Tea tree oil: a potential alternative for the management of methicillin-resistant *Staphylococcus aureus* (MRSA)

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Introduction

Complementary and alternative medicines occupy a privileged marketing position in many countries, including Australia, being able to carry low-level health claims while being relatively unfettered by regulatory requirements. Consequently, many enjoy widespread use for therapeutic purposes in the absence of definitive efficacy or safety data. Occasionally, the therapeutic properties of complementary and alternative medicines are scrutinised more closely and more thoroughly than their conventional counterparts, leading to the confirmation or discrediting of their properties.

While the scientific investigation of complementary and alternative medicines is at a nascent stage in Australia, certain therapies are being investigated formally. One of these is the essential oil of *Melaleuca alternifolia*, also known as tea tree or *Melaleuca* oil. Produced from steam distilled from the foliage of this Australian native plant, tea tree oil has been promoted since the 1920s as an antiseptic and disinfectant, more effective and less corrosive than the gold standard of the day, phenol or carbolic acid[1]. Its popularity dwindled during the era surrounding the discovery and development of penicillins, and recurred only relatively recently during the natural product renaissance of the late 1970s and 1980s. Today tea tree oil is available in many cosmetic and toiletry products as well as a range of therapeutic products.

Originally harvested from natural bush stands of *M. alternifolia*, tea tree oil is now produced on large-scale plantations, primarily in north-eastern New South Wales. The physical and chemical properties of tea tree oil may vary from batch to batch and are influenced by many factors, including provenance, cultivation conditions, production processes and storage conditions[2]. Quality control of these properties of this oil has been greatly assisted by the development of an international standard for tea tree oil[3]. The standard dictates compositional limits for 16 of the approximately 100 terpene components of the oil, including the major components terpinen-4-ol, α-terpinene and γ-terpinene that collectively comprise approximately 70% of the whole oil, and delineates many of the physical characteristics such as relative density, refractive index and optical rotation.

Notably, no specifications regarding the required levels of biological activity have been set, in part because these are still being defined and in part because, to date, there has been no evidence that the biological activities of oils that meet the international standard vary significantly. However, as the biological properties of tea tree oil become increasingly well-characterised and any potential for variation becomes apparent, this may become necessary.

In contrast to the apparent robustness of the biological properties of tea tree oil in the face of batch to batch variation, the formulation of tea tree oil into products may dramatically affect its biological properties[4], with certain product excipients known to compromise its antimicrobial activity[5].

The antimicrobial activity of tea tree oil is the most well-established biological property of the oil, with activity demonstrated against bacteria[6-9], fungi[10-13] and viruses[14]. Other biological properties described include anti-inflammatory properties[15,16] and, possibly, anti-tumoural activity[17].

Activity against methicillin-resistant *Staphylococcus aureus* (MRSA)

The first suggestion that tea tree oil may have had clinically useful antimicrobial activity against MRSA was made in 1987 by Walsh & Longstaff[18] who reported that these bacteria were susceptible to the oil. No additional characterisation occurred until 1995 when Carson *et al.*[19] tested the susceptibility of 64 isolates of MRSA (32 mupirocin-resistant) and found them uniformly susceptible, with MICs around 0.25% and MBCs of 0.5%. Several other groups have corroborated this activity[20-24], leading to speculation that tea tree oil may be a useful agent for the decolonisation of MRSA carriage or the treatment of skin wounds infected with MRSA.

Some clinical data to support this hypothesis came from a pilot study in which the efficacy of a 4% tea tree oil nasal ointment and a 5% tea tree oil body wash was compared to conventional treatment of mupirocin nasal ointment and Triclosan skin wash for the decolonisation of MRSA in hospital inpatients [25]. This small study, in which there were 15 patients in each group, did not show a significant difference between the two treatment groups; five patients and two patients were cleared, while three and eight remained colonised in the tea tree oil and conventional treatment groups, respectively. Five patients from the conventional treatment group and seven from the tea tree oil group did not complete the course of treatment. Use of the tea tree oil nasal ointment resulted in reports of adverse events ranging from mild swelling of the nasal mucosa to burning on application, but no patient numbers were given. No adverse events were recorded for either the tea tree oil body wash or the mupirocin nasal ointment, and one patient complained of skin tightness after using the Triclosan body wash.

Additional evidence that tea tree oil warrants further consideration for MRSA decolonisation came from a larger study in which 236 MRSA-positive patients were randomly assigned to a standard treatment or tea tree oil treatment regimen [26]. The standard treatment was a 4% chlorhexidine gluconate soap applied all over the body at least once a day and 2% mupirocin nasal ointment applied to the anterior nares three times a day, combined with 1% silver sulfadiazine cream applied to skin lesions, leg ulcers and wounds once a day. A 5% tea tree oil soap and a 10% tea tree oil cream for anterior nares and skin lesions, leg ulcers and wounds comprised the tea tree oil regimen. The application frequency was the same as for the standard treatment regimen and both regimens were used for 5 days. Swabs to test for clearance were taken 2 days and 14 days after treatment completion in 224 patients and the outcomes in these patients were evaluated. While mupirocin was significantly better than tea tree oil at eradicating nasal carriage, tea tree oil was significantly better for skin sites. Overall, there was no significant difference in the treatment regimens and no adverse effects were reported in either treatment group.

Sporadic reports of the successful treatment of MRSA infections by products containing tea tree oil have also appeared in the literature. A mixture of plant extracts, including tea tree oil, was used in the treatment of previously intractable MRSA osteomyelitis [27] with apparent success.

The formulation issues mentioned previously hold particular relevance for the future clinical evaluation of tea tree oil products. We have recently assessed the antibacterial activity of tea tree oil and tea tree oil products using the EN 1276 and EN 12054 European suspension test methods [4]. The tea tree oil products evaluated were a hygienic skin wash (HSW) and an alcoholic hygienic skin wash (AHSW), both containing 5% tea tree oil, and an alcoholic hand rub (AHR) containing 3% tea tree oil. These formulations were assessed in perfect conditions using the EN 12054 test, and in perfect conditions as well as in the presence of interfering substances with the EN 1276 test, against *S. aureus, Acinetobacter baumannii, Escherichia coli* and *Pseudomonas aeruginosa.*

With the EN 1276 test, the AHR achieved a ≥5 $\log_{10}$ reduction against all the test organisms within 1 minute contact time. The AHSW achieved this reduction with *A. baumannii* after 1 minute contact time and against the remaining test organisms after 5 minute contact time. Using the EN 12054 test, after 1 minute contact time, 5% tea tree oil in 0.001% Tween 80 and the AHSW achieved a reduction in *E. coli* and *P. aeruginosa* concentrations in excess of 4 $\log_{10}$, while the AHR achieved this reduction against all of the test organisms. In comparison, the HSW generally required longer contact times to achieve smaller reductions in test organism concentrations.

Oil concentrations and products that passed the European suspension test guidelines were subsequently evaluated *in vivo* using the European handwashing method (EN 1499) as well as *ex vivo* using freshly excised human skin samples [28]. Data from both the *in vivo* and *ex vivo* methods indicated that 5% tea tree oil in 0.001% Tween 80 and the AHSW were significantly more active than the non-medicated soft soap control after 1 minute of handwashing or rubbing.

Safety and toxicity

Just as clinical data to support the use of tea tree oil and tea tree oil products in the management of MRSA colonisation and infection are scarce, so too are safety and toxicity data for the oil. While the anecdotal data from 80 years of use suggest that the topical application of tea tree oil is safe, this is not a substitute for empirical safety data. Some formal toxicity studies have been conducted [29] but more are required. Most published reports of adverse reactions discuss irritant and allergic skin reactions to the oil [30], although cases of poisoning in children [31-33] and adults [34, 35] have occurred. Since tea tree oil is toxic if ingested and should only be used topically, formal studies of its acute and chronic effects on skin remain a priority.

Conclusions

Despite these limitations, the data from *in vitro* and *in vivo* work reported to date provide a strong impetus for comprehensively assessing the efficacy of tea tree oil in the management of MRSA colonisation and/or infection. However, the question of who would fund and conduct the required studies is a vexed one.

The fact that tea tree oil may be efficacious in the management of MRSA but may not be validated due to a lack of financial support highlights a critical issue in the future evaluation of many complementary and alternative medicines. Unless novel strategies that foster the rigorous evaluation of complementary and alternative medicines and allow investors to reap the commercial benefits of such work or substantial non-commercial funding sources become available, complementary and alternative medicines will remain largely uninvestigated.

Some initiatives to address this dilemma have begun. In 1992, the National Institutes of Health in the USA created an Office of Alternative Medicine and provided it with a budget of US$2 million. This agency has since become the National Center for Complementary and Alternative Medicine and has an operating budget in 2005 of US$123 million. In 1999, the Therapeutic Goods Administration in Australia established an Office of Complementary Medicines; however, it has no budget for research.

Ultimately, given the right circumstances, sufficient information will be available to resolve the validity of the claims made for tea tree oil. Whatever the outcome of current and future work, the whole process will hopefully broaden our outlook and serve as a template for the investigation of other complementary and alternative medicines.

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