytochemistry, molecular biology, pharmacology, formulation science, and clinical research will further clarify its mechanisms of action, strengthen the evidence supporting its therapeutic use, and facilitate the development of safe, standardized, and clinically effective lemongrass-derived anti-inflammatory products.

References

1. Aćimović, M., Čabarkapa, I., Cvetković, M., Stanković, J., Kiprovski, B., Gvozdenac, S., & Puvača, N. (2020). *Cymbopogon citratus* (DC.) Stapf: Chemical composition, antimicrobial and antioxidant activities, use in medicinal and cosmetic purposes.
2. Arthur, J. S. C., & Ley, S. C. (2013). Mitogen-activated protein kinases in innate immunity. *Nature Reviews Immunology, 13*(9), 679–692. https://doi.org/10.1038/nri3495
3. Avoseh, O., Oyedeji, O., Rungqu, P., Nkeh-Chungag, B., & Oyedeji, A. (2015). *Cymbopogon* species; ethnopharmacology, phytochemistry and the pharmacological importance. *Molecules, 20*(5), 7438–7453. https://doi.org/10.3390/molecules20057438
4. Bachiega, T. F., & Sforcin, J. M. (2011). Lemongrass and citral effect on cytokine production by murine macrophages. *Journal of Ethnopharmacology, 137*(1), 909–913. https://doi.org/10.1016/j.jep.2011.07.021
5. Bao, X. L., Yuan, H. H., Wang, C. Z., Fan, W., & Lan, M. B. (2015). Polysaccharides from *Cymbopogon citratus* with antitumor and immunomodulatory activity. *Pharmaceutical Biology, 53*(1), 117–124. https://doi.org/10.3109/13880209.2014.911921
6. Boukhatem, M. N., Ferhat, M. A., Kameli, A., Saidi, F., & Kebir, H. T. (2014). Lemon grass (*Cymbopogon citratus*) essential oil as a potent anti-inflammatory and antifungal drug. *Libyan Journal of Medicine, 9*, 25431. https://doi.org/10.3402/ljm.v9.25431
7. Campos, C. A., Lima, B. S., Trindade, G. G. G., Souza, E. P. B. S., Mota, D. S. A., Heimfarth, L., Quintans, J. S. S., Quintans-Júnior, L. J., Sussuchi, E. M., Sarmento, V. H. V., Carvalho, F. M. S., Marreto, R. N., Costa, R. M., Nunes, R. S., Araújo, A. A. S., Shanmugam, S., & Thangaraj, P. (2019). Anti-hyperalgesic and anti-inflammatory effects of citral with β-cyclodextrin and hydroxypropyl-β-cyclodextrin inclusion complexes in animal models. *Life Sciences, 229*, 139–148. https://doi.org/10.1016/j.lfs.2019.05.026
8. Chen, J., & Chen, Z. J. (2013). Regulation of NF-κB by ubiquitination. *Current Opinion in Immunology, 25*(1), 4–12. https://doi.org/10.1016/j.coi.2012.12.005
9. Cho, J. Y., Baik, K. U., Jung, J. H., & Park, M. H. (2003). In vitro anti-inflammatory effects of cynaropicrin, a sesquiterpene lactone, from *Saussurea lappa*. *European Journal of Pharmacology, 398*, 399–407.
10. Costa, G., Ferreira, J. P. B., Vitorino, C., Pina, M. E., Sousa, J. J. S., Figueiredo, I. V., & Batista, M. T. (2016). Polyphenols from *Cymbopogon citratus* leaves as topical anti-inflammatory agents. *Journal of Ethnopharmacology, 178*, 222–228. https://doi.org/10.1016/j.jep.2015.12.016
11. Figueirinha, A., Paranhos, A., Pérez-Alonso, J. J., Santos-Buelga, C., & Batista, M. T. (2008). Cymbopogon citratus leaves: Characterization of flavonoids by HPLC–PDA–ESI/MS/MS and an approach to their potential as a source of bioactive polyphenols. *Food Chemistry, 110*(3), 718–728. https://doi.org/10.1016/j.foodchem.2008.02.045
12. Francisco, V., Figueirinha, A., Neves, B. M., García-Rodríguez, C., Lopes, M. C., Cruz, M. T., & Batista, M. T. (2011). *Cymbopogon citratus* as source of new and safe anti-inflammatory drugs: Bio-guided assay using lipopolysaccharide-stimulated macrophages. *Journal of Ethnopharmacology, 133*(2), 818–827. https://doi.org/10.1016/j.jep.2010.11.018

13. Francisco, V., Figueirinha, A., Costa, G., Lopes, M. C., García-Rodríguez, C., Cruz, M. T., & Batista, M. T. (2011). Anti-inflammatory properties of polyphenols from *Cymbopogon citratus* by inhibition of NF-κB pathway. *Planta Medica, 77*, 1158. https://doi.org/10.1055/s-0031-1282839
14. Francisco, V., Costa, G., Figueirinha, A., Marques, C., Pereira, P., Neves, B. M., Lopes, M. C., García-Rodríguez, C., Cruz, M. T., & Batista, M. T. (2013). Anti-inflammatory activity of *Cymbopogon citratus* leaves infusion via proteasome and nuclear factor-κB pathway inhibition: Contribution of chlorogenic acid. *Journal of Ethnopharmacology, 148*(1), 126–134. https://doi.org/10.1016/j.jep.2013.03.077
15. Ganeshan, K., & Chawla, A. (2014). Metabolic regulation of immune responses. *Annual Review of Immunology, 32*, 609–634. https://doi.org/10.1146/annurev-immunol-032713-120236
16. García-Lafuente, A., Guillamón, E., Villares, A., Rostagno, M. A., & Martínez, J. A. (2009). Flavonoids as anti-inflammatory agents: Implications in cancer and cardiovascular disease. *Inflammation Research, 58*(9), 537–552. https://doi.org/10.1007/s00011-009-0037-3
17. Guimarães, L. G. L., Cardoso, M. G., Sousa, P. E., Andrade, J., & Vieira, S. S. (2011). Antioxidant and anti-inflammatory activities of essential oils from *Cymbopogon* species. *Industrial Crops and Products, 33*(2), 419–424.
18. Han, X., & Parker, T. L. (2017). Anti-inflammatory activity of essential oils from *Cymbopogon* species. *Journal of Functional Foods, 35*, 635–641. https://doi.org/10.1016/j.jff.2017.06.014
19. Heinrich, M., Barnes, J., Gibbons, S., & Williamson, E. M. (2012). *Fundamentals of Pharmacognosy and Phytotherapy* (2nd ed.). Elsevier.
20. Hussain, A. I., Anwar, F., Sherazi, S. T. H., & Przybylski, R. (2008). Chemical composition, antioxidant and antimicrobial activities of basil (*Ocimum basilicum*) essential oils depends on seasonal variations. *Food Chemistry, 108*(3), 986–995.
21. Kim, E. K., & Choi, E. J. (2010). Pathological roles of MAPK signaling pathways in human diseases. *Biochimica et Biophysica Acta (BBA) – Molecular Basis of Disease, 1802*(4), 396–405. https://doi.org/10.1016/j.bbadis.2009.12.009
22. Kim, H. P., Son, K. H., Chang, H. W., & Kang, S. S. (2004). Anti-inflammatory plant flavonoids and cellular action mechanisms. *Journal of Pharmacological Sciences, 96*(3), 229–245. https://doi.org/10.1254/jphs.CRJ04003X
23. Lawrence, T. (2009). The nuclear factor NF-κB pathway in inflammation. *Cold Spring Harbor Perspectives in Biology, 1*(6), a001651. https://doi.org/10.1101/cshperspect.a001651
24. Lee, I. T., & Yang, C. M. (2013). Role of NADPH oxidase/ROS in pro-inflammatory mediators and MAPK signaling. *Redox Biology, 1*(1), 1–11. https://doi.org/10.1016/j.redox.2013.01.010
25. Li, Q., & Verma, I. M. (2002). NF-κB regulation in the immune system. *Nature Reviews Immunology, 2*(10), 725–734. https://doi.org/10.1038/nri910
26. Libby, P. (2007). Inflammatory mechanisms: The molecular basis of inflammation and disease. *Nutrition Reviews, 65*(12 Pt 2), S140–S146. https://doi.org/10.1111/j.1753-4887.2007.tb00352.x
27. Liao, J. C., Deng, J. S., Chiu, C. S., Hou, W. C., Huang, S. S., Shie, P. H., Huang, G. J. (2015). Anti-inflammatory activities of *Cinnamomum cassia* constituents through suppression of NF-κB and MAPK signaling pathways. *Journal of Agricultural and Food Chemistry, 63*(15), 429–437.
28. Liu, T., Zhang, L., Joo, D., & Sun, S. C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy, 2*, 17023. https://doi.org/10.1038/sigtrans.2017.23
29. López-Lázaro, M. (2009). Distribution and biological activities of the flavonoid luteolin. *Mini-Reviews in Medicinal Chemistry, 9*(1), 31–59. https://doi.org/10.2174/138955709787001712
30. Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature, 454*(7203), 428–435. https://doi.org/10.1038/nature07201
31. Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029
32. Naik, M. I., Fomda, B. A., Jaykumar, E., & Bhat, J. A. (2010). Antibacterial activity of lemongrass (*Cymbopogon citratus*) oil against some selected pathogenic bacteria. *Asian Pacific Journal of Tropical Medicine, 3*(7), 535–538. https://doi.org/10.1016/S1995-7645(10)60129-0
33. Nathan, C. (2002). Points of control in inflammation. *Nature, 420*(6917), 846–852. https://doi.org/10.1038/nature01320
34. Nathan, C., & Ding, A. (2010). Nonresolving inflammation. *Cell, 140*(6), 871–882. https://doi.org/10.1016/j.cell.2010.02.029
35. Negrelle, R. R. B., & Gomes, E. C. (2007). *Cymbopogon citratus* (DC.) Stapf: Chemical composition and biological activities. *Revista Brasileira de Plantas Medicinais, 9*(1), 80–92. (Worldwide Journals)
36. Pan, M.-H., Lai, C.-S., & Ho, C.-T. (2010). Anti-inflammatory activity of natural dietary flavonoids. *Food & Function, 1*(1), 15–31. https://doi.org/10.1039/C0FO00103A

37. Pan, M.-H., Lai, C.-S., Wang, Y.-J., & Ho, C.-T. (2014). Acquired resilience to oxidative stress and inflammation: The role of phytochemicals. *Journal of Agricultural and Food Chemistry, 62*(30), 7406–7416. https://doi.org/10.1021/jf501362x
38. Park, E. J., & Pezzuto, J. M. (2002). Botanicals in cancer chemoprevention. *Cancer and Metastasis Reviews, 21*(3–4), 231–255. https://doi.org/10.1023/A:1021254725842
39. Reuter, S., Gupta, S. C., Chaturvedi, M. M., & Aggarwal, B. B. (2010). Oxidative stress, inflammation, and cancer: How are they linked? *Free Radical Biology and Medicine, 49*(11), 1603–1616. https://doi.org/10.1016/j.freeradbiomed.2010.09.006
40. Ríos, J. L., & Recio, M. C. (2005). Medicinal plants and antimicrobial activity. *Journal of Ethnopharmacology, 100*(1–2), 80–84. https://doi.org/10.1016/j.jep.2005.04.025
41. Rostagno, M. A., Palma, M., & Barroso, C. G. (2003). Pressurized liquid extraction of isoflavones from soybeans. *Analytica Chimica Acta, 522*(2), 169–177.
42. Saeed, M., Naveed, M., Arif, M., Kakar, M. U., Manzoor, R., El-Hack, M. E. A., Alagawany, M., Tiwari, R., Khandia, R., Munjal, A., Karthik, K., Dhama, K., Iqbal, H. M. N., & Dadar, M. (2018). Green tea (*Camellia sinensis*) and *L-theanine*: Medicinal values and beneficial applications in humans—A comprehensive review. *Biomedicine & Pharmacotherapy, 95*, 1260–1275.
43. Sakurai, H. (2012). Targeting of TAK1 in inflammatory disorders and cancer. *Trends in Pharmacological Sciences, 33*(10), 522–530. https://doi.org/10.1016/j.tips.2012.06.007
44. Santin, J. R., Lemos, M., Klein-Júnior, L. C., Machado, I. D., Costa, P., de Oliveira, A. P., Tilia, C., de Souza, J. P., de Oliveira, R. M. W., & Cechinel-Filho, V. (2009). Gastroprotective activity of essential oil of *Cymbopogon citratus*. *Journal of Ethnopharmacology, 125*(3), 522–524. https://doi.org/10.1016/j.jep.2009.07.022
45. Shah, G., Shri, R., Panchal, V., Sharma, N., Singh, B., & Mann, A. S. (2011). Scientific basis for the therapeutic use of *Cymbopogon citratus*, Stapf (Lemon grass). *Journal of Advanced Pharmaceutical Technology & Research, 2*(1), 3–8. https://doi.org/10.4103/2231-4040.79796
46. Shin, J. S., Noh, Y. S., Lee, Y. S., Cho, Y. W., Baek, N. I., Choi, M. S., Jeong, T. S., & Lee, K. T. (2020). Anti-inflammatory effects of natural phytochemicals through modulation of NF-κB and MAPK signaling pathways. *International Immunopharmacology, 84*, 106527. https://doi.org/10.1016/j.intimp.2020.106527
47. Surh, Y. J. (2003). Cancer chemoprevention with dietary phytochemicals. *Nature Reviews Cancer, 3*(10), 768–780. https://doi.org/10.1038/nrc1189
48. Tak, P. P., & Firestein, G. S. (2001). NF-κB: A key role in inflammatory diseases. *Journal of Clinical Investigation, 107*(1), 7–11. https://doi.org/10.1172/JCI11830
49. Wang, Q., Kuang, H., Su, Y., Sun, Y., Feng, J., Guo, R., & Chan, K. (2013). Naturally derived anti-inflammatory compounds from Chinese medicinal plants. *Journal of Ethnopharmacology, 146*(1), 9–39. https://doi.org/10.1016/j.jep.2012.12.039
50. Wright, C. W., Addae-Kyereme, J., Breen, A. G., Brown, J. E., Cox, M. F., Croft, S. L., Gökçek, Y., Kendrick, H., & Phillips, R. M. (2009). Synthesis and evaluation of citral derivatives for biological activity. *Journal of Natural Products, 72*(2), 289–294.
51. Xagorari, A., & Papapetropoulos, A. (2007). Inhibition of inflammatory signaling by natural compounds. *Current Medicinal Chemistry, 14*(21), 2220–2229. https://doi.org/10.2174/092986707781696635
52. Yang, Y., Kim, S. C., Yu, T., Yi, Y. S., Rhee, M. H., Sung, G. H., Yoo, B. C., & Cho, J. Y. (2014). Functional roles of p38 MAPK and its inhibitors in inflammatory responses. *Journal of Medicinal Food, 17*(11), 1201–1211. https://doi.org/10.1089/jmf.2014.3081
53. Zhang, J. M., & An, J. (2007). Cytokines, inflammation, and pain. *International Anesthesiology Clinics, 45*(2), 27–37. https://doi.org/10.1097/AIA.0b013e318034194e
54. Zhang, W., Xu, X., & Liu, Y. (2014). Plant-derived phenolic compounds as regulators of inflammatory pathways. *Molecules, 19*(8), 11379–11403. https://doi.org/10.3390/molecules190811379
55. Zhou, Y., Hong, Y., & Huang, H. (2016). Tristetraprolin and NF-κB signaling in inflammation. *Frontiers in Immunology, 7*, 294. https://doi.org/10.3389/fimmu.2016.00294