

The battle against multi-resistant strains: Renaissance of antimicrobial essential oils as a promising force to fight hospital-acquired infections

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SUMMARY. Hospital-acquired infections and antibiotic-resistant bacteria continue to be major health concerns worldwide. Particularly problematic is methicillin-resistant *Staphylococcus aureus* (MRSA) and its ability to cause severe soft tissue, bone or implant infections. First used by the Australian Aborigines, Tea tree oil and Eucalyptus oil (and several other essential oils) have each demonstrated promising efficacy against several bacteria and have been used clinically against multi-resistant strains. Several common and hospital-acquired bacterial and yeast isolates (6 *Staphylococcus* strains including MRSA, 4 *Streptococcus* strains and 3 *Candida* strains including *Candida krusei*) were tested for their susceptibility for Eucalyptus, Tea tree, Thyme white, Lavender, Lemon, Lemongrass, Cinnamon, Grapefruit, Clove Bud, Sandalwood, Peppermint, Kunzea and Sage oil with the agar diffusion test. Olive oil, Paraffin oil, Ethanol (70%), Povidone iodine, Chlorhexidine and hydrogen peroxide (H₂O₂) served as controls. Large prevailing effective zones of inhibition were observed for Thyme white, Lemon, Lemongrass and Cinnamon oil. The other oils also showed considerable efficacy. Remarkably, almost all tested oils demonstrated efficacy against hospital-acquired isolates and reference strains, whereas Olive and Paraffin oil from the control group produced no inhibition. As proven in vitro, essential oils represent a cheap and effective antiseptic topical treatment option even for antibiotic-resistant strains as MRSA and antimycotic-resistant *Candida* species. © 2009 European Association for Cranio-Maxillofacial Surgery

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INTRODUCTION

In recent decades, the incidence of hospital-acquired infections with antibiotic-resistant bacteria has increased remarkably. Notable amongst these infections is methicillin-resistant *Staphylococcus aureus* (MRSA) (Mulligan et al., 1993; Witte, 1999). MRSA carriers are more likely to have chronic skin lesions requiring multiple admissions, thereby potentially exposing other vulnerable patients (MacKinnon and Allen, 2000; Blok et al., 2001). This leads to significantly increased health care costs, due to the requirement for isolation and sterilization of facilities and instruments used for these patients during their hospital stay. Some hospitals may refuse admission to patients carrying MRSA, thereby compromising their ability to access appropriate health care. Carriage of highly resistant bacterial strains has important epidemiological, financial and logistical implications. Chronic infections with highly resistant strains have a profound effect on individual patients' sense of well-being, comfort, and quality of life (Tonge, 1997; Theaker et al., 2001).

Antibiotic resistance is not the sole domain of bacteria. Many strains of fungi and yeasts are resistant to, or

during the course of therapy, develop resistance to antimicrobials. *Candida* species are particularly problematic, as is seen in the example of *Candida krusei* which has been found frequently to be responsible for multiple drug-resistant opportunistic fungal infections (Pfaller et al., 2008). *C. krusei* is an extremely important pathogen, particularly in immuno-compromised patients such as transplant recipients and those with acquired-immunodeficiency syndrome (AIDS) (Capoor et al., 2005).

Antibiotic resistance is an evolving problem requiring new strategies to combat infection due to these strains. To date, systemic pharmacological approaches have had varying success. Our current pharmacopoeia is plagued by the development of resistance and by drug toxicity (Wright et al., 1998). Although not yet widely recognized by clinicians, there is mounting international literature evidence supporting the use of plant-derived essential oils against pathogenic microorganisms (Shapiro et al., 1994; Larrondo et al., 1995; Maudsley and Kerr, 1999; Warnke et al., 2004). Both clinical and in vitro studies have demonstrated the potent bactericidal, antimycotic and antifungal properties of some essential oils, including efficacy against antibiotic-resistant strains such as MRSA (Harkenthal et al., 1999; Peana et al.,

1999; Halcon and Milkus, 2004). We have previously reported significant clinical utility of essential oils. This included reduction of the malodour caused by head and neck tumour ulceration and promotion of ulcer healing and re-epithelization (Warnke et al., 2004, 2005, 2006).

Our aim was to evaluate antibacterial and antimycotic efficacy of different essential oils on frequently isolated and hospital-acquired bacterial strains including MRSA and yeast isolates, including *C. krusei*, by means of the agar diffusion test.

MATERIAL AND METHODS

Test group – essential oils

The following pure essential oils from different countries were selected for analysis: Thyme white oil (Australia), Lemon oil (Nepal), Lemongrass oil (Australia), Cinnamon oil (India), Tea tree oil (Australia), Eucalyptus oil (Australia), Grapefruit oil (Australia), Clove Bud oil (Australia), Lavender oil (France), Peppermint oil (Australia), Sage oil (Germany), Kunzea oil (Australia) and Sandalwood oil (Australia).

All oils were non-diluted and not chemically altered by any solvent or processing.

Control group – oils and antiseptics

To compare the antibacterial effects of essential oils with other oils such as Olive oil or industrial Paraffin oil and standard antiseptics such as Ethanol (70%), H₂O₂ (3%), Chlorhexidine (0.1%) and Povidone iodine (Betaisodona[®]) served as controls.

Bacterial and Candida strains

Several staphylococcal and streptococcal strains as well as *Candida* species were tested for their ability to grow in the presence of the essential oils and antiseptics. The isolates were common pathogenic microorganisms causing oral, dental or cutaneous infection. In addition to several hospital-acquired isolates such as MRSA and *C. krusei*, we also tested commercially available reference strains (American Type Culture Collection, ATCC). Each agar diffusion test was repeated minimum two times. The strains tested are presented in Table 1.

Agar diffusion test

A colony of each bacterial/candida strain to be tested was suspended in 10 ml 0.9% NaCl. Two millilitre of this mixture were uniformly distributed on agar and the excess fluid was removed afterwards. After drying the agar plates, test discs (6 mm in diameter) were applied with a sterile forceps after being loaded with 10 µl of essential oil.

The agar plates were incubated at 37 °C for 18 h. The streptococci were incubated in the presence of 5% CO₂. For evaluation the inhibition was measured on each plate. In areas smaller than 7 mm in diameter, the inhibitory effects were classified as “zero”.

Table 1 – Microbial strains tested. Clinical isolates from hospitalized patients are marked with an asterix (*)

Microbial strains
<i>Staphylococcus aureus</i> ATCC25923
<i>Staphylococcus aureus</i> VA 10465/02*
<i>Staphylococcus aureus</i> VA 10492/02 MRSA*
<i>Staphylococcus epidermidis</i> ATCC 155
<i>Staphylococcus epidermidis</i> VA 10421/02*
<i>Staphylococcus epidermidis</i> VA 10370/02*
<i>Streptococcus mutans</i> ATCC 35668
<i>Streptococcus pyogenes</i> ATCC 10389
<i>Streptococcus equisimilis</i> ATCC 35666
alpha-haemolysing – <i>Streptococcus</i> VA 20249/02*
<i>Candida albicans</i> ATCC 10231
<i>Candida albicans</i> VA 13642/02*
<i>Candida krusei</i> ATCC 6258

The microbiologists were “blinded” during the test and determination of the inhibition zones. They received no information about the substances tested. The test oils and the controls were delivered to them in neutral containers.

Evaluation

Each agar diffusion test was repeated at least two times (several oils were tested three times). The average values of the effective zone of inhibition were calculated and presented by essential oil and bacterial strain.

RESULTS

Test group: with the exception of Sandalwood and Grapefruit oil, all essential oils tested showed good antibacterial and antifungal activity against strains frequently responsible for infections of the oral mucosa and the dermis. The reference strains and also the hospital-acquired isolates were similarly susceptible to the inhibitory effect of the test oils. Inhibition zones had diameters ranging from 7 to 50 mm. The largest effective zones were measured for Thyme white oil (29–36 mm), Lemon oil (16–43 mm), Lemongrass oil (20–50 mm) and Cinnamon oil (24–46 mm) (see Fig. 1). These four essential oils showed consistent antibacterial effects against all bacterial strains tested including problematic strains such as MRSA and *C. krusei*. Sandalwood oil showed good efficacy against the bacteria tested, but not against the *Candida* strains. Tea tree oil had effective zones from 8 to 14 mm, Eucalyptus oil from 9 to 13 mm, Grapefruit oil from 0 to 10 mm, Clove Bud oil from 12 to 20 mm, Kunzea oil from 9 to 18 mm, Sandalwood oil from 0 to 12 mm, Peppermint oil from 9 to 18 mm, Sage oil from 7 to 13 mm and Lavender oil from 8 to 15 mm.

All average values of the effective zones are shown in Fig. 1a–d.

Controls: ethanol in concentration of 70% produced inhibition zones with a maximum of 9 mm diameter, while Olive and Paraffin oil had no effective zone. Povidone iodine, Chlorhexidine and H₂O₂ demonstrated effective zones of 14–16 mm and thereby inhibition of bacterial and *Candida* propagation.

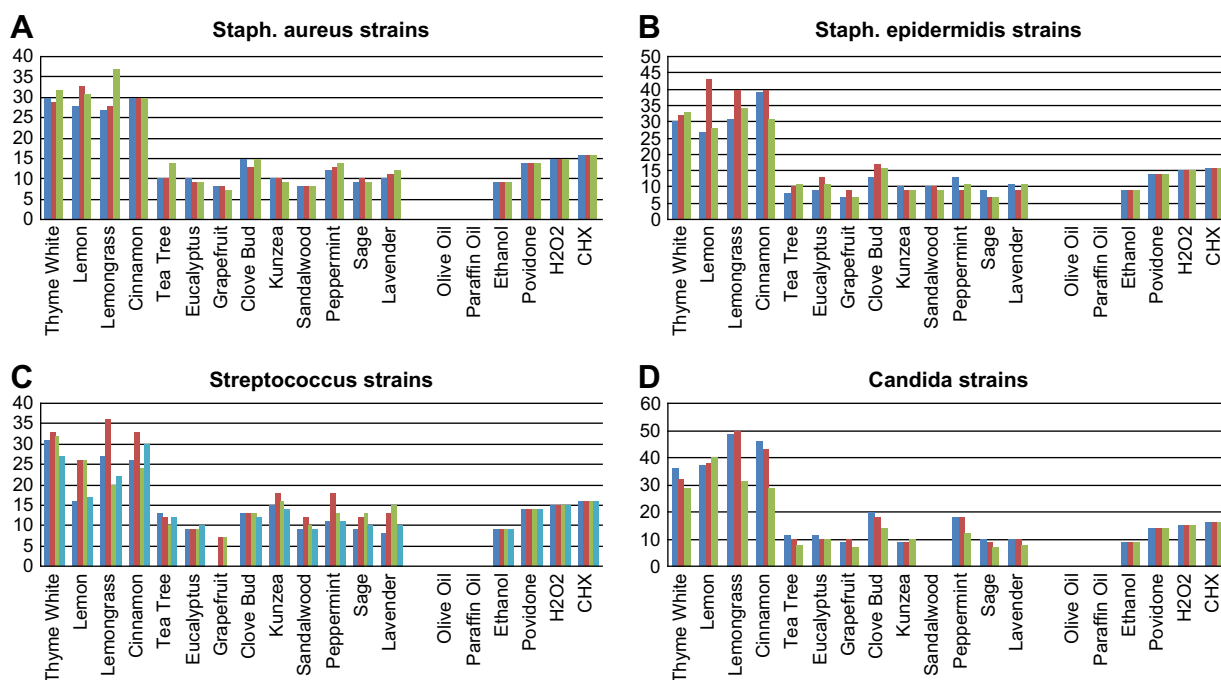


Fig. 1 – Inhibition zones (in mm) by test substances and test isolates on microbial strains. Clinical isolates from hospitalized patients are marked with an asterisk (*). (A) Blue: *Staphylococcus aureus* ATCC25923; red: *Staphylococcus aureus* VA 10465/02*; green: *Staphylococcus aureus* VA 10492/02 MRSA*. (B) Blue: *Staphylococcus epidermidis* ATCC 155; red: *Staphylococcus epidermidis* VA 10421/02*; green: *Staphylococcus epidermidis* VA 10370/02*. (C) Blue: *Streptococcus mutans* ATCC 35668; red: *Streptococcus pyogenes* ATCC 10389; green: *Streptococcus equisimilis* ATCC 35666; light blue: alpha-hemolysing – *Streptococcus* VA 20249/02*. (D) Blue: *Candida albicans* ATCC 10231; red: *Candida albicans* VA 13642/02*; green: *Candida krusei* ATCC 6258.

DISCUSSION

For hundreds, if not thousands of years, essential oils have been recognized for their therapeutic properties (Halcon and Milkus, 2004). Australian Aborigines used Tea tree oil to treat colds, sore throats, skin infections, and insect bites. Tea tree oil was soon adopted by the white settlers in the country and was sold commercially as a medicinal antiseptic from the early 20th century (Harkenthal et al., 1999). Various studies have demonstrated that essential oils are not only well tolerated, but hold therapeutic value in the treatment of acne, dandruff, head lice, and recurrent herpes labialis (Bassett et al., 1990; Carson et al., 2001; Satchell et al., 2002; McCage et al., 2002). Tea tree oil has also been shown to be effective against pathogenic oral bacteria and oropharyngeal candidiasis (Jandourek et al., 1998; Groppo et al., 2002). Takarada et al., (2004) tested the inhibition of growth of those bacteria responsible for caries and periodontal diseases from Manuka oil, Tea tree oil, Eucalyptus oil, Lavandula oil, and Rosmarinus oil. Manuka oil and Tea tree oil in particular had strong antibacterial activity.

In this study, the susceptibility to essential oils of several pathogenic bacterial and fungal isolates from the oral cavity and skin was proven in vitro. Twelve of thirteen essential oils tested demonstrated effective antimicrobial activity against bacterial and *Candida* strains. Sandalwood oil was effective against bacteria but did not show inhibition of the *Candida* strains tested in our study.

Another study (Prabuseenivasan et al., 2006) evaluated the antibacterial activity of 21 plant essential oils against four gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus vulgaris*) and two gram-positive bacteria, *Bacillus subtilis* and *S. aureus*. The majority of the oils showed antibacterial activity against the tested strains. However Cinnamon, Clove and Lime oils were found to be inhibiting both gram-positive and gram-negative bacteria.

A major criticism against the use of essential oils is that they are typically diluted in ethanol. This enables the oils to be delivered via a spray container and enhances the volatility of the oil and thereby its aroma. In response to criticism that the antimicrobial properties of essential oils are derived from their solvent, our experiment examined 70% ethanol as a control. Therefore, the antimicrobial activity seems to be mainly due to the essential oils and only partially to the solvent. As most essential oils consistently demonstrated inhibition zones larger than 70% ethanol alone, it is most likely that this effect is due to the oils. The antimicrobial activity is due to the oils and not to the solvent.

Povidone iodine, H₂O₂ and Chlorhexidine produced clearly visible zones of inhibition, between 14 and 16 mm. These disinfectants are commonly used in the oral cavity.

The other controls including both Olive oil and Paraffin oil resulted in neither a bacteriostatic nor bactericidal effect. Therefore the antimicrobial effect of the essential oils is not due to a simple physicochemical effect of an oily medium on microbial membranes. Otherwise, Olive

oil or Paraffin oil should have had an inhibitory effect on the microbes as well.

Four oils demonstrated exceptional inhibition zones from 16 to 50 mm: Thyme white oil, Lemon oil, Lemongrass oil and Cinnamon oil. No standard antiseptic in the control group demonstrated such dominant inhibitory effects. In the agar diffusion tests, the size of the effective inhibitory zone depends on the solubility and diffusion characteristics of the substances being tested. This makes the comparison of the different oils or controls difficult. Therefore, the results of this study may not directly reflect the extent of the antimicrobial potential of these essential oils. But as these effective zones were clearly visible, this is proof of their antimicrobial efficacy.

In contrast to standard antibiotics, the majority of the oils showed remarkable efficacy against all bacteria tested. The test bacteria were reference strains and isolates from hospitalized patients. *S. aureus* is commonly found in abscesses, but not in those of odontogenic origin (Warnke et al., 2008). In dentoalveolar and oropharyngeal abscesses, viridans-group streptococci play a dominant role (Warnke et al., 2008). These were also susceptible to the oils tested. The alpha-haemolytic streptococci strain (α -h Strept. VA 20249/02, Table 1) isolated from a hospitalized patient can cause severe inflammation. *Staphylococcus epidermidis* is often isolated from contaminated i.v. catheters and artificial heart valve replacements and is often difficult to treat with common antibiotics.

It is important to highlight the fact that MRSA also proved susceptible to the essential oils tested. This has important clinical implications as these strains result in a significant reduction in the quality of life of those affected and require specific precautions for relatives and clinic personnel.

Tea tree oil has been evaluated as an alternative topical decolonization agent for MRSA. Tea tree oil 4% in a nasal ointment and 5% in a body wash were compared with standard treatment of 2% mupirocin nasal ointment and triclosan body wash in patients with MRSA skin colonization. Tea tree oil appeared more efficacious than the standard treatment and was better tolerated by patients (Caelli et al., 2000). In a study of 105 clinical isolates of *S. aureus* using a broth microdilution method the MIC₉₀ of Tea tree oil was found to be 0.5% (Carson et al., 1995). A later study on 100 clinical isolates of MRSA found the MIC₉₀ of Tea tree oil to be 32% (El-som and Hide, 1999).

The demonstration of the antifungal properties of essential oils has broad potential significance. While it is difficult to extrapolate accurately based purely on in vitro data, it is clear that the essential oils examined in this study offer significant potential as a topical or intraoral therapy for Candida (and possibly other fungi/yeasts). Oropharyngeal candidiasis is the most common opportunistic infection among patients infected with human immunodeficiency virus (HIV). The use of many conventional drugs is hampered by lack of efficacy, emergence of resistance, adverse events, high costs and need for intravenous administration (Vazquez et al., 2006). Essential oils may have therapeutic value for

both dermatophytic and oral/mucosal infection in both immunocompetent and immuno-compromised patients (Jandourek et al., 1998). As *C. krusei* is a frequent multidrug-resistant opportunistic pathogen (Pfaller et al., 2008) especially in these immuno-compromised patients, its susceptibility to essential oils is important for the consideration of future therapeutic strategies.

Tea tree oil appears to be the most investigated of all essential oils in the literature. Investigations on other oils are rare. Thus we compared our findings with the existing literature: several mechanisms by which topical Tea tree oil facilitates healing in chronic Staphylococcus-infected wounds are suggested by laboratory and animal studies (Halcon and Milkus, 2004). Several components of Tea tree oil have been shown to contribute to its antibacterial activity. These include Terpinen-4-ol, 1,8 cineole, linalool, and alpha-terpineol (Hinou et al., 1989; Carson et al., 1996; May et al., 2000; Christoph et al., 2000). These components, particularly Terpinen-4-ol, have been shown to adversely affect the structural integrity of the bacterial cell wall. Following exposure to Tea tree oil, *S. aureus* demonstrates a loss of potassium ions and salt tolerance, as well as the development of and the presence of mesosome-like structures by electron microscopy. Inhibition of glucose-dependent respiration has also been demonstrated in bacteria exposed to Tea tree oil (Gustafson et al., 1998; Cox et al., 1998, 2000; Carson et al., 2002).

Hanbali et al., (2005) analyzed the chemical composition of the volatile oil constituent from *Pulicaria odora* L. The main constituents were thymol (47.83%) and its derivative isobutyrate (30.05%) which may represent the main active ingredients.

Tea tree oil has also been found to possess immunomodulatory effects. One study demonstrated that the oil promoted monocytic differentiation in vitro (Budhiraja et al., 1999). Other studies have shown that the main component of Tea tree oil, Terpinen-4-ol, suppresses inflammatory mediator production by monocytes activated in vitro (Hart et al., 2000; Warnke et al., 2006). This may explain the clinically observed anti-inflammatory properties of Tea tree oil – a factor also likely to assist in healing chronic wounds.

Whilst Tea tree oil has been reported to be generally well tolerated, little is known of its systemic pharmacokinetics or pharmacodynamics of essential oils in humans. In addition, available information regarding toxicology is limited to in vitro studies on cell lines or clinical case reports. There is also little information on the mechanisms of toxicity. However, several reports of systemic toxicity can be found in the literature (Halcon and Milkus, 2004). A 100% preparation of Tea tree oil was found to be ototoxic when applied in the ears of guinea pigs. However, no ototoxicity was seen with a 2% solution (Zhang and Robertson, 2000). de Groot and Weyland (1992) reported a case of contact dermatitis related to the chronic topical application of full strength Tea tree oil followed by its oral ingestion. In this report, 1,8 cineole or eucalyptol was found to be the offending substance (de Groot and Weyland, 1992). Other cases of allergic contact dermatitis related to eucalyptol have also been reported (Vilaplana and Romaguera, 2000). Cinnamon oil has

a significant potential to cause skin irritations (*Meding, 1993*). In contrast, other essential oils such as Eucalyptus or Sage oil have anti-inflammatory and calming properties when being used in upper respiratory tract infections (*Darshan and Doreswamy, 2004*).

We reported earlier the use of a mixture of Australian Eucalyptus oil and other essential oils for percutaneous treatment of two patients with osteomyelitis that had not resolved with surgery or multiple courses of antibiotics. The essential oil mixture was applied daily with visible signs of healing after only a few days. After a few weeks, the wounds had healed, cultures were clear and symptoms had resolved (*Sherry et al., 2001*). We have also used Australian essential oil mixtures in the treatment of malodorous cancer wounds (*Warnke et al., 2004, 2005*). The essential oil regimen was very successful in extinguishing tumour smell and also demonstrated wound healing and anti-inflammatory effects on superinfected ulcers (*Warnke et al., 2006*).

Both the in vitro studies and the case studies provide evidence in favour of the adjunctive use of essential oils in wound care. Our in vitro studies on essential oils have shown good microbicidal activity against *S. aureus*. In addition, essential oils have produced promising results in case studies and small clinical trials. Case reports have described promising results in the treatment of pulmonary tuberculosis (*Sherry et al., 2003, 2004; Warnke et al., 2004*). Combined, these studies present compelling evidence that essential oils could be a possible therapy for “difficult to treat” hospital-acquired infections with often multi-resistant strains.

There are, however, a number of barriers to their acceptance in general clinical practice. The chemical constituents of plant-derived products often vary, making standardization difficult (*Halcon and Milkus, 2004*). In addition, there is no standard and validated method of testing the effect of these products. This makes it difficult to establish in vitro efficacy in accordance with FDA guidelines (*Carson et al., 1995*).

Moreover, the essential oils seem to vary in their content of active components. We have found in previous tests remarkable differences in antimicrobial activity between essential oils of the same type, but from different producers. Also, the plant family is important. Therefore one Tea tree oil may not be equivalent to another Tea tree oil (*Carson et al., 2006*). There are also differences between oils regarding their country of origin. For example, Lemon oil from Nepal showed inhibition zones from 16 to 43 mm, whereas Lemon oil from Australia only demonstrated inhibition zones from 8 to 16 mm (previous study, data not shown). Thus, essential oils may not be suitable as a sole medication against serious infections due to composition changes. Therefore, additional pharmaceutical studies focussing on the oil contents and determination of the active ingredients respectively chemical substances are important.

However, the oils are inexpensive and are available worldwide. Significant pathogens are susceptible to a broad range of essential oils, as proven in this study. We suggest that essential oils may be a promising alternative for the treatment of localized infections even with severe hospital-acquired strains.

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