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Phytotherapeutic Potential of *Melaleuca*: An Integrative Review of Phytochemistry and Antimicrobial, Antifungal, Antioxidant, and Antiviral Mechanisms

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Abstract

Melaleuca alternifolia and other species of the Melaleuca genus stand out for the broad spectrum of pharmacological properties attributed to their bioactive compounds such as monoterpenes, sesquiterpenes, flavonoids, and polyphenols. This study aimed to critically review and analyze scientific evidence produced between 2005 and 2025 regarding the antimicrobial, antifungal, antioxidant, and antiviral activities of Melaleuca, correlating its phytochemistry with molecular mechanisms of action. For this purpose, an integrative literature review was conducted, comprising scientific articles indexed in Google Scholar, SciELO, PubMed, and ScienceDirect, selected based on relevance, timeliness, and methodological quality. The results demonstrate that the antimicrobial activity of Melaleuca is primarily related to the capacity of its monoterpenes, especially terpinen-4-ol, to disorganize bacterial membranes, induce oxidative stress, and interfere with essential metabolic processes. Antifungal evidence indicates action on ergosterol, the cell wall, microtubules, and pathways for generating reactive oxygen species, showing efficacy against clinical and phytopathogenic fungi. The antioxidant activity, in turn, involves mechanisms of hydrogen and electron transfer, chelation of pro-oxidant metals, and inhibition of lipid peroxidation, contributing to anti-inflammatory and wound-healing effects. The analyzed antiviral studies suggest that Melaleuca monoterpenes interact with the viral envelope, block fusion and cell entry steps, and modulate immune responses mediated by interferons, showing potential against various enveloped viruses. The integration of this evidence demonstrates that Melaleuca possesses a multi-target pharmacological profile, with convergent molecular mechanisms that justify its broad application in dermatology, phytotherapy, skin infections, and antiviral studies. It is concluded that the plant presents significant potential as a natural therapeutic agent, although robust clinical trials, phytochemical standardization, and safety studies are still necessary to consolidate its medicinais use. This work contributes by integrating phytochemical data, experimental evidence, and mechanisms of action, offering a solid scientific basis for future research and the development of Melaleuca-derived phytomedicines.

Keywords: *Melaleuca alternifolia*, phytochemistry, antimicrobial activity, phytomedicines, antiviral mechanisms

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INTRODUCTION

The species *Melaleuca* (Myrtaceae family), popularly known as tea tree, has a long history of medicinal use among Australian Aboriginal peoples, who used its leaves to treat wounds, inflammations, and respiratory infections [1]. Scientific interest in the plant intensified in the early 20th century when studies demonstrated that the essential oil of *Melaleuca alternifolia* exhibited antimicrobial activity superior to that of phenol, consolidating its therapeutic potential [2].

The chemical composition of *Melaleuca* is characterized by the presence of over a hundred bioactive compounds, mainly monoterpenes and sesquiterpenes, such as terpinen-4-ol, γ-terpinene, α-terpineol, 1,8-cineole, p-cymene, and sabinene, which are responsible for its broad pharmacological properties [3]. Other species of the genus, such as *M. quinquenervia*, stand out for the significant concentration of flavonoids, tannins, and polyphenols, expanding the spectrum of antioxidant, antiviral, and anti-inflammatory effects attributed to the plant [4].

The growing importance of phytomedicines in contemporary medicine reinforces the interest in studying plants like *Melaleuca*. According to Morais & Sharma (2020), approximately 80% of the world's population relies on plant-based treatments for basic health care, highlighting the need for research that evaluates natural compounds as immunomodulatory, antioxidant, antimicrobial, and antiviral agents [5]. Furthermore, according to the study, natural products rich in terpenoids, flavonoids, and alkaloids play an essential role in modulating the immune system, neutralizing free radicals, and intervening in the replicative cycle of pathogens, demonstrating high therapeutic potential.

This relevance also applies to the *Melaleuca* genus, whose chemical constituents exhibit antimicrobial, antifungal, antiviral, antiparasitic, and anti-inflammatory activity, confirmed in *in vitro* and *in vivo* studies [6]. Additionally, recent research points to promising interactions between *Melaleuca* terpene compounds and viral structures, suggesting possible applications in the control of enveloped viruses, including mechanisms related to SARS-CoV-2 [7].

The quality of the essential oil depends on factors, such as genetics, climate, soil, and extraction methods, which directly impact its composition and efficacy. In Brazil, the cultivation and processing of *Melaleuca* have gained economic and scientific relevance, especially due to the growing demand for essential oils in the cosmetic and pharmaceutical industries [8].

With over 250 cataloged species, the *Melaleuca* genus presents remarkable phytochemical diversity, reflected in its different biological activities. Species – such as *M. alternifolia*, *M. quinquenervia*, *M. leucadendra*, and *M. Cajuputi* – stand out for their traditional use and scientific confirmation of their therapeutic effects [9]. Thus, understanding the phytochemistry and the molecular mechanisms involved in these actions is essential to support clinical use and the development of new phytotherapeutic formulations.

Objective

This article aims to conduct an integrative review of the phytotherapeutic properties of *Melaleuca*, analyzing scientific studies published between 2005 and 2025. The goal is to understand the medicinal applications of the plant, highlighting its antimicrobial, antifungal, antiviral, anti-inflammatory, antioxidant, and other potentially therapeutic actions, as well as to discuss the relationship between chemical composition, essential oil quality, and pharmacological efficacy. The review also aims to synthesize evidence from different *Melaleuca* species and correlate their bioactive constituents with traditional and contemporary therapeutic uses.

VISUAL MODEL OF THE PRISMA FLOW DIAGRAM

From an initial total of 80 records identified in the databases, 31 articles met the eligibility criteria and were included in the final review, after removing duplicates and screening processes by title/abstract and full-text reading (Figure 1). *Source:* Developed by the author (2025).

Study Design

This is an integrative literature review, a method that allows for the synthesis of multiple published studies to generate new conclusions on a specific topic. The review structure followed the steps: (1) theme identification and research question selection; (2) establishment of inclusion and exclusion criteria; (3) identification of pre-selected and selected studies; (4) categorization of studies; (5) analysis and interpretation of results; and (6) presentation of the review/synthesis of knowledge.

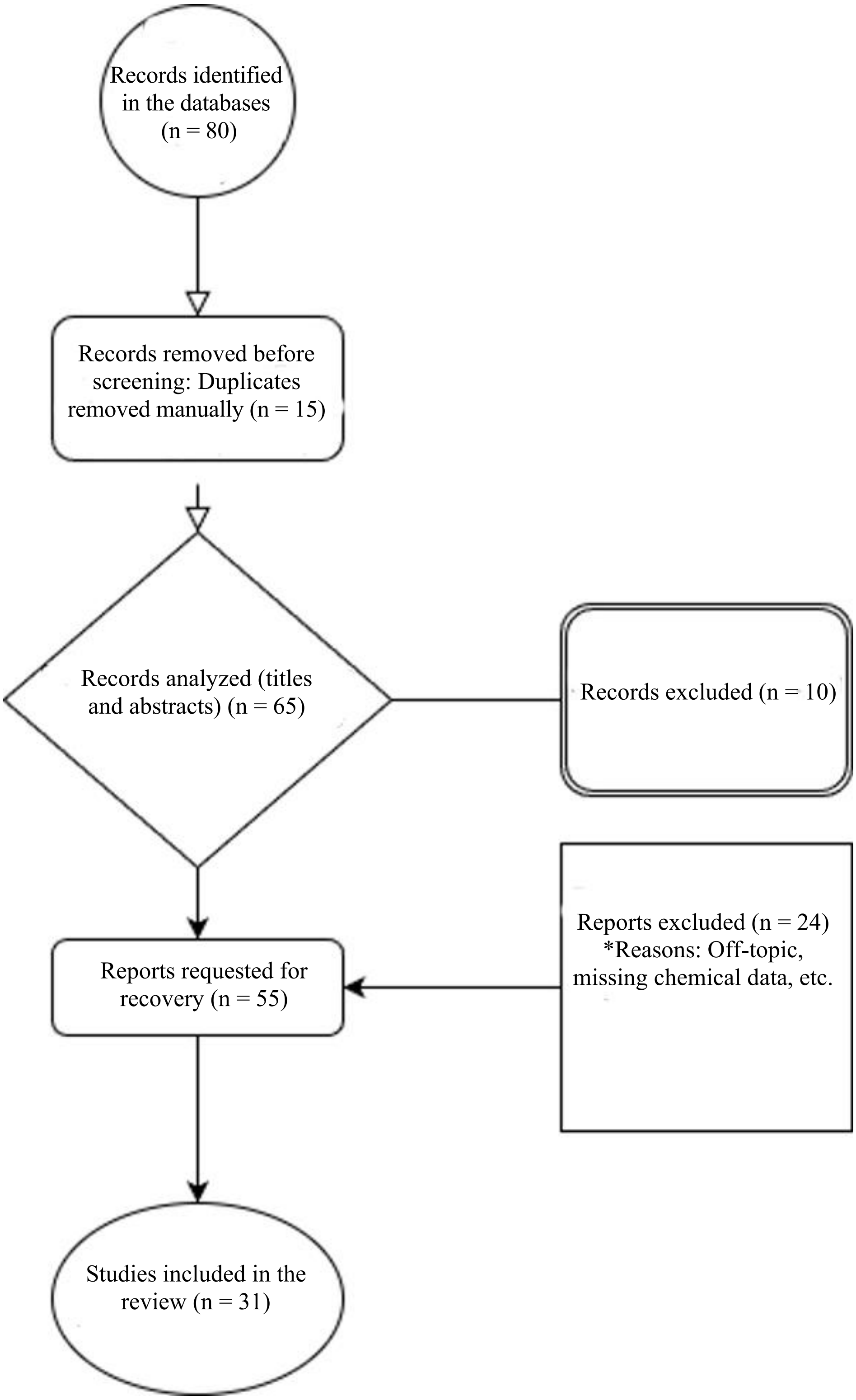

Figure 1. PRISMA flow diagram for study selection.

Search Strategy and Data Sources

The bibliographic survey was conducted in the electronic databases PubMed/MEDLINE, ScienceDirect, SciELO, and Google Scholar. The established time frame comprised publications from January 2005 to November 2025, ensuring the timeliness of the phytochemical and pharmacological data.

For the search, the following Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) were used, combined through the Boolean operators "AND" and "OR":

- *In English:* ("Melaleuca" OR "*Melaleuca alternifolia*" OR "Tea Tree Oil") AND ("Phytochemistry" OR "Essential Oil") AND ("Antimicrobial" OR "Antifungal" OR "Antiviral" OR "Antioxidant" OR "Mechanism of Action").

Eligibility Criteria (Inclusion and Exclusion)

The selection of studies followed strict criteria to ensure methodological quality:

- *Inclusion Criteria:* Included were original experimental articles (*in vitro* and *in vivo*), clinical trials, systematic reviews, and technical reports that addressed the correlation between *Melaleuca*'s phytochemistry and its biological activities. Studies published in English, Portuguese, and Spanish were considered.
- *Exclusion Criteria:* Excluded were duplicates, editorials, opinion articles without experimental basis, studies that did not identify the botanical species or the chemical composition of the oil, and publications outside the established time frame.

Study Selection and PRISMA Flow

The study selection followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA). The initial search in the electronic databases identified a total of 80 references. Subsequently, manual identification and removal of duplicates (n = 15) were performed, resulting in 65 articles for the screening stage.

In the screening phase, based on reading titles and abstracts, 10 studies were excluded for not directly addressing the relationship between phytochemistry and biological activity or for being outside the thematic scope. The remaining 55 articles were submitted to full-text reading for eligibility assessment. At this stage, 24 studies were excluded for not meeting the inclusion criteria (e.g., lack of clear data on the mechanism of action or undefined chemical composition). At the end of the process, 31 articles were selected to compose the final sample of this integrative review.

Illustration of Chemical Structures

The graphical representations of the molecular structures of the phytochemical compounds addressed in this review (Figures 1 to 6) were prepared with the aid of the molecular drawing software ChemDraw Professional (version 25.0, PerkinElmer Informatics, Waltham, MA, USA). The drawing of the structures followed chemical representation standards to ensure the accuracy and clarity of the structural information.

DEVELOPMENT

Chemical Characteristics of *Melaleuca*

The chemical composition of *Melaleuca*, especially *Melaleuca alternifolia*, is largely dominated by volatile compounds such as monoterpenes, sesquiterpenes, and their oxygenated derivatives. Studies show that the essential oil can contain over 100 chemical compounds, with 80–90% corresponding to monoterpenes with high pharmacological activity [10].

The most important component is terpinen-4-ol, present between 30 and 48% of the essential oil, according to the parameters established by the ISO 4730 standard (Oil of *Melaleuca* – terpinen-4-ol type) [11]. This compound is considered the main agent responsible for the oil's antimicrobial and antifungal action [12].

Other relevant compounds include:

- γ-terpinene (10–28%).
- α-terpinene (5–13%).
- 1,8-Cineole (eucalyptol) (up to 15%).

- α-terpineol.
- α-pinene.
- linalol.
- p-cymene.
- sabinene [7, 12].

In addition to volatile compounds, species – such as *M. Quinquenervia* – present a rich quantity of polyphenols, ellagitannins, flavonoids, phenolic acids, and triterpenic derivatives, which further expand the plant's therapeutic potential [13].

Molecular structure of terpinen-4-ol (Figure 2), the main oxygenated monoterpene present in *Melaleuca alternifolia* essential oil. The molecule features a carbocyclic ring with alcoholic substituents and methyl groups, conferring a high lipophilic character. *Source:* Developed by the author (2025).

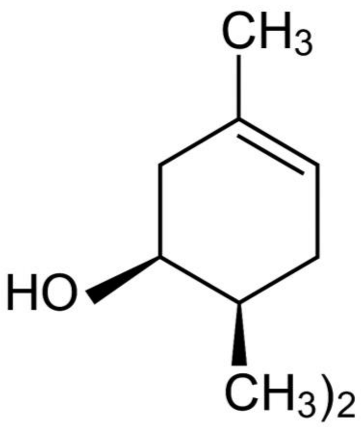

Figure 2. Chemical structure of terpinen-4-ol.

Terpinen-4-ol is a monocyclic monoterpene with an alcohol group attached to the ring, increasing its ability to interact with microbial cell membranes, promoting structural rupture and loss of cellular integrity.

Oxygenated monoterpene molecule with an epoxide ring, widely associated with expectorant, antimicrobial, and inflammation-modulating action.

1,8-Cineole (also known as eucalyptol) (Figure 3) is an oxide monoterpene with the molecular formula $C_{10}H_{18}O$. Its chemical structure consists of an oxirane ring (epoxide) fused to a cyclohexane ring, forming a bicyclic skeleton. It is a colorless, volatile liquid with a characteristic eucalyptus aroma, widely found in the essential oils of plants such as eucalyptus.

Monoterpene hydrocarbon of the cyclic terpene class, responsible for some of the antioxidant and antimicrobial properties of the essential oil.

γ-Terpinene (Figure 4) is a cyclic monoterpene with the molecular formula $C_{10}H_{16}$. Its chemical structure consists of a cyclohexene ring with two double bonds (positions 1 and 4) and two methyl groups attached to positions 4 and 6 of the ring. It is an unsaturated hydrocarbon, an oily liquid, found in the essential oils of various plants Monoterpene alcohol present in various species of the genus, with significant antifungal and anti-inflammatory action.

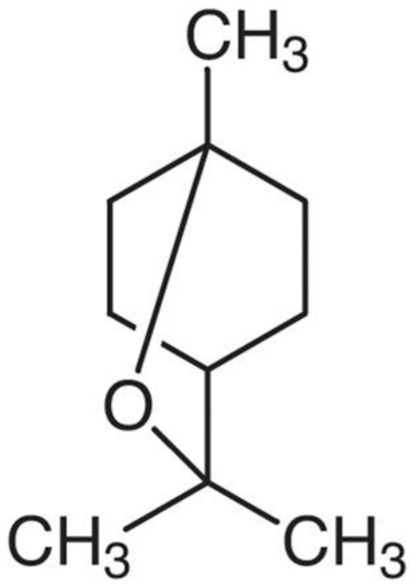

Figure 3. Chemical structure of 1,8-cineole (eucalyptol).

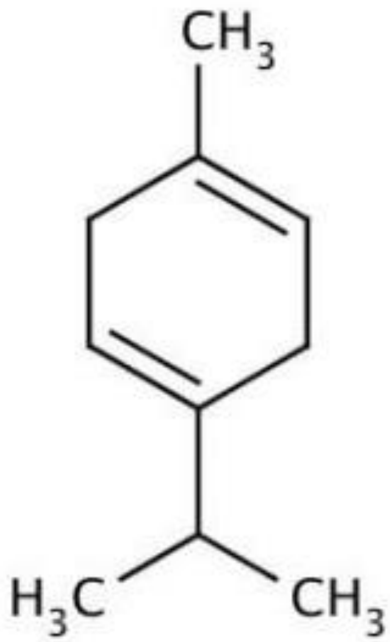

Figure 4. Chemical structure of γ-terpinene.

α-Terpineol is a cyclic monoterpenol (Figure 5) with the molecular formula $C_{10}H_{18}O$. Its chemical structure consists of a cyclohexene ring with a hydroxyl group (–OH) attached to carbon 1 and an isopropyl group attached to carbon 4 of the ring. It has a double bond between carbons 1 and 2. It is an oily, colorless liquid with a floral aroma and is found in the essential oils of various plants. Aromatic monoterpene related to antimicrobial activity and modulation of cell membrane permeability.

–Cymene (Figure 6) is an aromatic hydrocarbon (monoterpene) with the formula $C_{10}H_{14}$, featuring a benzene ring substituted with a methyl group ($–CH_3$) at the para position and an isopropyl group ($–CH(CH_3)_2$) also at the para position.

Bicyclic monoterpene associated with anti-inflammatory and antioxidant activity.

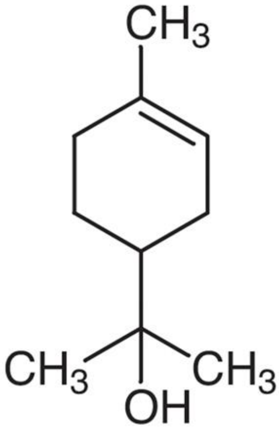

Figure 5. Chemical structure of α-terpineol.

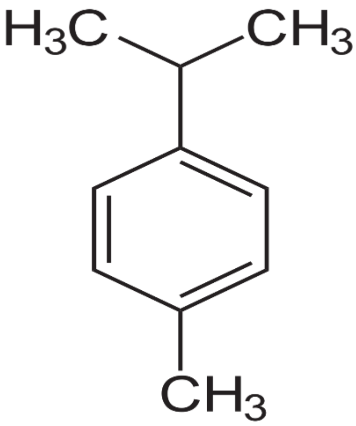

Figure 6. Chemical structure of p-cymene

Sabinene (Figure 7) is a bicyclic monoterpene with the formula $C_{10}H_{16}$, featuring a cyclobutane ring fused to a cyclopentene ring and an exocyclic double bond attached to a methylene group (=CH_2).

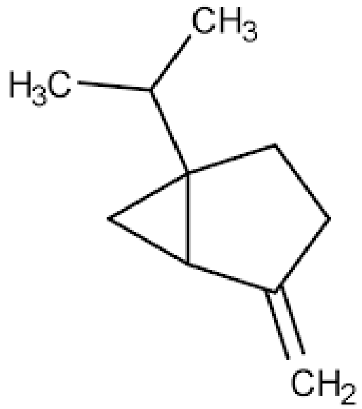

Figure 7. Chemical structure of sabinene.

Inserção Dos Flavonoides E Polifenóis

Melaleuca quinquenervia (or *M. quinquenervia*) is a shrub species belonging to the genus *Melaleuca* (Myrtaceae family), native to tropical and subtropical regions of Australia and parts of Oceania. The plant is characterized by alternate, simple, lanceolate to oblong leaves, with five prominent longitudinal veins – hence the epithet "quinquenervia" ("five-nerved").

The leaves are generally leathery, dark green on the adaxial surface and lighter on the abaxial surface, covered by glandular trichomes that store essential oils. The inflorescences are axillary or terminal spikes, composed of small white or creamy, hermaphroditic flowers, with numerous long stamens that give the bloom a "pom-pom" appearance. The fruit is a woody capsule that opens, releasing small winged seeds.

From a phytochemical perspective, *M. quinquenervia* is rich in essential oils, predominantly compounds, such as 1,8-cineole (eucalyptol), α-terpineol, terpinen-4-ol, and sabinene, which confer antimicrobial, anti-inflammatory, and antioxidant properties. These constituents are explored in traditional medicinal applications, the perfumery industry, and as an ingredient in hygiene products.
The species adapts to sandy or clay soils, often found in coastal areas, alluvial plains, and forest edges. It tolerates moderate salinity conditions and periods of drought, thanks to its efficient water regulation and the ability to resprout after fires or cutting.

Importance and Uses

Traditionally, indigenous communities use the leaves and bark of *M. quinquenervia* in the treatment of colds, respiratory infections, and skin wounds. In the pharmaceutical industry, the essential oils are studied for their biological activities, while in agronomy, the plant is employed in programs for the recovery of degraded areas due to its hardiness and capacity for nitrogen fixation in the soil.

Figure 8 Representation of the main phenolic compounds responsible for the antioxidant, antiviral, and anti-inflammatory properties of this species such as catechins, epigallocatechin gallate, and tannin derivatives.

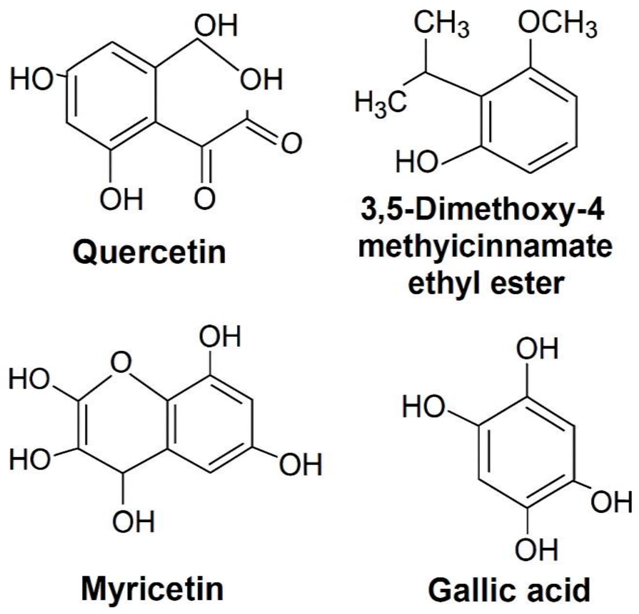

Figure 8. Chemical structures of flavonoids and polyphenols present in *M. quinquenervia*.

- *Flavonoids:* Compounds derived from the basic structure of 2-phenyl-chromone (15 carbons – C6-C3-C6), with variations such as flavones (e.g., luteolin), flavonols (e.g., quercetin), and flavanones. They possess phenolic hydroxyls that contribute to their antioxidant activity.
- *Polyphenols:* Molecules containing multiple hydroxyl groups attached to aromatic rings; they include phenolic acids (e.g., gallic acid, caffeic acid) and tannins (polymers of phenolic units). In *M. quinquenervia*, mainly phenolic acids and flavonoid derivatives with antioxidant and anti-inflammatory activity are identified.

Pharmacological Properties of *Melaleuca*

The available scientific literature demonstrates that *Melaleuca* possesses a broad spectrum of therapeutic properties, which vary according to its chemical constituents.

Antimicrobial Activity

The antimicrobial activity of *Melaleuca* is based on biochemical and structural processes that directly affect the microbial cell. The composition rich in oxygenated monoterpenes – mainly terpinen-4-ol, 1,8-cineole, α-terpineol, and γ-terpinene – allows these molecules to act as lipophilic agents capable of deeply penetrating the cytoplasmic membrane of bacteria and fungi, triggering the progressive destabilization of the phospholipid bilayer [14].

The diffusion of these molecules through the membrane alters the organization of phospholipids, increases lipid fluidity, and induces deformations that compromise the cell's physical stability. Following the insertion of terpenes, transient pores are formed, facilitating the leakage of essential constituents, including ions (K^+, Mg^{2+}), nucleotides, proteins, and internal metabolites. The efflux of these components results in loss of osmolarity, membrane depolarization, and failure to maintain the electrochemical gradient necessary for active transport and ATP synthesis, leading to cellular energy collapse [15].

The antimicrobial effect of *Melaleuca* constituents is also associated with the inhibition of fundamental processes for maintaining cell structure. Compounds – such as 1,8-cineole and α-terpineol – interfere with the organization of proteins involved in cell wall synthesis, impairing the polymerization of peptidoglycan in Gram-positive bacteria and the integrity of lipopolysaccharides in Gram-negative bacteria. This blockage compromises cell division, produces aberrant cells, and accelerates bacterial death [16].

In addition to structural damage, the antimicrobial action of *Melaleuca* includes mechanisms related to energy and respiratory metabolism. Membrane disorganization leads to the interruption of electron flow in the microbial respiratory chain, reducing oxidative phosphorylation and drastically decreasing intracellular ATP levels. This respiratory collapse intensifies cellular damage by favoring the accumulation of toxic intermediates and reactive oxygen species (ROS), which participate in the oxidation of proteins, lipids, and genetic material [17].

Biochemical evidence shows that polyphenols present in species – such as *M. quinquenervia* and *M. Styphelioides* – intensify this effect, as their phenolic groups favor controlled oxidation reactions, increasing the formation of superoxide radicals, peroxides, and highly reactive derivatives that affect vital structures of microorganisms [18]. This mechanism contributes to progressive oxidative stress within microbial cells, amplifying the lethal effects initiated by membrane perturbation.

Melaleuca also interferes with bacterial communication processes. Oxygenated monoterpenes reduce the expression of signaling molecules associated with quorum sensing, a mechanism essential for coordinating virulence, biofilm formation, and antimicrobial resistance. The reduction in the chemical density of quorum sensing facilitates the destruction of microbial colonies, reduces biofilm formation, and increases the susceptibility of pathogens to natural agents [19].

Microbiological tests reviewed in the period from 2005 to 2025 demonstrate that these convergent actions explain the efficacy of *Melaleuca* against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Propionibacterium acnes*, among other clinically relevant microorganisms [20]. The breadth of action was also observed in fungi, such as *Candida albicans* and *Trichophyton rubrum*, proving that antifungal activity follows similar cellular principles, with predominant involvement in membrane destruction and oxidative stress.

The integration of these mechanisms confirms that the antimicrobial effect of *Melaleuca* does not depend on a single pathway, but on the synergistic combination of structural perturbation, metabolic destabilization, respiratory interference, and induction of oxidative damage. This characteristic strengthens the use of the plant as a broad-spectrum phytomedicine and supports its application in the development of medicinal, cosmetic, and therapeutic formulations aimed at controlling bacterial and fungal infections of low, medium, and high complexity.

Antifungal Activity

The antifungal activity of *Melaleuca alternifolia* essential oil results from a complex interaction between its bioactive monoterpenes – mainly terpinen-4-ol, α-terpineol, and 1,8-cineole – and fundamental cellular structures of pathogenic fungi. The literature shows that these compounds exhibit multifactorial mechanisms of action, capable of simultaneously affecting the cytoplasmic membrane, cell wall, cytoskeleton, and essential intracellular processes for fungal survival [21].

The monoterpenes present in *Melaleuca* have high lipophilic affinity, which facilitates their penetration into the fungal lipid bilayer. This interaction promotes the structural disorganization of ergosterol – the predominant sterol in the fungal membrane – altering the membrane's fluidity, permeability, and stability. This process triggers the leakage of essential ions, compromising osmotic homeostasis, and eventual cell lysis. The mechanism is functionally analogous to that observed in polyenes, like amphotericin B, described in the literature as agents capable of generating "areas of tension" in the membrane by interacting with ergosterol [22].

In addition to direct action on the membrane, the essential oil interferes with the integrity of the fungal cell wall. Based on the structural model presented by Odds et al. (2003), it is observed that *Melaleuca* components destabilize the synthesis and organization of β-1,3-glucans, β-1,6-glucans, and chitin, which are determining elements for the rigidity and functionality of the cell wall [23]. The alteration of these metabolic pathways compromises morphological stability and cell division capacity, primarily affecting *Candida* genus yeasts and dermatophytes like *Trichophyton rubrum*.

Another relevant mechanism concerns interference with microtubules and cytoskeleton dynamics. Natural compounds can affect tubulin polymerization and block the formation of the mitotic spindle, a process similar to that observed with griseofulvin. Recent data suggest that *Melaleuca* monoterpenes can induce mitotic blockage, impairing replication and cell budding, contributing to the antifungal action against *Candida albicans* and *Aspergillus* species.

The induction of reactive oxygen species (ROS) is another critical factor in antifungal activity. The excessive production of ROS leads to the oxidation of membrane lipids, damage to structural proteins, and irreversible alterations in DNA. This phenomenon results in apoptosis or cell necrosis mediated by mitochondrial dysfunction, enhancing the efficacy of *Melaleuca* against resistant fungi, such as *Candida krusei* and *Fusarium* spp.

Additional studies show that *Melaleuca* exhibits relevant fungicidal activity against agricultural pathogens, such as *Macrophomina phaseolina*, *Colletotrichum gloeosporioides*, and *Fusarium* spp., acting as a sustainable alternative to conventional fungicides, mainly through the alteration of cell permeability and interruption of mycelial growth [24].

Thus, the antifungal activity of *Melaleuca* is characterized by a multifaceted profile, involving membrane-lytic actions, inhibition of cell wall synthesis, mitotic blockage, and induction of oxidative stress, conferring it a broad spectrum of action and therapeutic relevance.

Antioxidant Activity

The antioxidant activity of Melaleuca is attributed to the presence of phenolic compounds, flavonoids, and monoterpenes with free radical scavenging properties. Evidence indicates that components, such as terpinen-4-ol, γ-terpinene, and α-terpineol, exert significant antioxidant action through hydrogen transfer (HAT) and electron transfer (SET) mechanisms, biochemical processes essential for the stabilization of reactive molecules [25].

The antioxidant compounds in Melaleuca act by interrupting lipid peroxidation, a degenerative process responsible for structural damage to cell membranes. This effect occurs through the neutralization of peroxyl and hydroxyl radicals, limiting the formation of malondialdehyde (MDA) and other toxic byproducts. The reduction of these biomarkers is frequently associated with tissue protection in inflammatory and infectious environments.

In addition, the essential oil demonstrates the ability to modulate cytokine-mediated inflammatory pathways. The study by Rios JL (2016) [26] highlights that natural antioxidants have the potential to reduce the expression of TNF-α, IL-1β, and IL-6, cytokines involved in systemic and local inflammation. Melaleuca's modulating action on this signaling contributes to its application as an anti-inflammatory and healing agent.

Another antioxidant mechanism includes the ability to chelate pro-oxidant metal ions, such as Fe^{2+} and Cu^{2+}, preventing Fenton reactions and the subsequent formation of highly reactive hydroxyl radicals. By limiting these reactions, Melaleuca protects biomolecules, such as DNA, lipids, and proteins, against oxidative damage.

Additional protective effects include stabilization of cellular enzymes, prevention of DNA double-strand breaks, and decreased protein carbonylation. These reinforce the properties of Melaleuca's importance as a source of natural antioxidants, contributing to its effectiveness in healing processes, dermal protection, and modulation of oxidative stress in infections.

Thus, the antioxidant activity of Melaleuca involves combined mechanisms of radical neutralization, cytokine modulation, metal chelation, and biomolecular protection, justifying its therapeutic use in inflammations, infections, and degenerative processes [27].

Antiviral Activity

The antiviral activity of Melaleuca essential oil has been extensively investigated in studies involving medicinal plants with antimicrobial and antioxidant actions. The antiviral mechanism involves a combination of direct effects on viral structure and modulation of the host immune response, as highlighted by Schein JE, et al. (2002) [28].

The monoterpenes present in Melaleuca have an affinity for the lipid membrane of enveloped viruses, promoting the destabilization of the envelope and reducing viral structural integrity. This disorganization prevents the fusion of the viral envelope with the host cell membrane, a mechanism necessary for the entry of viruses such as HSV-1, HSV-2, influenza, and coronavirus. Thus, the essential oil acts as a physical and chemical blocker of the initial infection process.

In addition to inhibiting viral entry, evidence indicates that compounds from Melaleuca may impair intracellular replication. This effect occurs through interference with viral polymerases and modification of the intracellular environment, hindering the synthesis of structural proteins and enzymes essential for the replicative cycle. The oil's ability to alter the cellular redox state also contributes to viral inactivation, since moderately high levels of ROS can damage viral RNA or DNA genomes.

Another relevant mechanism involves the modulation of the immune response. The antioxidant and anti-inflammatory compounds of Melaleuca are able to stimulate the production of type I interferon (IFN-α and IFN-β), proteins fundamental to the initial antiviral response. This stimulation increases the activity of NK cells and macrophages, intensifying the elimination of viral particles and infected cells.

The combination of direct damage to the viral envelope, blockage of entry, replicative interference, and immunomodulation explains the effectiveness of Melaleuca against enveloped viruses and its application in cutaneous, respiratory, and mucosal infections. This set of mechanisms reinforces the relevance of the essential oil as a broad-spectrum natural antiviral agent, with potential for topical use in viral dermatoses and as a complementary therapeutic support.

RESULTS AND DISCUSSION

A review of publications between 2005 and 2025 shows that species of the genus Melaleuca possess a robust set of pharmacological properties attributed mainly to their monoterpenes and phenolic compounds. An integrated analysis of the studies demonstrates that the plant presents multiple convergent and synergistic biochemical mechanisms, which explain its broad spectrum of action in biological systems. The predominant presence of lipophilic molecules, such as terpinen-4-ol, 1,8-cineole, γ-terpinene, α-terpineol, p-cymene and sabinene, associated with flavonoids and polyphenols, supports the diversity of observed effects [1–21].

Antimicrobial Activity – Critical Synthesis of Findings

The antimicrobial action of *Melaleuca* is consistently reported as one of its most prominent functions. The literature demonstrates that its monoterpenes exert direct effects on the bacterial membrane, causing:

- disorganization of the phospholipid bilayer,
- formation of transient pores,
- loss of essential ions,
- cellular depolarization and energy collapse.

The ability of monoterpenes to cross membranes and interfere with the respiratory chain contributes to the inhibition of ATP production, leading to cell death. The induction of reactive oxygen species (ROS) amplifies this process, causing the oxidation of proteins, lipids, and nucleic acids.

These findings are consistent across Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* [29], reinforcing the use of *Melaleuca* as a broad-spectrum antimicrobial agent.

The body of evidence indicates that the essential oil does not have a single molecular target, but a multisystemic action that hinders the development of bacterial resistance. This gives the phytomedicine relevance for topical use in skin infections and as a complementary agent to conventional antibiotics.

ANTIFUNGAL ACTIVITY – IN-DEPTH ANALYSIS OF MECHANISMS

The antifungal activity reveals an equally multifaceted profile. The essential oil primarily interacts with the ergosterol of the fungal membrane, modifying its fluidity and stability. According to Albouchi F, et al. (2018) [30], alterations in ergosterol lead to structural fragility, increased permeability, and cytoplasmic leakage [11].

Furthermore, evidence suggests that *Melaleuca* interferes with cell wall synthesis, destabilizing β-1,3-glucans and chitin, which weakens the cellular structure and compromises fungal division and growth. The possible interference with microtubules and tubulin polymerization suggests a complementary mechanism similar to that observed in antifungals like griseofulvin [31].

The induction of intracellular ROS, verified in different experimental models, contributes to severe oxidative damage and fungal apoptosis. Such effects explain the action against clinically relevant species, such as *Candida albicans*, *C. tropicalis*, *C. krusei*, and dermatophytes, in addition to important phytopathogens like *Fusarium* and *Colletotrichum* [32].

The multi-target nature of *Melaleuca* strengthens its applicability in resistant fungal infections, especially in dermatomycoses and recurrent candidiasis.

ANTIOXIDANT ACTIVITY – BIOCHEMICAL INTERPRETATION AND THERAPEUTIC IMPLICATIONS

The monoterpenes and phenolic compounds of *Melaleuca* exhibit potent antioxidant activity based on Hydrogen Atom Transfer (HAT) and Single Electron Transfer (SET) mechanisms, confirmed by chemical and biochemical studies [33]. These processes neutralize free radicals, such as superoxide, peroxides, and hydroxyl radicals, interrupting chain reactions responsible for lipid peroxidation.

In addition to direct radical neutralization, the chelating capacity of pro-oxidant metal ions prevents Fenton reactions, significantly reducing cellular oxidative stress. The positive modulation of inflammatory cytokines suggests a complementary anti-inflammatory effect that explains the use of *Melaleuca* oil in:

- cutaneous wound healing,
- inflammation control,
- reduction of irritative processes,
- antioxidant support in the presence of infections.

Thus, the antioxidant action of *Melaleuca* acts both in host cell protection and as a modulator of the microenvironment during infectious processes.

ANTIVIRAL ACTIVITY – SYNTHESIS AND CRITICAL DISCUSSION

The antiviral activity described for *Melaleuca* involves direct mechanisms against enveloped viruses and the modulation of the innate immune response. Monoterpenes associate with the viral lipid envelope, causing:

- structural destabilization,
- loss of fusion capacity,
- inactivation of the viral particle.

These mechanisms have been observed in studies involving HSV-1, HSV-2, influenza virus, and *in silico* models that evaluate interactions with proteins related to SARS-CoV-2 [34].

In addition to direct inactivation, the antioxidant and immunomodulatory compounds of *Melaleuca* stimulate the production of type I interferons, intensifying the antiviral response. This dual effect – direct damage to the viral structure and strengthening of the immune response – suggests that *Melaleuca* has potential for topical use in herpetic lesions and as an adjuvant in mild cutaneous and respiratory viral infections.

General Considerations and Scientific Implications

The integration of the findings demonstrates that *Melaleuca* presents a complex and multifunctional pharmacological profile, with effects attributed to a combination of biochemical and cellular mechanisms. This multiplicity of targets explains:

- efficacy against resistant pathogens,
- clinical relevance in skin infections,
- broad therapeutic applicability,
- and the growing interest from the pharmaceutical and cosmetic industries.

The reviewed data suggest that *Melaleuca* is a promising source of bioactive compounds, justifying further clinical studies and integrative therapeutic approaches.

CONCLUSION

A review of scientific evidence published between 2005 and 2025 confirms that species of the genus Melaleuca represent a relevant source of bioactive compounds with broad therapeutic potential. The analyzed results demonstrate that the phytochemical complexity of the plant – composed mainly of monoterpenes, such as terpinen-4-ol, 1,8-cineole, γ-terpinene, α-terpineol, p-cymene, and sabinene, in addition to flavonoids and polyphenols – is directly related to the diversity of its pharmacological effects.

The observed antimicrobial, antifungal, antioxidant, and antiviral mechanisms show that Melaleuca does not act through a single molecular target, but rather through an integrated network of biochemical and cellular processes. This multipotentiality includes alterations in biological membranes, inhibition of essential metabolic pathways, modulation of the redox state, and stimulation of immune responses. This characteristic gives the essential oil a robust therapeutic profile and hinders the development of resistance by pathogens, highlighting its relevance for the development of phytotherapeutic products for topical and systemic use.

The consistency of the results reinforces the applicability of Melaleuca in clinical conditions of interest, such as superficial bacterial and fungal infections, detected inflammations, herpetic lesions, and disorders associated with oxidative stress. However, even with consolidated laboratory and preclinical evidence, there are still significant gaps in the literature, especially regarding the standardization of concentrations, broad-spectrum clinical validation, and the assessment of long-term safety in controlled human studies.

Thus, the body of proven information confirms that Melaleuca constitutes a promising therapeutic alternative, especially in the areas of dermatology, phytomedicine, and natural products. However, it is recommended that planned clinical studies, in-depth toxicological evaluations, and investigations into synergies between its chemical constituents be carried out to consolidate its therapeutic application with greater scientific precision. This article contributes to the integration of molecular mechanisms, experimental evidence, and the phytochemical basis of the species, providing solid support for future research and the rational development of phytotherapeutic formulations based on Melaleuca.

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