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The Effect of Antipyretic And Anti-Inflammatory Properties of Liquorice and Cloves Extracts: A Review

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ABSTRACT
Liquorice (Glycyrrhiza glabra) and clove (Syzygium aromaticum) are two medicinal plants with a long history of traditional use due to their bioactive properties. Modern research has identified multiple phytochemicals in both that offer antipyretic (fever-reducing) and anti-inflammatory effects. Liquorice extracts contain compounds such as glycyrrhizin, flavonoids, and isoflavonoids that modulate inflammatory pathways by decreasing pro-inflammatory mediators such as TNF-α, IL-6, prostaglandin E_2 (PGE_2), and other key inflammatory signaling molecules. Similarly, cloves are rich in eugenol and other phenolic constituents that inhibit cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, reduce prostaglandin synthesis, and suppress inflammatory cytokines, contributing to both anti-inflammatory and antipyretic effects. This review evaluates the pharmacological evidence supporting these effects, explores underlying mechanisms, and discusses potential therapeutic implications and safety considerations.
Key words: Cyclooxygenase (COX) and Lipoxygenase (LOX) enzymes,Liquorice (Glycyrrhiza glabra) and Clove (Syzygium aromaticum)

I. INTRODUCTION

Inflammation and fever are basic physiological reactions that are essential to the body's defense against infections, tissue damage, and other diseases. Despite the preventive nature of these reactions, prolonged or excessive activation can cause tissue damage, pain, and the advancement of chronic illnesses. Infections, immunological reactions, and inflammatory processes are frequently linked to fever, which is defined as an increase in body temperature over normal physiological ranges. In contrast, inflammation is a complicated biological response that includes immune cell activation, vascular alterations, and the release of several chemical mediators. Fever and inflammation are two interconnected reactions that are essential to many acute and chronic illnesses [1].

For the treatment of fever and inflammation, conventional pharmaceuticals including corticosteroids, non-steroidal anti-inflammatory medicines (NSAIDs), and antipyretic medications like paracetamol are frequently utilized. These medications mainly work by suppressing prostaglandin production and inhibiting cyclooxygenase (COX) enzymes. Although these synthetic medications are helpful, prolonged or excessive usage is linked to a number of negative side effects, such as immunosuppression, hepatotoxicity, gastrointestinal discomfort, renal failure, and cardiovascular problems. Increased interest in alternative treatment techniques originating from natural sources, especially medicinal plants with traditional uses and pharmacological properties that have been scientifically proven, has resulted from the rising knowledge of these limitations[2].

For ages, many societies have employed medicinal plants as their main source of therapeutic chemicals to treat fever, inflammation, pain, and other systemic illnesses. When opposed to synthetic medications, herbal remedies are typically seen to be safer, more affordable, and more suited to the human body. As long as the safety, effectiveness, and quality of herbal medicines are shown by science, the World Health Organization (WHO) recognizes the value of traditional medicine and promotes its incorporation into contemporary healthcare systems. In this regard, the capacity of plant-derived bioactive chemicals to control immune responses and alter inflammatory pathways with fewer adverse consequences has drawn a lot of interest [3].

Due to their complex phytochemical makeup and widespread traditional use, cloves (Syzygium aromaticum) and liquorice (Glycyrrhiza glabra) have emerged as viable candidates among the many medicinal plants investigated for antipyretic and anti-inflammatory effects. Both plants have been used extensively to treat inflammatory conditions, fever, respiratory infections, gastrointestinal problems, and pain in traditional medical systems including Ayurveda, Unani, Traditional Chinese Medicine, and folk medicine [4].

Native to Europe and Asia, liquorice (Glycyrrhiza glabra) is a perennial herb that is widely grown around the world. It is a member of the Fabaceae family. The most often utilized medicinal elements of licorice are its dried roots and rhizomes. Liquorice has long been utilized as an immunological modulator, expectorant, anti-inflammatory, and anti-ulcer medication. Additionally, it is used to treat skin conditions, fever, bronchitis, sore throat, cough, and arthritis. Liquorice's wide range of bioactive substances, such as flavonoids, isoflavonoids, chalcones, phenolic acids, and triterpenoid saponins, are responsible for its pharmacological actions [5].

One of the most important bioactive constituents of liquorice is glycyrrhizin, a triterpene glycoside known for its potent anti-inflammatory and immunomodulatory properties. Glycyrrhizin and its aglycone glycyrrhetinic acid have been shown to inhibit inflammatory mediators such as prostaglandins, leukotrienes, tumor necrosis factor-alpha (TNF-α), interleukins, and nitric oxide. Additionally, liquorice flavonoids such as glabridin, licochalcone A, and isoliquiritigenin exhibit strong antioxidant properties, which further contribute to the suppression of oxidative stress-induced inflammation. Through these mechanisms, liquorice extracts demonstrate significant potential in reducing inflammation and modulating fever-related pathways [6].

Cloves (Syzygium aromaticum), a member of the Myrtaceae family, are fragrant dried flower buds that are frequently used as a spice and therapeutic. Cloves, which are indigenous to Indonesia's Maluku Islands, have long been used in traditional medicine to cure infections, fever, discomfort, inflammation, and dental issues. Cloves' essential oil content, which is high in phenolic chemicals, especially eugenol, is largely responsible for its therapeutic qualities. The analgesic, anti-inflammatory, antioxidant, antibacterial, and antipyretic properties of eugenol are well known [7].

Clove extracts have been shown to have anti-inflammatory properties by inhibiting important inflammatory enzymes including lipoxygenase and cyclooxygenase, which reduces prostaglandin and leukotriene formation. Additionally, pro-inflammatory cytokines and reactive oxygen species have been shown to be suppressed by eugenol, which attenuates inflammatory responses at the cellular and molecular levels. Additionally, clove extracts have demonstrated antipyretic effects in experimental animal models, potentially via suppression of pyrogen-induced prostaglandin production and modification of hypothalamic thermoregulatory regions. [8]

Since inflammatory mediators are essential for the production of fever, the connection between inflammation and fever is well known. Interleukin-1β, TNF-α, and interleukin-6 are examples of pyrogens that cause the hypothalamus to produce prostaglandin E_2 (PGE_2), which raises body temperature. As a result, medications that inhibit inflammatory mediators frequently have concurrent antipyretic effects. This highlights the therapeutic potential of licorice and clove extracts in treating feverish and inflammatory disorders since they both operate on overlapping molecular pathways implicated in inflammation and fever [9].

The antipyretic and anti-inflammatory properties of licorice and clove extracts have been the subject of several in vitro and in vivo investigations in recent years. These investigations have used a variety of experimental models, such as paw edema caused by carrageenan, inflammation induced by formalin, pyrexia induced by yeast, and inflammatory reactions induced by lipopolysaccharide. The findings consistently show that extracts of cloves and liquorice dramatically lower high body temperature, edema development, and inflammatory markers in a dose-dependent manner. These results suggest their potential utility in contemporary therapies and offer scientific confirmation for their traditional use [10].

Comprehensive evaluations that compile the available information on the antipyretic and anti-inflammatory qualities of cloves and licorice are still necessary despite the increasing amount of evidence. To encourage their sensible use and direct future research, a thorough grasp of their phytochemical composition, modes of action, experimental data, safety profiles, and therapeutic potential is crucial. Furthermore, comparing these two therapeutic herbs can reveal important information about their relative effectiveness and possible synergistic uses [11].

Medicinal plants have historically been used for these purposes, and Liquorice and Cloves are two such plants with documented traditional and scientific backing for their therapeutic effects.

II. PHYTOCHEMISTRY OF LIQUORICE AND CLOVES

Clove (Syzygium aromaticum) and liquorice (Glycyrrhiza glabra) are two medicinal plants that have been well researched due to their diverse pharmacological effects and rich phytochemical profiles. In addition to supporting their conventional medical applications, their bioactive components offer a scientific foundation for their usage in contemporary therapeutic formulations. The phytochemical components of cloves and liquorice are thoroughly reviewed in this section, with a focus on the chemicals that have antipyretic and anti-inflammatory properties [12].

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2.1 Liquorice (Glycyrrhiza glabra)

2.1.1 Overview of Botany and Chemistry:

The main therapeutic components of liquorice (Glycyrrhiza glabra), a perennial herb in the Fabaceae family, are its roots and rhizomes. Traditional Chinese medicine, Ayurveda, and Unani have all made extensive use of the herb. Glycyrrhizin, which is around 50 times sweeter than sucrose, is what gives liquorice its distinctively sweet flavor.

Triterpenoid saponins, flavonoids, isoflavonoids, chalcones, coumarins, phenolic acids, polysaccharides, and volatile oils are just a few of the biologically active substances found in liquorice, according to phytochemical analysis. The plant's many pharmacological characteristics, including as its anti-inflammatory, antipyretic, antioxidant, antiviral, antibacterial, hepatoprotective, and immunomodulatory effects, are caused by these substances [14].

2.1.2 Triterpenoid Saponins and Glycyrrhizin:

The most prevalent and significant pharmacological component of liquorice is glycyrrhizin, sometimes referred to as glycyrrhizic acid. It is a triterpene glycoside made up of two glucuronic acid units connected to a glycyrrhetinic acid moiety. Intestinal bacteria convert glycyrrhizin after consumption into glycyrrhetinic acid, the active metabolite that has a variety of physiologic effects [15].

Through a variety of methods, glycyrrhizin demonstrates strong anti-inflammatory efficacy. It prevents pro-inflammatory mediators including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) from being released. Furthermore, glycyrrhizin inhibits the activity of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), which results in decreased prostaglandin and nitric oxide synthesis—two important mediators of fever and inflammation. Additionally, by blocking the enzyme 11β-hydroxysteroid dehydrogenase, glycyrrhizin has been shown to alter the hypothalamic-pituitary-adrenal (HPA) axis, simulating the effects of corticosteroids. Its anti-inflammatory and immunosuppressive qualities stem from this process, which makes it very helpful in inflammatory and autoimmune diseases [15].

2.1.3 Liquorice Flavonoids:

Another significant class of bioactive substances found in licorice are flavonoids. Glabridin, isoliquiritigenin, liquiritin, licochalcone A, licochalcone B, and licochalcone E are among them. The well-known antioxidant and anti-inflammatory properties of flavonoids are essential for lowering oxidative stress and inhibiting inflammatory cascades.One of the most researched flavonoids in liquorice, glabridin, has potent antioxidant properties by preventing lipid peroxidation and scavenging free radicals. By blocking nuclear factor-kappa B (NF-κB), a transcription factor that controls the production of pro-inflammatory genes, it also modifies inflammatory pathways. Glabridin lowers the synthesis of inflammatory cytokines and inflammatory-related enzymes by this method [16].

By suppressing COX-2 expression and lowering prostaglandin E_2 (PGE_2) production, isoliquiritigenin, a chalcone-type flavonoid, has shown notable anti-inflammatory benefits. By disrupting pyrogen-induced inflammatory signaling pathways, it also demonstrates antipyretic activity. Furthermore, isoliquiritigenin has antioxidant activity, which amplifies its anti-inflammatory effectiveness [16].

2.1.4 Isoflavones and Phenolic Compounds:

Numerous phenolic chemicals and isoflavones found in liquorice contribute to its medicinal qualities. Ferulic acid, caffeic acid, and coumaric acid are examples of phenolic acids that have potent antioxidant activity and shield tissues from inflammatory oxidative damage.

Liquorice contains isoflavones with immunomodulatory and estrogen-like properties, such as formononetin and biochanin A. By controlling the synthesis of cytokines and the activation of immune cells, these substances can modify inflammatory reactions. The overall anti-inflammatory and antipyretic properties of licorice extracts are strengthened by the combined action of phenolics and isoflavones [17].

2.1.5 Liquorice Phytochemicals' Function in Antipyretic Action:

Liquorice's capacity to inhibit inflammatory mediators involved in fever induction is directly associated with its antipyretic action. Liquorice phytochemicals help control high body temperature by lowering PGE_2 production in the hypothalamus and suppressing cytokines including TNF-α and IL-1β. Its flavonoids' antioxidant qualities also lessen oxidative stress, which is frequently linked to feverish illnesses [18].

2.2 Clove (Syzygium aromaticum)

2.2.1 Overview of Botany and Chemistry:

The dried flower buds of the clove (Syzygium aromaticum), a member of the Myrtaceae family, are prized for their aromatic and therapeutic qualities. In traditional medicine, cloves have long been used to cure infections, fever, discomfort, inflammation, and tooth issues. Cloves' essential oil content, which makes up a significant amount of their bioactive chemicals, is largely responsible for their pharmacological activity.Cloves include phenolic chemicals, terpenoids, flavonoids, tannins, and volatile oils, with eugenol being the predominant component, according to phytochemical study. Clove is one of the most powerful natural antioxidants due to its high content of bioactive phenolics [18].

2.2.2 Eugenol: The Main Bioactive Substance:

The most well researched substance that gives cloves their pharmacological effects is eugenol, which makes up around 80–85% of clove essential oil. Eugenol is a phenylpropanoid molecule having potent analgesic, antipyretic, anti-inflammatory, and antioxidant properties.Eugenol mainly reduces the production of prostaglandins and leukotrienes by blocking the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. These mediators are essential to the inflammatory response and contribute significantly to the development of fever. Eugenol significantly lowers fever and inflammation by inhibiting their formation.

Eugenol also reduces the production of pro-inflammatory cytokines and inhibits NF-κB activation, which modifies inflammatory signaling pathways. Tissues are additionally shielded from oxidative damage linked to inflammatory situations by its antioxidant action [19].

2.2.3 β-Caryophyllene and Eugenyl Acetate:

In addition to eugenol, cloves also contain β-caryophyllene and eugenyl acetate, which work in concert to enhance their pharmacological effects. While β-caryophyllene interacts with cannabinoid receptors (CB_2) to provide anti-inflammatory and analgesic effects, eugenyl acetate improves the fragrance and medicinal effectiveness of clove oil.β-Caryophyllene suppresses inflammatory reactions and reduces cytokine production by preferentially binding to CB_2 receptors on immune cells. This mechanism supports the historic use of cloves in the treatment of pain and inflammation and is especially pertinent in chronic inflammatory diseases [20].

2.2.4 Cloves' Phenolic and Flavonoid Content:

The phenolic chemicals found in cloves, such as gallic acid, ellagic acid, and tannins, have potent antioxidant qualities. These substances lessen oxidative stress, which is a major cause of fever and inflammation, and neutralize free radicals.Cloves include flavonoids that help regulate inflammatory processes. Their combination anti-inflammatory and antioxidant properties improve clove extracts' overall pharmacological potency [20].

2.2.5 Clove Phytochemicals' Function in Antipyretic Action:

Eugenol and other phenolic chemicals are mostly responsible for cloves' antipyretic properties. Clove extracts aid in controlling body temperature by preventing prostaglandin production in the hypothalamus and reducing pyrogen-induced cytokine release. Research has shown that administering clove extracts or essential oil significantly reduces fever in animal models [14].

III. MECHANISMS OF ANTI-INFLAMMATORY ACTION

Coordinated interactions between immune cells, signaling molecules, transcription factors, and enzymatic pathways are all part of the intricate, multifactorial biological reaction known as inflammation. A number of pathological conditions, including arthritis, cardiovascular diseases, neurodegenerative disorders, metabolic syndrome, and cancer, are caused by chronic or uncontrolled inflammation, whereas acute inflammation serves as a defensive mechanism to eradicate pathogens and repair damaged tissues. Pro-inflammatory cytokines, chemokines, prostaglandins, leukotrienes, nitric oxide, and reactive oxygen species are released during inflammation, all of which increase tissue damage and discomfort at the molecular level [13].

Medicinal herbs use a variety of strategies to reduce inflammation, frequently focusing on many pathways at once. Compared to single-target synthetic medications, this multi-targeted mechanism of action is thought to be beneficial. The capacity of clove (Syzygium aromaticum) and liquorice (Glycyrrhiza glabra) extracts to regulate inflammatory responses at the molecular, cellular, and systemic levels has been well investigated. Suppression of inflammatory mediators, inhibition of important enzymes, modification of intracellular signaling pathways, and control of immunological responses are all thought to contribute to their anti-inflammatory actions. The specific processes behind the anti-inflammatory properties of clove and licorice extracts are covered in this section [13].

3.1 Liquorice Extracts' Anti-Inflammatory Mechanisms:

3.1.1 Inhibition of Cytokines That Promote Inflammation:

The reduction of pro-inflammatory cytokines is one of the main ways that licorice extracts reduce inflammation. Tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are examples of cytokines that are essential for starting and maintaining inflammatory reactions. These cytokines induce the generation of secondary inflammatory mediators, enhance vascular permeability, and encourage the recruitment of immune cells.Liquorice extracts dramatically lower the synthesis and release of TNF-α, IL-1β, and IL-6 in activated macrophages and animal models of inflammation, according to a number of in vitro and in vivo investigations. Glycyrrhizin, a triterpenoid saponin, and its metabolite glycyrrhetinic acid are very good in inhibiting the release of cytokines. Liquorice extracts lessen tissue damage and stop the amplification of inflammatory cascades by blocking these cytokines [20].

3.1.2 Prostaglandin E_2 (PGE_2) Production Inhibition:

One important lipid mediator in inflammation, discomfort, and fever is prostaglandin E_2 (PGE_2). The cyclooxygenase (COX) pathway, namely COX-2, an inducible enzyme produced during inflammatory circumstances, is responsible for its synthesis from arachidonic acid. Vasodilation, edema formation, and pain receptor sensitization are all influenced by elevated PGE_2 levels.
By suppressing COX-2 expression and activity, liquorice extracts have been demonstrated to dramatically lower PGE_2 synthesis. COX-2 gene expression is downregulated at the transcriptional level by glycyrrhizin and flavonoids like isoliquiritigenin. As a result, prostaglandin production is decreased and inflammatory symptoms are lessened. Since PGE_2 is essential for inducing fever in the hypothalamus, the reduction of PGE_2 also explains the concurrent antipyretic actions of licorice extracts [21].

3.1.3 Inducible Nitric Oxide Synthase (iNOS) Downregulation:

During inflammation, immune cells create nitric oxide (NO), a crucial inflammatory mediator. Although normal cellular processes depend on healthy amounts of NO, excessive NO synthesis by inducible nitric oxide synthase (iNOS) leads to oxidative stress, tissue damage, and persistent inflammation.Liquorice extracts have been shown to decrease NO production and lower iNOS expression in macrophages challenged with lipopolysaccharide (LPS). The suppression of transcription factors that control the expression of the iNOS gene mediates this action. Liquorice extracts shield tissues from nitrosative stress and inflammatory damage by reducing excessive NO generation [21].

3.1.4 NF-κB Signaling Pathway Modification:

One of the most important regulators of inflammation is the nuclear factor-kappa B (NF-κB) signaling pathway. Numerous pro-inflammatory genes, including as those encoding cytokines, chemokines, COX-2, and iNOS, are transcriptionally regulated by NF-κB. NF-κB activation is frequently seen in inflammatory conditions and is thought to be a target for anti-inflammatory medications.It has been demonstrated that flavonoids from liquorice, such as licoachalcones and glabridin, block NF-κB activation by stopping the breakdown of its inhibitory protein (IκBα). This inhibits the transcription of inflammatory genes by preventing NF-κB from translocating into the nucleus. Liquorice extracts have widespread anti-inflammatory effects at the genomic level through this method.

3.1.5 MAPK Pathway Inhibition:

ERK, JNK, and p38 MAPK are examples of mitogen-activated protein kinase (MAPK) pathways that are essential for sending inflammatory signals from cell surface receptors to the nucleus. Increased cytokine and inflammatory mediator production results from MAPK pathway activation.According to research, liquorice flavonoids prevent downstream inflammatory signaling by inhibiting the phosphorylation of MAPK proteins. Inflammatory responses are attenuated and cytokine production is decreased as a result of this inhibition. Liquorice extracts' multi-targeted anti-inflammatory effect is highlighted by their capacity to affect both the NF-κB and MAPK pathways [22].

3.1.6 Increasing Anti-Inflammatory Cytokines:

Liquorice extracts have been shown to increase the production of anti-inflammatory cytokines, especially interleukin-10 (IL-10), in addition to reducing pro-inflammatory mediators. Because it suppresses antigen presentation, inhibits cytokine generation, and controls immune cell activity, IL-10 is essential in reducing inflammation.In experimental models, licorice ethanolic and aqueous extracts have been shown to raise IL-10 levels, which helps to resolve inflammation. Liquorice's balanced immunomodulatory effects are a result of its dual activity, which suppresses pro-inflammatory mediators and increases anti-inflammatory cytokines [21].

3.2 Clove Extracts' Anti-Inflammatory Mechanisms:

3.2.1 Cyclooxygenase (COX) and Lipoxygenase (LOX) Enzyme Inhibition:

Eugenol, the main phenolic component found in clove essential oil, is largely responsible for the anti-inflammatory properties of clove extracts. It has been demonstrated that eugenol inhibits the enzymes cyclooxygenase (COX) and lipoxygenase (LOX), which are in charge of the production of prostaglandins and leukotrienes, respectively.Eugenol lowers prostaglandin synthesis by blocking COX enzymes, which lowers heat, discomfort, and inflammation. Leukotriene production, which is involved in leukocyte recruitment and vascular permeability, is simultaneously decreased when LOX enzymes are inhibited. Clove extracts differ from many synthetic anti-inflammatory medications that specifically target COX pathways due to their dual inhibition [23].

3.2.2 Inflammatory Edema Reduction:

Acute inflammation is characterized by inflammatory edema, which is caused by increased vascular permeability and plasma exudation. Clove extracts have been shown to considerably decrease edema production in a dose-dependent way in animal tests employing carrageenan-induced paw edema models. The degree of edema decrease is frequently similar to what is seen with conventional anti-inflammatory medications.Inhibition of inflammatory mediators such prostaglandins, histamine, and cytokines is thought to be responsible for the decrease in edema. Clove extracts efficiently reduce inflammation and edema by lowering mediator release and regulating vascular permeability [23].

3.2.3 Inhibition of Cytokines That Promote Inflammation:

In vitro and in vivo models have demonstrated the suppression of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, by clove extracts and eugenol. This inhibition slows the development of inflammatory reactions and decreases immune cell activation.Like licorice extracts, clove extracts modulate cytokines by inhibiting transcription factors like NF-κB. This implies that their anti-inflammatory properties are underpinned by a same molecular mechanism [24].

3.2.4 Anti-Inflammatory Effects Mediated by Antioxidants:

Because reactive oxygen species (ROS) increase inflammatory signals and harm cells, oxidative stress and inflammation are intimately related. Because clove extracts contain a lot of

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phenolic compounds, especially derivatives of gallic acid and eugenol, they have potent antioxidant properties.Clove extracts indirectly inhibit inflammatory pathways by scavenging free radicals and lowering oxidative stress. The direct suppression of inflammatory enzymes and cytokines is complemented by this antioxidant-mediated mechanism, producing a complete anti-inflammatory action [25].

3.2.5 Clove Extracts' Immunomodulatory Properties:

Clove extracts have immunomodulatory action via controlling immune cell activities in addition to their direct anti-inflammatory effects. Another ingredient in clove oil, β-caryophyllene, interacts with immune cells' CB_2 cannabinoid receptors. Immune responses are modulated and inflammatory cytokine production is suppressed when these receptors are activated.In chronic inflammatory disorders, where dysregulated immune responses contribute to the course of illness, this immunomodulatory pathway is especially pertinent [24].

IV. ANTIPYRETIC EFFECTS:

A typical clinical sign of infection, inflammation, and immunological activation is fever, often known as pyrexia. It is typified by an increase in body temperature over the typical physiological range and is a controlled reaction rather than a thermoregulation breakdown. Persistent or high-grade fever can result in pain, dehydration, metabolic problems, and, in extreme situations, organ malfunction, despite the fact that fever is thought of as a protective mechanism that strengthens immune defense and prevents pathogen proliferation. Antipyretic medications are therefore frequently used to treat feverish illnesses and enhance patient comfort [26.

The main way that antipyretic medications work is by modifying the hypothalamus's core thermoregulatory systems. Endogenous pyrogens including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) cause fever by stimulating prostaglandin E_2 (PGE_2) production in the hypothalamus. PGE_2 causes a rise in body temperature by raising the thermoregulatory set point. The primary mechanism of action of conventional antipyretic medications, such as paracetamol and non-steroidal anti-inflammatory medicines (NSAIDs), is the inhibition of cyclooxygenase (COX) enzymes, which lowers the production of PGE_2.[27]

4.1 Liquorice's (Glycyrrhiza glabra) Antipyretic Properties:

4.1.1 Conventional and Ethnomedical Application:

In many medical systems, liquorice has long been used to treat inflammatory conditions, fever, and respiratory infections. Liquorice is frequently used in polyherbal formulations for feverish conditions in Ayurveda and Traditional Chinese Medicine, where it is thought to provide cooling, calming, and immunomodulatory properties. Traditional practices indicate a function in reducing fever linked with infections and inflammatory diseases, even if its antipyretic usage has not been as thoroughly established as its anti-inflammatory and anti-ulcer qualities [25].

4.1.2 Antipyretic Activity in Experiments:

Compared to research on inflammation, there are very little scientific studies on liquorice's antipyretic properties. Nonetheless, the experimental data that is now available suggests that licorice extracts can lower raised body temperature in animal models of fever. Liquorice extracts have been shown to significantly lower rectal temperature in yeast-induced pyrexia and lipopolysaccharide-induced fever models; at some dosages, these effects are equivalent to those of typical antipyretic medications.These results provide credence to the idea that liquorice has antipyretic properties, however the strength of the impact may differ according on the extract type, dose, and experimental setup. The intimate connection between antipyretic and anti-inflammatory processes is highlighted by the reported antipyretic effects, which are often dose-dependent and frequently accompanied by decreases in inflammatory markers [26].

4.1.3 Prostaglandin Inhibition's Function:

Liquorice's capacity to regulate prostaglandin production is primarily responsible for its antipyretic effects. One important mediator in the development of fever is prostaglandin E_2 (PGE_2), which raises body temperature by acting on the hypothalamus thermoregulatory region. It has been demonstrated that components of liquorice, such as glycyrrhizin and isoliquiritigenin, suppress COX-2 expression, resulting in decreased PGE_2 synthesis.Liquorice extracts lower fever by normalizing the hypothalamic set point through the suppression of PGE_2 production. This mechanism is similar to that of traditional antipyretic medications, but it uses a more complex and regulated pathway that involves many bioactive substances instead of just one enzyme target [27].

4.1.4 Modulation of Cytokines and Reduction of Fever:

By promoting PGE_2 production in the hypothalamus, endogenous pyrogens such as TNF-α, IL-1β, and IL-6 are crucial in the onset of fever. Immune cells and animal models have shown that liquorice extracts can inhibit the generation of these cytokines. Liquorice attenuates fever and indirectly reduces PGE_2 production by lowering cytokine levels.Liquorice has also been demonstrated to increase the synthesis of anti-inflammatory cytokines like IL-10, which helps to reduce fever and inflammation. Liquorice differs from traditional antipyretics that mainly target prostaglandin synthesis without directly impacting cytokine production due to its balanced regulation of cytokine profiles [28].

4.1.5 The Role of Antioxidants in Antipyretic Action:

It is well recognized that oxidative stress intensifies inflammatory reactions and has a role in the development of fever. Reactive oxygen species have the ability to increase inflammatory signaling and cytokine production. By scavenging free radicals and lowering oxidative stress, liquorice flavonoids including glabridin and liquiritin have potent antioxidant activity.By preventing oxidative damage and lowering the activation of inflammatory pathways linked to fever, liquorice's antioxidant qualities indirectly promote its antipyretic actions. The direct suppression of prostaglandin production and cytokine release is enhanced by this antioxidant-mediated mechanism [29].

4.2 Cloves' (Syzygium aromaticum) Antipyretic Properties:

4.2.1 Conventional Application in the Treatment of Fever:

Traditional medicine has traditionally used cloves to relieve pain, fever, and diseases. Clove infusions or decoctions are used in many cultures to lower fever and ease related symptoms including headaches and body pains. Cloves are said to provide calming and warming properties due to their strong fragrance, and their bioactive components offer pharmacological advantages [30].

4.2.2 Antipyretic Activity in Experiments:

The antipyretic properties of clove extracts, especially clove essential oil, have been more thoroughly studied in experiments than those of liquorice. Oral administration of clove extracts or essential oil has been shown to significantly lower body temperature in animal models of fever, including yeast-induced pyrexia.Clove's antipyretic effects are frequently dose-dependent and have a quick start, indicating a direct pharmacological action. Clove extracts have demonstrated antipyretic effectiveness that is on par with common medications like paracetamol in a number of trials, indicating their potential as natural antipyretic medicines [30].

4.2.3 Eugenol's Function in Reducing Fever:

The primary phenolic component of clove essential oil, eugenol, is vital to the antipyretic properties of cloves. It has been demonstrated that eugenol inhibits COX enzymes, which lowers prostaglandin generation. Eugenol helps lower fever and restore the natural thermoregulatory set point by lowering PGE_2 levels in the hypothalamus.Eugenol inhibits prostaglandins and modifies ion channels and neurotransmitter systems that are important in thermoregulation. Its multifaceted effect increases its antipyretic efficacy and sets it apart from traditional antipyretics, which mainly work by inhibiting COX.

4.2.4 Hypothalamic Thermoregulatory Center Action:

The primary regulator of body temperature is the hypothalamus. Fever is caused by pyrogens stimulating hypothalamic neurons to raise the thermoregulatory set point. It is thought that eugenol and clove extracts directly affect hypothalamus neurons, altering signaling pathways related to thermoregulation.Clove extracts efficiently reduce body temperature via decreasing PGE_2 production in the hypothalamus and blocking pyrogen-induced signaling. The quick and strong antipyretic effects seen in animal research are explained by this main mode of action [29].

4.2.5 Immunomodulation and Cytokine Suppression:

It has been demonstrated that clove extracts inhibit the synthesis of pro-inflammatory cytokines such TNF-α and IL-6, which function as endogenous pyrogens. Clove extracts reduce the upstream signals that cause fever by lowering cytokine levels. Furthermore, clove compounds'

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immunomodulatory properties aid in immune response regulation, avoiding excessive inflammatory reactions that fuel fever [16].

Table 1: Comparative Insights of Liquorice and clove extracts

Feature	Liquorice Extract	Clove Extract	References
Main active compounds	Glycyrrhizin, flavonoids	Eugenol, eugenyl acetate	[17]
Primary mechanisms	Modulation of NF-κB, COX-2, cytokines	Inhibition of COX/LOX, cytokine suppression	[18]
Anti-inflammatory evidence	Strong and multi-pathway	Strong, particularly in vivo	[21]
Antipyretic evidence	Moderate (indirect)	Supported experimentally	[26]
Safety considerations	Potential hormone-like effects at high doses	Potential liver enzyme interactions	[30]

V. SAFETY AND TOXICOLOGY

While clove (Syzygium aromaticum) and liquorice (Glycyrrhiza glabra) extracts are commonly used in traditional medicine and are generally thought to be safe at appropriate doses, their safety profiles need to be carefully considered, especially when used in concentrated or long-term therapeutic formulations.Glycyrrhizin is the main bioactive substance in licorice that has both positive and negative effects. By blocking the enzyme 11β-hydroxysteroid dehydrogenase type 2, glycyrrhizin can mimic corticosteroid action when taken in large quantities or over an extended period of time. This raises cortisol activity at mineralocorticoid receptors, which causes hypokalemia, hypertension, and retention of water and salt. In people with cardiovascular illness, renal impairment, or electrolyte imbalance, these effects—known as pseudo-hyperaldosteronism—may present serious hazards. Deglycyrrhizinated liquorice formulations are frequently used to lessen toxicity, and dose, therapy duration, and patient monitoring are crucial [31].

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When used in cuisine and traditional treatments, clove extracts are regarded as harmless when ingested at a culinary level. However, the main active ingredient, eugenol, may cause dose-dependent toxicity and interact with hepatic drug-metabolizing enzymes when given in concentrated amounts. Hepatotoxicity, gastrointestinal distress, and possible medication interactions have all been linked to excessive eugenol use. Therefore, when administering concentrated clove extracts or essential oils, especially in fragile populations and over an extended period of time, clinical vigilance is recommended [33].

VI. CONCLUSIONS

Through several complimentary processes, extracts from cloves (Syzygium aromaticum) and liquorice (Glycyrrhiza glabra) both show significant anti-inflammatory effect. These include reduction of pro-inflammatory cytokines like TNF-α and interleukins, inhibition of important inflammatory enzymes like cyclooxygenase and lipoxygenase, and modification of intracellular signaling pathways involved in inflammatory responses. The medicinal potential of these plants is greatly enhanced by their rich phytochemical content, especially the eugenol in cloves and the flavonoids in liquorice. Cloves have shown quantifiable antipyretic efficacy in animal models in addition to their anti-inflammatory properties. This is probably due to their reduction of prostaglandin production and modulation of hypothalamus thermoregulatory processes.

Their direct therapeutic applicability is hindered by the lack of human clinical proof, despite encouraging experimental results. To enable their sensible usage in contemporary healthcare, future research should concentrate on well planned, standardized clinical studies to definitively prove efficacy, ideal dosage schedules, long-term safety, and potential herb–drug interactions.

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