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Essential oils as topical anti-infective agents: A systematic review and meta-analysis

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Highlights

- Eighteen clinical trials investigated essential oil effectiveness; among which five on acne treatment, five on methicillin resistant *S. aureus* (MRSA) decolonization and eight on topical fungal infections
- Essential oils significantly lowered level of new MRSA emergence compared to routine care
- In treatment of topical fungal infections, efficacy of essential oils were non-inferior compared to a standard treatment but superior to a placebo
- Essential oils could be considered as viable alternatives for the decolonization of MRSA, acne treatment and topical fungal infections
- Considerable heterogeneity among the included studies calls standardization of essential oils for future studies

Abstract

Objective: This study summarized evidence on efficacy and safety of essential oils (EOs) in the treatment of topical infections.

Design and Setting: Systematic review of clinical trials conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline. Electronic databases of the Cochrane, Pub Med, EMBASE, Web of Science, and Scopus were searched from inception to November 2018.

Intervention: Essential oil of any type, standard treatment and placebo

Main outcome measures: Outcomes of the study include total acne count, ace severity index, reduction in total acne surface area, number of non-inflammatory acne lesions

and inflammatory acne lesions, microbial cure rate, microbial decolonization rate, and new microbial emergence.

Results: Non-significant but higher proportion of MRSA was cleared in EOs group (69% [95%CI: 34%, 96%]) compared to routine care (45% [95%CI: 36%, 53%]). Essential oils significantly lowered level of new MRSA emergence (9% [95% CI: 5%, 14%], $I^2=86.59\%$) compared to routine care (53% [95%CI: 30%, 75%], $I^2=86.59\%$). Four of the five studies on acne treatment showed equal or superior efficacy of EOs and the remaining one showed inferior efficacy to a control. In treatment of topical fungal infections, efficacy of essential oils were non-inferior compared to a standard treatment but superior to a placebo.

Conclusion: Essential oil could be considered as alternative treatment for acne, decolonization of MRSA, and topical fungal infections yet the low quality and heterogeneity among the studies calls for further studies.

Key words: Tea tree oil, clinical trial, aromatherapy, alternative therapy

1. Introduction

Essential oils (EOs) are one of the most common natural products used for various medical purposes and since early human being ^{1 2}. Common EO producing plants families includes, Lamiaceae (*Ocimum citratus*), Poaceae (*Cymbopogon citratus*) , Verbenaceae (*Aloysia citriodora*), Asteraceae (*Echinops kebericho*), Umbelliferae (*Carum nigrum*), Zingiberaceae (*Zingiber officinale*) ³ . Their use in dermatology, cosmetic products and popularity as self-care natural medicine products is recently increasing ⁴. Combined with their popular use in dermatology, their easy availability, and emergence of antimicrobial resistance, commercial EOs are increasingly an option for therapy ⁵. Essential oils are considered means of treatment for resistant and difficult-to-treat strains which synergize the antimicrobial activity of conventional antimicrobial agents when combined with conventional antimicrobial agents ⁶. This synergistic activity

was attributed to membrane disruption property of the EOs ⁷. Their antimicrobial efficacy study in human particularly have shown promising results as in mouth wash for oral mal-odour ⁸, reduced gingival inflammation and dental plaque ^{9 10} and acute external otitis.

Of the 98 EOs recommended for dermatological use, 88 are endorsed for treating skin infections of which 73 are used for bacterial infections, 49 specifically for acne, 34 for fungal infections, and 16 for viral infections as outlined by Orchard and Vuuren (2017) ⁵. The review described the details of commercial EOs use as potential antimicrobials to treat skin diseases and focuses on *in vitro* antimicrobial activities. Currently, several clinical studies were conducted to evaluate the efficacy of these EOs ¹⁰⁻¹³. Except for dental infection ¹⁴, there is no systematic review summarizing the clinical studies conducted on anti-infective use of EOs. The studies are worth summarizing to direct future studies and establish evidence based medicine. The aim of the current study is to synthesize the findings of clinical studies/trials on EOs that have been conducted to treat topical infections.

2. Methods

2.1. Study design

Systematic review of clinical trials conducted using best available evidence and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline. PRISMA checklist was used to ensure inclusion of relevant information. The protocol was registered in the International Prospective Registry of Systematic review with registration number (PROSPERO = 2018 CRD42018106478) ¹⁵.

2.2. Search Strategy

Electronic databases of the Cochrane, PubMed, EMBASE, Web of Science, and Scopus were searched from inception to November 2018. The search syntax was

developed based on guidance from the Cochrane handbook in Table 1. Other sources including Google Scholar, the meta register of controlled trials, bibliography of retrieved publications, and conference proceedings were also searched.

2.3. Selection of Papers, Inclusion and Exclusion Criteria

Two reviewers (SD and AM) independently performed a literature search and examined relevant studies and then sequentially screened their titles and abstracts for eligibility. Full-text articles were examined using predefined eligibility criteria for inclusion. A screening guide was used to ensure that all review authors reliably apply the selection criteria. All clinical studies with parallel or cross-over design investigating EOs effectiveness in topical infectious were included. *In vitro* antimicrobial activity studies, studies on non-infectious skin disease conditions, and studies as mouth wash were excluded.

2.4. Methodological quality assessment

Cochrane risk of bias tool was used to assess randomized controlled studies while the Newcastle-Ottawa quality assessment score (NOS) for non-randomized studies. The bias was graded as low, high or unclear.

2.5. Outcome, intervention, data extraction and management

Data on methods, participants, interventions, and outcomes were. Outcomes of the study include total acne count, acne severity index, reduction in total acne surface area, number of non-inflammatory acne lesions and inflammatory acne lesions, microbial cure rate, microbial decolonization rate, and new microbial emergence. Adverse events were considered secondary outcomes. Intervention of the study includes essential oil of any type, standard treatment and placebo. For each dichotomous outcome the number of participants experiencing the event and the number of patients randomized in each treatment group were extracted.

2.6. Statistical analyses

Analyses were performed using STATA version 13.0 (Statacorp, LP, college station, TX). Odds ratios (OR) and 95% confidence intervals (CI) were pooled using the

metan command. Heterogeneity was assessed using I^2 statistic and Chi square test. Random-effects model (REM) employed using DerSimonian and Laird method ¹⁶. The subgroup analysis was done based on the type of intervention.

3. Results

3.1. Characteristics of included studies

A total of 1,060 articles were identified of which 883 articles remained after de-duplications. Titles and abstracts screening reduced the number of articles to 849. With further screening for inclusion and exclusion criteria, 33 remained for full-texts examination. Fifteen articles were further excluded based on the predefined inclusion/exclusion criteria. The reasons for exclusion were: dental infection , review articles , study protocols , *in vitro* study , Spanish language article , head lice infestation , and duplicate publication . Finally, eighteen articles were included among which, five studies on acne ¹⁷⁻²¹, five on methicillin resistant *S. aureus* (MRSA) decolonization ²²⁻²⁶ and eight on topical fungal infections ^{13 27-33}. A PRISMA flow diagram depicted number of studies retrieved, screened, excluded and included in the study (Fig. 1).

3.2. Risk of bias assessment of included studies

The quality of included studies ranges from low to moderate in accordance with authors' risk of bias assessment, Fig 2 and Fig 3.

3.3. Essential oils in the treatment of acne

Five studies enrolled a total of 256 participants in clinical trials. Two studies were placebo controlled ^{17 18}, one placebo and standard treatment controlled ²¹, one standard treatment controlled ¹⁹ and the other one was uncontrolled ²⁰. The standard were Lactobacillus-fermented *Chamaecyparis obtusa* (LFCO) ¹⁹ and benzoyl peroxide 10% lotion ²¹. Three studies used *Melaleuca alternifolia* (tea tree oil (TTO)) while the others used *Ocimum gratissimum* and copaiba EOs. The primary outcomes include acne surface area reduction, total lesion count, acne severity index, inflammatory acne

lesion, non-inflammatory acne lesion and reduction in investigator's global assessment (IGA). Efficacy is determined using total numbers of facial acne lesions (TLC)²⁰, IGA score²⁰ histopathological changes¹⁹, TLC and ASI¹⁸, reduction in the total surface¹⁷, product activity (reciprocal value of the number of days taken to achieve a 50% reduction in lesion count)²¹. The characteristic of included studies and summary of the finding is presented in table 2.

Four of the five studies demonstrated effectiveness of EO in acne treatment and the remaining study demonstrated effectiveness but was inferior to the control. In uncontrolled study showed significant improvement when baseline and end of treatment values compared²⁰. Essential oils showed better efficacy compared to placebo in two of the included studies^{18 19}. Of the included studies, one identified a base with better product activity as alcohol and cetomacrogol blend bases (hydrophilic)²¹. One study revealed LFCO as rapid and effective for treating acne lesions compared to TTO where histopathological findings correlated well with the clinical acne grade and treatment response¹⁹. The effectiveness of the EO could be attributed to their antibacterial and anti-inflammatory effect³⁴. The *in vitro* antibacterial activity of different EOs were observed against acne associated bacteria like *Propionibacterium acnes* and *Staphylococcus epidermidis*³⁵. Both antibacterial and anti-inflammatory activities are considerably important in acne therapy. Treatment approaches where antibacterial effects and anti-inflammatory effect were addressed by one component would be future alternative approaches. Evidence-based review of botanicals dermatologic use reported that TTO could be potentially used in acne treatment¹² yet the included studies were of low quality³⁶. Essential oils could be future preferred alternative provided the limitation in the included studies are addressed⁵.

3.4. Essential oils in decolonization of methicilin resistant *Staphylococcus aureus*

Five studies enrolled and evaluated 620 participants^{22 23 25 26 37} of which four were randomized controlled trials^{22 23 26 37} and the remaining uncontrolled trial²⁵. Two studies used routine care (2% mupirocin ointment & triclosan body wash or mupirocin 2%,

chlorhexidine gluconate 4% soap, silver sulfadiazine 1% cream)²³ as control. In other two studies the saline gauze²⁶ and JBS²² were the controls. The primary outcomes include number of patients cleared of MRSA and with new MRSA. The characteristic of the included studies was summarized in table 3. Essential oils showed significantly better efficacy in decolonization of MRSA compared to routine care. Control of MRSA within health-care settings and populations poses a problem and managed by mupirocin³⁸. Mupirocin and chlorhexidine gluconate are current standard agents for MRSA decolonization³⁹. MRSA strains have developed resistance to mupirocin^{40 41}, and chlorhexidine gluconate⁴² which call the search for new treatments.

Meta-analysis showed the proportion of MRSA cleared in the whole intervention was 55% (95%CI: 35%, 75%), $I^2=88.16\%$). Though non-significant a higher proportion of MRSA was cleared in EOs (TTO) group compared to routine care (Fig 4).

The proportion of new MRSA developed was 21% ([95%CI: 9%, 36%], $I^2= 86.59\%$) in whole intervention type. Subgroup analysis showed significantly lower level of new MRSA occurrence in TTO group compared to routine care, Fig 5. Dryden et al., 2004 showed significantly lower proportion of number of patients with MRSA in TTO (49% [95%CI: 38%, 60%]) compared to standard care (78% [95%CI: 68%, 86%]).

3.5. Essential oils in the treatment of topical fungal infections

Eight studies enrolled a total of 631 participants with fungal infections for evaluation of EOs effectiveness^{13 27-33}. Three^{13 29 31} enrolled participants with dandruff, two with tinea pedis^{28 32}, one with pityriasis³³, one with toenail onychomycosis³⁰, and one with seborrheic dermatitis²⁷. The treatment outcomes of EOs were compared to standard treatment of 2% ketoconazole^{13 33}, 2% butanafine³⁰, and placebo^{27-29 32}. The characteristics of included studies were summarized in table 4. Essential oils showed

equal or non-inferior efficacy to standard treatment and better efficacy to a placebo in treating topical fungal infections. Essential oils improved clinical symptoms in all of the included studies and conversion to negative cultures. This study included three or more additional studies yet no conclusive evidence was generated as result of significant heterogeneity and different operationalization of the same outcome. The finding merits future studies with improved quality, standardized formulation, strength, clearly formulated primary outcomes, and duration of follow up. Future studies should primarily generate a standard formulation and focus on clearly defined outcome.

4. Summary and conclusion

This review demonstrated clinical use of EOs in the treatment of topical infectious. A total of eighteen clinical trials were retrieved, of which five were in treatment of acne, five in MRSA decolonization and eight in the treatment of topical fungal infections which revealed EOs as promising which deserve further investigation. Considerable heterogeneity amongst the included studies gave a lesson for future studies to be standardized. Heterogeneity in the studies come from differences in outcome variables, duration of treatment, dosage strength, differences in controls used, type of EOs, characteristics of the patients in the study, and geographical origin of EOs. Outcomes varied among the studies, even the same primary outcome variables had been differently operationalized. Some of studies involve no controls at all and/or used different controls; some used placebo as controls while others standard treatment. Geographical variation could result in differences in the constituents of EO both qualitatively and quantitatively, which affect the clinical outcome.

Tea tree oil is commonly studied, characterized and an international standard has been formulated⁴³. The origin of the plant, Australia, could have contributed to its intensive study because of technologies while most EOs from developing countries was less frequently studied. It is worthy to note that the clinical utilization of EOs requires more in-depth studies as EO contains multi-components and single active component is not identified. The studies have to focus on identifying the most active component. The increasing popularity of EOs and the prevalence of EO-based self-care practices

targeting a wide variety of ailments in the United States and developing countries alert healthcare professionals to address concerns about the agents' safety and efficacy. Proper literature evaluation requires the ability to discern the quality of EO, the safety of administration, and validity of its use ⁴. A prescription with EOs could reduce and reserve future over-use of antibiotics ⁴⁴.

In conclusion, this review analyzed data from clinical trials conducted in human with topical infections. Based on the review, EOs could be considered alternatives for the decolonization of MRSA, acne treatment and topical fungal infections. The low quality and heterogeneity among the studies necessitate the need for further studies.

Abbreviations/Acronyms

ASI: Acne severity index

CFU: Colony forming unit

EO: Essential oil

ICU: Intensive care unit

JBS: Johnson's Baby Soft wash

LFCO: Lactobacillus-fermented *Chamaecyparis obtusa*

MRSA: Methicilin resistant *Staphylococcus aureus*

TLC: Total acne lesions count

TTO: Tea tree oil

Declarations

Ethical clearance and consent for participation

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Consent for publication

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Data availability statement

The data supporting the conclusions of this article are included within the article and its supplementary files.

Conflict of interests

The authors declare no conflict of interests

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Authors' contributions: SD and AM conceived the research idea. SD drafted earlier version of the manuscript. SD and AM searched, screened and extracted the data. AA and HL assisted in screening and extraction of the data. EM, AH, JB and PEA revised and developed the drafted manuscript. All authors read and approved the final manuscript.

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Fig 1: Flow diagram of retrieved, screened, included and excluded studies

Fig 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Fig 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Fig 4: Proportion of MRSA cleared, essential oil TT O versus routine care

Fig 5: Proportion of new MRSA emergence in EO (TTO) versus placebo versus routine care

Table 1: Search syntax used

	Search
1.	[Essential oil]OR [Volatile oil]OR [Aromatherapy]OR [alternative treatment]
2.	Mycosis OR dermatitis OR furuncles OR cellulitis OR ecthyma, erysipelas OR erythrasma OR acne OR impetigo OR actinomycosis OR boils OR carbuncles OR dandruff
3.	[Clinical trial] OR [Randomized controlled trial] OR [Clinical study] OR [Controlled trial] OR [Prospective study]
4.	1 AND 2 AND 3

Table 2: Characteristic of the included studies and summary of the finding of Essential oils use for treatment of acne

	Study	Study duration	Study Design, Country	Findings			Adverse effect
				Intervention	No of pts	Result	
1	da Silva et al, 2012 ¹⁷	3 wk	CCT, India	1.0% copaiba	10	SA reduction = 86.494	Not reported
				Placebo	10	SA reduction = 13.931	Not reported
2	Enshai et al, 2007 ¹⁷	6 wk	RCT, South Korea	5% TTO	30	Reduction TLC= 43.64 Reduction ASI=40.49	Pruritus (10%), little burning sensation (1) & minimal scaling (1)
				Placebo	30	Reduction TLC= 43.64, Reduction ASI=14.18	minimal pruritus (2) & little burning sensation (2)
3	Kwon et al, 2014 ²⁰	8 wks	RCT, Split-face trial Australia	5% TTO	34	IAC by 38.2% ‘	Not reported
				5% LFCO	34	IAL reduced by 65.3% , NIAL reduced by 52.6% & LFCO superior to TTO in onset time of efficacy	Not reported
4	Malhi et al, 2017 ²⁰	12 wks	CT, Nigeria	TTO gel (200 mg/g) and face wash (7 mg/g) BID	14	Reduction IGA =0.5, Reduction TLC = 13	moderate scaling, peeling (1) dryness (1), and minor itch (1)
5	Orafidiya et al, 2002 ²¹	4 wk		2% <i>Ocimum gratissimum</i> oil		5% oil in alcohol, gave highest activity	Mild skin burning’ sensation (98%) & Moderate skin reaction in 5%

				10% benzoyl peroxide			
				Placebo		No 50% reduction	

Where, IGA= Investigator global assessment, TTO= Tea tree oil, RCT= Randomized controlled trial, CCT= Controlled clinical trial, CT= Clinical trial, TLC = Total lesion count, SA = Surface area, ASI = Acne severity index, IAL= Inflammatory acne lesions, NIAL= Non-inflammatory acne lesions, DA= Product activity, wks = weeks, LFCO = Lactobacillus-fermented *Chamaecyparis obtuse*

Table 3: Characteristic of the included studies and summary of the finding of Essential oils in MRSA decolonization

		Design, Country	Intervention of type	Duration of intervention	Treatment outcome		
					No of Patients	No of Patients cleared of MRSA	Adverse effect
1.	Blackwood et al., 2013 ²²	RCT, ICUs, Ireland	5% TTO	Median (IOR) 8 (4, 13)	195	-	Safe and well tolerated
			JBS	Median (IQR) 6 (3, 11)	196	-	Not reported
2.	Caelli et al., 2001 ²⁴	RCT, Referral hospital, Australia	IC	Mean (range) 5.6 (2-14)	15	5	Mild swelling of nasal mucosa, burning
			RC	Mean (range) 10.7 (1-34)	15	2	Skin tightness (1)
3.	Edmondson et al., 2011 ²⁵	Case serious, Australia	3.3% TTO	12 week	11	11	Pain in 3 of 12
4.	Lee et al., 2014 ²⁶	RCT, Hong Kong	10% TTO	4week	16	14	Not reported
			Saline gauze	4week	16	0	-
5.	Dryden et al., 2014 ²³	Royal Hampshire County Hospital, UK	10%TTO cream & 5% body lotion	14 days	110	46	Not reported
			ST	14 days	56	114	-

Where= RC= Routine care = 2% mupirocin ointment & triclosan body wash, IC= intervention care (4% TTO ointment & 5% TTO), JBS = Johnson's Baby Soft wash, ST= standard treatment (Mupirocin 2%, chlorhexidine gluconate 4% soap, silver sulfadiazine 1% cream)

Table 4: Characteristic of the included studies and summary of the finding of essential oils in topical fungal infections

	Study	Disease	Design, country		Intervention	Treatment outcome		
						Dose	No of participants	Results
1.	Carmo et al., 2013 ³³	Pityriasis versicolor	RCT, Brazil	Forty days	Cymbopogon citratus 1.25 μ L/mL	Shampoo 3xweek & cream 2x day	47	60% cure
					2% ketoconazole		29	80% cure
2.	Chaijan et al., 2018 ¹³	Dandruff	CT, Iran	One month	Myrtus communis L.	8x in a month	37	ASF reduced 2.92 $\pm$ 0.98 No significant difference between the efficacy, side effects
					2% ketoconazole	8x in a month	37	ASF reduced from 2.92 $\pm$ 0.98
3.	Tong et al., 1992 ³²	Tinea pedis	RCT, Australia		10% TTO		37	Conversion =30% Clinical improvement
					1% tolnaftate		33	Conversion =85% Clinical improvement
					Placebo		34	Conversion =21% Clinical improvement
4.	Chaisripipt et al,	Dandruff	RCT, Thailand	2 wk	10% lemongrass oil	-	30	10% lemongrass oil reduced dandruff

	2015 ³¹							81% at 14
5.	Syed et al., 1999 ³⁰	Toenail onychomycosis	RCT	16wk	5% TTO		40	80% cured (4)
					2% butenafine		20	None cured
6.			RCT, Sydney	4wk	5%TTO	Daily	63	Total area Total severe 6.9+2.04, =91.0+38.5 =48.9+19.5 43.5+21.3
	Satchell et al., 2002a ²⁹	Dandruff			Placebo	Daily	62	Total area Total severe 7.0+1.92, =99.9+35.5 =53.6+21.5 49.1+24.7
7.	Satchell et al., 2002b ²⁸	Tinea pedis		4 wk	25% TTO		36	14 cured
					50%TTO		38	18 cured
					Placebo		46	14 cured
8.			Skin Diseases Research Center, Iran	4 wk	5%TTO gel		23	At 4 wk: It Erythma% 0.55+0.2, 0.0+0.0, P
	Roy et al, 2013 ²⁷	Seborrheic dermatitis			Placebo		19	At 4 week Erythma% 1.9+0.90, 1.8+0.3, P