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Original Article

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Investigation of molecular mechanisms and therapeutic potential of thyme *(Thymus vulgaris)* extract in bronchitis

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Abstract

Background: Bronchitis is a common inflammatory airway disease characterized by cough, mucus hypersecretion, and airway inflammation. Limitations of conventional therapies have increased interest in herbal medicines with anti-inflammatory and mucoregulatory properties. *Thymus vulgaris* has been traditionally used for respiratory disorders, yet its molecular mechanisms in bronchitis require comprehensive evaluation. **Objective:** This review work aimed to summarize and critically analyze experimental and clinical evidence regarding the effects and molecular mechanisms of *Thymus vulgaris* extract in bronchitis. **Methods:** A narrative review of in vitro, in vivo, and clinical studies published in peer-reviewed journals was conducted. Studies investigating anti-inflammatory, antioxidant, mucolytic, and clinical effects of thyme extract in bronchitis or airway inflammation were included. **Results:** The findings indicate that *Thymus vulgaris* exerts its therapeutic effects through multiple molecular pathways. Key mechanisms include inhibition of the NF-κB signaling pathway, resulting in reduced expression of pro-inflammatory cytokines (IL-1β, IL-6, IL-8), downregulation of MUC5AC gene expression leading to decreased mucus hypersecretion, modulation of the arachidonic acid pathway via inhibition of 5-lipoxygenase, and attenuation of oxidative stress through antioxidant activity. Clinical trials demonstrated significant reductions in cough frequency and bronchitis severity scores, with good tolerability. **Conclusion:** *Thymus vulgaris* extract shows promising multi-target effects in the management of bronchitis, particularly acute bronchitis. Although current evidence supports its use as a complementary therapy, further large-scale, well-designed clinical trials with standardized extracts are required to confirm its efficacy and safety.

Introduction

Bronchitis is an inflammatory disorder of the respiratory tract characterized by inflammation, swelling, and increased mucus production in the airways (bronchi). The condition can be acute or chronic and, depending on the severity and cause, can lead to persistent cough, excessive sputum production, shortness of breath, and reduced quality of life. Acute bronchitis is often caused by viral infections, while chronic bronchitis is often associated with long-term damage from environmental factors such as smoking or air pollution. Common treatments include anti-inflammatory drugs, bronchodilators, and in some cases antibiotics, but problems such as side effects and poor response to treatment have increased interest in exploring alternative mechanisms, including natural compounds [1-3].

Thyme (*Thymus vulgaris* L.) has a long history of use in traditional medicine for the treatment of respiratory diseases, including cough, bronchitis, and airway inflammation. The medicinal properties of thyme are mainly attributed to its bioactive compounds, such as thymol, carvacrol, and other phenolic and essential compounds, which have shown antibacterial, anti-inflammatory, antioxidant, expectorant, and antiviral activities in early studies (Molecular and Experimental Review). These compounds can affect molecular pathways related to inflammation, immune response, and regulation of mucus secretion in the airways [4-8].

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Thymus vulgaris is an herbaceous, perennial, aromatic plant of the Lamiaceae family (mints) that is widely distributed in the Mediterranean and temperate regions of the world. The plant usually grows as a small shrub, between 10 and 40 cm tall, with woody stems in the lower part and herbaceous stems in the upper part. The stems are often branched, quadrangular, and covered with fine hairs, which is a characteristic feature of plants in this family [9-12].

Thyme leaves are small, opposite, narrow, and elliptical to linear, and usually have a recurved margin. The leaf surface is dark green to gray-green, and due to the presence of essential oil glands, they have a fragrant odor and a distinctive pungent taste. These essential oil glands contain bioactive compounds such as thymol and carvacrol, which play an important role in the medicinal properties of the plant [1, 8-10].

Thyme flowers are small, bisexual, and white, pink, or pale purple in color, and appear in clustered inflorescences at the ends of the stems. The calyx is tubular and persistent, and the corolla is bilobed, which is consistent with the general structure of mint plants. Flowering usually occurs in spring and summer, and this plant is highly sought after by honeybees and is considered an important nectar plant (Figure 1).

Figure 1: Botanical characteristics of *Thymus vulgaris* L.

Thyme fruit is a nut-like berry containing four small brown or black seeds. It is commonly propagated by seed, cuttings, or division of the plant and is highly adaptable to dry environmental conditions, full sunlight, and light, well-drained soils. Thyme's resistance to drought and adverse environmental conditions makes it a suitable plant for cultivation in water-scarce areas [2-9].

In terms of genetic diversity, the genus Thymus includes numerous species that differ in essential oil composition and morphological characteristics. These differences can affect the amount and type of active compounds and, consequently, the medicinal effects of the plant. Therefore, accurate knowledge of the botanical characteristics of thyme plays an important role in the standardization of extracts and its therapeutic application in various diseases, including respiratory disorders [10-15].

For example, in vitro studies have shown that thyme extract is able to inhibit the activity of NF-κB transcription factors and reduce the expression of proinflammatory cytokines such as IL-1β and IL-8 in human bronchial epithelial cells, as well as reduce mucus secretion (MUC5AC); these findings support the traditional use of thyme in the treatment of respiratory inflammatory diseases and suggest possible biological mechanisms for its therapeutic effects. Evidence has also shown that thyme extract can reduce inflammatory responses in animal models of lung injury induced by oxidant agents and particulate matter, reduce the production of ROS (reactive oxygen species) and modulate the expression of genes associated with inflammation and cell death, which may contribute to the improvement of lung function [8-18].

In addition to preclinical data, placebo-controlled clinical trials have also shown positive effects of a combination of thyme extract with ivy leaf extract (Hedera helix) on the symptoms of acute bronchitis with phlegmy cough. These studies reported that patients treated with the herbal extract combination had a more rapid and significant reduction in the number of cough attacks and severity of symptoms compared to the placebo group, with no significant difference in the incidence of adverse events. These results suggest that thyme extract, especially in combination formulations, can be considered as an effective and well-tolerated herbal treatment option for the management of bronchitis symptoms in adults [9].

The biological mechanisms behind the effects of thyme extend beyond anti-inflammatory activity. Thyme compounds may have antimicrobial activities against bacterial and viral agents, although direct clinical evidence for a direct anti-infective effect in bronchitis is more limited. Thyme may also help relieve congestion and improve cough by improving mucus clearance mechanisms and increasing the efficiency of epithelial cilia. Together, these multiple activities suggest that thyme extract may have a multifaceted role in the management of airway inflammation and facilitating mucus secretion [19-24].

However, it should be noted that much of the available evidence is still from small studies or in combination with other herbal extracts, and larger, more carefully designed clinical trials are needed to definitively confirm the effects of thyme extract on different types of bronchitis, especially chronic bronchitis. This is essential to determine the appropriate dosage, duration of treatment, precise mechanisms, and long-term safety [5, 18-20].

Our goal is to comprehensively review the available scientific evidence on the effect of thyme *(Thymus vulgaris)* extract on bronchitis, focusing on plant mechanisms, active compounds, anti-inflammatory and expectorant effects, and preclinical and clinical evidence.

Material and Method

A systematic review of in vitro, in vivo, and clinical studies published in peer-reviewed journals was conducted. Studies that investigated the anti-inflammatory, antioxidant,

mucolytic, and clinical effects of thyme extract in bronchitis or airway inflammation were included.

Result

The in vitro study investigated the effects of a hydroalcoholic extract of thyme *(Thymus vulgaris)* on human bronchial and tracheal epithelium in an LPS-induced inflammation model. The results showed that thyme extract reduced the activation of the NF-κB pathway (both p65 and p52 subunits) and consequently reduced the expression of the proinflammatory cytokines IL-1β and IL-8 in epithelial cells. The extract also reduced the secretion of MUC5AC, indicating a reduction in excessive mucus secretion in airway inflammation. These findings are scientific and were performed using human cell lines, which supports the anti-inflammatory molecular mechanisms of thyme extract. The researchers concluded that thyme extract could have a therapeutic effect in chronic inflammatory lung disorders associated with increased mucus, although direct human studies are needed [1-5].

In an animal study, a commercial syrup based on thyme and ivy extracts (Bronchipret) was evaluated in a model of lung inflammation in Wistar rats. The results showed that the combination of extracts significantly reduced the increase in leukocytes in lung tissue and bronchoalveolar lavage fluid, and also reversed the hyperplasia of goblet cells that leads to increased mucus secretion. In vitro studies also showed that the syrup analog version could inhibit the release of leukotrienes and reduce the activity of 5-lipoxygenase, a mechanism that may contribute to the anti-inflammatory effects. The few studies that has quantitatively investigated the effects of thyme extract on the healing of lung inflammation in animal models and supports its subsequent clinical use in acute bronchitis [18, 20-24].

The clinical trial evaluated a combination of dried thyme extract and primrose root in adult patients with acute bronchitis and productive cough. 361 patients were randomly assigned to receive treatment or placebo for 11 days. Results showed that the treatment group had a greater reduction in the number of cough attacks per day than the placebo group (about 67% vs. 51%), and this reduction was significantly greater on days 7–9. Bronchitis symptoms (based on the Bronchitis Severity Score) also improved more quickly after treatment, and the treatment group had a higher response rate than the control group. The study suggests that thyme-based formulations can significantly reduce the clinical symptoms of acute bronchitis. Another study from the same research group investigated the effects of a combination of liquid extracts of thyme and ivy leaves in patients with acute bronchitis. In this randomized trial, patients were treated with the combination syrup or placebo. The results were similar to the previous study: the number of coughing attacks per day was significantly reduced and the treatment group improved more quickly than the placebo group. The main symptoms of bronchitis were also improved more effectively according to the BSS. The treatment was well tolerated and there was no significant increase in side effects, which supports the safety of thyme extract in clinical use [17-22].

In some basic studies, the researchers investigated the effect of thyme extract on β_2 receptors and mucociliary clearance. The results showed that thyme extract has broncho lytic (airway-opening) properties and positive effects on mucus clearance by improving ciliary function, which may help explain the expectorant effects and facilitate mucus discharge in respiratory diseases. These results indicate the functional importance of thyme compounds in enhancing mucus clearance and facilitating breathing, although this remains to be confirmed in humans [21-25]. Some studies investigated the anti-inflammatory and mucus-regulating mechanisms of a combination of thyme and marigold root in a model of pulmonary inflammation. Treatment with this combination significantly reduced the infiltration of polynuclear cells into the lung and caused a decrease in MUC5AC protein and goblet cell numbers. In vitro findings also confirmed that the reduction of MUC5AC is not only through anti-inflammatory effects, but also through independent pathways, providing further insight into the molecular mechanisms [12-16].

The observational works were conducted in real pharmacies to investigate the effect of a combination of thyme and ivy extracts on cough symptoms and quality of life in patients with acute bronchitis or similar symptoms. The results showed that the combination was able to rapidly and sustainably reduce cough and its frequency, and also improve sleep disturbances associated with cough [13-15, 21-25].

Molecular mechanisms of thyme's effect on bronchitis

Bronchitis is an inflammatory disease of the airways in which excessive activation of innate immune pathways, increased production of proinflammatory cytokines, accumulation of inflammatory cells, and excessive mucus secretion play a key role. Preclinical and clinical evidence suggests that thyme extract and its active compounds, especially thymol and carvacrol, can play a role in modulating these processes simultaneously through multiple molecular pathways (Figure 2).

- **Inhibiting the NF-κB pathway and reducing inflammation**

One of the most important molecular mechanisms of thyme's effect is the inhibition of the activation of the NF-κB pathway. This pathway plays a key role in regulating the expression of inflammatory genes in bronchial epithelial cells and immune cells. In vitro studies have shown that thyme extract, by preventing the phosphorylation and nuclear translocation of the p65 subunit, leads to a decrease in the expression of proinflammatory cytokines such as IL-1β, IL-6, and IL-8. The reduction of these cytokines inhibits the recruitment of neutrophils and reduces mucosal inflammation in the airways. This effect is of great clinical importance, especially in acute

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bronchitis, where inflammation plays a dominant role p25, 28-31]. Animal studies have shown that thyme-based compounds are able to reduce the infiltration of inflammatory cells into lung tissue and inhibit mucosal edema. These effects are exerted in part by inhibiting the arachidonic acid pathway and reducing the production of leukotrienes. Since leukotrienes are key mediators of inflammation and bronchospasm, this mechanism could play an important role in improving respiratory function in patients with bronchitis [2, 31-40].

- **Inhibiting mucus production through regulation of MUC5AC**

One of the main features of bronchitis is increased mucus secretion and airway obstruction. Cellular studies have shown that thyme extract can significantly reduce the expression of the MUC5AC gene, which is responsible for mucus production in goblet cells. This effect has been reported to be partly dependent on and partly independent of the inhibition of the NF-κB pathway. Reduced mucus production improves mucus clearance and reduces cough severity in patients with bronchitis [8-16].

- **Modulating the arachidonic acid pathway and inhibiting leukotrienes**

Compounds in thyme are able to inhibit the activity of the enzyme 5-lipoxygenase (5-LOX). This enzyme plays a role in the production of leukotrienes, which are considered to be the most important inflammatory mediators in airway inflammation. Reducing the production of leukotrienes leads to a decrease in the infiltration of inflammatory cells, a decrease in mucosal edema, and an improvement in airflow in the bronchial tubes. This mechanism is particularly important in reducing bronchospasm and submucosal inflammation [9-17, 41-47].

- **Antioxidant effects and reduction of oxidative stress**

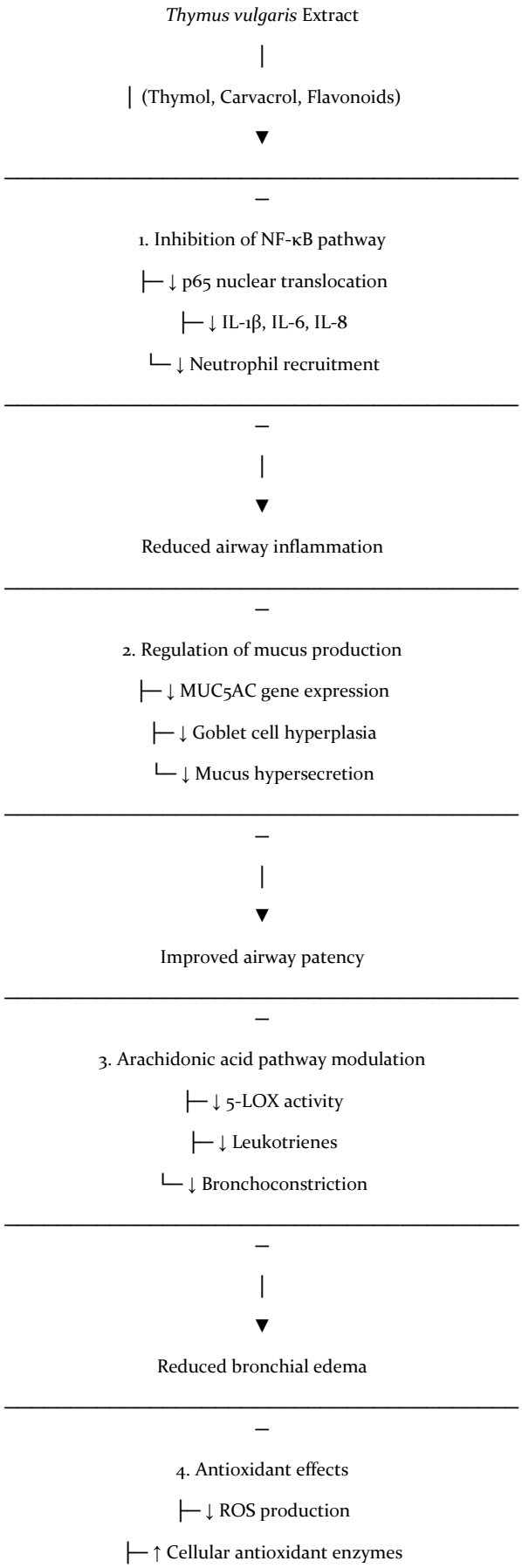
Oxidative stress is one of the factors exacerbating inflammation in bronchitis. Thymol and carvacrol have strong antioxidant activity and can prevent oxidative damage to lung epithelial cells by reducing the production of reactive oxygen species (ROS) and increasing the activity of cellular antioxidant enzymes. This effect maintains the integrity of the airway epithelial barrier and reduces the secondary inflammatory response [18].

- **Improves mucus clearance and cilia function**

Thyme extract has positive effects on the mucociliary clearance system. Studies have shown that thyme compounds can increase the activity of epithelial cilia while reducing mucus viscosity. This dual effect facilitates the clearance of secretions from the airways and plays an important role in reducing phlegmy cough [9-12, 28-41].

- **Indirect antimicrobial effects**

Although bronchitis is often of viral origin, the phenolic compounds in thyme have antibacterial and antiviral activity. These effects may help reduce inflammation indirectly by reducing microbial load and inhibiting ongoing immune system stimulation. Thymol and carvacrol work by damaging the cell membranes of microorganisms and inhibiting their vital enzymes [21, 23-25].



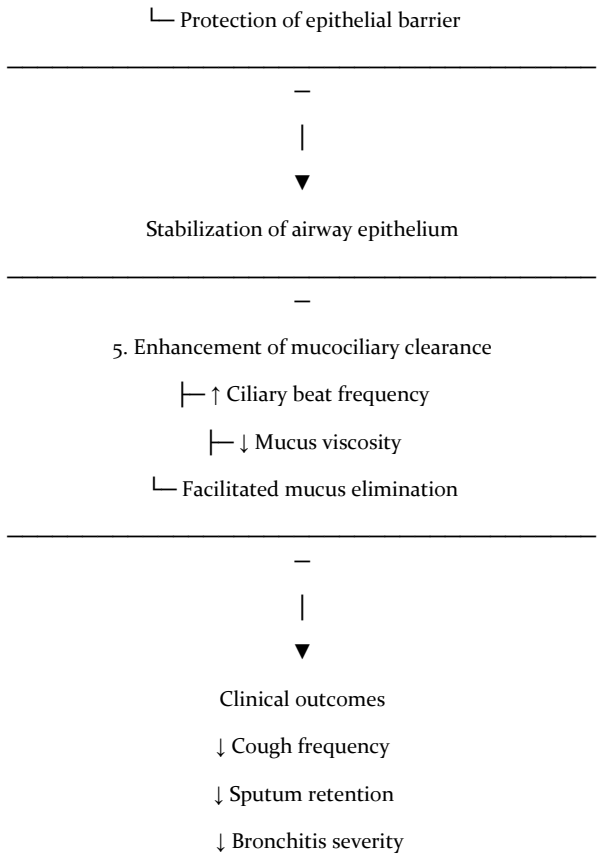


Figure 2: Diagram of the molecular effect of thyme extract on bronchitis

Discussion

The findings of the present review indicate that thyme extract *(Thymus vulgaris)* has significant potential in reducing symptoms and modulating pathophysiological processes associated with bronchitis. Evidence from in vitro, animal, and clinical trials suggests that the therapeutic effects of thyme are due to its multitargeted action on inflammatory pathways, mucus secretion, oxidative stress, and airway epithelial function [1-4, 24-27].

One of the most important findings of the reviewed studies is the inhibition of the NF-κB pathway by thyme extract. Excessive activation of this pathway plays a pivotal role in the pathogenesis of bronchitis, especially in acute bronchitis, and leads to increased expression of inflammatory cytokines, neutrophil recruitment, and exacerbation of mucosal inflammation. Inhibition of this pathway by active thyme compounds such as thymol and carvacrol could be a suitable explanation for the reduction of inflammatory markers observed in cellular and animal studies.

In addition to inflammation, increased mucus secretion and goblet cell hyperplasia are hallmarks of bronchitis, which play an important role in airway obstruction and exacerbation of cough. Evidence suggests that thyme extract can modulate mucus production by reducing MUC5AC gene expression and regulating goblet cell differentiation. This finding is clinically important, as reducing mucus not only improves lung ventilation, but also helps reduce the frequency and severity of cough [17-26].

Oxidative stress is also known to be an exacerbating factor in airway diseases. The antioxidant activity of thymol and carvacrol may help maintain the integrity of the lung epithelial barrier by reducing the production of reactive oxygen species and protecting epithelial cells. This is particularly important in chronic bronchitis or cases associated with air pollution and particulate matter.

At the clinical level, results from randomized trials have shown that formulations containing thyme extract, especially in combination with other medicinal plants such as ivy or marigold, can significantly reduce cough severity, number of cough attacks and bronchitis severity score. Notably, the good tolerability and low side effects of these compounds make them a suitable option for complementary therapy.

Despite these promising results, there are also limitations in the existing studies. Many trials have used combination formulations, making it difficult to accurately isolate the contribution of thyme extract. Also, variability in dose, duration of treatment, and study design limits direct comparison of results. Therefore, larger clinical trials with standardized thyme extracts appear necessary.

Overall, the results of this review suggest that thyme may effectively modulate inflammation and clinical symptoms of bronchitis through multiple molecular mechanisms, although more evidence is needed to generalize these findings to chronic bronchitis [8-24,14-31].

Conclusion

Based on the reviewed evidence, thyme extract *(Thymus vulgaris)* is a promising herbal option in the management of bronchitis. This medicinal plant can help improve the pathophysiology of this disease by inhibiting key inflammatory pathways, reducing mucus production, modulating the immune response, and reducing oxidative stress.

Findings suggest that inhibition of the NF-κB pathway and reduction of proinflammatory cytokine expression are among the main mechanisms of action of thyme. In addition, upregulation of the expression of genes related to mucus secretion and improvement of the function of the mucus clearance system play an important role in reducing clinical symptoms such as cough and congestion. Available clinical studies have confirmed the efficacy and safety of formulations containing thyme extract, especially in acute bronchitis. However, the lack of well-designed studies focusing on thyme extract alone is a major challenge in interpreting the results.

Finally, it can be concluded that thyme has significant potential as a complementary or supportive therapy in the management of bronchitis. Future clinical trials with standardized extracts, determination of optimal dosage, and

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investigation of long-term effects are necessary to establish the therapeutic position of this herb (Figure 3).

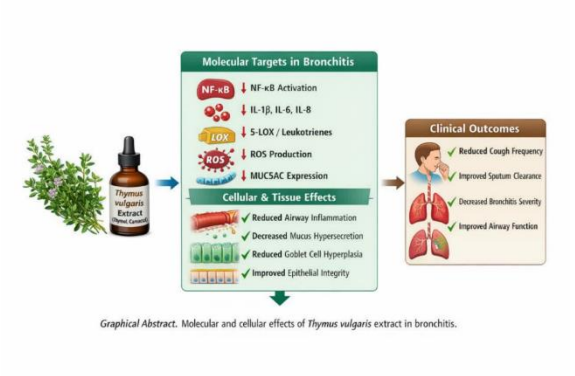

Figure 3: Graphical abstract

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Declarations:

Authors' Contribution:

- All Authors Conceptualization, data collection, interpretation, drafting of the manuscript and intellectual revisions
- The authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed

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