From Tradition to Therapy: *Plectranthus amboinicus* as a Remedy for Respiratory Inflammation

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Abstract: The respiratory tract is the anatomical pathway through which air travels during respiration and plays a critical role in gas exchange. While inflammation is a necessary immune response for combating infections in this system, severe inflammation can be detrimental and even fatal. Pathogenic microorganisms frequently expose the respiratory tract, necessitating a prompt and robust immune response, particularly through inflammation, to swiftly eliminate these threats. To reduce the intensity and duration of pulmonary inflammation, extensive research has been conducted to explore the pathophysiological mechanisms and therapeutic strategies associated with lung inflammation. Among these strategies, natural products have garnered significant attention for their chemical composition and pharmacologic properties, particularly their potential therapeutic applications in treating respiratory inflammation. Traditional herbal remedies widely use *Plectranthus amboinicus* because of its effectiveness in reducing respiratory inflammation. Numerous studies have demonstrated the potential of this plant for treating pulmonary disorders because of its phytochemical and pharmacognostic properties, specifically the activity of its essential compounds against airway inflammation. This review focuses on the phytochemistry, extraction techniques, phytocompound analyses, pharmacological activities in respiratory disorders, and clinical efficacy of *P. amboinicus* as a conventional herbal treatment for lung inflammation.

Keywords: Anti-inflammation, Antioxidant, Lung inflammation, *Plectranthus amboinicus*, Respiratory disease, Traditional herb

INTRODUCTION

Inflammation is an innate physiological reaction of the body that occurs in response to many stimuli, including infection, trauma, and hypersensitivity. The inflammatory response is a multifaceted process that encompasses an array of mechanisms aimed at preventing infections and facilitating tissue healing. In the pulmonary system, inflammation is commonly promoted by microorganisms or through exposure to chemicals, pollutants, irritants, and allergens. Throughout the process of inflammation, various types of inflammatory cells become engaged. Each generation of cytokines and mediators contributes to affecting the responses of other cells involved in the process of an inflammatory reaction. The coordination of these cellular and molecular components contributes to the progression of the inflammatory process. From a clinical perspective, instances of acute inflammation are observed in patients with pneumonia and acute respiratory distress syndrome (ARDS), whereas chronic inflammation is exemplified by asthma and chronic obstructive pulmonary disease (COPD). Since the essential function of the pulmonary system is facilitating gas exchange, an excessive inflammatory response could represent a significant risk to an individual's life. With regard to the continuous exposure of the lung to deleterious bacteria, a prompt and vigorous immune response, primarily characterized by inflammation, becomes imperative to expeditiously eradicate the intruders. Preserving lung homeostasis implies a precise equilibrium between inflammatory and anti-inflammatory processes [1].

Macrophages circulate in the airways, alveoli, and lung interstitium and can also migrate into the pulmonary microvasculature. The function of macrophages is crucial for regulating both acute and chronic inflammatory reactions. However, despite their ability to proliferate inside the lung, the quantity of macrophages is insufficient for successful defense against infections [2]. The defensive role of macrophages is enhanced by dendritic cells. Collectively, they possess the ability to engage in the phagocytosis of bacteria, particulate matter, and apoptotic cells. Nevertheless, macrophages constitute the primary source of cytokines, chemokines, and diverse inflammatory mediators that either enhance or inhibit the immune response. After experiencing an offensive response, macrophages and epithelial cells release chemokines and cytokines, which facilitate the formation of neutrophils and the onset of localized inflammation [3].

Cytokines can be classified into two distinct categories: proinflammatory and anti-inflammatory. The primary proinflammatory cytokines include tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8), and the interferon-inflammatory response. TNF-α and IL-1β are widely recognized as crucial proinflammatory cytokines. They play a significant role in promoting several inflammatory processes, including antigen presentation, the upregulation of adhesion molecules on endothelial cells, the activation of inflammatory cells, and the induction of matrix-degrading enzymes such as collagenase. Prominent anti-inflammatory cytokines include interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), and IL-1 receptor antagonist (IL-1ra), which act as natural antagonists of the IL-1 receptor. The secretion of anti-inflammatory cytokines by alveolar macrophages decreases the inflammatory response within the pulmonary system [3, 4].

Redness, swelling, heat, discomfort, and loss of function are the macroscopic hallmarks of inflammation. At the microscopic level, it manifests as vasodilation, increased vascular permeability, and the infiltration of inflammatory cells. The primary purpose of inflammatory responses is to eliminate and expel harmful chemicals while also isolating and containing them in a confined area. Moreover, the process of inflammation contributes to activating the immune system to facilitate healing and restoration. Neutrophils are the primary cellular component involved in acute lung inflammation, whereas chronic reactions are characterized primarily by the presence of macrophages and lymphocytes. Chronic inflammation arises when acute inflammation is not fully resolved. Chronic inflammatory responses assist in removing necrotic debris and apoptotic cells that are associated with acute inflammation. Additionally, they play crucial roles in defending against persistent infections and preventing their dissemination. Furthermore, chronic inflammatory responses contribute to the healing and repair of damaged lung tissue. The primary cellular components implicated in this process are macrophages and lymphocytes. Cytokines are synthesized by a diverse range of both immunological and nonimmune cellular entities. The synthesis of these cytokines can determine the magnitude and nature of the inflammatory reaction. In the context of chronic lung inflammation, there is a prevalence of profibrotic and immunoregulatory Th2 cytokines. Chemokines are of utmost importance in the regulation of cell trafficking, angiogenesis, and the inflammatory response [5, 6].

Inflammation is a prominent characteristic of numerous respiratory disorders, including pneumonia, ARDS, asthma, and COPD. A range of diverse strategies have been implemented to intervene in immune responses in the lungs. In addition to investigating cytokines, cytokine receptors, and cell-surface molecules, therapeutic interventions targeting cellular signal transmission and gene activation have been investigated. To comprehend the forthcoming modalities of treatment, it is necessary for physicians to possess a fundamental understanding of the underlying biological mechanisms of inflammation.

The present approach to managing respiratory tract inflammation as a supplementary therapy involves specifically targeting inflammatory cytokines. Corticosteroids are frequently prescribed as the preferred pharmacological intervention for mitigating the intensity of symptoms in individuals experiencing acute or chronic airway inflammation. Nevertheless, the use of corticosteroids over an extended period could give rise to undesirable side effects that have the potential to negatively affect patient well-being and patient satisfaction [7]. Alternative therapeutic drugs that have comparable clinical efficacy while providing improved safety profiles are urgently needed. The utilization of traditional herbal medicine in the treatment of respiratory problems has been a longstanding practice across several cultures. Many studies conducted over several decades have investigated the pharmacological activities of these herbal remedies, particularly their efficacy in mitigating lung inflammation. The bioactivity and pharmacological advantages of the principal phytocompounds present in *P. amboinicus* were assessed in an array of studies, including *in vitro*, *in vivo*, and clinical investigations. These studies aimed to explore the potential therapeutic applications of these compounds, particularly in the treatment of respiratory tract inflammation.

The *Plectranthus* genus encompasses more than 300 species that are distributed across Tropical Africa, Asia, and Australia. *P. amboinicus* (Lour.) Spreng. is a natural plant that originates in Asia and is distributed in America. It is a member of the Lamiaceae family and is frequently used in traditional botanical medicine to treat inflammation as well as respiratory infections [8, 9] Common names for this plant include Indian borage, Country borage, Broad-leaved thyme, Cuban oregano, Oregano Brujo, French thyme, Mexican mint, mother of herbs, and Spanish thyme. Herbal plants are also referred to as mothers [8].

P. amboinicus, widely recognized as an ancestral plant used in folkloric medicines, has been found to be effective in various therapeutic applications. These include wound healing, treatment of headaches, eye inflammation, flatulence or dyspepsia, diarrhea, fever, cough, obstruction, or inflammation of airways with or without infection, with no observed adverse effects [10]. The literature search conducted in this study revealed a total of 76 volatile compounds and 30 nonvolatile compounds. These compounds encompass a wide range of chemical classes, such as monoterpenoids, diterpenoids, triterpenoids, sesquiterpenoids, phenolics, flavonoids, esters, alcohols, and aldehydes. These substances are classified into many categories of phytochemicals [11].

PHYTOCHEMISTRY

The extraction process involved the use of several solvents to extract the shade-dried greenery of *P. amboinicus* powder. The most phytocompounds were found in the water fraction of the extract (19.2% w/v), followed by the alcohol fraction (15.2% w/v), the chloroform fraction (4.14% w/v), and the petroleum ether fraction (2.79% w/v) [12]. A broad spectrum of bioactive chemicals has been identified in the leaf extract of *P. amboinicus*. However, the composition of the elements is subject to variation based on numerous factors, including regional characteristics, climate conditions, various phases of leaf collection, and the techniques employed for extraction and identification [12, 13]. Understanding the pharmacological properties of plants and comparing their effects to those of other research requires first determining where the plants came from and how they were processed. This review only examines the primary bioactive components predominantly present in the leaf extract of *P. amboinicus*.

Carvacrol

Carvacrol, an oxygenated monoterpene, is the primary essential oil mostly present in the leaves of *P. amboinicus*. Carvacrol is often produced by a variety of aromatic plants that are utilized in traditional medicine for treatment/prevention and as culinary spices [12]. The beneficial therapeutic properties of carvacrol have been substantiated and include antioxidant, antibacterial, antifungal, antiparasitic, anticancer, diabetes-preventive, cardioprotective, and antiobesity effects. Several studies have identified carvacrol and thymol, which are oxygenated monoterpenes, as the primary compounds. β-Caryophyllene, a sesquiterpene hydrocarbon, and γ-terpinene, a monoterpene hydrocarbon, are additional essential oil molecules predominantly derived from the leaves, although in lesser quantities than the two aforementioned compounds [12].

Thymol

Thymol has strong anti-inflammatory characteristics, which are particularly important for respiratory tract irritation. Thymol (150 μM) was found to diminish lipopolysaccharide (LPS)–induced inflammation in mouse macrophages, whereas 84 μg/ml in J774A.1 cells inhibited LPS- and IFN-γ-induced inflammation by reducing nitric oxide mRNA expression [14, 15]. Thymol (10 and 20 μg/ml) inhibited elastase release in human polymorphonuclear neutrophils, a pulmonary inflammation-related enzyme [16]. Like nonsteroidal anti-inflammatory drugs (NSAIDs), thymol decreases the activity of cyclooxygenases (COXs), especially COX-1 [17]. In addition to inhibiting T-cell immunological responses, it modulates cytokine ratios, which are important in respiratory inflammation. Thymol (40 μg/ml) reduced LPS-induced inflammation in mouse mammary epithelial cells by inhibiting the MAPK and NF-κB pathways. These results indicate that thymol has the potential to be a therapeutic agent for respiratory inflammatory conditions [18].

Phenolic acid

Phenolic acids have been detected in the leaves of *P. amboinicus*, constituting a portion of its nonvolatile constituents. The primary component consists of rosmarinic acid, followed by caffeic acid [19]. This study demonstrated robust antioxidant activity by evaluating the ability of these compounds to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH•) radicals effectively. The radical-scavenging activity of *P. amboinicus* can be attributed primarily to the presence of rosmarinic acid, which is abundant in the leaf extract. While caffeic acid has more radical-scavenging activity than rosmarinic acid does, it is important to note that the quantity of caffeic acid present in the extract is rather limited [19].

Flavonoids

Several bioactive flavonoid chemicals, including luteolin, quercetin, and crisimaritin, have been identified in *P. amboinicus* foliage [19, 20]. The leaf extract of *P. amboinicus* was shown to contain quercetin as the primary flavonoid constituent. Furthermore, the acetone extract resulted in a greater yield of quercetin than did the ethyl acetate extract [21]. Luteolin and quercetin have antioxidant, anticancer, and anti-inflammatory properties. Multiple studies have provided evidence indicating that these substances effectively impede the growth of tumors in various *in vivo* experimental models [9, 21–24].

Steroids and terpenoids

β-Sitosterol is a steroid derived from the leaves of *P. amboinicus* [25]. The primary terpene constituents are thymol, geraniol, eugenol, linalool, carvacrol, caryophyllene, γ-terpinene, and p-cymene. *P. amboinicus* was found to contain 2.35% volatiles, seven of which were identified as terpene alcohols. These included 1-octen-3-ol, terpinene-4-ol, linalool, and nerolidol. Carvacrol has a distinctive pungent spicy-woody aroma that enhances the pronounced oregano-like odor. In conjunction with the notable relative proportions of α-bergamotene and caryophyllene, which impart citrus and spicy-woody aromas, respectively, these compounds collectively contribute to the distinct and potent aromatic fragrance of *P. amboinicus* [10, 11, 26].

EXTRACTION TECHNIQUES

P. amboinicus, generally referred to as Indian Borage or Mexican Mint [10], is an aromatic herb that is rich in cultural heritage in terms of its traditional therapeutic properties. The extraction of active chemical substances from leaves is highly important in various industries, including the pharmaceutical, cosmetic, and food industries [27]. Various techniques are employed to isolate important components from *P. amboinicus* leaves, each of which has distinct advantages and influences the composition of the resulting extract. Hydro/steam distillation, hexane extraction, supercritical carbon dioxide extraction, chloroform extraction, and ethyl acetate extraction are well recognized as prevalent extraction procedures in several fields.

Hydro/Steam Distillation

Hydro/steam distillation is a conventional method employed for the extraction of essential oils from aromatic plants, such as the leaves of *P. amboinicus*. In the specific circumstances at hand, leaves undergo a process of controlled steam distillation. The vaporization process causes the volatile components, including essential oils, found in the leaves to be transformed into a gaseous state. As a result, the extracted solution is rich in aromatic chemicals, including thymol, carvacrol, and terpenes [28, 29]. Furthermore, this technique has the potential to retain specific heat-sensitive chemicals that are inherent in the leaves, enhancing the overall medicinal attributes of the extract.

Hexane Extraction Procedure

The hexane extraction method is employed to isolate lipophilic substances from the leaves of *P. amboinicus* by incorporating the nonpolar solvent hexane. A solution containing several lipids and lipid-soluble phytochemicals is expected to be produced by this process. Nevertheless, the practicality of this method for the extraction of highly polar substances, such as polyphenols and water-soluble vitamins, might be questionable [30].

Supercritical Carbon Dioxide (SC–CO_2) Extraction

The SC–CO_2 technique is a contemporary and ecologically friendly approach utilized for the extraction of plant components. Under specific combinations of temperature and pressure, carbon dioxide may achieve a supercritical state, exhibiting characteristics that resemble both a liquid and a gas. In this experimental protocol, SC-CO_2 is employed as a solvent for the purpose of extracting diverse chemicals from the leaves of *P. amboinicus*. Through the manipulation of extraction parameters, the selective characteristics of supercritical carbon dioxide (SC–CO_2) extraction enable the extraction of diverse groups of chemical compounds. Essential oils, terpenoids, polyphenols, and other volatile and nonvolatile substances can all be present in the extracted solution [31, 32].

Chloroform Extraction Procedure

The reduced use of chloroform extraction can be attributed to safety concerns arising from its toxic nature and probable carcinogenic properties. Throughout history, chloroform has been employed for the purpose of extracting particular chemicals that strongly attract chloroform. This methodology has the potential to provide a solution that encompasses chlorophyll, certain carotenoids, and lipophilic constituents. Nevertheless, the utilization of this approach for current extraction practices is restricted by the inherent associated risks and environmental concerns associated with it [33, 34].

Ethyl Acetate Extraction

The ethyl acetate extraction technique was used to separate chemicals from *P. amboinicus* leaves by exploiting the solvent ethyl acetate. Medium-polarity ethyl acetate is an appropriate solvent for the extraction of various chemicals, such as flavonoids, polyphenols, and terpenoids. The resulting extract is expected to include a significant amount of phytochemicals with moderate polarity [35].

In summary, the technique used to extract *P. amboinicus* leaves is dependent on the particular desired components, safety factors, and intended application of the extract. Every extraction method has the potential to yield a distinct combination of phytochemicals, essential oils, lipids, and other active components that may possess medicinal properties. The selection of an appropriate extraction method is a common practice among researchers and enterprises and is guided mostly by the desired attributes of the end product and the overall considerations of safety and environmental effects associated with the extraction process.

ESSENTIAL SUBSTANCES

A literature review of *P. amboinicus* elucidated the existence of various categories of phytocompounds that can be categorized into two distinct groups: volatile and nonvolatile compounds.

Volatile Composition

P. amboinicus has a diverse array of 76 distinct chemical constituents in its volatile makeup. Gas chromatography combined with mass spectrometry (GC–MS) is widely regarded as the preferred method for the identification of volatile chemicals. This methodology enables the accurate determination and measurement of the volatile constituents present in *P. amboinicus* [10, 35].

Nonvolatile Composition

P. amboinicus consists of a nonvolatile composition comprising a total of thirty chemicals that have been discovered. Liquid chromatography combined with mass spectrometry (LC–MS) is employed for the identification and analysis of nonvolatile substances. The aforementioned method enables the isolation and analysis of the nonvolatile phytochemicals present in *P. amboinicus* [36]. The primary volatile components of plants are essential oils that contribute to the distinctive scent and flavor of the plant. The nonvolatile components include a diverse array of chemicals that have potential bioactive effects, including phenolic compounds, flavonoids, and alkaloids [20].

To further understand *P. amboinicus* and its medicinal properties, researchers are currently engaged in the development of novel extraction methodologies. The employed methodologies are specifically designed to improve the productivity and integrity of the isolated substances, thereby leading to a more comprehensive chemical composition analysis of the botanical sample.

Supercritical fluid extraction (SFE) is a new technology that uses supercritical carbon dioxide as a solvent. SFE has several advantages over conventional procedures, including greater selectivity and efficient extraction of both volatile and nonvolatile chemicals. Additionally, this approach reduces the consumption of potentially harmful solvents, hence ensuring their sustainability in the environment. Furthermore, investigators are also examining the feasibility of extraction methodologies facilitated by the use of nanotechnology. The utilization of nanoparticles and nanocarriers has been shown to improve the solubility and stability of bioactive chemicals, therefore augmenting their therapeutic effects of *P. amboinicus* extract [31, 32, 37, 38].

In addition, advancements in analytical methodologies, such as GC–MS and high-performance liquid chromatography (HPLC), have facilitated the precise determination and measurement of specific constituents within *P. amboinicus* extracts. The utilization of analytical tools is necessary to gain a comprehensive understanding of the intricate chemical composition and the possible synergistic impacts of the constituents present in the plant [39].

The comprehensive therapeutic potential of *P. amboinicus* can be elucidated by integrating advanced extraction techniques with sophisticated analytical approaches, as demonstrated by researchers. The findings of this study hold significant potential for advancing the fields of natural medicines, pharmaceutical drugs, and nutraceutical foods, with a wide range of implications for medical and wellness purposes [20]. *P. amboinicus* has great potential as a subject for further investigation in the fields of pharmacology and medicine, primarily because of its rich assortment of phytochemical compounds.

The stems and green leaf explants of *P. amboinicus* contain biological components that result in the production of an essential oil consisting of 76 volatile compounds. The presence of two primary phenolic chemicals, carvacrol and thymol, in substantial quantities is well documented, and their significance in culinary applications has been recognized from a pharmacological perspective [20, 40]. The purity and quantity of an essential oil's chemical compounds are directly related to its biological functions. Essential oils are characterized by the significant presence of oxygenated monoterpenes, monoterpene hydrocarbons, sesquiterpene hydrocarbons, and oxygenated sesquiterpenes. The extraction of essential oil from *P. amboinicus* is typically conducted via a hydrodistillation method employing a Clevenger-type apparatus for 3–4 hours. Alternative extraction methods, such as hexane extraction, steam distillation, and supercritical CO_2 extraction, have also been used in various studies. The oil yield obtained through hexane extraction was the highest (6.52%), whereas steam distillation resulted in a lower oil yield (0.55%), and supercritical CO_2 extraction yielded an intermediate oil quantity (1.4%) [35].

The chemical composition of *P. amboinicus* consists of 30 nonvolatile chemicals, which include phenolic acids, flavonoids, monoterpene hydrocarbons, sesquiterpene hydrocarbons, oxygenated monoterpenes, and esters [37]. Flavones, mainly cirsimaritin, salvigenin, and chrysoeriol, have been identified beneath plants. Moreover, the aqueous extract derived from *P. amboinicus* contains carvacrol, which has a diverse array of bioactive polyphenols, such as rosmarinic acid, rutin, caffeic acid, gallic acid, *p*-coumaric acid, and quercetin [40].

According to the literature, the leaf extracts of *P. amboinicus* include several compounds, such as tannins, flavonoids, saponins, polyuronides, and steroid glycosides. GC–MS analysis confirmed the presence of approximately eleven phytocompounds, which accounted for 97.6% of the total extract. The principal nonvolatile elements detected in the chemical composition were linalool, carvacrol, geranyl acetate, and nerol acetate, which made significant contributions [38].

Figures 1 and 2 provide examples of the most prevalent volatile and nonvolatile constituents.

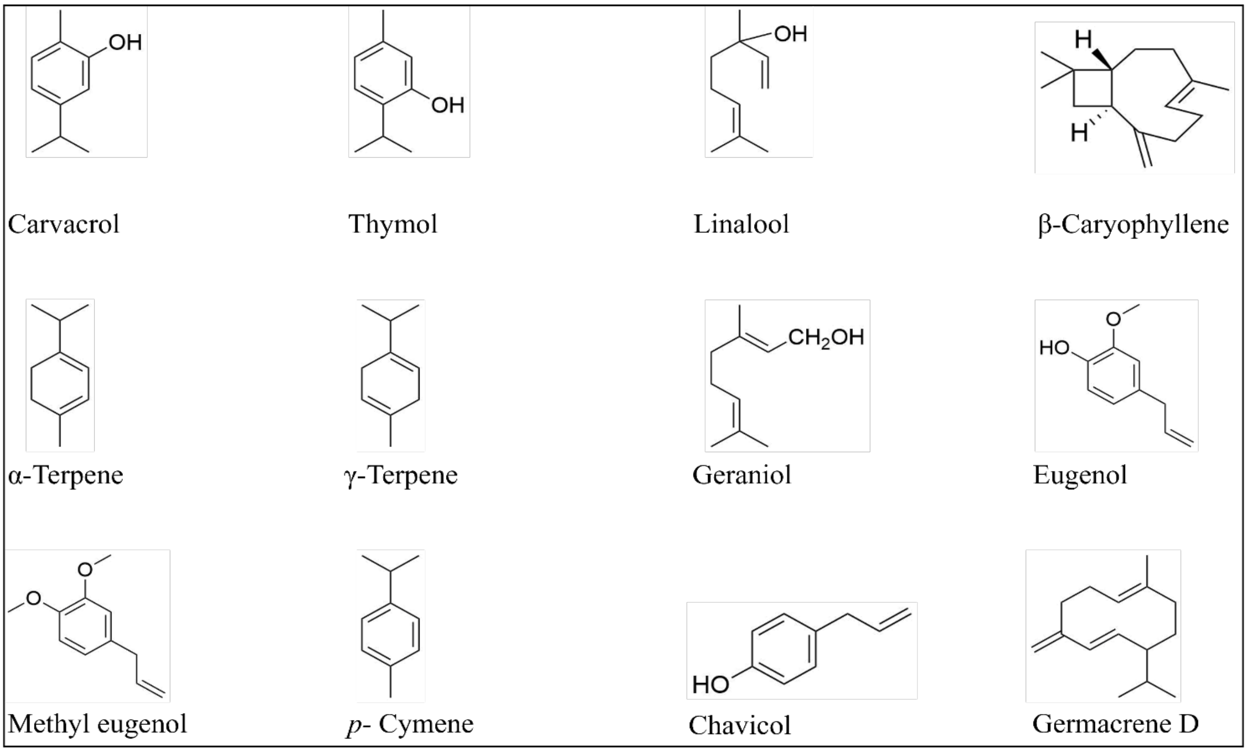

Figure 1. Major volatile constituents

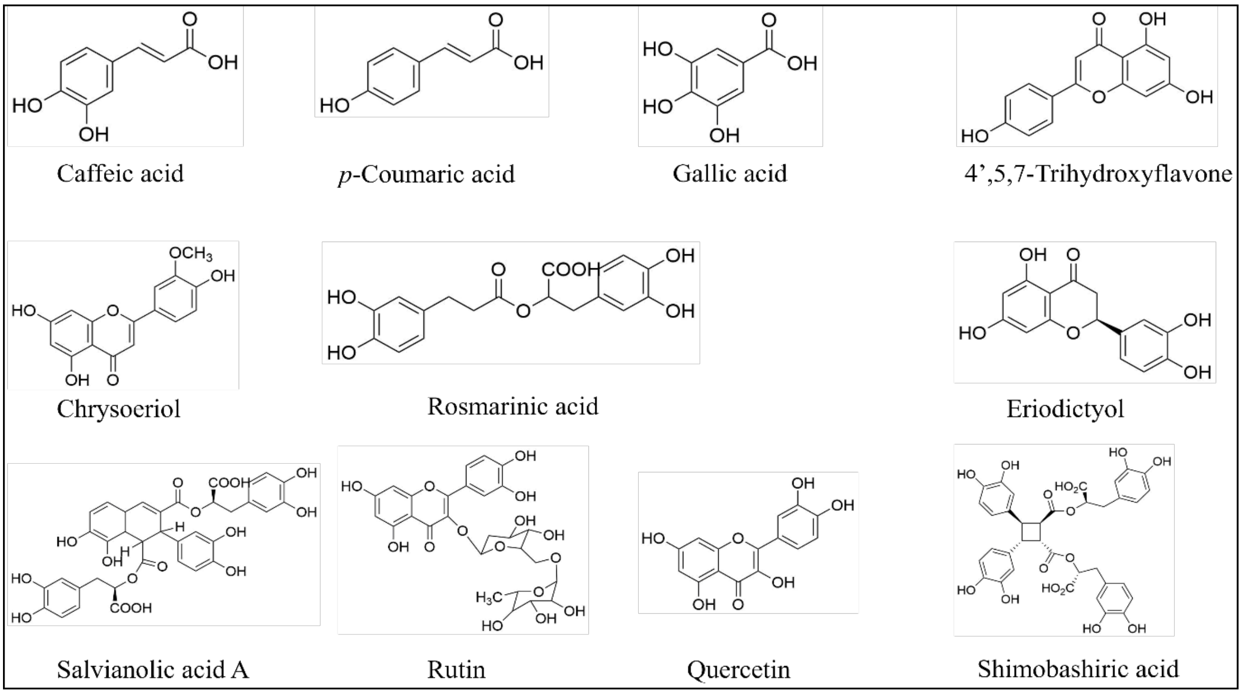

Figure 2. Major nonvolatile constituents

THE PRESENT INVESTIGATION DETERMINED THE PHARMACOLOGICAL ACTIVITY OF SEVERAL RELEVANT SUBSTANCES IN TERMS OF RESPIRATORY CONDITIONS

Carvacrol

The biological activity of *P. amboinicus* may be attributed to carvacrol. Carvacrol has numerous biological effects, including antibacterial, anticancer, antimutagenic, antigenotoxic, analgesic, antispasmodic, anti-inflammatory, antiangiogenic, antiparasitic, antiplatelet, Ache inhibitory, antielastase, insecticidal, and hepatotoxic effects [39]. The potential of carvacrol as an anti-inflammatory drug for respiratory inflammation has been documented in numerous *in vitro* investigations. Its mechanism of action may be attributed to its ability to reduce IL-1β, IL-4, IL-8, and malondialdehyde (MDA) levels [40, 41]. Furthermore, carvacrol has exhibited potential pharmacological activity by acting as an antagonist of acetylcholine-induced currents in both the nicotine-sensitive acetylcholine receptor (AChR) and the morantel-sensitive AChR subtypes [42].

Thymol

Thymol has been shown to have many pharmacological effects, such as antioxidant advantages; free radical scavenging; anti-inflammatory, analgesic, antispasmodic, antibacterial, antifungal and antiseptic effects; and potential for anticancer therapy [43]. Previous studies have demonstrated that thymol can mitigate ovalbumin (OVA) hyperresponsiveness (AHR) and allergic airway inflammation in mice. This effect is achieved through a reduction in inflammatory cell infiltration and the suppression of pathological alterations, which can be attributed to its ability to prevent NF-κB activation [43-45]. Thymol has demonstrated notable efficacy in mitigating pulmonary fibrosis induced by BLM through its substantial antioxidant and anti-inflammatory effects. The upregulation of lung miR-29a expression, coupled with the downregulation of TGF-β and PI3K/Akt signaling, merits further investigation as a potential molecular mechanism underlying the antifibrotic actions of thymol [46].

Linalool

Linalool has been demonstrated to be effective against a variety of germs and fungi and to exhibit local anesthetic activity. This activity is thought to be related to the effects that linalool has on nicotinic receptor-ion channels. The distinguishing features of linalool, which manifests as antibacterial, anti-inflammatory, analgesic, and antihyperalgesic qualities, render it potentially valuable for addressing infectious illnesses that are frequently accompanied by inflammation and pain [47].

Terpinene

The therapeutic administration of terpinene was associated with a decrease in neutrophil migration, as well as a reduction in the production of IL-1β and TNF-α. Additionally, during acute lung injury, γ-terpinene decreases neutrophil migration into lung tissue, regardless of the extent of protein extravasation in the lung [48]. The anti-inflammatory effects are facilitated by a reduction in the concentrations of proinflammatory mediators, including nitric oxide (NO), interleukins, TNF-α, and prostaglandin E2 (PGE2) [49].

Geraniol

Geraniol has various pharmacological effects, including anticancer, anti-inflammatory, antioxidative, and antibacterial effects. Numerous studies have examined the potential preventive effects of geraniol in a mouse model of acute lung damage generated by intranasal injection of lipopolysaccharide (LPS). The administration of geraniol significantly improved pathological damage and reduced pulmonary cell death. It also decreases the wet/dry (W/D) weight ratio of the lungs, myeloperoxidase (MPO) activity, and the synthesis of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) [50].

Eugenol

Several *in vivo* investigations have demonstrated the beneficial effects of eugenol on acute lung injury. The intratracheal instillation of LPS in mice demonstrated that eugenol possesses anti-inflammatory properties, effectively mitigating the LPS-induced inflammatory reaction. The protective mechanism of eugenol can be partially due to its ability to suppress the generation of proinflammatory cytokines by modulating inflammation and the redox state [51].

Cymene

Cymene has various pharmacological effects, including antioxidant, anti-inflammatory, antiparasitic, antidiabetic, antiviral, antitumor, antibacterial, and antifungal effects. In addition to contributing to its known properties, p-cymene has been shown to have analgesic, antinociceptive, immunomodulatory, vasorelaxant, and neuroprotective effects. The anticancer properties of this substance are associated with multiple pharmacological mechanisms, including the suppression of apoptosis and the induction of cell cycle arrest [52]. The administration of p-cymene substantially decreased the overall number of inflammatory cells present in the bronchoalveolar lavage fluid. Additionally, it resulted in a decrease in the level of NF-κB protein within the lungs, an increase in superoxide dismutase (SOD) activity, and an inhibition of MPO activity. Histological investigations revealed that the presence of p-cymene resulted in significant inhibition of neutrophil activity in lung tissue following LPS induction [53].

Chavicol

The administration of chavicol significantly suppressed cancer cell proliferation, viability, motility, and infiltration. The potential mechanism of action may involve the initiation of cell apoptosis through the production of oxidative stress, depletion of glutathione, and dysregulation of the cell cycle. Chavicol has been found to enhance the immune response and trigger apoptosis through its ability to modulate the mitochondrial signaling pathway and affect the p53 protein. In a laboratory-based investigation, the bioactive chemical chavicol demonstrated significant anticancer effects against lung cancer cells (A549) in an *in vitro* setting [54].

p-Coumaric acid

p-Coumaric acid (*p*-CA) is widely recognized as an effective substance for the treatment of pulmonary inflammatory illnesses because of its remarkable capacity to mitigate pulmonary inflammation generated by cigarette smoke. The inhibition of pulmonary inflammation by *p*-CA was observed through the suppression of NF-κB activity, which in turn modulated the expression of proinflammatory mediators [55]. *p*-CA has demonstrated an anticancer effect both *in vitro* and *in vivo*. The application of *p*-CA prior to therapy induces the transmission of oxidative stress in the setting of inflammatory lung damage and in A549 cells [56].

Quercetin

Quercetin has demonstrated potential as an efficient adjuvant for mitigating the adverse effects of cigarette smoke exposure, according to findings from both *in vitro* and *in vivo* studies. Furthermore, it has been shown to be efficacious in preserving pulmonary function and tidal volume [57]. Furthermore, the compound quercetin inhibited the translocation of NF-κB into the nucleus. It also results in decreased secretion of the inflammatory cytokines TNF-α, IL-1, and IL-6. Additionally, quercetin reduces the oxidative stress and inflammation generated by ROS through the suppression of NOX2 production [58].

Rutin

Rutin has been shown to have many pharmacological effects, such as antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective, and cardioprotective effects. The investigation also included an examination of anti-asthmatic activity and other related effects. The administration of rutin notably reduced the airway and immediate-phase response, as well as the levels of histamine, phospholipase A2, and eosinophil peroxidase. The recruitment of neutrophils and eosinophils to the lung was diminished. Furthermore, the compound quercetin inhibited the translocation of NF-κB into the nucleus. It also resulted in decreased levels of the inflammatory cytokine TNF-α, as well as IL-1 and IL-6. Additionally, quercetin reduces the oxidative stress and inflammation generated by ROS through the suppression of NOX2 production [59].

Gallic acid

Gallic acid has notable anti-inflammatory and antioxidative properties, as well as various additional pharmacological benefits, such as antitumor, antibacterial, antidiabetic, antiobesity, antimicrobial, and antimyocardial ischemic activities. The primary mechanism through which gallic acid exerts its anti-inflammatory effects is predominantly through the activation of the mitogen-activated protein kinase (MAPK) and NF-κB signaling pathways. Therefore, it attenuates the inflammatory response by decreasing the secretion of inflammatory cytokines, chemokines, and adhesion molecules and decreasing cellular infiltration [60]. With respect to the treatment of respiratory conditions, a study was conducted to explore the potential benefits of gallic acid in mitigating elastase-induced lung inflammation and emphysema. Specifically, this study aimed to test the protective effects of gallic acid against conditions resembling the exacerbation of COPD in a mouse model [61].

Rosmarinic acid

Rosmarinic acid has an interesting variety of biological effects, including antiviral, antibacterial, antioxidant, antimutagenic, and anti-inflammatory effects. Numerous *in vitro* and *in vivo* investigations have documented the anti-inflammatory properties of rosmarinic acid in the context of inflammatory disorders [62]. A previous study examined the impact of rosmarinic acid on lung damage caused by diesel-expelled particles (DEPs). The daily oral administration of rosmarinic acid effectively suppressed the development of lung damage characterized by neutrophilic inflammation and interstitial edema induced by exposure to DEPs. The apparently favorable effects of rosmarinic acid have been shown to be associated with a reduction in the localized expression of IL-1β, keratinocyte chemoattractant (KC), macrophage inflammatory protein (MIP)-1α, and monocyte chemoattractant protein (MCP)-1. Similarly, the expression of inducible nitric oxide synthase (iNOS) mRNA was found to be suppressed by rosmarinic acid in the presence of DEPs [63].

Examples of phytocompounds in *P. amboinicus* with pharmacological activities relevant to respiratory tract inflammation are summarized in Table 1.

Table 1. Phytocompounds in *Plectranthus amboinicus* with pharmacological activities related to respiratory tract inflammation.

Phytocompounds	Pharmacological Activities
Carvacrol	Carvacrol reduces respiratory inflammation by inhibiting pro-inflammatory markers consisting of IL-1β, IL-4, IL-8, and malondialdehyde (MDA) and functions as an antagonist on acetylcholine receptors that are involved in inflammatory pathways [40, 42, 43].
Thymol	Thymol decreases the infiltration of inflammatory cells, inhibiting the activation of NF-κB, and reducing pulmonary fibrosis through its antioxidant and anti-inflammatory properties. These effects include increasing the expression of miR-29a and decreasing the activity of TGF-β and PI3K/Akt signaling pathways [44–47].
Linalool	Linalool, which is recognized for its potential antibacterial, anti-inflammatory, analgesic, and anti-hyperalgesic properties, is effective in the treatment of infectious diseases that are associated with inflammation and pain by modulating nicotinic receptor-ion channels, which in turn alleviates respiratory inflammation [48].
Terpinene	Terpinene reduces neutrophil migration and levels of pro-inflammatory mediators including IL-1β, TNF-α, nitric oxide (NO), and prostaglandin E2 (PGE2), which minimizes respiratory inflammation [49–50].
Geraniol	Reduced pathological lung damage, pulmonary cell death, lung wet/dry weight ratio, myeloperoxidase (MPO) activity, and production of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α are some of the mechanisms in which geraniol alleviates respiratory inflammation [51].
Eugenol	Eugenol suppresses the production of pro-inflammatory cytokines and regulates the inflammatory response and redox state, which relieves respiratory inflammation [52].
Cymene	Cymene decreases NF-κB protein levels, increase superoxide dismutase (SOD) activity, inhibit myeloperoxidase (MPO) activity, and reduce inflammatory cells in bronchoalveolar lavage fluid [54].
Chavicol	Through regulating mitochondrial signaling and p53 protein pathways, causing apoptosis in lung cancer cells, and boosting the immune response, chavicol reduces inflammation in the respiratory tract. As well as initiating oxidative stress and cell cycle dysregulation, the process additionally suppresses cell proliferation, viability, and motility [55].
p-Coumaric acid	NF-κB activity is inhibited and pro-inflammatory mediators are modulated by *p*-CA, which effectively treats pulmonary inflammatory conditions by reducing inflammation caused by cigarette smoke. *p*-CA induces oxidative stress in inflammatory lung damage and A549 cells and has anticancer effects *in vitro* and *in vivo* [56–57].
Quercetin	Quercetin reduces the negative consequences of cigarette smoke exposure by preserving pulmonary function, lowering tidal volume, and blocking NF-κB nuclear translocation. The production of NOX2 is suppressed, which in turn decreases oxidative stress and inflammation induced by ROS. Additionally, the secretion of inflammatory cytokines (TNF-α, IL-1, IL-6) is lowered [58–59].
Rutin	Rutin reduces airway inflammation and immediate-phase reactions, decreases histamine, phospholipase A2, and eosinophil peroxidase levels, and inhibits neutrophil and eosinophil recruitment. The compound hinders NF-κB translocation, lowers inflammatory cytokines (TNF-α, IL-1, IL-6), and reduces oxidative stress and inflammation by inhibiting NOX2 synthesis [60].
Gallic acid	Gallic acid possesses anti-inflammatory, antioxidant, anticancer, antibacterial, antidiabetic, anti-obesity, antimicrobial, and anti-myocardial ischemia activities. Anti-inflammatory effects are primarily mediated by MAPK and NF-κB signaling pathways, decreasing cytokines, chemokines, adhesion molecules, and cellular infiltration. This compound exhibits potential in reducing elastase-induced lung inflammation and emphysema [61–62].
Rosmarinic acid	Rosmarinic acid demonstrates antiviral, antibacterial, antioxidant, antimutagenic, and anti-inflammatory characteristics. The suppression of neutrophilic inflammation, interstitial edema, and the expression of inflammatory markers consisting of IL-1β, KC, MIP-1α, MCP-1, and iNOS mRNA effectively mitigates lung injury caused by diesel-exhaust particles [63–64].

CLINICAL USE OF *PLECTRANTHUS AMBOINICUS* AS A TREATMENT AGENT FOR INFLAMMATION OF THE RESPIRATORY TRACT

P. amboinicus is an evergreen herb that has traditionally been employed for medicinal purposes. The therapeutic potential of this substance has undergone extensive research in recent years, particularly in the domain of respiratory problems. The active compounds demonstrate anti-inflammatory, bronchodilator, and immunomodulatory effects, suggesting their potential therapeutic value in the prevention and management of respiratory diseases [11].

With respect to therapeutic effectiveness in addressing respiratory problems, the botanical material has demonstrated the ability to alleviate respiratory manifestations, including coughing, wheezing, and dyspnea, in patients with conditions such as asthma, bronchitis, and COPD. Furthermore, research has demonstrated the efficacy of this substance in alleviating upper respiratory tract infections by reducing both the duration and severity of symptoms. This can be attributed to its remarkable expectorant properties, which can be attributed to the presence of carvacrol and thymol components. The greenery of this species is recognized for its essential oils, flavonoids, terpenes, and cinnamic derivative products [9], which have been found to exhibit anti-inflammatory and chemotherapeutic properties [64–66]. Consistent with these findings, the green foliage of *P. amboinicus* exhibited favorable bronchodilator activity throughout the experiment [67].

The use of essential oils derived from the aerial components of *P. amboinicus* for the treatment of asthma has been reported in Eastern Cuba [68]. The oral administration of a concoction or extract derived from leaves, in combination with other herbal substances, is utilized as a means to manage asthma symptoms. The aforementioned decoction is additionally employed for the treatment of catarrhal illnesses, wherein it effectively alleviates the excessive accumulation of viscous phlegm or mucus within an airway or bodily cavity [69]. The potential explanation for this phenomenon may be attributed to the significant presence of carvacrol and thymol [68–70], which are the primary constituents of the plant's essential oils. These compounds possess notable expectorant properties and have been traditionally employed in the treatment of diverse respiratory ailments. The use of a decoction of *P. amboinicus* juice, either as a beverage or for bathing purposes, may hold potential as a viable therapeutic option for influenza, cough, bronchitis, and throat ailments [10].

The therapeutic efficacy of *P. amboinicus* in treating respiratory tract diseases, specifically the common cold, has been confirmed through a randomized, double-blind, controlled trial [71]. During the study, participants were administered either a placebo or tablets containing *P. amboinicus* at doses of 300 mg or 600 mg per day for 15 days. The efficacy of extensive fluids and antipyretics was evaluated in the context of fever or malaise. Compared with individuals in the other groups, individuals in the initial week of therapy who received a dosage of 600 mg presented a significant decrease in cough frequency. Furthermore, the administration of this dosage resulted in the complete cessation of cough symptoms. During that period, the aforementioned group exhibited superior outcomes in terms of reducing cough intensity and increasing expectoration volume. Consequently, the cohort that exhibited the most remarkable proportion of patients achieving favorable overall responses was the group administered a dosage of 600 mg. The safety profile of the intervention was found to be well tolerated, with adverse effects being predominantly modest and primarily associated with usual illness symptoms. Pillics containing *P. amboinicus* had a dose-dependent effect on patients suffering from the common cold, resulting in more favorable outcomes than standard treatment methods.

CONCLUSION

P. amboinicus is a botanical artifact that contains a considerable abundance of both volatile and nonvolatile chemicals and consequently shows substantial promise because of its bioactive characteristics. The diverse range of phytocompounds found in plants plays a crucial role in influencing their biological activities. This characteristic renders plants an intriguing area to investigate for future research in the domains of pharmacology and therapeutics, particularly in conjunction with the management of respiratory tract inflammation. There is an impressive amount of evidence substantiating the bioactivity of the primary phytocompounds present in *P. amboinicus*, such as terpenes, flavonoids, and phenolic acids. These compounds have been shown to be capable of various pharmacologic activities, primarily manifesting as anti-inflammatory effects, antioxidation, analgesic properties, antitumor activity, and immune enhancement. These assertions have been supported by both *in vitro* and *in vivo* studies. The medicinal properties of *P. amboinicus* have been extensively recognized by several ethnic groups globally, both as a traditional remedy and as a therapeutic intervention for respiratory ailments. One intriguing therapeutic application involves the utilization of clinical efficacy against inflammation in the respiratory tract, encompassing both the upper and lower regions of the airways. This beneficial effect is attributed to the modulation of many intracellular pathways associated with inflammation. Numerous *in vitro* studies have demonstrated the pharmacological activities and mechanisms of action underlying the remarkable efficacy of *P. amboinicus* in mitigating the inflammatory biomarkers associated with lung injury generated by diverse agents. A clinical trial, specifically a randomized controlled trial, has provided evidence of the clinical advantages of the use of *P. amboinicus* tablets in the treatment of respiratory tract illnesses. This treatment has been shown to effectively reduce the severity of symptoms and shorten the recovery period. Additionally, the use of daily doses of *P. amboinicus* tablets has been deemed safe, as indicated by a satisfactory safety profile. Additional clinical research is needed to explore the clinical advantages of various outcomes related to respiratory illnesses. Moreover, investigations are needed to assess the clinical benefits of preventing lung cancer resulting from chronic pulmonary inflammation.

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