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# Tea Tree (*Melaleuca alternifolia* (Maiden & Betche) Cheel) Oil: An important medicinal essential oil

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## Abstract

*Melaleuca alternifolia* (Maiden & Betche) Cheel oil (Tea Tree Oil, TTO) is an essential oil appropriate for medicinal and cosmetic usage. Tea tree oil is composed of complex formulation with more than 100 components; however, the most pharmaceutically active one is terpinen-4-ol. TTO can be implemented for decolonization of multi-resistant *Staphylococcus aureus*, anti-tumor therapy and antifungal activity based on different doses and exposure-duration proportionate with the targeted species. Antioxidant activity is related to α-terpinene, α-terpinolene and γ-terpinene. Hypersensitivity may occur as mild dermatitis or being aggravated to hepatitis and central nervous system reactions due to chronic or acute poisoning. Acne treatment prognosis shows significant improvement after TTO application proceeding by *Propionibacterium acnes* colony destruction. Plus, TTO usage psoriasis is also possible. Further investigations have premised TTO's insecticidal effects performed by anticholinesterase activity. Destructive ability of the oil on *Pityrosporum ovale* is also indisputable and including TTO as the active ingredient has been highly beneficial for curing scalp dandruff. Expeditious antiviral activity is also considered as the promising characteristic suggested for this oil. Still, little information is available about feasibility of *in vivo* utilization.

**Keywords**

Dermo-cosmetic, *Melaleuca alternifolia*, pharmacological properties, tea tree oil, terpinen-4-ol.

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## INTRODUCTION

Dominant member of Australian domestic forest, *Melaleuca alternifolia* is an ever-green woody shrub from Mytraceae family. In 1770, the name of tea tree mentioned by Captain James Cook due to its aromatic scent (Saller *et al.*, 1998). Tea tree oil, obtained by steam distillation from leaves, have been consumed by native Australian people, Aboriginals, for its germicidal property (Carson and Riley, 1998). First scientific examination about TTO's antiseptic activity had been performed by Penfold *et al.* (Penfold and Grant, 1925). First officially approved tilt of the oil's chemical composition was discovered and published by Brophy et al. (Brophy *et al.*, 1989). Six distinct chemotypes based on genetic differences may exhibit variable antimicrobial ranges; terpinen-4-ol chemotype is the one used in commercial oil production (Keszei *et al.*, 2010). While terpinen-4-ol is the core of biological activities, 1,8-cineole is assumed to be the beginner of dermatologic hypersensitivity; a prevalence side effect in topical applications (Carson *et al.*, 2019). TTO's mode of action may show sharp switch from bacteriostatic to bactericidal according to the applied concentration (Oliva *et al.*, 2018). High selectivity among different strains emphasizes oil's destructive effect on pathogenic microorganisms (Cueva *et al.*, 2010). Synergism is, also, another crucial term used while analyzing TTO performance (D'Arrigo *et al.*, 2010, Mickiene *et al.*, 2011). Bacterial resistance linked with frequent antibiotic prescription creates a demand for alternative agents. TTO, with remarkable antibacterial spectrum, not only does it exhibit acceptable range of *in vivo* activity against MRSA and resistant *Escherichia coli* strains, but also preparation of TTO containing sanitizing products for ICU personals is feasible (Blackwood *et al.*, 2013). TTO, with an unknown mechanism, declines the count of lesions originated by *Tobacco mosaic* (Bishop, 1995) plus application of this oil speeds up re-epithelization in recurrent *Herpes labialis* (RHL) involution (Carson *et al.*, 2001); and, also, it can be preferred for curing fungal infections in a dose-dependent manner (K. A. Hammer *et al.*, 2003). As an excellent antioxidant, it accelerates the rate of tissue renovation (Kim *et al.*, 2004). Improvement observed in subcutaneous mesothelioma prognosis after topical TTO administration revealed anti-cancer potential of the oil as well. TTO is accepted as an ideal active ingredient for cosmetology in order that it can cover both infectious and

inflammatory related skin disconfirms. The usage of TTO in pharmaceutical industry is not limited to the 'active ingredient' section; it also is preferable as a natural preservative option (Zhang *et al.,* 2018). In this review, tea tree oil was evaluated according to its botanical and chemical properties as well as biological activity.

## DISCUSSION

*Melaleuca alternifolia* is an evergreen, little sclerophyllous with woody texture reaching up to 7 meters, which is covered with paper-like bark and decorated with flowers, each attached to a separate bract and collected in bottlebrush shaped clusters (Altman, 1988). Seeds can be observed with naked eye, being protected by a round-shaped woody capsule (Craven, 1999). Tea tree is not the only member of *Melaleuca* genus, it represents 330 other species. Important for determining ecological properties of wetlands, Myrtaceae family constitutes a dominant part of Australian natural flora (Franklin *et al.,* 2007; Edwards *et al.,* 2019) and most of them contain aromatic extracts stored in glandular sacs under their leaves (Serbesoff-King, 2003). After *M. alternifolia*, *M. cajuputi* and *M. leucadendron* are famous species due to their essential oil. Although it is possible to obtain equivalent extracts from different *Melaleuca* plants (Falci *et al.,* 2015), only tea tree oil (TTO) can provide a high degree of germicidal efficacy (Sharifi-Rad *et al.,* 2017). *M. alternifolia* grows in the coastal regions of the country from port Macquarie to New South Wales. Aborigines used to implement it as an antiseptic agent in their traditional medicines (Edmondson *et al.,* 2011); prepared pomades were utilized for accelerating wound healing prognosis plus persistent respiratory discomforts were suppressed with the aid of TTO (Cox *et al.,* 2001; Carson *et al.,* 2019). Moreover, there were healing lakes localized under tea trees where leaves naturally fell down and gave the water disinfecting ability (Craven, 1999). All knowledge and practical skills were conveyed from one generation to another, but the chain of transition was cleaved at some point (Carson *et al.,* 2019). At 1770's, Captain James Cook and his sailors named this tree as 'tea tree' due to its spicy smell (Ian Southwell, 1999). First medical research was published in 1920s to 1930s, performed by Penfold *et al.* (Penfold and Grant, 1925), a comparison-based study carried out between essential oils with antibacterial activity and phenol. Acquisition of optimistic outcomes from TTO, 11-13 times more effective than phenol, supervised bias toward natural germicidal

products. During Second World War TTO was added to navy's first aid kits due to its wide antibacterial spectrum (Lis-Balchin *et al.,* 2000). *Obstetrics and Gynecology* published a journal authored by Pefia (Pefia, 1962) named "*Melaleuca alternifolia* oil – its use for Trichomonal Vaginitis and other Vaginal Infections". 0.5% diluted preparations of TTO as washing solution cured all cases after six sessions. In 1985, three discrete studies were performed by Belaiche (Belaiche, 1985) on vaginal *Candida albicans* cystitis and onychomycosis in which TTO speeded up treatment prognosis associated with a safe regimen. In addition, topical treatment of toenail onychomycosis with 100% *Melaleuca* oil can be as effective as 1% clotrimazole solution (Buck *et al.,* 1994). After successful feedbacks from first synthetic antibiotics (*e.g.* penicillin) popular notion was inclined to artificial choices, but occurrence of resistance, disturbance of natural flora and subsequent superinfections caused by arbitrary prescriptions was discouraging (Carson and Riley, 1998; Larson and Jacob, 2012). Cross-contamination caused by aerosol microbes may be a questionable situation after dental surgeries. Although, there is no doubt that chlorhexidine digluconate performs expeditiously among famous disinfectant agents, however; utilization of TTO as a mouthwash before manual or ultrasonic scaling suppresses the microbial colonies dramatically (Shetty *et al.,* 2013). Success of a TTO containing washing gel, due to its anti-inflammatory activity, in chronic gingivitis management in comparison with chlorhexidine was also remarkable (Hart *et al.,* 2000; Soukoulis and Hirsch, 2004). TTO has been mentioned among first-line agents of veterinary medical history (Mozelsio *et al.,* 2003). Studies suggested TTO usage as air sanitizer against airborne microbes (influenza virus, *E. coli* and *Pseudomonas fluorescens*) for animal houses, stables (May, 2000; Mickiene *et al.,* 2011) and air tunnel system of industrial environments (Pyankov *et al.,* 2008, 2012). TTO disinfectant products can be implemented by caregivers for preventing nosocomial infections prevalence (Blackwood *et al.,* 2013). In 1970, plantation of tea tree has been established (Carson *et al.,* 2019). Conditions of natural environment, soil type, climate, humidity and water content, must be imitated while cultivation (Rodney *et al.,* 2015). Sandy loam is proposed as the native soil texture with high amount of moisture and slightly acidic pH circulating around 5.0. In addition, tea tree desires a mild subtropical weather that may has annual raining height between 1200 and 1600 mm. It is crucial to maintain the soil temperature above 17 $^{o}$C, because the temperature reduction may trigger

'dormancy' of the tree (Colton and Murtagh, 1999). Surprisingly, *M. alternifolia* prefers dense tree orientation. However, the spacing pattern does not affect the oil components, but it shows boosting effect on oil yield (Small, 1981). Pest damaging in natural lands is uncommon due to low leaf/wood ratio. Increased leaf ratio in cultivation area is accompanied by greater demand for suitable pesticide. Attention must have be given to *Purana tigrina*, mites and psyllids; the most dangerous ones for oil yield (Campbell and Maddox, 1999). Using any type of chemical materials in wrong dose, rate or technique may lead to impurity creation (Rowe, 1999; Larkman, 2016). Visual examination can be applied for determining oil purity. While TTO is colorless in its pure form, any discoloration is considered as the presence of impurity. Examination of odor abnormality, caused by inappropriate distillation methods, is a crucial step in QC (Rowe, 1999). Appropriate time for harvesting may vary, from 1 to 3 years, depending on the growth conditions. Quality peak time for *M. alternifolia* can be determined as nine months after planting, preferring dry seasons to minimize the risk of fungal infection development. Tree should be cut 15-30 cm above the soil level to assure tree re-growth. TTO is extracted from leaves and not woody terminal branches mainly by steam distillation. Solvent extraction is another method in which ethanol is used as the solvent; however, a sharp drop in terpene concentration turns it into an undesirable option. New methods such as microwave heating are also available. Additionally, more precise techniques may be applied to *in vitro* media; such as microwave technology (Carson *et al.,* 2019) and Static Headspace Gas Chromatography (HS-GC) (Homer *et al.,* 2000). TTO's chemical composition needs to be controlled before marketing to assure the concentration of pharmacologically active terpenes. Naturally growing trees may expose to different environmental factors triggering genetic mutation and subsequent intra-specific variation (Sharififar *et al.,* 2007). Even though morphological characteristics are similar among different foliar chemotypes, ecological and chemical properties show significant differences (Bustos-Segura *et al.,* 2017). Six foliar chemotypes, based on dissimilarity of terpinen-4-ol, terpinolene and 1,8-cineole concentrations (Keszei *et al.,* 2010), are currently accepted by **The International Standard, ISO 4730**. Similar *in vitro* and *in vivo* bioactivity is expected from oils with identical chemotype (Homer *et al.,* 2000). Differences between biosynthetic pathways for terpene production may be the reason for chemotype variation (Keszei *et al.,*

2010), which is significantly complex (Padovan *et al.,* 2017). The only commercially valuable chemotype is the one with highest terpinen-4-ol as well as lowest 1,8-cineole and *d*-limonene level. Geographical separation is observable according to dominant TTO chemotype (Homer *et al.,* 2000); however different sources can be used for this purpose even if chemotype variability is detected (Keszei *et al.,* 2010).

Functional groups are important in determining pharmaceutical value of an essential oil (Kumari *et al.,* 2018). TTO is composed of cyclic monoterpenes; half of them are oxygenated and the other half remains as simple hydrocarbons (Noumi *et al.,* 2011). Terpenes are single structural units of terpene ($C_5H_8$, isoprene) polymers (Dorman and Deans, 2000). First official list of 'chemical composition of tea tree oil' was published by Brophy et al. It has a complex formulation with more than 100 components; main constituents are as follows: terpinen-4-ol, 1,8-cineole, α-terpineol, terpinolene, α- and γ-terpinene involving 90% of the whole composition (Brophy *et al.,* 1989). Catechins and polyphones are critical components managing the antibacterial action in cooperation with terpinen-4-ol and 1,8-cineole. Bacterial cell membrane is damaged by these compounds, leading to vital defects in respiration, permeability, and osmoregulation (Kumari *et al.,* 2018). Presence of trace components, sabinene, globulol and viridiflorol, creates a favorable synergism effect (Mickiene *et al.,* 2011). TTO, with density between 0.885 and 0.906, exhibits low aqueous solubility. Surfactant, Tween 20 and Tween 80 from 0.001% to 0.5% (v/v), addition to agar medium would be beneficial (Kumari *et al.,* 2018); however, involvement of suspending agents may cause turbidity and decrease the accuracy of 'inhibition zone' measurements. Presence of triphenyl tetrazolium chloride (TTC) in the bacterial culture puts out a tricky point; TTC 0.005% (w/v) changes from transparent to red color simultaneously with bacterial colonization; a 'growth detector' (Hammer *et al.,* 1998). Terpinen-4-ol is considered as the active part responsible for antimicrobial activity, and 1,8-cineole acts as a skin and mucous irritant (Mondello *et al.,* 2006); however, recent researches have proved that calculating the best ratio between these two dominant terpenes is the most appropriate perspective for achieving maximum potency associated with minimum hypersensitivity (Mickiene *et al.,* 2011). A premise about the interaction between different oil constituents was suggested after discriminative examinations of TTO's components. While terpineol-4-ol was found to be effective

against *Pseudomonas aeruginosa*, this predestinate result could not be achieved in the complete-oil testing (Papadopoulos *et al.,* 2006; Rodney *et al.,* 2015). It may, also, explain the empowered bactericidal activity resulted from cooperation of the two essential oils. *Melaleuca alternifolia* and *Cymbopogon citrarus* are two plants with remarkable antimicrobial feedbacks; an underestimate MIC (0.05%) expressed by the combined agent indicated increased antimicrobial activity against *S. aureus, P. mirabilis, C. albicans*, and *E. coli*. On the other hand, *P. aeruginosa* and *E. faecium* colonies were more stable in the media inoculated by mixed product with MIC increased from 5.0% to 8.0% (Mickiene *et al.,* 2011).

TTO can be consumed as a bactericidal agent against both gram-negative and gram-positive pathogens and shows sufficient destructive activity by obstructing cellular respiration interfered with enzymatic reactions in cell membrane together with increasing permeability of cytoplasmic membrane established by measuring the amount of propidium iodide uptake (Hammer *et al.,* 1998) as well as morphological examination of treated organism (Carson *et al.,* 2002). It may also cause potassium leakage and destroy chemiosmotic control of microorganism. This premise is empowered by presence of nucleic acid residue in extracellular fluid. Target sensitivity can vary depending on penetration rate of monoterpenes (Cox *et al.,* 2001). Moreover, diabetic gangrene, leg ulcer, and catarrh are cases that have been treated by this oil. Presence of blood or any other organic material augments antibacterial ability of the oil (Edmondson *et al.,* 2011). TTO shows an acceptable decolonization degree at 1% concentration, in specific cases higher concentrations up to 5% in term of MIC may be needed. (Mickiene *et al.,* 2011). It is classified as a bactericidal agent, but bacteriostatic effect is also observable at higher concentrations (Oliva *et al.,* 2018). Although mupirocin is the first-line drug for MRSA decolonization, frequent application in prophylaxis manner elevates resistance risk (Caelli *et al.,* 2000). Colonization of multi drug resistance (MDR) *Staphylococcus aureus* in Intensive Care Units (ICU) is among most life-threatening situations for hospitalized patients. Laboratory trials revealed that TTO can be preferred for MRSA treatment; however clinical trials did not support it. A randomized controlled study was designed to determine the effect of *M. alternifolia* oil on MRSA decolonization in patients without systemic infection. Including 1080 patients hospitalized in ICU, a comparison protocol has been followed between 5% TTO body wash and Johnson's baby soft wash for 21 months. While results were not adequate,

clinical improvement may be reached by preferring a leave-on medication with higher TTO concentration (Blackwood *et al.,* 2013*).* A limitation mentioned in MRSA infectious lesions treatment is healing rate. In this theme, TTO might be helpful by decreasing the size of the lesions as well as the healing period (Edmondson *et al.,* 2011). TTO as a volatile agent with remarkable colony clearance potency can be utilized in its vapor form for pneumonia treatment caused by *Klebsiella pneumoniae* (Oliva *et al.*, 2018). This oil can speed up recovery speed by deactivating pro-inflammatory mediators and preventing or curing present fungal infections. A study was performed around killing capacity of thirteen phenolic acid structures premising that sensitivity of pathogenic *E. coli* O157:H7 (CECT 5947) is twice more than non-pathogenic *E. coli* (ATCC) 25922 (Cueva *et al.,* 2010). This conclusion can be expanded to the plants containing phenolic structures such as *Melaleuca alternifolia.* Moreover, combination of TTO with tobramycin can express high bactericidal capacity and subsequent post antibiotic effect (PAE), even at doses lower than MIC. In addition to empowered bioactivity, diminished drug dosage increases drug tolerability and patient compliance (D'Arrigo *et al.,* 2010). TTO in phosphate-buffered saline (PBS) solution was tested on salt adapted *Enterococcus faecalis* sample with 6.5% NaCl, triggering cross protection; a reduction in TTO's colony eradication ability. It can be explained by TTO's mode of action; empowered cell membrane will suppress antibacterial activity of all agents with mutual side of action (Lim and Hammer, 2015). Another study suggested equivalent efficacy of TTO and 3% Sodium hypochlorite. Sodium hypochlorite is the number one root canal irrigant agent utilized during dental operations. TTO with significant *in vitro* activity gives hope for replacing old-fashion medications with undesirable effects (Sheth *et al.,* 2013). While occurrence of single-step mutation leading to bacterial resistance was uncommon, gradual increase after several sub-culturing with underestimated TTO concentration was observable (McMahon *et al.,* 2007; Hammer *et al.,* 2008,). Antimicrobial spectrum can be a challenging characteristic while applying on a particular area with sensitive microflora like vagina. While TTO might be helpful for treatment of discomforts caused by *Bacteroides, Prevotella, Fusobacterium* and *Peptostreptococcus* with $MIC_{90}$ less than 0.5% (v/v), the natural microflora of vagina stays untouched due to high $MIC_{90}$ reaching up to 2% in lactobacilli (Carson and Riley, 1998). Furthermore, antibacterial property of this oil can protect the irritated skin

patches from pathogenic microorganisms like *Staphylococcus aureus* and accelerate healing process (Edmondson *et al.,* 2011). TTO can also be used as a sanitizing agent for nurses and devices (Blackwood *et al.,* 2013). Being in direct contact with the infected patients, there is a huge necessity for effective hand washers to break the transmission chain of the intended pathogen. TTO can be defined as a preferable agent for this purpose; expanded antimicrobial spectrum distinguishing between host and transient microorganisms plus lipophilic nature enabling oil penetration to the skin's outer layers. (Carson and Riley, 1998). Fungal infections caused by 'filamentous fungi' after traumatic events (Fanfair *et al.,* 2012) are treated by surgical discharge of infected tissue and subsequent support with systemic antifungal agents, especially when the rotten tissue is out of access or too tiny (Austin *et al.,* 2014). Usage of topical antifungal agents, such as Dakin's solution, seems to be rational for accelerating healing process with minimizing systemic toxicity (Barsoumian *et al.,* 2013). Antifungal achievements of TTO are mainly related to terpinen-4-ol (Brophy *et al.,* 1989). Several fungal species can be target for TTO with dose-variation (Hammer *et al.,* 2003); highlighted performance of 2% butenafine hydrochloride TTO solution in curing toenail onychomycosis (Syed *et al.,* 1999) and *in vitro* activity against *Madueralla mycetomatis* are vital examples (van de Sande *et al.,* 2007). *Exophialia* spp., *Actinomucor* spp. and *Fusarium* spp. were strains with highest susceptibility, while Aspergillus *terreus* and *Absidia* spp were resistant even in 100% oil concentration. Increasing exposure time, mutually, increased efficacy. (Homeyer *et al.,* 2015). There has been a growing concern about prevalence of resistant to common antifungal therapies, especially among immune deficient and cancerous patients, (Hammer *et al.,* 2003); infections generated by *C. albicans* strains have been highly insistent to treatment with azoles (Casalinuovo *et al.,* 2004). TTO has been reported to display potent antifungal performance against azole-resistant yeast types (Mondello *et al.,* 2003) and specific species of oral Candidiasis (Bagg *et al.,* 2006). The planktonic *C. albicans* are susceptible to TTO components, terpinen-4-ol and α-terpinol, with $MIC_{50}$ 0.5% and 0.25% (Ramage *et al.,* 2012). Local treatment is a preferable option for strengthening *in situ* pharmacological action as well as minimizing the systemic toxicity. Curing superficial cancerous tissues with topical chemotherapy drugs, imiquimod and 5-fluorouracil, is also possible, but limitations leading to little patient satisfaction are present: low-rate

elimination, local unwanted effects, and long duration of treatment. Moreover, treatment prognosis may show variation depending on the nature of cancerous tissue (Greay *et al.,* 2010). Nowadays natural therapeutic agents such as TTO and ingenol mebutate are at the center of attention for pre-clinical trials. While topical application of 10% diluted TTO together with dimethyl sulphoxide (DMSO) to subcutaneous AE17 mesothelioma suppressed the tumor's size and growth rate, skin irritation can be considered as a disadvantage. The complexity of the mechanism became clear after analyzing the involved cells by flow cytometry, immunohistochemistry, and transmission electron microscopy. TTO starts a local immunization. Although, first expression about the mechanism is T cell mediated anti-tumor cytotoxicity, subsequent examinations eliminate this option. Skin irritation is the weak point in topically applied TTO. After *i.p.* administration of Gr –1 mAb, a reduction in neutrophil concentration together with skin irritation was observed; however, cytotoxicity degree of the medication did not diminish. High specificity in mode of action can be another breakpoint of novel cancer therapy methods (Ireland *et al.*, 2012). Unsatisfied amount of the oil (3-5%) was combined with prolonged therapy interval to compensate the shortage of the agent. Although skin irritation was suppressed, it also underachieved the pharmaceutical effect as well (Greay *et al.,* 2010). *In situ* observations of the target tissue emphasized the importance of the penetration degree for a successful treatment. Layers that were close to the exposure area showed higher level of destruction. The effect of DMSO on penetrability was also notable (Ireland *et al.,* 2012). Moreover, five pharmaceutically valuable parts of the oil were isolated and examined. None of them could reach the desirable concentration in epidermal and dermal layers by themselves; while using these five terpenes as a unit showed enough penetration. (Greay *et al.,* 2010). *M. alternifolia* essential oil is one of the momentous extracts with remarkable antioxidant property. An evaluation by three methods gave hopeful background information. TTO was examined by DPPH$^{\bullet}$ (2,2-diphenylpicrylhydrazyl) and TBARS (thiobarbituric acid reactive substances) assays together with Hydroxyl Radical Scavenging Activity. Intended substance was compared to well-known antioxidant agents such as quercetin, α-lipoic acid, vitamin C and E. Earlier premise was completely supported by the final outcomes. District investigation with the aim of recognizing the responsible compounds for this task made a clear point

to phenol functional groups (Zhang *et al.*, 2018). Studies clarified TTO compositions with the highest antioxidant property: α-terpinene, α-terpinolene and γ-terpinene (Kim *et al.*, 2004). Little information is available about essential oil's antiviral activity. Investigations concerning healing capacity of TTO on lesions caused by *Tobacco mosaic* suggested its efficacy on decreasing lesion numbers within 10 days after inoculation with an unknown mechanism (Bishop, 1995). Moreover, while average time required for re-epithelialization after recurrent *Herpes labialis* (RHL) contamination for TTO treated group was 9 days, control group with placebo needed 12.5 days; plus, a modest reduction was highlighted in median duration of culture positivity. viral titer appeared lower in the TTO group (Carson *et al.*, 2001).

Jacobs *et al.* (Jacobs and Hornfeldt, 1994) reported a case of systemic toxicity after TTO ingestion; 23-month-old white patient suffering from disorientation showed complete recovery after 5 hours of hospitalization. Reversible systemic toxicity may be related to suppressed central nervous system activity. Systemic contact dermatitis, semi-consciousness or comatose are serious conditions associated with TTO ingestion. Apart from the nature of the oil constituents, appearance of toxic reactions may be linked to inappropriate storing. Inauguration of specified storage standards about air and light availability in storage milieu must have been established for preventing the formation of impurities such as peroxides and p-cymene (Southwell, 2006). Decreased amount of terpinene coincidently with increased cymene concentration indicates variation in oil composition (Pazyar *et al.*, 2013). Dose adjustment is also essential (Hammer *et al.*, 2006); for example, fungal nail infection, as an acute-type of infection, needs high TTO concentrations, treatment prognosis is considerably long and the risk of toxicity is assumed to be high (Syed *et al.*, 1999). Although TTO usage in antimicrobial products is widespread, there is no clarity about the exact toxic dose. Two main detoxifying procedures in TTO metabolism are glycine and glucuronide conjugative pathways in which metabolites can cause acute hepatotoxicity (Meesters *et al.*, 2009). Infraclass analysis revealed that authentic TTO triggered hypersensitivity; therefore, hypersensitivity associated with intended TTO ascended concurrent with aging. Furthermore, terpinolene, α-terpinene and terpinen-4-ol were the least stable terpenes against aging (Avonto *et al.*, 2016). Although toxicity after topical application may be under control, direct contact with inner layers shows unpredictable interactions. Analyzing fibroblasts, keratinocytes, osteoblasts and

HUVECs suggested a perception about the relationship between toxicity and concentration; cell viability was suppressed by increasing the dose. Different $LD_{50}$s were obtained from different cell types; HUVECs showed highest resistance with 13.4% $LD_{50.}$ In addition, single cell destruction was more obvious compared to the whole tissue. Long-term application together with concentration under 25% may give us both efficacy and safety (Homeyer *et al.,* 2015). Analysis of TTO influence on treatment prognosis ascended bias toward being optimistic about Dermocosmetics studies (Kulkarni, 2012). *M. alternifolia* extract destroys *Propionibacterium acnes* colonies; a commercial microorganism causing acne (Kabir Mumu and Mahboob Hossain, 2018). TTO can compete with benzoyl peroxide and topical erythromycin with low toxicity (Hammer, 2015). The main reason of dandruff is overgrowth of a yeast type named *Pityrosporum ovale* (Piérard-Franchimont *et al.,* 2006; Turner *et al.,* 2012). In a 4-week research, satisfactory results were obtained in a group with 126 members using 5% TTO product. A high degree of curing with well-tolerated toxicity profile made the oil successful in this competition with placebo-controlled group. Dilution of the oil with daily shampoo or direct application of a few drops to the hair scalp can be helpful in long term (Satchell *et al.,* 2002). Moreover, *M. alternifolia* leaf extract exhibits antiseptic property, an advantage while curing dermatitis (Davis, 1999). In a study searching for replacements for corticosteroids in dermatitis treatment, suppressed allergic contact dermatitis caused by nickel up to 40.5% was linked with anti-eczematic properties of TTO. Initial TTO concentration was 50%, but erythema development leaded to dose reduction to 20%. Comparison of anti-eczematic effectiveness among TTO, zinc oxide and clobetasol butylate determined high potential of the oil. Although, skin hypersensitivity associated with nickel was well-treated with TTO, augmenting effect of the oil on histamine-induced weal (52.5%) emphasized the necessity of etiological analysis for this pathologic condition. (Wallengren, 2011). Head mice or scabies, named *Pediculosis capitis*, is a persistent parasitic infection with severe itching. Skin lesions appearing as holes and secondary infections are the consequences of untreated *Pediculosis capitis*. (Leung *et al.,* 2005; Nutanson *et al.,* 2008). *Melaleuca alternifolia* extract as shampoo is a preferable option. Not only for head scalp but also all affected body parts can be treated (Walton' *et al.*, 2000). This insecticidal effect is the result of anticholinesterase activity of TTO (Mills *et*

*al.*, 2004). A chronic skin disease with high genetic tendency showing itself before 20's called psoriasis. Existence of red or brown patches with different sizes is a strong sign of psoriasis, but morphometric details like vasodilation of the problematic area must be analyzed. Pathophysiological examinations premise TNF-α as the reason for underlying inflammatory reaction. *Melaleuca alternifolia* oil, with antioxidant efficacy, can control over-expression of TNF-α, PGE 2, IL-1 and IL-8 (Pazyar and Yaghoobi, 2012). Anti-psoriatic 5% TTO transdermal patches based on micro-emulsion technology were design for direct and continuous drug delivery (Sonia and Anupama, 2011).

## CONCLUSION

Naturally obtained medical agents are always one step ahead. *M. alternifolia* oil has been proceeding successfully in considerable numbers of assessments. Even though the promising abilities as an antimicrobial, anti-inflammatory and anti-tumor agent are well-known, *in vivo* evaluations must be done to assure the safety and reproductivity.

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