International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

Tea Tree Oil (*Melaleuca Alternifolia*): A Comprehensive Review of Phytochemistry, Pharmacological Activities, Therapeutic Applications and Safety Consideration.

Sonawane Harshada
Sonawane Vijay, Solunke Suresh, Shendge Sujit
Dattakala college of pharmacy daund (pune) affiliated with savitribai phule pune university

Date of Submission: 12-10-2026 Date of Acceptance: 24-10-2026

ABSTRACT
Tea tree, which is known as Melaleuca alternifolia and is a member of the Myrtaceae family, is a principal source of tea tree oil (TTO), a complex essential oil made up of more than 100 volatile compounds. The main components of this oil are terpinen-4-ol, γ-terpinene, α-terpinene and 1,8-cineole. The present review looks at the botanical characteristics, the methods of cultivation, the ways in which it is extracted, its phytochemical composition, the quality standards, the pharmacological actions, the therapeutic uses, the mechanisms of action, the formulations, safety and the clinical evidence relating to TTO. Experimental research has shown that TTO possesses antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant and antiparasitic properties, the mechanisms involved being membrane disruption and the modulation of inflammatory mediators. It has been studied as a treatment for acne, dandruff, seborrheic dermatitis, superficial fungal infections, minor skin infections, wound care and oral health. Traditional formulations consist of creams, gels, ointments, lotions and mouthwashes, whereas more advanced systems such as nanoemulsions, nanogels, hydrogels and encapsulated formulations are designed to enhance stability, delivery and therapeutic effectiveness. In preclinical and clinical studies, promising results have been obtained in certain applications. Yet the differences in chemical composition, chemotype, concentration, formulation and the methods used in the studies make it difficult to compare the results. Concerns regarding safety involve skin irritation, allergic sensitization and toxicity when taken by mouth. Further research is required in order to deal with standardization, optimize the dose, examine long-term safety, carry out mechanistic validation and conduct high-quality clinical trials. Future studies should concentrate on standardized preparations, advanced delivery systems and combination therapies if safe, reproducible and evidence-based therapeutic uses of TTO are to be established.

KEYWORDS: *Melaleuca alternifolia*; tea tree oil; terpinen-4-ol; essential oil; pharmacological activities; antimicrobial activity

I. 1.INTRODUCTION

Tea tree oil is made up of approximately 100 different components, most of which are monoterpenes, sesquiterpenes and alcohols derived from these (Carson, Hammer, and Riley 2006a). The chemical makeup of tea tree oil is well established, and the international standard ISO 4730 for Melaleuca oil, specifically the terpinen-4-ol type (i.e. tea tree oil), includes a chromatographic profile that specifies the minimum and maximum percentage levels for 14 different components (Nguyen, Nguyen, and Nguyen 2026a). The three principal components—terpinen-4-ol, c-terpinene and a-terpinene—make up about 70% of the oil, whereas other components such as q-cymene, terpinolene, a-terpineol and a-pinene account for about 15% (Nguyen, Nguyen, and Nguyen 2026b) . Since there is very little information available regarding the antifungal effects of the various components of tea tree oil, the present study was conducted with the aim of investigating the *in vitro* susceptibility of a number of medically important fungi to these components, employing a range of investigative methods (Hammer, Carson, and Riley 2003).

Melaleuca alternifolia (Maiden and Betche)
Cheel is an evergreen tree species native to Australia and belongs to the Myrtacedefamily . This species

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

is recognized as the primary source of tea tree oil (TTO), an essential oil extracted from the leaves of the tree through a process called steam distillation ((PDF) Tea Tree (Melaleuca alternifolia (Maiden & Betche) Cheel) Oil an important medicinal essential oil 2026).

The Aboriginal communities have traditionally used this plant as part of remedies .In recent years, there has been growing interest in using TO as a natural antimicrobial agent in health and personal care products, especially as a possible alternative to synthetic antimicrobials currently used (Turpin et al. 2022) .

(Masyita et al. 2022).

The oil can be classified into one of six

Chemotypes , which can be distinguished using gas chromatography .The main components of the oil include terpinen-4-ol, alphaterpinene, gamma-terpinene , and 1,8-cineole. The percentage of each component varies depending on the chemotype of the oil (Borotová et al. 2022a). An international standard has been established asa guideline for the major constituents in commercially available TTO: 30% 48% terpinen-4-ol, 5% -13% alpha-terpinene, 10% 28% gamma-terpinene, trace amounts to 15% 1,8-cineole, and 1.5% 5% terpinolene(Enzyme-assisted polysaccharides extraction from Calocybe indica: Synergistic antibiofilm and oxidative stability of essential oil nanoemulsion | Request PDF n.d.).

Terpinen-4-ol, the main component in TTO, is highly valued due to its reported strong antimicrobial and anti-inflammatory properties. Alpha-terpinene, gamma-terpinene, and 1,8-cineole have also been found to affect bacterial growth and, to a lesser extent, fungal growth(Mondello et al. 2006) .

Currently, TTO is used in creams and topical treatments at concentrations ranging from 1% to 10% (semisolid oil-water emulsion) (Bao and Burgess 2018).

The inclusion of TTO in personal care products is intended to reduce dependence on synthetic antimicrobials currently in use . One such antimicrobial agent is the paraben family(Caioni et al. 2023) .

II. BOTANICAL PROFILE

Parameter	Description
Common name	Tea tree
Common synonym	Australian tea tree
Botanical name	*Melaleuca alternifolia* (Maiden &Betche) Cheel
Family	Myrtaceae
Genus	*Melaleuca*
Plant type	Evergreen shrub or small tree
Origin	Australia
Distribution	Mainly eastern Australia; cultivated in other regions for essential-oil production
Plant height	Generally up to about 7 m, depending on growing conditions
Stem/Bark	Woody; bark characteristically papery and layered
Leaves	Narrow, linear to lanceolate, aromatic, rich in oil glands
Flowers	Small, white to cream-coloured flowers, typically arranged in spikes
Fruit	Small woody capsules containing numerous seeds
Essential oil	Obtained mainly from the leaves and terminal branches by steam / hydrodistillation
Oil appearance	Usually clear to pale yellow liquid
Characteristic Odour	Strong, fresh, medicinal/terpenic aroma
Major constituents	Terpinen-4-ol, γ-terpinene, α-terpinene, α-terpinolene, 1,8-cineole and other monoterpenes
Traditional uses	Topical applications for minor skin conditions, wounds and infections
Common contemporary uses	Cosmetic, personal-care and topical formulations
Important consideration	Composition varies with plant material, geographical origin, cultivation, harvesting and processing conditions

(Tea Tree Oil Laboratory Guidance Document n.d.)

2.1 BOTANICAL DISCRIPTION

Melaleuca alternifolia is an evergreen aromatic shrub or small tree belonging to the family Myrtaceae(Borotová et al. 2022b). The species is native to Australia and is particularly associated

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

with wet or swampy environments in parts of New South Wales and Queensland . Its narrow aromatic leaves contain numerous secretory structures responsible for the production of the essential oil(Barbosa 2013) .

The flowers are generally white or cream coloured and occur in characteristic cylindrical or spike-like inflorescences. Following flowering, small woody capsules develop and contain numerous tiny seeds(Shepherd et al. 2020) .The combination of its narrow aromatic leaves, papery bark and distinctive flower clusters assists in botanical identification(Paparella et al. 2022) .

2.2GEOGRAPHICAL DISTRIBUTION

Tea tree, which is *Melaleuca alternifolia,* is native to Australia and is found naturally in lowlying, swampy, subtropical coastal areas along the Clarence and Richmond Rivers in northeastern New South Wales and in southern Queensland (Carson, Hammer, and Riley 2006b). Unlike some of the other species in the Melaleuca genus, *M. alternifolia* does not occur naturally outside of Australia (Carson, Hammer, and Riley 2006c). In the past, tea tree oil was taken from wild stands of the plant that produced the correct chemotype. As commercial demand increased, cultivation gradually moved from the wild bush stands to planned plantations (Carson, Hammer, and Riley 2006d). Commercial plantations were set up in the 1970s and 1980s, which enabled mechanised cultivation and the production in larger quantities of a product of consistent quality. Today, tea tree plantations are located in Western Australia, Queensland and New South Wales, with the greatest number of them situated in the Lismore area of New South Wales (Creating a viable farm forestry industry in Australia. What will it take? n.d.). The commercial plants are usually grown from seedlings in greenhouses before being transplanted into the fields at a high density. The first harvest is generally achieved within 1 to 3 years, the exact time depending on the climatic conditions and the rate of plant growth(Proietti et al. 2022) .

2.3CULTIVATION & HARVESTING

The oil is primarily made by steam distilling the leaves and young terminal branches.TTO was made from natural plant growth in bush areas, which are believed to be *M.alternifolia,* and these plants produced oil with the correct chemical type (Carson, Hammer, and Riley 2006e).The plant material was manually cut and usually distilled right there using simple, portable, wood-burning stills set up in the bush.The native area of *M.alternifolia* is low-lying, swampy, subtropical coastal land near the Clarence and Richmond Rivers in northeastern New South Wales and southern Queensland.Unlike many other Melaleuca species, it does not grow naturally anywhere else in the world.The plant material was manually cut and often distilled on the spot using makeshift, mobile, wood-fired stills.The industry operated this way for many years (Carson, Hammer, and Riley 2006f) .

Changes in the concentration, composition, and yield of oil in coppice growth of tea tree (*Melaleuca alternifolia)* were assessed when plants were harvested in different months (Variation in oil concentration and economic return from tea-tree (Melaleuca alternifolia Cheel) oil n.d.-a). Oil concentrations in leaves were lower when plants were harvested in July-September than in other months, but biomass yields were higher. Consequently, there was no consistent effect of harvest month on oil yield(Park, Garland, and Close 2022) . Oil yield varied as much between the same month in different years, as between months within a year. The oil concentration in one harvest was positively related to the biomass yield at the previous harvest of the same plants, suggesting that a carryover of energy reserves contributed to oil production (Variation in oil concentration and economic return from tea-tree (Melaleuca alternifolia Cheel) oil n.d.-b). The oil concentration was also positively related to the mean air temperatures over the 3 months before harvest (Najafian 2025). The proportion of the economically significant compounds in oil, terpinen-4-01 and 1,8-cineole, was not affected by either the month of harvest or regrowth cycle, but other compounds did change. There was a significant loss of monoterpene olefins from oil which was present at high concentrations (Understanding the role of key metabolic genes, transcription factors, and trichome-related genes in-terms of temperature-stress management techniques in the rose-scented Geranium (Pelargonium graveolens) using transcriptomic analysis | Request PDF n.d.).

III. SOURCE AND EXTRACTION

3.1 PLANT MATERIAL USED:

The essential oil of *Melaleuca* is obtained mainly from the above-ground parts of the plant, especially leaves and terminal branchlets or branches (Carson, Hammer, and Riley 2006g). Although the total above-ground biomass may be utilized in large-scale commercial plantations, the leaves are considered

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

the main source of volatile compounds that give tea tree oil its specific properties (Carson, Hammer, and Riley 2006h). The plant material that may be harvested for oil contains leaves and young terminal branches, and the proportion of foliage to branch material may affect the composition and oil yield of the final product (Çelik 2026). Tea tree oil obtained from the foliage of *M. alternifolia* is characterized by a high content of volatile terpenoids and is used in commercial essential-oil production as the main type of plant material. (Ebrahimi et al. 2026a)

3.2 METHODS OF EXTRATION :

Tea tree oil (TTO) is an essential oil which is obtained primarily from the leaves of *Melaleuca alternifolia*(an overview | ScienceDirect Topics n.d.). The main and commercially used method for producing it is steam distillation; in this process steam takes the volatile components of the oil from the plant material and the vapour is then condensed so that the oil can be separated out from the water phase(an overview | ScienceDirect Topics n.d.). Other techniques such as hydrodistillation, solvent extraction, supercritical fluid extraction, microwave-assisted extraction and ultrasound-assisted extraction have also been studied in order to improve extraction efficiency, selectivity and the preservation of the volatile constituents (Sun et al. 2025).

A. Steam Distillation

The usual commercial process for producing TTO involves exposing fresh leaves and terminal branches to steam, causing the essential-oil components to vaporize (Extraction Methods n.d.-a). The vapour is then condensed and the oil that results is separated out from the aqueous distillate. The amount of oil obtained is typically about 1–2% of the weight of the wet plant material (Extraction of Bioactive Compounds from Medicinal Plants and Herbs | IntechOpen n.d.).

B. Hydrodistillation

In hydrodistillation the plant material is heated directly in the presence of water and the volatile components are given off along with the vapour and are then condensed in order to obtain the essential oil (Extraction Methods n.d.-b). This method has been used in the case of *M. alternifoli*a and is especially useful for extraction on a laboratory scale, even though it is less favoured than steam distillation when it comes to large-scale commercial production (Nabi et al. 2025).

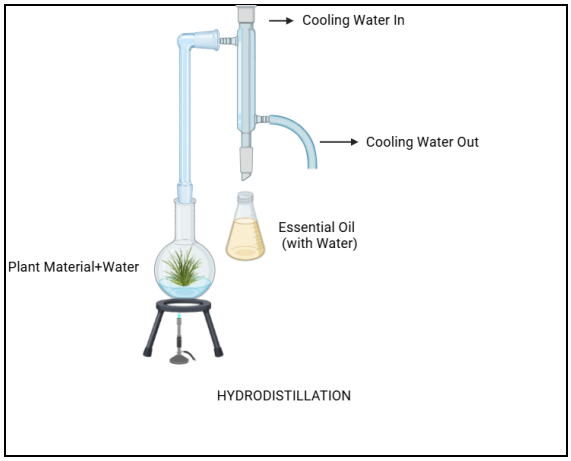

Figure 1hydrodistillation

C. Supercritical Fluid Extraction

Supercritical CO_2 extraction has been looked at as an alternative method for recovering the volatile compounds from *M. alternifolia*; it can do so at fairly moderate temperatures and enables selection during extraction to be controlled by means of both pressure and temperature (de Aguiar et al. 2023). It might thus help to reduce some of the thermal degradation linked with conventional distillation, but it is not the commercially established method for producing TTO (Pandey et al. 2023).

D. Microwave-Assisted Extraction

Microwave-assisted extraction has been looked at as an alternative method for obtaining tea tree oil since microwave energy is able to speed up heating and mass transfer and may therefore reduce the time taken for extraction (Wang et al. 2026). Yet, even with its potential benefits, it has not been adopted by the industry on a commercial scale (Human factors in digital manufacturing technology adoption: a workforce perspective | The International Journal of Advanced Manufacturing Technology | Springer Nature Link n.d.)

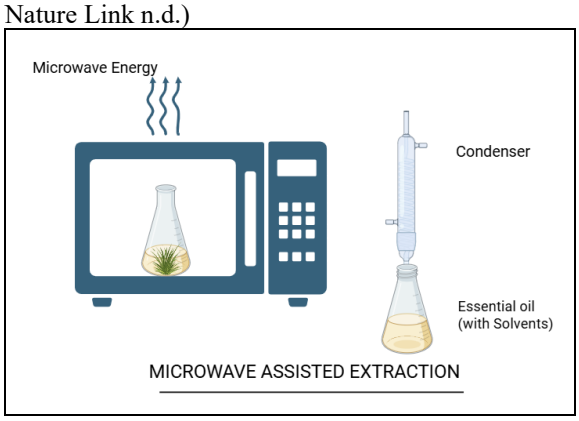

Figure 2 microwave assisted extraction

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

E. Solvent Extraction
Solvent extraction is capable of recovering volatile and other extractable components from plant material, but the extract obtained in this way will not have the same composition as that obtained by conventional steam distillation of TTO (Lee et al. 2024). For this reason, it is more suitable for use in experimental or analytical extraction than in standard commercial TTO production (Bitwell et al. 2023).

3.3 THE FACTORS WHICH INFLUENCE THE QUALITY OF TEA TREE OIL:

The quality and chemical make-up of tea tree oil (TTO) can vary greatly for a number of reasons related to genetic factors, the environment, harvesting, processing and storage (Nguyen, Nguyen, and Nguyen 2026c).
Changes in these factors can affect the concentration of the main components such as terpinen-4-ol, γ-terpinene, α-terpinene , 1,8-cineole and p-cymene, and as a result influence the general quality and properties of the oil (Kačániová et al. 2026).
. The genetic factors and chemotype:
The various chemotypes of *M. alternifolia* yield oils which have different chemical compositions, and the terpinen-4-ol chemotype is especially important for commercial TTO production (Borotová et al. 2022c).
. Geographical and environmental conditions:
The place where a plant comes from, the climate and the conditions under which it grows can affect the relative amounts of the volatile components; oils obtained from plants that are grown .Therefore, their composition will differ if they are harvested in different areas (Kim and Kim 2026).
. The kind of plant material and the age of the leaves:
The chemical make-up of the oil obtained can be influenced by the part of the plant used, the composition of the biomass and the age of the leaves; differences can appear whether the leaves alone, or the leaves together with the branchlets, are processed.4. Harvesting season (Rodrigues et al. 2024):
Seasonal changes can have an effect on the concentration of the volatile components, so the time at which harvesting is done is a significant factor in determining the consistency of the TTO (Karka and Kesen 2026).
. Extraction conditions:
The method used for extracting the oil, particularly the distillation process and the duration of distillation, can influence the composition of the oil obtained… There are differences in the relative amounts of some of the components when steam distillation and laboratory hydrodistillation are used (Park et al. 2026).
. Storage conditions:
TTO can undergo changes in composition as a result of storage, and exposure to light, heat, oxygen or air as well as moisture can cause oxidation and lead to a modification of its chemical composition; during storage the amount of p-cymene tends to increase while that of α terpinene and γ-terpinene decreases. It should therefore be stored whenever possible in cool, dark and dry conditions with as little exposure to air as possible (Impact of different storage conditions on the quality of selected essential oils | Request PDF n.d.).

IV. PHYTOCHEMICAL AND CHEMICAL COMPOSITION

Tea tree oil (TTO) is complex volatile mixture of monoterpenes and oxygenated monoterpenes, with small proportion of sesquiterpenes. More than 100 compounds have been identified in TTO, including terpinen-4-ol, γ-terpinene, α-terpinene, 1,8-cineole, terpinolene, p-cymene, αpinene and α-terpineol as the main constituents Terpinen-4-ol is usually the main compound of commercial tea tree oils, but its content may vary significantly depending on a chemotype, geography of growing, abiotic factors during harvesting and storage. Such variations may lead to differences in bioactivity of the essential oil (Lam et al. 2020)
The essential oil make-up of *Melaleuca alternifolia* shows a great deal of variation and therefore there are different chemotypes. Six chemotypes which occur in nature have been identified, the main basis for this being the dominant terpene components: terpinen-4-ol, terpinolene and 1,8-cineole. Of these, one is dominated by terpinen-4-ol, one by terpinolene, and four have 1,8-cineole-rich profiles (Webb et al. 2013).
Tea tree oil for commercial use is based mainly on the terpinen-4-ol chemotype since of its distinctive chemical composition. The different chemotypes are mostly the result of genetic factors and are also connected with geographical distribution (Ebrahimi et al. 2026b). Genetic studies carried out recently have demonstrated that variations in the terpene synthase genes are of great importance in determining the various chemotypes of *M. alternifolia*(Voelker, Mauleon, and Shepherd 2023)

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

The quality of tea tree oil is determined by means of internationally recognized specifications, especially those set out in ISO 4730, which specify the characteristics of terpinen-4-ol type tea tree oil (ISO 4730:2017 n.d.). The present standard, ISO 4730:2025, includes specifications designed to aid in the assessment of both the quality and identity of tea tree oil . Chemical analysis is primarily carried out using gas chromatography coupled with flame ionization detection (GC-FID) or mass spectrometry (GC-MS) in order to establish the qualitative and quantitative makeup of the oil's main volatile components (Standard - Essential oil of Melaleuca, terpinen-4-ol type (tea tree oil) ISO 4730:2025 - Swedish Institute for Standards, SIS n.d.).
HPTLC, infrared spectroscopy and chromatographic fingerprinting are also suitable for use in the authentication of the product and for the detection of adulteration (Islam et al. 2020). These analytical methods are able to tell the genuine *M. alternifolia* oil apart from that of other Melaleuca species or from adulterated products and aid in maintaining consistent quality control (Vázquez, Tabanca, and Kendra 2023).

V. PHARAMACOLOGICAL ACTIVITIES

5.1 ANTIMICROBIAL ACTIVITY

Tea tree oil (TTO) has broad-spectrum antimicrobial properties and is effective against a number of Gram-positive and Gram-negative bacteria (Mohammed et al. 2024a). The reason for its antibacterial action lies in its lipophilic terpene components, especially terpinen-4-ol, since this compound is able to interact with the bacterial cell membrane and as a result cause a disruption of the membrane's integrity, resulting in the leakage of the cell's internal components and the inhibition of microbial growth (Cordeiro et al. 2020a). It has shown activity against organisms including Staphylococcus aureus, Streptococcus pyogenes and Escherichia coli (Chouhan, Sharma, and Guleria 2017) . Because of its antimicrobial properties, TTO has been studied for use in topical formulations and in other pharmaceutical applications (Carson, Hammer, and Riley 2006i).

5.2 ANTIFUNGAL ACTIVITY

Tea tree oil (TTO) has broad-spectrum antifungal properties against a number of pathogenic fungi, such as Candida albicans, Malassezia furfur, dermatophytes and other filamentous fungi; its antifungal effect is mainly due to the disruption of the integrity of the fungal cell membrane and to a change in membrane permeability (Roana et al. 2021). Terpinen-4-ol is regarded as one of the main factors responsible for this activity. It has also been stated that TTO inhibits the germ-tube formation of C. albicans, a process which is important for virulence (Cordeiro et al. 2020b). These results indicate that TTO might be used in topical formulations for the treatment of superficial fungal infections and dandruff-related problems. (Garg et al. 2020a)

5.3 ANTIBACTERIAL ACTIVITY

Tea tree oil (TTO) has antibacterial properties and is effective against a wide range of both Gram-positive and Gram-negative bacteria; this effect is primarily because of terpinen-4-ol, which can interact with and damage the bacterial cell membrane, increasing the membrane's permeability and as a result causing the leakage of the cell's contents… It has been found to have inhibitory actions against several important pathogens, including Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli and Pseudomonas aeruginosa (Cox et al. 2001a). Because of its antibacterial characteristics, TTO has been studied for use in topical formulations and in other pharmaceutical applications, especially in cases where local antimicrobial action is needed. (Williamson, Carter, and Howden 2017)

5.4 ANTI-INFLAMMATORY ACTIVITY

Tea tree oil (TTO) has anti-inflammatory properties, these mainly being due to its main component terpinen-4-ol (Nogueira et al. 2014a). It has been found that both TTO and terpinen-4-ol are able to inhibit the production of inflammatory mediators such as TNF-α, IL-1β, IL-8 and prostaglandin E2 (PGE2) in activated immune cells (Nogueira et al. 2014b). Moreover, terpinen-4-ol has shown an ability to suppress inflammatory responses in experimental models, indicating its possible function in reducing inflammation linked to microbial and skin-related conditions (Ninomiya et al. 2013) . Nevertheless, clinical evidence regarding the anti-inflammatory effects of TTO in humans is still very limited and further research is needed (Costello et al. 2024)

5.5 ANTIOXIDANT ACTIVITIES

Tea tree oil (TTO) shows antioxidant properties by scavenging free radicals and by inhibiting lipid peroxidation (Yasin et al. 2021). This antioxidant capacity has been shown in various tests, including those for DPPH radical scavenging, hydroxyl radical scavenging and TBARS assays. Of the compounds contained in TTO, α-terpinene, α-terpinolene and γ-

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

terpinene have been found to make a significant contribution to its antioxidant activity (Baliyan et al. 2022) . Since these characteristics indicate that TTO has the potential to be used as a natural antioxidant and preservative in pharmaceutical, food and cosmetic formulations, it may be so applied. Yet, since most of the evidence is derived from in-vitro studies, further research is needed if the antioxidant effects of TTO are to be confirmed in clinical situations. (Rathee et al. 2023)

5.6 ANTIVIRAL ACTIVITY

Evidence indicates that tea tree oil has antiviral activity, notably against herpes simplex virus (HSV-1 and HSV-2) and influenza A virus in vitro (Schnitzler, Schön, and Reichling 2001). The antiviral effect appears to be due in part to the terpene constituents of TTO, including terpinen-4-ol, terpinolene and α-terpineol(Garozzo et al. 2009). Studies on HSV have shown that TTO primarily acts on free virus particles before or during their interaction with host cells . TTO has been reported to inhibit an early stage of the replication cycle of influenza A virus, possibly interfering with viral entry or uncoatingprocesses . However, most of the evidence is preclinical and further clinical studies are needed to establish its therapeutic antiviral efficacy in humans. (Agelidis and Shukla 2015)

5.7 ANTIPARASITIC ACTIVITY

The tea tree oil (TTO) has proven antiparasitic activity against a number of medically relevant parasites, primarily ectoparasites such as Demodex mites, scabies mites and lice. Its antiparasiticactivity is primarily related to its terpene constituents, particularly terpinen-4-ol, which likely act on the parasite (Bezabh et al. 2022)

VI. THERAPEUTIC APPLICATIONS

Tea tree oil (TTO) has been investigated for a variety of topical therapeutic applications due to its antimicrobial, antifungal and anti-inflammatory properties (Wróblewska, Szymańska, and Winnicka 2021). Its major applications include the management of acne, dandruff and seborrheic dermatitis, superficial fungal infections, minor skin infections and oral health conditions. TTO is generally incorporated into topical formulations such as creams, gels, shampoos, mouthwashes and other personal-care preparations (Dall'Oglio et al. 2022)

6.1 ACNE

TTO has been investigated as a topical agent for mild to moderate acne because of its antimicrobial and anti-inflammatory properties. Clinical studies have reported reductions in acne lesions following topical application of tea tree oil preparations, although further studies are required to establish standardized concentrations and long-term safety. (Nurzyńska-Wierdak, Pietrasik, and Walasek-Janusz 2022)

6.2 DANDRUFF AND SEBORRHEIC DERMATITIS

Tea tree oil has been incorporated into shampoos and scalp preparations for dandruff and seborrheic dermatitis. Its antifungal activity, particularly against Malassezia species, together with its anti-inflammatory properties, may contribute to improvement in scalp symptoms. (Satchell, Saurajen, Bell, and R. S. Barnetson 2002)

6.3 SUPERFICIAL FUNGAL INFECTIONS

TTO has been investigated for topical management of superficial fungal infections, including tinea pedis (athlete's foot) and onychomycosis. Its antifungal activity against dermatophytes and other fungi provides a basis for its use in topical preparations; however, clinical evidence varies according to the condition and formulation used.(Crawford and Hollis 2007)

6.4 ORAL HEALTH

TTO-containing oral preparations have been investigated for their antimicrobial effects against oral microorganisms. Experimental and clinical studies have explored their potential use as an adjunct in oral hygiene and management of plaque-associated conditions. However, tea tree oil should not be swallowed because oral ingestion can cause toxicity. (Zhang et al. n.d.)

6.5 WOUND AND SKIN INFECTIONS

Due to its antimicrobial and anti-inflammatory properties, tea tree oil has been studied as an agent for treating minor wounds and superficial infections (Nascimento et al. 2023a). Its primary active component, terpinen-4-ol, may suppress the development of microorganisms and reduce inflammatory responses in the affected area. Topical preparations containing TTO have therefore been investigated as an adjunct to standard-of-care treatments for minor skin abrasions, cuts and localized superficial infections (Mondello et al. 2022). Nevertheless, while preliminary evidence suggests potential benefits, the effectiveness for promoting wound healing remains inconclusive, and appropriate dilution with carrier agents is critical to avoid adverse effects such as skin irritation or sensitization.(Orchard and van Vuuren 2019)

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

VII. MECHANISM OF ACTION

7.1 EFFECTS ON MICROBIAL CELL MEMBRANES

The antimicrobial action of tea tree oil is mainly due to its interaction with the membranes of micro-organisms. Because of its lipophilic components, especially terpinen-4-ol, it is able to penetrate the lipid-containing membrane and change its structure and permeability (Cox et al. 2001b). This causes the leakage of material from within the cell, leads to a disruption of functions associated with the membrane and results in a loss of cellular homeostasis, and finally causes the inhibition of microbial growth or kills the cells. Effects similar to this membrane disruption have also been reported in both bacterial and fungal cells(Yu et al. 2024)

7.2 ANTI-INFLAMMATORY MECHANISMS

The main reason for the anti-inflammatory effects of tea tree oil is its ability to regulate the production of inflammatory mediators. Terpinen-4-ol has been found to decrease the production of various mediators, including TNF-α, IL-1β, IL-8 and PGE_2, in activated inflammatory cells. Moreover, tea tree oil and its components might also affect the cellular signalling pathways that are involved in inflammatory responses, thus leading to a reduction in local inflammation and the related tissue responses (Hart et al. 2000).

7.3 OTHER SUGGESTED MOLECULAR MECHANISMS

Apart from causing membrane disruption and affecting inflammation, other mechanisms have also been suggested for tea tree oil. The substances contained in it might interfere with microbial respiration, ion transport and cellular metabolism, thus leading to antimicrobial effects (Cox et al. 2001c). Moreover, the components of TTO may also affect the oxidative processes and the signalling pathways which are involved in the interactions between the host and the microorganism. Nevertheless, these mechanisms are not fully established and could differ depending on the microorganism, the concentration and the individual constituents in the oil (Li et al. 2016)

VIII. FORMULATION &PHARMACEUTICAL APPLICATIONS

8.1 CREAMS AND GELS

Tea tree oil (TTO) is usually included in topical creams and gels in order to aid its application to the skin and to give it local antimicrobial and anti-inflammatory effects. Putting it into a semisolid base also helps with handling and decreases the amount of direct exposure to the highly concentrated oil. Gels containing TTO have been studied especially in the case of acne and superficial skin infections, and those with about 5% TTO have shown promising topical activity(Nascimento et al. 2023b)

Creams and gels can likewise enhance the physical stability and the controlled release of TTO. It is nevertheless essential to make an appropriate choice of emulsifiers, gelling agents and TTO concentration since the oil is volatile and could lead to irritation when used in higher concentrations. Furthermore, nanoemulsion-based emulgels have been studied in order to improve the dispersion of TTO, skin permeation and antimicrobial efficacy as compared to conventional formulations (Milutinov et al. 2023)

8.2 OINTMENTS AND LOTIONS

Tea tree oil can be included in ointments and lotions for use on the skin in cases of superficial skin conditions due to its antimicrobial and anti-inflammatory properties (Nascimento et al. 2023c). Ointment bases allow the oil to remain in contact with the skin for a longer period, while lotions are easier to apply over large or hairy areas (Oliveira and Almeida 2023). Preparations containing TTO have been studied for use in conditions such as minor skin infections, inflammatory skin disorders and superficial fungal infections (Nascimento et al. 2023d)

The effectiveness of such formulations is influenced by various factors including TTO concentration, the type of vehicle, solubility, stability and skin compatibility (Tapfumaneyi et al. 2025). Since tea tree oil is volatile and oxidation can increase its sensitizing potential, it is important to use appropriate formulation methods and packaging conditions if product quality is to be maintained and irritation is to be minimized . Controlled topical delivery systems have therefore been investigated in order to improve stability and to keep an appropriate concentration of TTO at the site of application (Nascimento et al. 2023e).

8.3 MOUTHWASHES AND ORAL FORMULATIONS

Tea tree oil has been looked into in a number of oral formulations, especially in the form of mouthwashes and rinses, since it has antimicrobial properties against oral micro-organisms (Ripari et al. 2020). Mouthwashes containing tea tree oil have been studied for their possible effect in reducing dental plaque, gingival inflammation and the number of

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

oral microbes. The lipophilic components of tea tree oil might interact with the membranes of microbial cells and disrupt the growth of oral bacteria (Menat et al. n.d.).

Clinical studies have shown that oral preparations containing tea tree oil might offer antimicrobial and plaque-controlling effects if they are used in addition to normal oral hygiene. Tea tree oil has also been studied with regard to microorganisms linked to periodontal diseases, such as Porphyromonasgingivalis and Prevotella intermedia (SALVATORI et al. 2017). Yet it is necessary to take into account the concentration of the formulation, the length of exposure, and safety, and tea tree oil should not be swallowed since this can lead to toxic effects (Hammer et al. 2006).

8.4 NANOFORMULATIONS AND ADVANCED DELIVERY SYSTEMS

Since tea tree oil has certain limitations in terms of formulation—such as its high volatility, poor solubility in water, and susceptibility to oxidation—research has been carried out into nanoformulation methods in order to enhance its stability, dispersibility, controlled release, and therapeutic efficacy(Nguyen, Nguyen, and Nguyen 2026d) .

Nanoemulsions and nanoemulgels are able to decrease the size of the droplets of TTO and enhance its distribution in aqueous formulations. It has been shown that TTO nanoemulgels have better skin permeability and antimicrobial activity than conventional formulations (Jacob and Nair 2026a).

Furthermore, other advanced systems such as liposomes, polymeric nanoparticles, nanofibers and encapsulated delivery systems can protect TTO from degradation and allow for a more controlled release of its active ingredients (Adepu and Ramakrishna 2021).

The use of materials like chitosan and sodium alginate for the encapsulation of TTO has also been studied with a view to employing it in wound-dressing applications, since sustained release and better stability could enhance its antimicrobial activity . Nano-enabled delivery systems as a whole are a promising method of overcoming the physicochemical limitations of conventional TTO formulations and of extending its pharmaceutical uses (Froelich et al. 2023).

IX. SAFETY ,TOXICITY& ADVERSE EFFECTS

9.1 REGARDING SKIN IRRITATION AND SENSITIZATION

Tea tree oil is usually applied topicaly in the form of diluted preparations; yet it may cause skin irritation in people who are susceptible. Known reactions consist of erythema, a burning sensation, itching and dermatitis. The risk could go up if the tea tree oil is exposed to air, light or heat, since oxidation may lead to the formation of compounds which have a greater sensitising potential(Ambrogio et al. 2022a) .

It is therefore necessary to ensure that topical tea tree oil formulations are appropriately diluted, packed in suitable containers, and protected from excessive exposure to both light and air in order to maintain their safety and stability. In addition, patch testing should also be considered in cases where essential oils are being used in people with a history of sensitivity to them (Carson, Hammer, and Riley 2006j).

9.2 ALLERGIC REACTIONS

Tea tree oil can cause allergic contact dermatitis in sensitized individuals, particularly after repeated topical exposure. The reaction may present as redness, itching, swelling, burning or eczematous skin lesions at the site of application (Ambrogio et al. 2022b). The allergenic potential of tea tree oil is strongly influenced by oxidation, as prolonged exposure to air can produce oxidation products that are more potent sensitizers than several constituents of fresh oil (Nguyen, Nguyen, and Nguyen 2026e)

Several oxidized components, including terpinen-4-ol oxidation products, α-terpinene, terpinolene and limonene derivatives, have been associated with contact allergy. Therefore, properly stored, fresh and appropriately formulated tea tree oil is preferable, particularly for individuals with sensitive skin or a previous history of fragrance or essential-oil allergy(de Groot and Schmidt 2016) .

9.3 TOXICITY AFTER TAKING IT BY MOUTH

If tea tree oil is taken orally it is toxic and even fairly small quantities can cause adverse effects. It has been linked to symptoms including drowsiness, confusion, ataxia, weakness, nausea and vomiting. In some serious instances central nervous system depression and impaired consciousness may happen(Morris et al. 2003) .

Since tea tree oil is a strong essential oil, it must not be taken internally unless it has been specially formulated and prescribed for a suitable medical purpose. It follows that products which contain TTO should be stored safely and kept out of children's reach in order to reduce the risk of accidental ingestion (Nguyen, Nguyen, and Nguyen 2026f).

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

9.4 DRUG INTERACTIONS AND PRECAUTIONS

Limited information is available about clinically relevant drug interactions with topical tea tree oil (TTO). Due to the topical application, systemic exposure to TTO is usually lower compared to oral medications. However, the concurrent use of TTO with other topical preparations, especially irritating or sensitizing agents, may lead to an increased risk of local adverse effects, such as dermatitis(Carson, Hammer, and Riley 2006k) .

Tea tree oil should be used with caution on damaged or highly sensitive skin, and it should not be applied in its pure form. Oxidized or poorly stored products may exhibit an enhanced sensitizing effect. Ingestion of TTO should also be avoided, and the oil should be kept away from children and pets due to its potential toxicity after oral exposure . Patients using various topical or dermatological preparations should consult a healthcare professional if they experience irritation or an allergic reaction(Rutherford et al. 2007) .

9.5 SPECIAL POPULATION CONSIDERATIONS

Special precautions may be needed when using tea tree oil in children, pregnant/nursing women, and people with sensitive skin. Tea tree oil should not be taken by mouth in children, due to the risk of neurologic and GI toxicity if it is ingested. Topical products should be diluted and used with caution in young children, as their skin may be more sensitive to irritants(Kairey et al. 2023a) .

Limited data are available concerning the safety of tea tree oil use in pregnancy or lactation, so extensive or oral use should be avoided unless information on safety is available and its use is warranted by a healthcare provider. Individuals with a history of allergic contact dermatitis or sensitivity to essential oils should also use TTO cautiously, as oxidized tea tree oil may have increased sensitizing potential(Kairey et al. 2023b) .

X. CLINICAL STUDIES

Clinical research on tea tree oil (TTO) has been carried out through experiments in vitro, on animals and in human clinical trials. These studies have examined its antimicrobial, antifungal, anti-inflammatory and other therapeutic effects. Even though some studies have shown promising results, the quality and strength of the existing clinical evidence differ according to the condition and the formulation being studied (Carson, Hammer, and Riley 2006l).

10.1 *IN VITRO* STUDIES

Studies carried out in a laboratory setting have shown that tea tree oil (TTO) has considerable antimicrobial, antifungal and antibiofilmpropertiesTo examine these effects researchers have used a number of methods, including disk diffusion, broth microdilution and biofilm assays. The degree of activity depends on the type of microorganism, the concentration of TTO and its chemical composition(Mohammed et al. 2024b) .

Borotová and others in 2022 examined the effect of *Melaleuca alternifolia*essential oil on a number of Gram-positive and Gram-negative bacteria as well as on Candida species. The oil exhibited considerable antimicrobial activity, the inhibition zones for Enterococcus faecalis and Candida albicans being about 10.67 mm. The study further showed that free-floating bacterial cells were generally more susceptible than yeast and biofilm-forming microorganisms. Antibiofilm properties were found to act against Pseudomonas fluorescens and Salmonella enterica, indicating the potential of TTO as an antimicrobial agent (Borotová et al. 2022d).

A further in vitro study looked at the effects of TTO on clinical isolates of Pseudomonas aeruginosa associated with cystic fibrosis. This study assessed both free-swimming bacteria and existing biofilms and also investigated the effect of combining TTO with antibiotics that are commonly used. These results offered evidence of the antimicrobial and antibiofilm properties of TTO with respect to bacterial isolates that are relevant from a clinical point of view (Borisova et al. 2025)

Broad in vitro evidence shows that TTO is able to inhibit a wide variety of microorganisms; yet the results from laboratory studies cannot be directly regarded as equivalent to clinical efficacy. It is necessary to carry out further animal and human studies in order to determine its therapeutic effectiveness and to identify the suitable formulations (Carson, Hammer, and Riley 2006m)

10.2 ANIMAL STUDIES

Animal studies have contributed significantly to understanding the therapeutic potential of *Melaleuca alternifolia*(tea tree) oil (TTO). Most preclinical trials have focused on the antimicrobial, anti-inflammatory and wound-healing effects of TTO in murine models. (Carson, Hammer, and Riley 2006n)

Antimicrobial and anti-inflammatory activity

In a mouse model of Group A Streptococcus infection, administration of a water-soluble

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

concentrate of *M. alternifolia* led to reduced skin damage and mortality in infected mice. It also reduced inflammatory cytokine production and accelerated bacterial clearance, indicating a combined antimicrobial and anti-inflammatory mechanism (Tsao et al. 2010)

- Wound-Healing Activity

A rat wound model was used to assess the wound-healing activity of tea tree oil incorporated into a chitosan-based topical preparation. Topical application was evaluated daily for 14 days, with wound contraction and granulation tissue formation used as indicators of healing. The tea tree oil formulation showed potential to increase wound healing as compared with the untreated wound group(Oran et al. 2023)

More recently, a 2% form of *M. alternifolia* essential-oil cream was evaluated in a mouse model of Staphylococcus aureus-infected wounds. Topical treatment decreased wound severity, wound size and bacterial load, supporting their potential for use in infected wounds management (Alves et al. 2024)

- Other Experimental Effects

Topical 10% TTO/DMSO has also been tested in mice bearing subcutaneous tumours. Repeated topical treatment resulted in regression of experimental mesotheliomas and delayed melanoma growth. Investigation suggested that the mechanism involved direct cytotoxicity against tumour cells plus local immune-cell reactions. These findings are preclinical and should not be considered to indicate any benefit for human cancer treatment(Nordenberg et al. 1986) .

Overall, animal studies have shown the biological activity of TTO, particularly in the context of infected wounds, inflammation and experimental antimicrobial models. However, differences in animal models, concentration, formulations and routes of administration limit their direct extrapolation to human treatment. Thus, controlled clinical studies are essential to establish the therapeutic efficacy and safety (Mohammed et al. 2024c).

10.3 CLINICAL TRIALS

Clinical trials have investigated tea tree oil (TTO) derived from *Melaleuca alternifolia*in various cases relatingto the skin, infectious diseases and oral health. Randomised controlled trials have looked into different concentrations and formulations including gels, shampoos, creams, mouthwashes and nanoemulsion preparations(Kairey et al. 2023c) .

- Acne Vulgaris

A randomized, double-blind, placebo-controlled study of 60 patients with mild to moderate acne vulgaris examined the use of a 5% TTO gel over a period of 45 days; the group treated with TTO showed a significant reduction in the total number of acne lesions and in the acne severity index compared to the placebo group, although the adverse effects were generally well tolerated .A previous randomized clinical trial with 124 patients examined 5% TTO gel against 5% benzoyl peroxide. Bothtreatments were found to reduce inflammatory and noninflammatory acne lesions but TTO took longer tobegin working. This study noted fewer side effects related to treatment with TTO(Enshaieh et al. 2007) .

- Dandruff and Seborrheic Dermatitis

Dandruff is a common scalp problem that results in flakes of skin. It is often accompanied by itching. The exact cause is not known but may involve an overgrowth of Malassezia yeast, oily skin and changes in the skin's barrier. Dandruff does not result in redness or swelling. Seborrheic dermatitis is a chronic form of eczema that affects areas rich in oil glands such as the scalp, face and upper chest. It results in red, scaly patches with greasy yellow or white scales. It can also cause itching. Seborrheic dermatitis like dandruff can be associated with Malassezia yeast and changes in the skin barrier. Stress, cold weather and certain illnesses can exacerbate the condition. Treatment for both conditions include medicated shampoos with ingredients such as zinc pyrithione, selenium sulfide, ketoconazole or coal tar. In severe cases, doctors may prescribe topical steroids or antifungal creams.A clinical trial involving 126 participants examined the use of 5% TTO shampoo once a day for four weeks. While the group who used the TTO showed a greater degree of improvement in the severity of the dandruff compared to the group given the placebo, it also experienced reductions in the level of itching and greasiness. The study noted no adverse effects to report (Borda and Wikramanayake 2015).

-Tinea Pedis

TTO has also been the subject of clinical trials for use against superficial fungal infections. In a randomised, placebo-controlled study with 158 patients suffering from interdigital tinea pedis, 25% and 50% solutions of TTO were applied twice a day for four weeks. While both concentrations resulted in greater clinical responses compared to the placebo, the 50% formulation showed a higher mycological cure rate than the placebo. A small

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

number of the participants who received TTO developed dermatitis(Satchell, Saurajen, Bell, and R. S. C. Barnetson 2002a) .

A previous trial which tested 10% TTO cream for tinea pedis showed no statistically significant difference in culture conversion between TTO and placebo, though tolnaftate had a higher mycological cure rate. This implies that clinical efficacy can be dependent on concentration, formulation and study design(Satchell, Saurajen, Bell, and R. S. C. Barnetson 2002b) .

-Advanced Formulations

More recent clinical studies have looked at TTO in the use of advanced delivery systems. In a randomizedclinical trial with 100 patients suffering from acne vulgaris, a gel based on a TTO nanoemulsionandcontainingadapalene was compared with the existing 0.1% adapalene gel over a period of 12 weeks. The TTOnanoemulsion formulation resulted in greater reductions in both total and inflammatory as well as non-inflammatory acne lesions while dryness was also reported more frequently in the group using the TTOnanoemulsion(Piskin and Uzunali 2007).

- Overall Clinical Evidence

A systematic review from 2023 looked at 46 randomized controlled trials which involved the use of TTO in thefields of dentistry, dermatology, infectious diseases, ophthalmology and podiatry.[70] While it found promisingevidence for certain applications, the review stated that overall the quality of the evidence varied from poorto modest and that it was necessary to conduct larger and more well-designed clinical trials. The adverseeffects were generally minor though higher topical concentrations were associated with a greater number oflocal reactions. (PubMed CentralClinical trials do indeed indicate that TTO may be used, particularly in the case of acne, dandruff and somesuperficial fungal infections. However, since there is variation among the trials with respect to TTOcomposition, concentration, formulation, the length of treatment and the quality of the studies, it is difficult tomake direct comparisons between them (Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: A randomized, placebo-controlled, blinded study n.d.).

10.4 EVIDENCE-BASED ASSESSMENT OF THERAPEUTIC EFFICACY ESSAY

Melaleuca alternifolia (tea tree) oil (TTO) has been evaluated for its therapeutic efficacy in vitro, in animals, and in randomized clinical trials. In vitro studies have demonstrated antimicrobial and antifungal activities, while animal studies have provided evidence for antimicrobial, antiinflammatory, and wound-healing properties. However, these findings cannot be directly extrapolated to humans (Carson, Hammer, and Riley 2006o).

Limited evidence from human studies supports the use of TTO for the treatment of acne vulgaris, dandruff, and some superficial fungal infections. Clinical trials have shown that specific preparations and concentrations of TTO may be effective, such as 5% TTO gel for acne and 5% TTO shampoo for dandruff. Nevertheless, treatment results are often inconsistent, and for fungal infections, differences in preparation, concentration, and duration of treatment have influenced the outcomes (Nascimento et al. 2023f).

A systematic review of randomized controlled trials revealed the efficacy of TTO across various conditions including dermatological, dental, infectious, and others, but with significant variability between studies in terms of design and quality. Thus, the current evidence base indicates therapeutic potential of TTO for selected topical applications, but does not establish it as a universally efficacious treatment. Further research with standardized TTO preparations, appropriate formulations, and large-scale clinical trials is needed to advance the evidence base(Tea tree oil: a systematic review of randomized clinical trials - Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews - NCBI Bookshelf n.d.) .

In conclusion, the available evidence suggests that TTO has a promising but condition-specific therapeutic profile. However, the strongest clinical support is found in the context of selected topical dermatological applications (Ernst and Huntley 2000a).

Evidence Based Assessment of Therapeutic Effectiveness

Laboratory, animal and randomized clinical trials have examined the therapeutic efficacy of *Melaleuca alternifolia* (tea tree) oil (TTO). The laboratory studies have shown that it has antimicrobial and antifungal properties, and the animal studies have given evidence of its antimicrobial, anti-inflammatory, and wound-healing effects. Yet the results from these studies cannot be directly applied to humans (Carson, Hammer, and Riley 2006p).

The amount of evidence from studies involving humans in support of the use of TO for the treatment

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

of acne vulgaris, dandruff, and certain superficial fungal infections is limited. Clinical trials have shown that specific preparations and concentrations of TTO may be effective, such as 5% TTO gel for acne and 5% TTO shampoo for dandruff. Nevertheless, treatment results are often inconsistent, and for fungal infections, differences in preparation, concentration, and duration of treatment have influenced the outcomes(Nascimento et al. 2023g) .

A systematic review of randomized controlled trials revealed the efficacy of TTO across various conditions including dermatological, dental, infectious, and others, but with significant variability between studies in terms of design and quality. Thus, the current evidence base indicates therapeutic potential of TTO for selected topical applications, but does not establish it as a universally efficacious treatment. Further research with standardized TTO preparations, appropriate formulations, and large-scale clinical trials is needed to advance the evidence base(Ernst and Huntley 2000b) .

Overall, the evidence available suggests that TTO has a promising therapeutic profile, but only for certain conditions. However, the strongest clinical support is found in the context of selected topical dermatological applications(Ernst and Huntley 2000c) .

XI. THE CURRENT CHALLENGES AND RESEARCH GAPS

Even though there has been a great deal of research into *Melaleuca alternifolia* (tea tree) oil (TTO), some difficulties still exist before its therapeutic uses can be fully confirmed. The main research gaps are as follows; (Carson, Hammer, and Riley 2006q)

. The variation in chemical composition

The chemical make-up of TTO depends on its chemotype, place of origin, the conditions under which it is cultivated, the methods used for harvesting it, the way it is extracted and the storage conditions. This variation may affect its biological activity and causes it to be difficult to compare the different studies. Further research is needed in order to establish clearer links between chemical composition and therapeutic activity(Waheed et al. 2024) .

. The standardisation of tea tree oil

Even though international standards specify the acceptable ranges for a number of main constituents, there is still a need for standardized methods that link particular chemotypes and constituent profiles with pharmacological effects. In future studies it is essential to clearly state the source, chemical composition, chemotype and quality parameters of the TTO used in the experiments and clinical trials(Abraham and Kellogg 2021) .

. Clinical evidence of a limited quality

A great deal of research has been carried out at both the in vitro and preclinical levels, while for a number of the suggested uses the clinical evidence is still comparatively limited. A systematic review of 46 randomized controlled trials found the overall quality of the evidence to vary from poor to modest, thus underscoring the necessity for larger, well-designed and adequately reported clinical trials (Venturella et al. 2021).

. Dose, formulation and exposure–response relationship

The therapeutic effects of TTO are influenced by concentration, formulation, method of administration and the length of exposure. Yet the concentrations that are most therapeutic for various indications have not been clearly defined. Future research should aim at establishing exposure–response relationships and at finding concentrations which produce a therapeutic effect while at the same time minimizing irritation and sensitization(Stokes et al. 2024) .

. Safety and Use Over an Extended Period

TTO is commonly used in topical preparations, but oxidation may increase its ability to cause sensitization and higher concentrations could lead to local adverse reactions. More systematic studies should be carried out to assess the effects of long-term exposure, repeated application, its impact on susceptible groups and formulation-dependent toxicity (Kairey et al. 2023d).

. The development of advanced drug delivery systems

TTO is both volatile and has very little solubility in water, which can cause difficulties in terms of formulation and stability. Nanoemulsions, nanogels, hydrogels, lipid-based carriers and other advanced delivery systems might help to improve stability, provide controlled release and allow for local delivery. Nevertheless, these systems still need further optimization and clinical validation before they can be widely used in a therapeutic context (Jacob and Nair 2026b).

. The use of combination therapy and antimicrobial resistance

It will be necessary to carry out further research in order to find out if TTO can be effectively combined with conventional antimicrobial drugs to produce

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

additive or synergistic effects, especially in the case of biofilms and drug-resistant microorganisms; suitable clinical studies also need to be conducted in order to see if such combinations offer any real therapeutic benefits (Oliveira et al. 2024).

. The need for mechanistic and translational research

Even though a number of molecular mechanisms have been suggested, the relationship between the various constituents of TTO, their molecular targets and the clinical outcomes is not fully understood. Future research must combine chemical profiling, pharmacological mechanisms, pharmacokinetics and clinical outcomes if laboratory findings are to be translated into therapeutic applications based on solid evidence(Cemali et al. 2025) .

. Future Research Priorities

Future studies should concentrate on standardised TTO preparations, clinical trials tailored to specific indications, validated advanced formulations, evaluations of long-term safety and patient-centred outcomes. There would also be an improvement in reproducibility and enable meaningful comparisons between studies if there was greater consistency in the reporting of TTO composition and the experimental methods used (Zhang and Jiang n.d.).

XII. FUTURE PERSPECTIVES

Scientific interest in tea tree oil (TTO) has continued because of its wide antimicrobial properties and its possible uses in dermatology, in oral health, in wound care and in pharmaceutical formulations. Research in the future should aim at turning the promising results obtained in the laboratory into therapeutic products that are standardised, safe and have been validated by clinical trials(Nascimento et al. 2023h) .

. The development of standardized preparations

Future research should develop more closely linked relationships between chemotype, chemical composition and pharmacological activity; detailed chemical profiling together with standardised reporting of terpinen-4-ol and other major components will increase reproducibility and make it easier to compare the different studies (Shapira et al. 2016).

.New Drug Delivery Systems

The development of nanoemulsions, nanogels, liposomes, polymeric nanoparticles, hydrogels and microencapsulated systems could enhance the stability, allow for controlled release and enable local delivery of TTO. These systems might also contribute to a reduction in volatility and help minimise direct exposure to high concentrations of the oil. Recent research shows that there is growing interest in new methods of delivering TTO for use in pharmaceuticals(Lal et al. 2023).

. Combination Therapy

Future studies should look into combining TTO with conventional antimicrobial agents and with other natural bioactive compounds. Such combined approaches could be especially useful in the case of biofilms and drug-resistant microorganisms. Nevertheless, the synergistic effects must be verified by means of standardized experimental methods and then assessed in clinical trials (Grassi et al. 2017).

. The expansion of clinical research

It will be necessary to carry out more large-scale, randomized, and well-controlled clinical trials in order to establish the efficacy of TTO for particular therapeutic indications. The trials carried out in the future should involve standardized TTO preparations being compared with established standard treatments and with appropriate placebo controls. The 2023 systematic review of randomized trials had emphasized the need for larger and better-reported clinical studies(Kairey et al. 2023e)

. Personalized and Situation-Specific Formulations

Future versions of the product could be developed in accordance with the particular therapeutic needs, for example for acne, dandruff, superficial fungal infections, wound care or oral infections. Improving the concentration, the carrier system, the release profile and the length of treatment might lead to better therapeutic results while at the same time reducing irritation and sensitization(Garg et al. 2020b)

. Mechanism-Based Drug Development

Further research needs to determine the specific molecular targets which are responsible for the biological effects of TTO and its main components. The combination of molecular biology, metabolomics, proteomics and computational methods could aid in clarifying the structure–activity relationships and in identifying promising constituents or combinations for use in drug development(Pan et al. 2024).

. The safety and long-term evaluation

Future studies should offer more evidence concerning long-term topical exposure, repeated administration, sensitization, formulation-dependent toxicity and its effects on susceptible groups. Safety assessment should be incorporated into the process of developing the formulation rather than being carried out only after therapeutic efficacy has already been established (Zhao et al. 2024).

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

. Translating findings from the laboratory to clinical use

One of the main priorities for the future is to overcome the gap between research carried out in vitro and clinical research. The use of standardized experimental procedures, animal models that have been validated and clinical trials that are properly designed can help turn promising findings into practical pharmaceutical applications. The fact that more research is now being focused on pathogens that are relevant to clinical situations, biofilms and strains that are resistant to drugs offers opportunities for this type of translational approach(Nair and Weiskirchen 2024).

. Sustainable production and quality control[91]

Future development should also take into account the sustainable cultivation of *M. alternifolia*, the use of efficient extraction methods and environmentally responsible production practices. The incorporation of quality control, chemotype identification and sustainable manufacturing could help to ensure a consistent supply of pharmaceutical-grade TTO(Nguyen, Nguyen, and Nguyen 2026g)

. Overall Future Outlook [93]

The future of research into TTO will depend on combining standardized phytochemistry, advanced drug delivery methods, mechanistic pharmacology, safety evaluation and highquality clinical research(Bae and Park 2020).

By adopting such multidisciplinary strategies, it may be possible to transform TTO from a traditional and complementary product which is currently widely used into one that is more accurately characterized and based on evidence(Ebrahimi et al. 2026c).

XIII. CONCLUSION

Oil derived from *Melaleuca alternifolia*(commonly known as Australian tea tree) is a chemically complex essential oil which has great pharmacological potential. The main components of it, especially terpinen-4-ol, are responsible for a wide variety of biological actions such as antibacterial, antifungal, anti-inflammatory, antioxidant and antiparasitic effects. Experimental research has shown that it is active against a number of microorganisms of clinical importance and has given some indication of the possible ways in which it works. Clinical studies have found that tea tree oil has beneficial effects when used topically in certain cases, especially in the treatment of acne vulgaris, dandruff and various superficial fungal infections(Carson, Hammer, and Riley 2006r). Yet, due to differences in the chemical composition, concentration, formulation and the methods employed in the studies, it is difficult to make direct comparisons between them.Consequently, the existing clinical evidence only supports the therapeutic potential of tea tree oil for certain conditions and does not prove its effectiveness in all cases.The latest developments in nanoemulsions, nanogels, hydrogels and other advanced delivery systems offer the possibility of enhancing the stability, delivery and therapeutic effectiveness of tea tree oil. However, more research is still needed if standardised preparations are to be established, therapeutic concentrations are to be optimised, the molecular mechanisms are to be made clear and long-term safety is to be assessed(Figueiredo 2019). *Melaleuca alternifolia* is a promising natural source of bioactive compounds which have potential uses in pharmaceutical and therapeutic contexts. It will be necessary to carry out future multidisciplinary research combining phytochemical standardization, advanced formulation, pharmacological investigation and well-designed clinical trials if its biological potential is to be turned into safe, reproducible and evidence-based therapeutic products(de Assis et al. 2020).

REFERENCES

[1]. Abraham, Evelyn J., and Joshua J. Kellogg. 2021. “Chemometric-Guided Approaches for Profiling and Authenticating Botanical Materials.” *Frontiers in Nutrition* 8:780228. doi:10.3389/fnut.2021.780228.

[2]. Adepu, Shivakalyani, and Seeram Ramakrishna. 2021. “Controlled Drug Delivery Systems: Current Status and Future Directions.” *Molecules* 26(19):5905. doi:10.3390/molecules26195905.

[3]. Agelidis, Alex M., and Deepak Shukla. 2015. “Cell Entry Mechanisms of HSV: What We Have Learned in Recent Years.” *Future Virology* 10(10):1145–54. doi:10.2217/fvl.15.85.

[4]. de Aguiar, Ana Carolina, Renata Vardanega, Juliane Viganó, and Eric Keven Silva. 2023. “Supercritical Carbon Dioxide Technology for Recovering Valuable Phytochemicals from Cannabis Sativa L. and Valorization of Its Biomass for Food Applications.” *Molecules* 28(9):3849. doi:10.3390/molecules28093849.

[5]. Alves, Lully Gabrielly Silva, Beatriz Gomes Vila Nova, Raissa Guará Assunção, Leticia Cely Tavares da Silva, Gabrielle Chaves Sá,

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

Lucas Dos Santos Silva, Marcos Andrade Silva, Amanda Vitória Sevidanes de Santana, Thays Rodrigues de Jesus, Flávia Ritchelle Coutinho Lucena, Marcos Aurélio Dos Santos da Silva, Luís Cláudio Nascimento da Silva, Izabel Cristina Portela Bogéa Serra, and Afonso Gomes Abreu. 2024. "Melaleuca Alternifolia Essential Oil in a Natural Product-Based Formulation: Antimicrobial and Healing Effects in Staphylococcus Aureus-Infected Wounds." *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V* 202:114416. doi:10.1016/j.ejpb.2024.114416.

[6]. Ambrogio, Francesca, Caterina Foti, Gerardo Cazzato, Edoardo Mortato, Stella Mazzoccoli, Anna Paola De Caro, Nicoletta Cassano, Gino Antonio Vena, Gianfranco Calogiuri, and Paolo Romita. 2022a. "Spreading Allergic Contact Dermatitis to Tea Tree Oil in an Over-the-Counter Product Applied on a Wart." *Medicina* 58(5):561. doi:10.3390/medicina58050561.

[7]. Ambrogio, Francesca, Caterina Foti, Gerardo Cazzato, Edoardo Mortato, Stella Mazzoccoli, Anna Paola De Caro, Nicoletta Cassano, Gino Antonio Vena, Gianfranco Calogiuri, and Paolo Romita. 2022b. "Spreading Allergic Contact Dermatitis to Tea Tree Oil in an Over-the-Counter Product Applied on a Wart." *Medicina* 58(5):561. doi:10.3390/medicina58050561.

[8]. de Assis, Karoll M. A., Renaly I. de A Rêgo, Demis F. de Melo, Laryssa M. da Silva, João A. Oshiro-Júnior, Fábio R. Formiga, Vinícius C. Pires, Ádley A. N. de Lima, Attilio Converti, and Bolívar P. G. de L Damasceno. 2020. "Therapeutic Potential of Melaleuca Alternifolia Essential Oil in New Drug Delivery Systems." *Current Pharmaceutical Design* 26(33):4048–55. doi:10.2174/1381612826666200305124041.

[9]. Bae, You Han, and Kinam Park. 2020. "Advanced Drug Delivery 2020 and beyond: Perspectives on the Future." *Advanced Drug Delivery Reviews* 158:4–16. doi:10.1016/j.addr.2020.06.018.

[10]. Baliyan, Siddartha, Riya Mukherjee, Anjali Priyadarshini, Arpana Vibhuti, Archana Gupta, Ramendra Pati Pandey, and Chung-Ming Chang. 2022. "Determination of Antioxidants by DPPH Radical Scavenging Activity and Quantitative Phytochemical Analysis of Ficus Religiosa." *Molecules* 27(4):1326. doi:10.3390/molecules27041326.

[11]. Bao, Quanying, and Diane J. Burgess. 2018. "Perspectives on Physicochemical and In Vitro Profiling of Ophthalmic Ointments." *Pharmaceutical Research* 35(12):234. doi:10.1007/s11095-018-2513-3.

[12]. Barbosa, Luiz. 2013. "Chemistry and Biological Activities of Essential Oils from Melaleuca L. Species." *Agriculturae Conspectus Scientificus (Poljoprivredna Znanstvena Smotra)*. https://www.academia.edu/118954422/Chemistry_and_Biological_Activities_of_Essential_Oils_from_Melaleuca_L_Species.

[13]. Bezabh, Solomon Abrha, Wubshet Tesfaye, Julia K. Christenson, Christine F. Carson, and Jackson Thomas. 2022. "Antiparasitic Activity of Tea Tree Oil (TTO) and Its Components against Medically Important Ectoparasites: A Systematic Review." *Pharmaceutics* 14(8):1587. doi:10.3390/pharmaceutics14081587.

[14]. Bitwell, Chibuye, Singh Sen Indra, Chimuka Luke, and Maseka Kenneth Kakoma. 2023. "A Review of Modern and Conventional Extraction Techniques and Their Applications for Extracting Phytochemicals from Plants." *Scientific African* 19:e01585. doi:10.1016/j.sciaf.2023.e01585.

[15]. Borda, Luis J., and Tongyu C. Wikramanayake. 2015. "Seborrheic Dermatitis and Dandruff: A Comprehensive Review." *Journal of Clinical and Investigative Dermatology* 3(2):10.13188/2373-1044.1000019. doi:10.13188/2373-1044.1000019.

[16]. Borisova, Dayana, Tanya Strateva, Svetoslav G. Dimov, Borjana Atanassova, Tsvetelina Paunova-Krasteva, Tanya Topouzova-Hristova, Svetla T. Danova, Rositsa Tropcheva, and Stoyanka Stoitsova. 2025. "Diversification of Pseudomonas Aeruginosa After Inhaled Tobramycin Therapy of Cystic Fibrosis Patients: Genotypic and Phenotypic Characteristics of Paired Pre- and Post-Treatment Isolates." *Microorganisms* 13(4):730. doi:10.3390/microorganisms13040730.

[17]. Borotová, Petra, Lucia Galovičová, Nenad L. Vukovic, Milena Vukic, Eva Tvrdá, and Miroslava Kačániová. 2022a. "Chemical and

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

Biological Characterization of Melaleuca Alternifolia Essential Oil." *Plants* 11(4):558. doi:10.3390/plants11040558.

[18]. Borotová, Petra, Lucia Galovičová, Nenad L. Vukovic, Milena Vukic, Eva Tvrdá, and Miroslava Kačániová. 2022b. "Chemical and Biological Characterization of Melaleuca Alternifolia Essential Oil." *Plants* 11(4):558. doi:10.3390/plants11040558.

[19]. Borotová, Petra, Lucia Galovičová, Nenad L. Vukovic, Milena Vukic, Eva Tvrdá, and Miroslava Kačániová. 2022c. "Chemical and Biological Characterization of Melaleuca Alternifolia Essential Oil." *Plants* 11(4):558. doi:10.3390/plants11040558.

[20]. Borotová, Petra, Lucia Galovičová, Nenad L. Vukovic, Milena Vukic, Eva Tvrdá, and Miroslava Kačániová. 2022d. "Chemical and Biological Characterization of Melaleuca Alternifolia Essential Oil." *Plants* 11(4):558. doi:10.3390/plants11040558.

[21]. Caioni, Giulia, Elisabetta Benedetti, Monia Perugini, Michele Amorena, and Carmine Merola. 2023. "Personal Care Products as a Contributing Factor to Antimicrobial Resistance: Current State and Novel Approach to Investigation." *Antibiotics* 12(4):724. doi:10.3390/antibiotics12040724.

[22]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006a. "*Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[23]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006b. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[24]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006c. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[25]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006d. "*Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[26]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006e. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[27]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006f. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[28]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006g. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[29]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006h. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[30]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006i. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[31]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006j. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[32]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006k. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[33]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006l. "*Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[34]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006m. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology*

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

Reviews 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[35]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006n. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[36]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006o. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[37]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006p. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[38]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006q. *"Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[39]. Carson, C. F., K. A. Hammer, and T. V. Riley. 2006r. "*Melaleuca Alternifolia* (Tea Tree) Oil: A Review of Antimicrobial and Other Medicinal Properties." *Clinical Microbiology Reviews* 19(1):50–62. doi:10.1128/CMR.19.1.50-62.2006.

[40]. Çelik, Sadiye Ayşe. 2026. "Influence of Harvesting Method on Essential Oil Composition, Antioxidant Activity, and Operational Efficiency in Anatolian Sage (Salvia Fruticosa Mill.)." *Molecules* 31(12):2023. doi:10.3390/molecules31122023.

[41]. Cemali, Sadık Hüseyin, Samet Poyraz, Samet Belveren, Senanur Taş, Mehmet Ali Tamer, Naciye Yaktubay Döndaş, H. Ali Döndaş, and Jose Miguel Sansano. 2025. "Recent Insights in Multi-Target Drugs in Pharmacology and Medicinal Chemistry." *Chemmedchem* 20(18):e202500447. doi:10.1002/cmdc.202500447.

[42]. Chouhan, Sonam, Kanika Sharma, and Sanjay Guleria. 2017. "Antimicrobial Activity of Some Essential Oils—Present Status and Future Perspectives." *Medicines* 4(3):58. doi:10.3390/medicines4030058.

[43]. Cordeiro, Laísa, Pedro Figueiredo, Helivaldo Souza, Aleson Sousa, Francisco Andrade-Júnior, Daianne Medeiros, Jefferson Nóbrega, Daniele Silva, Evandro Martins, José Barbosa-Filho, and Edeltrudes Lima. 2020a. "Terpinen-4-Ol as an Antibacterial and Antibiofilm Agent against Staphylococcus Aureus." *International Journal of Molecular Sciences* 21(12):4531. doi:10.3390/ijms21124531.

[44]. Cordeiro, Laísa, Pedro Figueiredo, Helivaldo Souza, Aleson Sousa, Francisco Andrade-Júnior, Daianne Medeiros, Jefferson Nóbrega, Daniele Silva, Evandro Martins, José Barbosa-Filho, and Edeltrudes Lima. 2020b. "Terpinen-4-Ol as an Antibacterial and Antibiofilm Agent against Staphylococcus Aureus." *International Journal of Molecular Sciences* 21(12):4531. doi:10.3390/ijms21124531.

[45]. Costello, Joseph P., Nikhil N. Patel, Justin A. Chen, Marissa C. Tandron, Brandon Goldenberg, and Michael G. Baraga. 2024. "Tibial Tubercle Osteotomy (TTO): A Review of Impactful Papers in the Literature." *Journal of Orthopaedics* 60:89–95. doi:10.1016/j.jor.2024.08.011.

[46]. Cox, Sean D., Cindy M. Mann, Julie L. Markham, John E. Gustafson, John R. Warmington, and S. Grant Wyllie. 2001a. "Determining the Antimicrobial Actions of Tea Tree Oil." *Molecules : A Journal of Synthetic Chemistry and Natural Product Chemistry* 6(2):87–91. doi:10.3390/60100087.

[47]. Cox, Sean D., Cindy M. Mann, Julie L. Markham, John E. Gustafson, John R. Warmington, and S. Grant Wyllie. 2001b. "Determining the Antimicrobial Actions of Tea Tree Oil." *Molecules : A Journal of Synthetic Chemistry and Natural Product Chemistry* 6(2):87–91. doi:10.3390/60100087.

[48]. Cox, Sean D., Cindy M. Mann, Julie L. Markham, John E. Gustafson, John R. Warmington, and S. Grant Wyllie. 2001c. "Determining the Antimicrobial Actions of Tea Tree Oil." *Molecules : A Journal of Synthetic Chemistry and Natural Product Chemistry* 6(2):87–91. doi:10.3390/60100087.

[49]. Crawford, Fay, and Sally Hollis. 2007. "Topical Treatments for Fungal Infections of

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

the Skin and Nails of the Foot." *The Cochrane Database of Systematic Reviews* 2007(3):CD001434. doi:10.1002/14651858.CD001434.pub2.

[50]. Dall'Oglio, Federica, Maria Rita Nasca, Carlo Gerbino, and Giuseppe Micali. 2022. "An Overview of the Diagnosis and Management of Seborrheic Dermatitis." *Clinical, Cosmetic and Investigational Dermatology* 15:1537–48. doi:10.2147/CCID.S284671.

[51]. Ebrahimi, Nader, Hadiseh Shokouhi, Marzieh Omrani, Maryam Manzari Tavakoli, Andia Vojdani, Christine Carson, Parvaneh Mehrbod, and Saeid Ghavami. 2026a. "Phytochemistry and Pharmacology of *Melaleuca Alternifolia*: Bridging Aboriginal Heritage with Contemporary Science." *Biochimica et Biophysica Acta (BBA) - General Subjects*1870(5):130917. doi:10.1016/j.bbagen.2026.130917.

[52]. Ebrahimi, Nader, Hadiseh Shokouhi, Marzieh Omrani, Maryam Manzari Tavakoli, Andia Vojdani, Christine Carson, Parvaneh Mehrbod, and Saeid Ghavami. 2026b. "Phytochemistry and Pharmacology of *Melaleuca Alternifolia*: Bridging Aboriginal Heritage with Contemporary Science." *Biochimica et Biophysica Acta (BBA) - General Subjects* 1870(5):130917. doi:10.1016/j.bbagen.2026.130917.

[53]. Ebrahimi, Nader, Hadiseh Shokouhi, Marzieh Omrani, Maryam Manzari Tavakoli, Andia Vojdani, Christine Carson, Parvaneh Mehrbod, and Saeid Ghavami. 2026c. "Phytochemistry and Pharmacology of *Melaleuca Alternifolia*: Bridging Aboriginal Heritage with Contemporary Science." *Biochimica et Biophysica Acta (BBA) - General Subjects* 1870(5):130917. doi:10.1016/j.bbagen.2026.130917.

[54]. Enshaieh, Shahla, Abolfazl Jooya, Amir Hossein Siadat, and Fariba Iraji. 2007. "The Efficacy of 5% Topical Tea Tree Oil Gel in Mild to Moderate Acne Vulgaris: A Randomized, Double-Blind Placebo-Controlled Study." *Indian Journal of Dermatology, Venereology and Leprology* 73(1):22–25. doi:10.4103/0378-6323.30646.

[55]. Enzyme-assisted polysaccharides extraction from Calocybe indica: Synergistic antibiofilm and oxidative stability of essential oil nanoemulsion | Request PDF. n.d. *ResearchGate*. doi:10.1016/j.ijbiomac.2023.124843.

[56]. Ernst, E., and A. Huntley. 2000a. "Tea Tree Oil: A Systematic Review of Randomized Clinical Trials." *Forschende Komplementarmedizin Und Klassische Naturheilkunde = Research in Complementary and Natural Classical Medicine* 7(1):17–20. doi:10.1159/000057164.

[57]. Ernst, E., and A. Huntley. 2000b. "Tea Tree Oil: A Systematic Review of Randomized Clinical Trials." in *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*. Centre for Reviews and Dissemination (UK).

[58]. Ernst, E., and A. Huntley. 2000c. "Tea Tree Oil: A Systematic Review of Randomized Clinical Trials." *Forschende Komplementarmedizin Und Klassische Naturheilkunde = Research in Complementary and Natural Classical Medicine* 7(1):17–20. doi:10.1159/000057164.

[59]. Extraction Methods. n.d.-a. Retrieved October 13, 2026. https://www.edenbotanicals.com/extraction-methods?srsltid=AU7gw4WJ_DloTPSAi5zxuEw16j2hO5uaRsEzaCIdAQHh51tkxtZMWGgO.

[60]. Extraction Methods. n.d.-b. Retrieved October 13, 2026. https://www.edenbotanicals.com/extraction-methods?srsltid=AU7gw4X-oaFOaj_pm3k1V6a4ARVfam8kMCNKv8l7ym9J5XT6w70JoFsE.

[61]. Extraction of Bioactive Compounds from Medicinal Plants and Herbs | IntechOpen. n.d. Retrieved October 13, 2026. https://www.intechopen.com/chapters/77433.

[62]. Figueiredo, Maria. 2019. "Chemical Composition and Oil Concentration of Tea Tree Leaf Oil Grown in South Africa During a One-Year Vegetative Cycle." *Journal of Essential Oil Research* 18:52–53. doi:10.1080/10412905.2006.12067120.

[63]. Froelich, Anna, Emilia Jakubowska, Monika Wojtyłko, Barbara Jadach, Michał Gackowski, Piotr Gadziński, Olga Napierała, Yulia Ravliv, and Tomasz Osmałek. 2023. "Alginate-Based Materials Loaded with Nanoparticles in Wound Healing."

Pharmaceutics 15(4):1142. doi:10.3390/pharmaceutics15041142.

[64]. Garg, Abhinava, Ganti S. Sharma, Amit K. Goyal, Goutam Ghosh, Sudam Chandra Si, and Goutam Rath. 2020a. "Recent Advances in Topical Carriers of Anti-Fungal Agents." *Heliyon* 6(8):e04663. doi:10.1016/j.heliyon.2020.e04663.

[65]. Garg, Abhinava, Ganti S. Sharma, Amit K. Goyal, Goutam Ghosh, Sudam Chandra Si, and Goutam Rath. 2020b. "Recent Advances in Topical Carriers of Anti-Fungal Agents." *Heliyon* 6(8):e04663. doi:10.1016/j.heliyon.2020.e04663.

[66]. Garozzo, A., R. Timpanaro, B. Bisignano, P. M. Furneri, G. Bisignano, and A. Castro. 2009. "In Vitro Antiviral Activity of Melaleuca Alternifolia Essential Oil." *Letters in Applied Microbiology* 49(6):806–8. doi:10.1111/j.1472-765X.2009.02740.x.

[67]. Grassi, Lucia, Giuseppantonio Maisetta, Semih Esin, and Giovanna Batoni. 2017. "Combination Strategies to Enhance the Efficacy of Antimicrobial Peptides against Bacterial Biofilms." *Frontiers in Microbiology* 8:2409. doi:10.3389/fmicb.2017.02409.

[68]. de Groot, Anton C., and Erich Schmidt. 2016. "Tea Tree Oil: Contact Allergy and Chemical Composition." *Contact Dermatitis* 75(3):129–43. doi:10.1111/cod.12591.

[69]. Hammer, K. A., C. F. Carson, and T. V. Riley. 2003. "Antifungal Activity of the Components of Melaleuca Alternifolia (Tea Tree) Oil." *Journal of Applied Microbiology* 95(4):853–60. doi:10.1046/j.1365-2672.2003.02059.x.

[70]. Hammer, K. A., C. F. Carson, T. V. Riley, and J. B. Nielsen. 2006. "A Review of the Toxicity of Melaleuca Alternifolia (Tea Tree) Oil." *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 44(5):616–25. doi:10.1016/j.fct.2005.09.001.

[71]. Hart, P. H., C. Brand, C. F. Carson, T. V. Riley, R. H. Prager, and J. J. Finlay-Jones. 2000. "Terpinen-4-Ol, the Main Component of the Essential Oil of Melaleuca Alternifolia (Tea Tree Oil), Suppresses Inflammatory Mediator Production by Activated Human Monocytes." *Inflammation Research: Official Journal of the European Histamine Research Society ... [et Al.]* 49(11):619–26. doi:10.1007/s000110050639.

[72]. Human factors in digital manufacturing technology adoption: a workforce perspective | The International Journal of Advanced Manufacturing Technology | Springer Nature Link. n.d. Retrieved October 13, 2026. https://link.springer.com/article/10.1007/s00170-025-16524-5.

[73]. Impact of different storage conditions on the quality of selected essential oils | Request PDF. n.d. *ResearchGate*. doi:10.1016/j.foodres.2011.12.028.

[74]. Islam, Md Khairul, Tomislav Sostaric, Lee Yong Lim, Katherine Hammer, and Cornelia Locher. 2020. "Sugar Profiling of Honeys for Authentication and Detection of Adulterants Using High-Performance Thin Layer Chromatography." *Molecules* 25(22):5289. doi:10.3390/molecules25225289.

[75]. ISO 4730:2017. n.d. Retrieved October 13, 2026. https://www.iso.org/standard/69082.html.

[76]. Jacob, Shery, and Anroop B. Nair. 2026a. "Nanoemulgels as Advanced Topical Drug Delivery Systems: Mechanistic Insights and Therapeutic Applications in Skin Disorders, Infections, Wound Healing, and Cancer." *Pharmaceuticals* 19(2):247. doi:10.3390/ph19020247.

[77]. Jacob, Shery, and Anroop B. Nair. 2026b. "Nanoemulgels as Advanced Topical Drug Delivery Systems: Mechanistic Insights and Therapeutic Applications in Skin Disorders, Infections, Wound Healing, and Cancer." *Pharmaceuticals* 19(2):247. doi:10.3390/ph19020247.

[78]. Kačániová, Miroslava, Stefania Garzoli, Minhang Qiao, Zhaojun Ban, Li Li, Jian Lou, Joel Horacio Elizondo-Luevano, Wissem Mnif, Rania Ben Saad, Anis Ben Hsouna, and Alessandro Bianchi. 2026. "Deciphering Chemical Composition of *Eucalyptus Globulus* Essential Oil and Its Bioactivities Compared with 1,8-Cineole and α-Pinene: *In Vitro* and *in Situ* Antimicrobial, Antibiofilm, and Insecticidal Perspectives." *Biocatalysis and Agricultural Biotechnology* 75:104138. doi:10.1016/j.bcab.2026.104138.

[79]. Kairey, Lana, Tamara Agnew, Esther Joy Bowles, Bronwyn J. Barkla, Jon Wardle, and Romy Lauche. 2023a. "Efficacy and Safety of *Melaleuca Alternifolia* (Tea Tree) Oil for

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

Human Health—A Systematic Review of Randomized Controlled Trials." *Frontiers in Pharmacology* 14:1116077. doi:10.3389/fphar.2023.1116077.

[80]. Kairey, Lana, Tamara Agnew, Esther Joy Bowles, Bronwyn J. Barkla, Jon Wardle, and Romy Lauche. 2023b. "Efficacy and Safety of *Melaleuca Alternifolia* (Tea Tree) Oil for Human Health—A Systematic Review of Randomized Controlled Trials." *Frontiers in Pharmacology* 14:1116077. doi:10.3389/fphar.2023.1116077.

[81]. Kairey, Lana, Tamara Agnew, Esther Joy Bowles, Bronwyn J. Barkla, Jon Wardle, and Romy Lauche. 2023c. "Efficacy and Safety of *Melaleuca Alternifolia* (Tea Tree) Oil for Human Health-A Systematic Review of Randomized Controlled Trials." *Frontiers in Pharmacology* 14:1116077. doi:10.3389/fphar.2023.1116077.

[82]. Kairey, Lana, Tamara Agnew, Esther Joy Bowles, Bronwyn J. Barkla, Jon Wardle, and Romy Lauche. 2023d. "Efficacy and Safety of *Melaleuca Alternifolia* (Tea Tree) Oil for Human Health—A Systematic Review of Randomized Controlled Trials." *Frontiers in Pharmacology* 14:1116077. doi:10.3389/fphar.2023.1116077.

[83]. Kairey, Lana, Tamara Agnew, Esther Joy Bowles, Bronwyn J. Barkla, Jon Wardle, and Romy Lauche. 2023e. "Efficacy and Safety of Melaleuca Alternifolia (Tea Tree) Oil for Human Health—A Systematic Review of Randomized Controlled Trials." *Frontiers in Pharmacology* 14:1116077. doi:10.3389/fphar.2023.1116077.

[84]. Karka, Hicran Uzun, and Songul Kesen. 2026. "Effects of Different Harvesting Seasons on the Physical, Chemical, and Aromatic Properties of Tea Leaves." *Food Chemistry: X* 37:104145. doi:10.1016/j.fochx.2026.104145.

[85]. Kim, Minju, and Songmun Kim. 2026. "Climate Zone of Geographical Origin Associations with Essential Oil Composition, Yield, and Chemotype Distribution in Coriandrum Sativum L.: A Multivariate Analysis of 48 Global Accessions." *Molecules* 31(11):1950. doi:10.3390/molecules31111950.

[86]. Lal, Diwya Kumar, Bhavna Kumar, Abdulaziz S. Saeedan, and Mohd Nazam Ansari. 2023. "An Overview of Nanoemulgels for Bioavailability Enhancement in Inflammatory Conditions via Topical Delivery." *Pharmaceutics* 15(4):1187. doi:10.3390/pharmaceutics15041187.

[87]. Lam, Nelson Siukei, Xinxin Long, Xin-zhuan Su, and Fangli Lu. 2020. "*Melaleuca Alternifolia* (Tea Tree) Oil and Its Monoterpene Constituents in Treating Protozoan and Helminthic Infections." *Biomedicine & Pharmacotherapy* 130:110624. doi:10.1016/j.biopha.2020.110624.

[88]. Lee, Ji-Eun, Jayakodyge Thilini Madushani Jayakody, Jae-Il Kim, Jin-Woo Jeong, Kyung-Min Choi, Tae-Su Kim, Chan Seo, Iman Azimi, Ji-Min Hyun, and Bo-Mi Ryu. 2024. "The Influence of Solvent Choice on the Extraction of Bioactive Compounds from Asteraceae: A Comparative Review." *Foods* 13(19):3151. doi:10.3390/foods13193151.

[89]. Li, Wen-Ru, Hai-Ling Li, Qing-Shan Shi, Ting-Li Sun, Xiao-Bao Xie, Bin Song, and Xiao-Mo Huang. 2016. "The Dynamics and Mechanism of the Antimicrobial Activity of Tea Tree Oil against Bacteria and Fungi." *Applied Microbiology and Biotechnology* 100(20):8865–75. doi:10.1007/s00253-016-7692-4.

[90]. Masyita, Ayu, Reka Mustika Sari, Ayun Dwi Astuti, Budiman Yasir, Nur Rahma Rumata, Talha Bin Emran, Firzan Nainu, and Jesus Simal-Gandara. 2022. "Terpenes and Terpenoids as Main Bioactive Compounds of Essential Oils, Their Roles in Human Health and Potential Application as Natural Food Preservatives." *Food Chemistry: X* 13:100217. doi:10.1016/j.fochx.2022.100217.

[91]. Menat, Alfred, Cecília Rozan, Helena Barroso, Luís Proença, Madalena Salema-Oom, João Botelho, Abdesselam Zhiri, and Ana Cristina Manso. n.d. "Effect of a Tea Tree Oil Mouthwash on Plaque-Induced Gingivitis When Comparing to Chlorhexidine: An Exploratory Randomised Clinical Trial." *Frontiers in Oral Health* 7:1727735. doi:10.3389/froh.2026.1727735.

[92]. Milutinov, Jovana, Veljko Krstonošić, Dejan Ćirin, and Nebojša Pavlović. 2023. "Emulgels: Promising Carrier Systems for Food Ingredients and Drugs." *Polymers* 15(10):2302. doi:10.3390/polym15102302.

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

[93]. Mohammed, Afrah E., Reham M. Aldahasi, Ishrat Rahman, Ashwag Shami, Modhi Alotaibi, Munerah S. BinShabaib, Shatha S. ALHarthi, and Kawther Aabed. 2024a. "The Antimicrobial Activity of Tea Tree Oil (Melaleuca Alternifolia) and Its Metal Nanoparticles in Oral Bacteria." *PeerJ* 12:e17241. doi:10.7717/peerj.17241.

[94]. Mohammed, Afrah E., Reham M. Aldahasi, Ishrat Rahman, Ashwag Shami, Modhi Alotaibi, Munerah S. BinShabaib, Shatha S. ALHarthi, and Kawther Aabed. 2024b. "The Antimicrobial Activity of Tea Tree Oil (Melaleuca Alternifolia) and Its Metal Nanoparticles in Oral Bacteria." *PeerJ* 12:e17241. doi:10.7717/peerj.17241.

[95]. Mohammed, Afrah E., Reham M. Aldahasi, Ishrat Rahman, Ashwag Shami, Modhi Alotaibi, Munerah S. BinShabaib, Shatha S. ALHarthi, and Kawther Aabed. 2024c. "The Antimicrobial Activity of Tea Tree Oil (Melaleuca Alternifolia) and Its Metal Nanoparticles in Oral Bacteria." *PeerJ* 12:e17241. doi:10.7717/peerj.17241.

[96]. Mondello, Francesca, Flavia De Bernardis, Antonietta Girolamo, Antonio Cassone, and Giuseppe Salvatore. 2006. "In Vivo Activity of Terpinen-4-Ol, the Main Bioactive Component of Melaleuca Alternifolia Cheel (Tea Tree) Oil against Azole-Susceptible and -Resistant Human Pathogenic Candida Species." *BMC Infectious Diseases* 6:158. doi:10.1186/1471-2334-6-158.

[97]. Mondello, Francesca, Stefano Fontana, Maria Scaturro, Antonietta Girolamo, Marisa Colone, Annarita Stringaro, Maura Di Vito, and Maria Luisa Ricci. 2022. "Terpinen-4-Ol, the Main Bioactive Component of Tea Tree Oil, as an Innovative Antimicrobial Agent against Legionella Pneumophila." *Pathogens* 11(6):682. doi:10.3390/pathogens11060682.

[98]. Morris, Marilyn C., Aaron Donoghue, Jennifer A. Markowitz, and Kevin C. Osterhoudt. 2003. "Ingestion of Tea Tree Oil (Melaleuca Oil) by a 4-Year-Old Boy." *Pediatric Emergency Care* 19(3):169–71. doi:10.1097/01.pec.0000081241.98249.7b.

[99]. Nabi, Md. Hassan Bin, Md. Monir Ahmed, Md. Suhel Mia, Sumon Islam, and Wahidu Zzaman. 2025. "Essential Oils: Advances in Extraction Techniques, Chemical Composition, Bioactivities, and Emerging Applications." *Food Chemistry Advances*8:101048. doi:10.1016/j.focha.2025.101048.

[100]. Nair, Dileep G., and Ralf Weiskirchen. 2024. "Advanced In Vitro Models for Preclinical Drug Safety: Recent Progress and Prospects." *Current Issues in Molecular Biology* 47(1):7. doi:10.3390/cimb47010007.

[101]. Najafian, Sharareh. 2025. "Preservation of Essential Oil Quality in Endangered Ziziphora Tenuior L. under Different Storage Conditions." *Scientific Reports* 15:40535. doi:10.1038/s41598-025-24422-9.

[102]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023a. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

[103]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023b. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

[104]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023c. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

[105]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023d. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

[106]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023e. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

[107]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023f. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

[108]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023g. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

[109]. Nascimento, Tânia, Diana Gomes, Ricardo Simões, and Maria da Graça Miguel. 2023h. "Tea Tree Oil: Properties and the Therapeutic Approach to Acne—A Review." *Antioxidants* 12(6):1264. doi:10.3390/antiox12061264.

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 5, Sep.-Oct.2026, pp:1069-1095 www.ijprajournal.com ISSN:2456-4494

[110]. Nguyen, Huy Loc, Hong Minh Xuan Nguyen, and Thi Bich Ngoc Nguyen. 2026a. "Nano-Enabled Advances in Tea Tree Essential Oil *(Melaleuca Alternifolia):* Composition, Bioactivity, and Emerging Roles in Food Protection." *Materials* 19(13):2915. doi:10.3390/ma19132915.

[111]. Nguyen, Huy Loc, Hong Minh Xuan Nguyen, and Thi Bich Ngoc Nguyen. 2026b. "Nano-Enabled Advances in Tea Tree Essential Oil *(Melaleuca Alternifolia*): Composition, Bioactivity, and Emerging Roles in Food Protection." *Materials* 19(13):2915. doi:10.3390/ma19132915.

[112]. Nguyen, Huy Loc, Hong Minh Xuan Nguyen, and Thi Bich Ngoc Nguyen. 2026c. "Nano-Enabled Advances in Tea Tree Essential Oil *(Melaleuca Alternifolia):* Composition, Bioactivity, and Emerging Roles in Food Protection." *Materials* 19(13):2915. doi:10.3390/ma19132915.

[113]. Nguyen, Huy Loc, Hong Minh Xuan Nguyen, and Thi Bich Ngoc Nguyen. 2026d. "Nano-Enabled Advances in Tea Tree Essential Oil *(Melaleuca Alternifolia)*: Composition, Bioactivity, and Emerging Roles in Food Protection." *Materials* 19(13):2915. doi:10.3390/ma19132915.

[114]. Nguyen, Huy Loc, Hong Minh Xuan Nguyen, and Thi Bich Ngoc Nguyen. 2026e. "Nano-Enabled Advances in Tea Tree Essential Oil *(Melaleuca Alternifolia)*: Composition, Bioactivity, and Emerging Roles in Food Protection." *Materials* 19(13):2915. doi:10.3390/ma19132915.

[115]. Nguyen, Huy Loc, Hong Minh Xuan Nguyen, and Thi Bich Ngoc Nguyen. 2026f. "Nano-Enabled Advances in Tea Tree Essential Oil *(Melaleuca Alternifolia)*: Composition, Bioactivity, and Emerging Roles in Food Protection." *Materials* 19(13):2915. doi:10.3390/ma19132915.

[116]. Nguyen, Huy Loc, Hong Minh Xuan Nguyen, and Thi Bich Ngoc Nguyen. 2026g. "Nano-Enabled Advances in Tea Tree Essential Oil *(Melaleuca Alternifolia)*: Composition, Bioactivity, and Emerging Roles in Food Protection." *Materials* 19(13):2915. doi:10.3390/ma19132915.

[117]. Ninomiya, Kentaro, Kazumi Hayama, Sanae A. Ishijima, Naho Maruyama, Hiroshi Irie, Junichi Kurihara, and Shigeru Abe. 2013. "Suppression of Inflammatory Reactions by Terpinen-4-Ol, a Main Constituent of Tea Tree Oil, in a Murine Model of Oral Candidiasis and Its Suppressive Activity to Cytokine Production of Macrophages in Vitro." *Biological & Pharmaceutical Bulletin* 36(5):838–44. doi:10.1248/bpb.b13-00033.

[118]. Nogueira, M. N. M., S. G. Aquino, C. Rossa Junior, and D. M. P. Spolidorio. 2014a. "Terpinen-4-Ol and Alpha-Terpineol (Tea Tree Oil Components) Inhibit the Production of IL-1β, IL-6 and IL-10 on Human Macrophages." *Inflammation Research: Official Journal of the European Histamine Research Society ... [et Al.]* 63(9):769–78. doi:10.1007/s00011-014-0749-x.

[119]. Nogueira, M. N. M., S. G. Aquino, C. Rossa Junior, and D. M. P. Spolidorio. 2014b. "Terpinen-4-Ol and Alpha-Terpineol (Tea Tree Oil Components) Inhibit the Production of IL-1β, IL-6 and IL-10 on Human Macrophages." *Inflammation Research: Official Journal of the European Histamine Research Society ... [et Al.]* 63(9):769–78. doi:10.1007/s00011-014-0749-x.

[120]. Nordenberg, J., L. Wasserman, E. Beery, D. Aloni, H. Malik, K. H. Stenzel, and A. Novogrodsky. 1986. "Growth Inhibition of Murine Melanoma by Butyric Acid and Dimethylsulfoxide." *Experimental Cell Research* 162(1):77–85. doi:10.1016/0014-4827(86)90427-1.

[121]. Nurzyńska-Wierdak, Renata, Dominika Pietrasik, and Magdalena Walasek-Janusz. 2022. "Essential Oils in the Treatment of Various Types of Acne—A Review." *Plants* 12(1):90. doi:10.3390/plants12010090.

[122]. Oliveira, M. S., M. S. A. Paula, Millena Machado Cardoso, N. P. Silva, Luciana Cláudia Diniz Tavares, Taleessa Vieira Gomes, Dayanne Lopes Porto, Cícero Flávio Soares Aragão, Rodrigo Luiz Fabri, Guilherme Diniz Tavares, and Ana Carolina Morais Apolônio. 2024. "Exploring the Antimicrobial Efficacy of Tea Tree Essential Oil and Chitosan against Oral Pathogens to Overcome Antimicrobial Resistance." *Microbial Pathogenesis* 196:107006. doi:10.1016/j.micpath.2024.107006.

[123]. Oliveira, Rita, and Isabel F. Almeida. 2023. "Patient-Centric Design of Topical Dermatological Medicines." *Pharmaceuticals* 16(4):617. doi:10.3390/ph16040617.

[124]. Oran, Nazan Tuna, Nurten Alan, Pinar Akokay, Sibel Büyükçoban, and Bekir Uğur Ergür. 2023. "The Healing Effect of Topical Tea Tree Oil on Pressure Ulcers in a Rat Model." *Journal of Wound Care* 32(Sup3a):xiv–xxi. doi:10.12968/jowc.2023.32.Sup3a.xiv.

[125]. Orchard, Ané, and Sandy F. van Vuuren. 2019. "Carrier Oils in Dermatology." *Archives of Dermatological Research* 311(9):653–72. doi:10.1007/s00403-019-01951-8.

[126]. Pan, Shanshan, Luan Yin, Jie Liu, Jie Tong, Zichuan Wang, Jiahui Zhao, Xuesong Liu, Yong Chen, Jing Miao, Yuan Zhou, Su Zeng, and Tengfei Xu. 2024. "Metabolomics-driven Approaches for Identifying Therapeutic Targets in Drug Discovery." *MedComm* 5(11):e792. doi:10.1002/mco2.792.

[127]. Pandey, Vinay Kumar, Anjali Tripathi, Shivangi Srivastava, Aamir Hussain Dar, Rahul Singh, Alvina Farooqui, and Sneha Pandey. 2023. "Exploiting the Bioactive Properties of Essential Oils and Their Potential Applications in Food Industry." *Food Science and Biotechnology* 32(7):885–902. doi:10.1007/s10068-023-01287-0.

[128]. Paparella, Antonello, Bhagwat Nawade, Liora Shaltiel-Harpaz, and Mwafaq Ibdah. 2022. "A Review of the Botany, Volatile Composition, Biochemical and Molecular Aspects, and Traditional Uses of Laurus Nobilis." *Plants* 11(9):1209. doi:10.3390/plants11091209.

[129]. Park, Chanjoo, Sandra M. Garland, and Dugald C. Close. 2022. "The Effect of the Height of Coppicing and Harvest Season on the Yield and Quality of the Essential Oil of Kunzea Ambigua." *Plants* 12(1):20. doi:10.3390/plants12010020.

[130]. Park, Chanjoo, Nahyun Kim, Soo-Kyeong Jang, and Mi-Jin Park. 2026. "Effect of Distillation Time on the Yield and Chemical Composition of Leaf Essential Oil from Abies Koreana." *Plants* 15(7):1123. doi:10.3390/plants15071123.

[131]. (PDF) Creating a viable farm forestry industry in Australia. What will it take? n.d. Retrieved October 13, 2026. https://www.researchgate.net/publication/282355769_Creating_a_viable_farm_forestry_industry_in_Australia_What_will_it_take.

[132]. (PDF) Tea Tree (Melaleuca alternifolia (Maiden & Betche) Cheel) Oil an important medicinal essential oil. 2026. *ResearchGate*. doi:10.54994/emujpharmsci.1030526.

[133]. (PDF) Tea Tree Oil Laboratory Guidance Document. n.d. Retrieved October 13, 2026. https://www.researchgate.net/publication/328175728_Tea_Tree_Oil_Laboratory_Guidance_Document.

[134]. Piskin, Suleyman, and Erol Uzunali. 2007. "A Review of the Use of Adapalene for the Treatment of Acne Vulgaris." *Therapeutics and Clinical Risk Management* 3(4):621–24.

[135]. Proietti, Simona, Valentina Scariot, Stefania De Pascale, and Roberta Paradiso. 2022. "Flowering Mechanisms and Environmental Stimuli for Flower Transition: Bases for Production Scheduling in Greenhouse Floriculture." *Plants* 11(3):432. doi:10.3390/plants11030432.

[136]. Rathee, Priyanka, Renu Sehrawat, Pooja Rathee, Anurag Khatkar, Esra Küpeli Akkol, Sarita Khatkar, Neelam Redhu, Gizem Türkcanoğlu, and Eduardo Sobarzo-Sánchez. 2023. "Polyphenols: Natural Preservatives with Promising Applications in Food, Cosmetics and Pharma Industries; Problems and Toxicity Associated with Synthetic Preservatives; Impact of Misleading Advertisements; Recent Trends in Preservation and Legislation." *Materials* 16(13):4793. doi:10.3390/ma16134793.

[137]. Ripari, Francesca, Alessia Cera, Monica Freda, Giulia Zumbo, Francesca Zara, and Iole Vozza. 2020. "Tea Tree Oil versus Chlorhexidine Mouthwash in Treatment of Gingivitis: A Pilot Randomized, Double Blinded Clinical Trial." *European Journal of Dentistry* 14(1):55–62. doi:10.1055/s-0040-1703999.

[138]. Roana, Janira, Narcisa Mandras, Daniela Scalas, Paolo Campagna, and Vivian Tullio. 2021. "Antifungal Activity of Melaleuca Alternifolia Essential Oil (TTO) and Its Synergy with Itraconazole or Ketoconazole against Trichophyton Rubrum." *Molecules* 26(2):461. doi:10.3390/molecules26020461.

[139]. Rodrigues, Tânia, Ana Lima, Tanner Wortham, Filipe Arruda, Alexandre Janeiro, José Baptista, and Elisabete Lima. 2024. "Essential Oil Composition and Anti-Cholinesterase Properties of Cryptomeria Japonica Foliage Harvested in São Miguel Island (Azores) in Two Different Seasons."

Plants 13(23):3277. doi:10.3390/plants13233277.

[140]. Rutherford, Tim, Rosemary Nixon, Mei Tam, and Bruce Tate. 2007. "Allergy to Tea Tree Oil: Retrospective Review of 41 Cases with Positive Patch Tests over 4.5 Years." *The Australasian Journal of Dermatology* 48(2):83–87. doi:10.1111/j.1440-0960.2007.00341.x.

[141]. SALVATORI, C., L. BARCHI, F. GUZZO, and M. GARGARI. 2017. "A Comparative Study of Antibacterial and Anti-Inflammatory Effects of Mouthrinse Containing Tea Tree Oil." *Oral & Implantology* 10(1):59–70. doi:10.11138/orl/2017.10.1.059.

[142]. Satchell, Andrew C., Anne Saurajen, Craig Bell, and Ross St C. Barnetson. 2002a. "Treatment of Interdigital Tinea Pedis with 25% and 50% Tea Tree Oil Solution: A Randomized, Placebo-Controlled, Blinded Study." *The Australasian Journal of Dermatology* 43(3):175–78. doi:10.1046/j.1440-0960.2002.00590.x.

[143]. Satchell, Andrew C., Anne Saurajen, Craig Bell, and Ross St C. Barnetson. 2002b. "Treatment of Interdigital Tinea Pedis with 25% and 50% Tea Tree Oil Solution: A Randomized, Placebo-Controlled, Blinded Study." *The Australasian Journal of Dermatology* 43(3):175–78. doi:10.1046/j.1440-0960.2002.00590.x.

[144]. Satchell, Andrew C., Anne Saurajen, Craig Bell, and Ross StC Barnetson. 2002. "Treatment of Dandruff with 5% Tea Tree Oil Shampoo." *Journal of the American Academy of Dermatology* 47(6):852–55. doi:10.1067/mjd.2002.122734.

[145]. Schnitzler, P., K. Schön, and J. Reichling. 2001. "Antiviral Activity of Australian Tea Tree Oil and Eucalyptus Oil against Herpes Simplex Virus in Cell Culture." *Die Pharmazie* 56(4):343–47.

[146]. Shapira, Shiran, Shlomo Pleban, Diana Kazanov, Peter Tirosh, and Nadir Arber. 2016. "Terpinen-4-Ol: A Novel and Promising Therapeutic Agent for Human Gastrointestinal Cancers." *PLoS ONE* 11(6):e0156540. doi:10.1371/journal.pone.0156540.

[147]. Shepherd, Kelly A., Brendan J. Lepschi, Eden A. Johnson, Andrew G. Gardner, Emily B. Sessa, and Rachel S. Jabaily. 2020. "The Concluding Chapter: Recircumscription of Goodenia (Goodeniaceae) to Include Four Allied Genera with an Updated Infrageneric Classification." *PhytoKeys* 152:27–104. doi:10.3897/phytokeys.152.49604.

[148]. Standard - Essential oil of Melaleuca, terpinen-4-ol type (tea tree oil) ISO 4730:2025 - Swedish Institute for Standards, SIS. n.d. Retrieved October 13, 2026. https://www.sis.se/en/produkter/chemical-technology/products-of-the-chemical-industry/essential-oils/iso-47302025/.

[149]. Stokes, Daniel J., Bryant P. Elrick, Melissa L. Carpenter, Yazdan Raji, Kade S. McQuivey, Seth L. Sherman, and Rachel M. Frank. 2024. "Tibial Tubercle Osteotomy: Indications, Outcomes, and Complications." *Current Reviews in Musculoskeletal Medicine* 17(11):484–95. doi:10.1007/s12178-024-09915-w.

[150]. Sun, Shicai, Ying Yu, Yunju Jo, Jung Ho Han, Yingqi Xue, Minkyoung Cho, Sung-Jin Bae, Dongryeol Ryu, Wonyoung Park, Ki-Tae Ha, and Shiwei Zhuang. 2025. "Impact of Extraction Techniques on Phytochemical Composition and Bioactivity of Natural Product Mixtures." *Frontiers in Pharmacology* 16:1615338. doi:10.3389/fphar.2025.1615338.

[151]. Tapfumaneyi, Pronalis, Khanh Phan, Yicheng Huang, Kewaree Sodsri, Sarika Namjoshi, Howard Maibach, and Yousuf Mohammed. 2025. "Solute–Vehicle–Skin Interactions and Their Contribution to Pharmacokinetics of Skin Delivery." *Pharmaceutics* 17(6):764. doi:10.3390/pharmaceutics17060764.

[152]. Tea Tree Oil - an overview | ScienceDirect Topics. n.d. Retrieved October 13, 2026. https://www.sciencedirect.com/topics/medicine-and-dentistry/tea-tree-oil.

[153]. Tea tree oil: a systematic review of randomized clinical trials - Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews - NCBI Bookshelf. n.d. Retrieved October 14, 2026. https://www.ncbi.nlm.nih.gov/books/NBK68347/.

[154]. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: A randomized, placebo-controlled, blinded study. n.d. Retrieved October 14, 2026. https://www.researchgate.net/publication/11258278_Treatment_of_interdigital_tinea_pedis_with_25_and_50_tea_tree_oil_solution_A_r

andomized_placebo-controlled_blinded_study.

[155]. Tsao, N., C. F. Kuo, H. Y. Lei, S. L. Lu, and K. J. Huang. 2010. "Inhibition of Group A Streptococcal Infection by Melaleuca Alternifolia (Tea Tree) Oil Concentrate in the Murine Model." *Journal of Applied Microbiology* 108(3):936–44. doi:10.1111/j.1365-2672.2009.04487.x.

[156]. Turpin, Gerry, Edita Ritmejerytė, Joanne Jamie, Darren Crayn, and Phurpa Wangchuk. 2022. "Aboriginal Medicinal Plants of Queensland: Ethnopharmacological Uses, Species Diversity, and Biodiscovery Pathways." *Journal of Ethnobiology and Ethnomedicine* 18:54. doi:10.1186/s13002-022-00552-6.

[157]. Understanding the role of key metabolic genes, transcription factors, and trichome-related genes in-terms of temperature-stress management techniques in the rose-scented Geranium (Pelargonium graveolens) using transcriptomic analysis | Request PDF. n.d. *ResearchGate*. doi:10.1016/j.indcrop.2023.116673.

[158]. Variation in oil concentration and economic return from tea-tree (Melaleuca alternifolia Cheel) oil. n.d.-a. *ResearchGate*. doi:10.1071/EA9900675.

[159]. Variation in oil concentration and economic return from tea-tree (Melaleuca alternifolia Cheel) oil. n.d.-b. *ResearchGate*. doi:10.1071/EA9900675.

[160]. Vázquez, Aimé, Nurhayat Tabanca, and Paul E. Kendra. 2023. "HPTLC Analysis and Chemical Composition of Selected Melaleuca Essential Oils." *Molecules* 28(9):3925. doi:10.3390/molecules28093925.

[161]. Venturella, Giuseppe, Valeria Ferraro, Fortunato Cirlincione, and Maria Letizia Gargano. 2021. "Medicinal Mushrooms: Bioactive Compounds, Use, and Clinical Trials." *International Journal of Molecular Sciences* 22(2):634. doi:10.3390/ijms22020634.

[162]. Voelker, Julia, Ramil Mauleon, and Mervyn Shepherd. 2023. "The Terpene Synthase Genes of *Melaleuca Alternifolia* (Tea Tree) and Comparative Gene Family Analysis among Myrtaceae Essential Oil Crops." *Plant Systematics and Evolution* 309(3):13. doi:10.1007/s00606-023-01847-1.

[163]. Waheed, Marwa, Muhammad Bilal Hussain, Farhan Saeed, Muhammad Afzaal, Aftab Ahmed, Rushba Irfan, Noor Akram, Faiyaz Ahmed, and Gebremichael Gebremedhin Hailu. 2024. "Phytochemical Profiling and Therapeutic Potential of Thyme (Thymus Spp.): A Medicinal Herb." *Food Science & Nutrition* 12(12):9893–9912. doi:10.1002/fsn3.4563.

[164]. Wang, Zening, Changtong Lu, Gaolei Xi, Yibo Ning, Xueying Cao, Lei Li, Haoyang Chen, Zhifei Chen, Yongzhen Zhao, Tianxin Shen, Tao Jia, and Xiuhua Zhao. 2026. "A Highly Effective Extraction Method for Tea Essential Oil by Microwave-Assisted Hydrodistillation for Antioxidant Application." *New Journal of Chemistry* 50(25):10652–61. doi:10.1039/d6nj00981f.

[165]. Webb, Hamish, Robert Lanfear, John Hamill, William J. Foley, and Carsten Külheim. 2013. "The Yield of Essential Oils in Melaleuca Alternifolia (Myrtaceae) Is Regulated through Transcript Abundance of Genes in the MEP Pathway." *PLoS ONE* 8(3):e60631. doi:10.1371/journal.pone.0060631.

[166]. Williamson, Deborah A., Glen P. Carter, and Benjamin P. Howden. 2017. "Current and Emerging Topical Antibacterials and Antiseptics: Agents, Action, and Resistance Patterns." *Clinical Microbiology Reviews* 30(3):827–60. doi:10.1128/CMR.00112-16.

[167]. Wróblewska, Magdalena, Emilia Szymańska, and Katarzyna Winnicka. 2021. "The Influence of Tea Tree Oil on Antifungal Activity and Pharmaceutical Characteristics of Pluronic® F-127 Gel Formulations with Ketoconazole." *International Journal of Molecular Sciences* 22(21):11326. doi:10.3390/ijms222111326.

[168]. Yasin, Mursleen, Adnan Younis, Talha Javed, Ahsan Akram, Muhammad Ahsan, Rubab Shabbir, Muhammad Moaaz Ali, Ayesha Tahir, Enas M. El-Ballat, Mohamed S. Sheteiwy, Reda Helmy Sammour, Christophe Hano, Fahad A. Alhumaydhi, and Mohamed A. El-Esawi. 2021. "River Tea Tree Oil: Composition, Antimicrobial and Antioxidant Activities, and Potential Applications in Agriculture." *Plants* 10(10):2105. doi:10.3390/plants10102105.

[169]. Yu, Shiqian, Jiajin Sun, Haiming Chen, Weijun Chen, Qiuping Zhong, Ming Zhang, Jianfei Pei, Rongrong He, and Wenxue Chen.

2024. "Disruption of Cell Membranes and Redox Homeostasis as an Antibacterial Mechanism of Dielectric Barrier Discharge Plasma against Fusarium Oxysporum." *International Journal of Molecular Sciences* 25(14):7875. doi:10.3390/ijms25147875.

[170]. Zhang, Chenjiao, Bowen Liu, Jingchao Hu, Li Zhao, and Han Zhao. n.d. "The Effect of Local Application of Tea Tree Oil Adjunctive to Daily Oral Maintenance and Nonsurgical Periodontal Treatment: A Systematic Review and Meta-Analysis of Randomised Controlled Studies." *Oral Health & Preventive Dentistry* 22:b5458585. doi:10.3290/j.ohpd.b5458585.

[171]. Zhang, Haofuzi, and Xiaofan Jiang. n.d. "Importance of Clinical Trials and Contributions to Contemporary Medicine: Commentary." *Annals of Medicine* 57(1):2451190. doi:10.1080/07853890.2025.2451190.

[172]. Zhao, Lin, Jiamei Chen, Bai Bai, Guili Song, Jingwen Zhang, Han Yu, Shiwei Huang, Zhang Wang, and Guanghua Lu. 2024. "Topical Drug Delivery Strategies for Enhancing Drug Effectiveness by Skin Barriers, Drug Delivery Systems and Individualized Dosing." *Frontiers in Pharmacology* 14:1333986. doi:10.3389/fphar.2023.1333986.