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

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ABSTRACT

Objective: This study summarized evidence on the 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 the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline. Electronic databases of the Cochrane, PubMed, 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, 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.
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 oils 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.

1. Introduction

Essential oils (EOs) are one of the most common natural products used for various medical purposes since early human being.[1,2] Common EO-producing plant families include 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 the emergence of antimicrobial resistance, commercial EOs are increasingly an option for therapy.[5] Essential oils are

Abbreviations: 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

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considered a 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 the membrane disruption property of the EOs.[7] Their antimicrobial efficacy study in humans 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. To date, several clinical studies have been 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 was to synthesize the findings of clinical studies/trials on EOs that have been conducted to treat topical infections.

2. Methods

2.1. Study design

This systematic review of clinical trials was conducted using best available evidence and reported in accordance with the 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) was used 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 retrieved. Outcomes of the study included 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 included 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) was 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 1060 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 were five studies on acne,[17–21] five on methicilin 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, Figs. 2 and 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

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

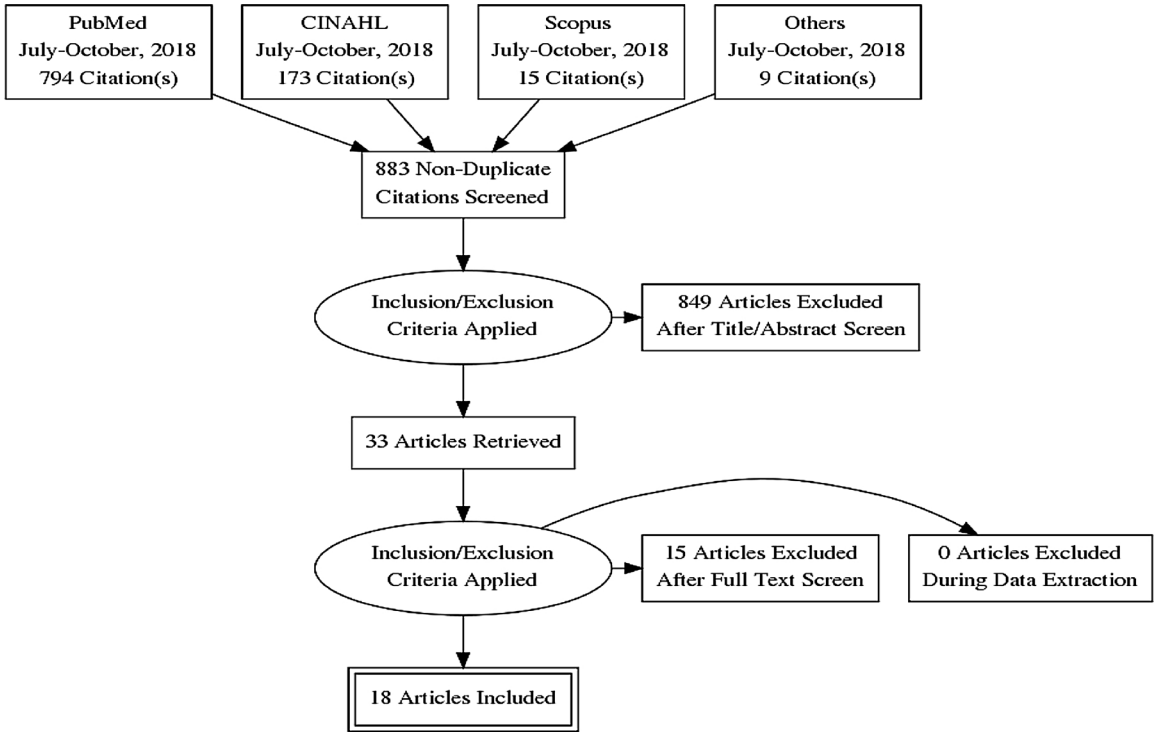

Fig. 1. Flow diagram of retrieved, screened, included and excluded studies.

other one was uncontrolled.[20] The standards 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 included 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 was determined using total numbers of facial acne lesions (TLC),[20] IGA score[20] histopathological changes,[19] TLC and ASI,[18] reduction in the total surface,[17] 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 the uncontrolled study significant improvement were found when baseline and end-of-treatment values were compared.[20] 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 response.[19] The effectiveness of the EOs could be attributed to their antibacterial and anti-inflammatory effect.[34] 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 for dermatologic use reported that TTO could be potentially used in acne treatment[12] yet the included studies were of low quality.[36] Essential oils could be a future preferred alternative provided the limitations in the included studies are addressed.[5]

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, an uncontrolled trial.[25] Two studies used routine care (2% mupirocin ointment and+ triclosan body wash or mupirocin 2%,

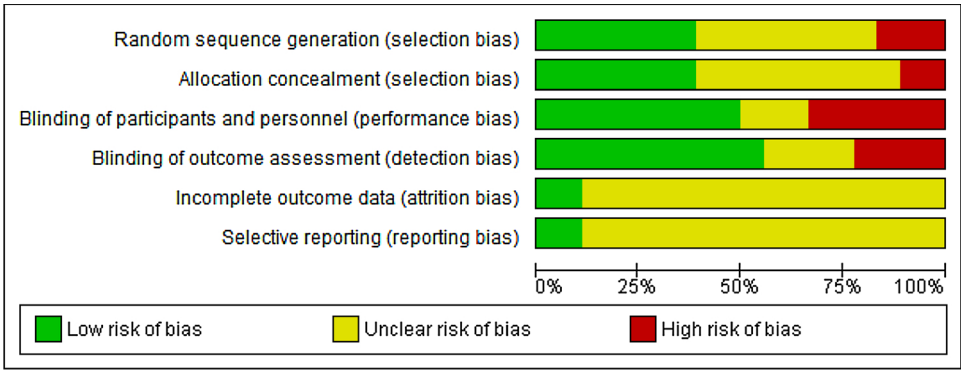

Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

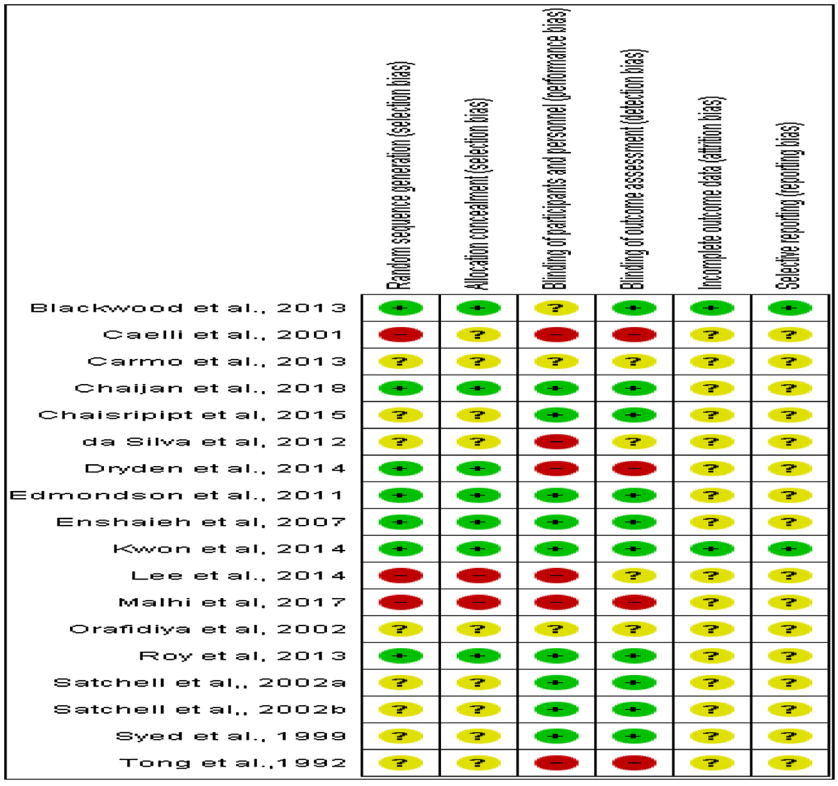

Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

chlorhexidine gluconate 4% soap, silver sulfadiazine 1% cream)[23] as control. In two other studies, the saline gauze[26] and JBS[22] were the controls. The primary outcomes included 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 is managed by mupirocin.[38] Mupirocin and chlorhexidine gluconate are current standard agents for MRSA decolonization.[39] MRSA strains have developed resistance to mupirocin,[40,41] and chlorhexidine gluconate [42] which call for 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 the whole intervention type. Subgroup analysis showed significantly lower level of new MRSA occurrence in the 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 pityriasis,[33] one with toenail onychomycosis,[30] and one with seborrheic dermatitis.[27] The treatment outcomes of EOs were compared to standard treatment of 2% ketoconazole,[13,33] 2% butanafine,[30] 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(s).

4. Summary and conclusion

This review demonstrated the clinical use of EOs in the treatment of topical infectious. A total of eighteen clinical trials were retrieved, of which five were in the treatment of acne, five in MRSA decolonization and eight in the treatment of topical fungal infections, which revealed EOs as promising and 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 the studies involved no controls at all and/or used different controls; some used placebo as controls while others used 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 formulated.[43] The origin of the plant, Australia, could have contributed to its intensive study because of available technologies while most EOs from developing countries were less frequently studied. It is noteworthy that the clinical utilization of EOs requires more in-depth studies as EOs contain multi-components and single active component not identified. The studies have to focus on identifying the most active component(s). The increasing popularity of

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	Enshaieh 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% *Ocimum gratissimum* 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	Other findings
1	Blackwood et al., 2013[22]	RCT, ICUs, Ireland	5% TTO	Median (IOR) 8 (4, 13)	195	–	Safe and well tolerated	17 new MRSA
			JBS	Median (IQR) 6 (3, 11)	196	–	Not reported	22 new MRSA
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	6 new MRSA
			RC	Mean (range) 10.7 (1-34)	15	2	Skin tightness (1)	8 new MRSA
3	Edmondson et al., 2011[25]	Case serious, Australia	3.3% TTO	12 week	11	11	Pain in 3 of 12	8 healed
4	Lee et al., 2014 [26]	RCT, Hong Kong	10% TTO	4week	16	14	Not reported	16 healed M(SD) = 93(201) CFU/ml
			Saline gauze	4week	16	0	–	M(SD) = 10,312 (3054) CFU/ml
5	Dryden et al., 2014[23]	Royal Hampshire County Hospital, UK	10%TTO cream & 5% body lotion	14 days	110	46	Not reported	Nasal carriage cleared = 36/74
			ST	14 days	56	114	–	Nasal carriage cleared = 58/74

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).

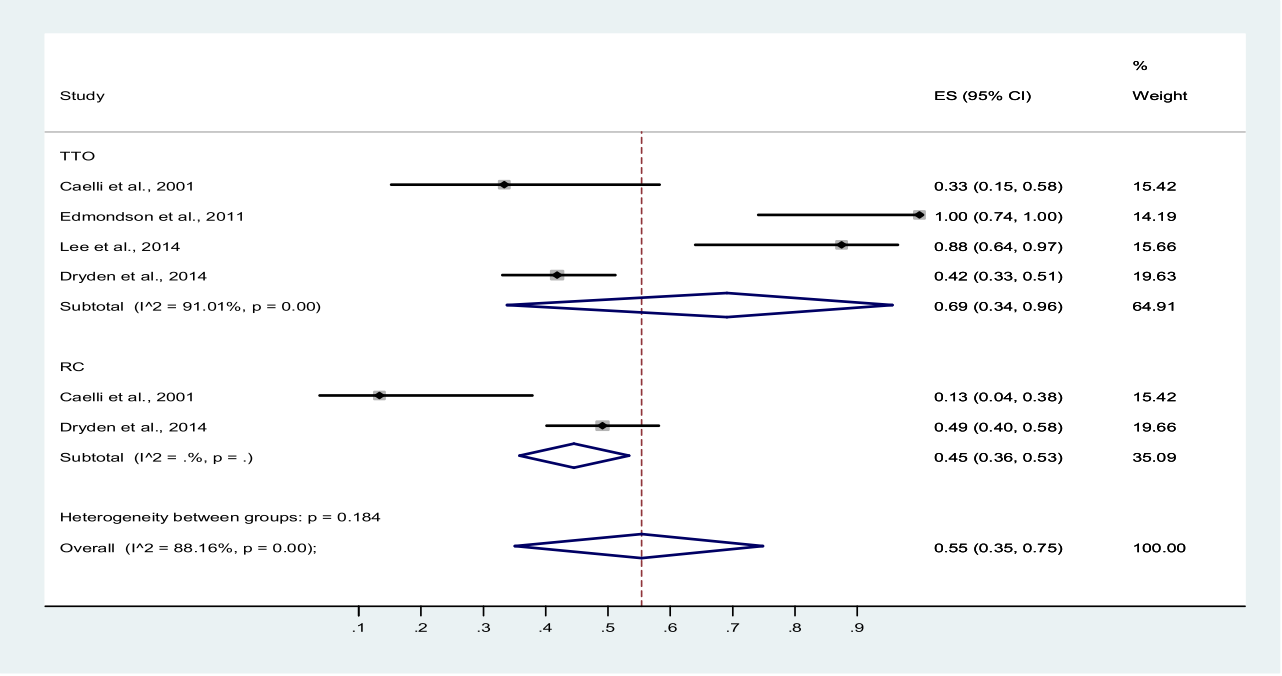

Fig. 4. Proportion of MRSA cleared, essential oil TT O versus routine care.

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 further studies.

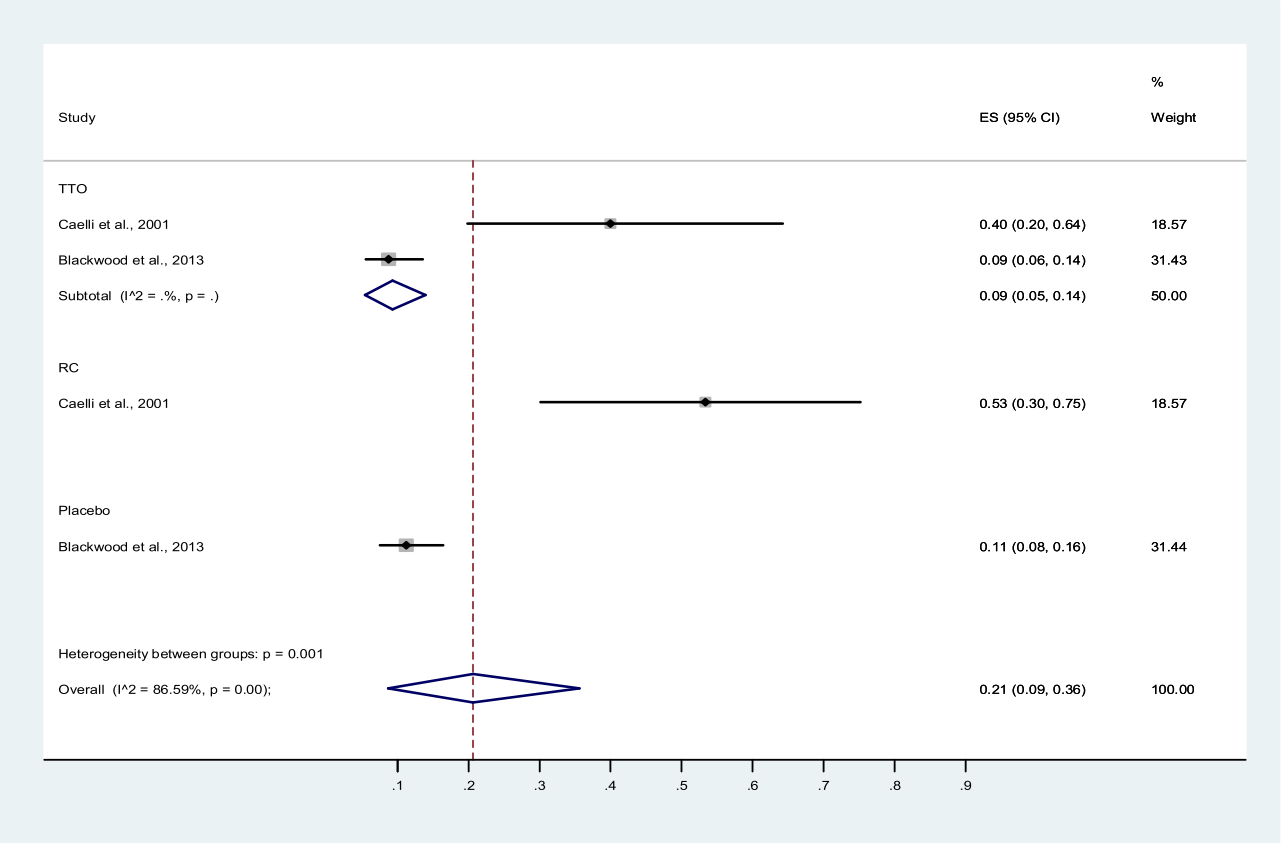

Fig. 5. Proportion of new MRSA emergence in EO (TTO) versus placebo versus routine care.

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 μL/mL	Shampoo 3xweek & cream 2x day	47	60% cure rate
					2% ketoconazole		29	80% cure rate
2.	Chaijan et al., 2018[13]	Dandruff	CT, Iran	One month	Myrtus communis L.	8x in a month	37	ASF reduced to 0.62± from 2.92±0.98 No significant differences between the groups in terms of efficacy, satisfaction rate and side effects
					2% ketoconazole	8x in a month	37	ASF reduced to 0.86±0.89 from 2.92±0.98
3.	Tong et al.,1992[32]	Tinea pedis	RCT, Australia		10% TTO		37	Conversion to negative culture = 30% Clinical improvement = 24/37
					1% tolnaftate		33	Conversion to negative culture = 85% Clinical improvement = 19/33
					Placebo		34	Conversion to negative culture = 21% Clinical improvement = 14/34
4.	Chaisripipt et al, 2015[31]	Dandruff	RCT, Thailand	2 wk	10% lemongrass oil	–	30	10% lemongrass oil reduced dandruff by 75% at 7 day and 81% at 14 day
5.	Syed et al., 1999[30]	Toenail onychomycosis	RCT	16wk	5% TTO		40	80% cured & mild inflammation (4)
					2% butenafine		20	None cured
6.	Satchell et al,, 2002a[29]	Dandruuff	RCT, Sydney	4wk	5%TTO	Daily	63	Total area score = 13.0 + 2.59, Total severity index = 6.9 + 2.04, Whole scalp lesions = 91.0 + 38.0, Scaliness = 48.9 + 19.5, Itchiness = 43.5 + 21.3
					Placebo	Daily	62	Total area score = 13.9 + 2.39, Total severity index = 7.0 + 1.92, Whole scalp lesions = 99.9 + 35.3, Scaliness = 53.6 + 21.9, Itchiness = 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.	Roy et al, 2013[27]	Seborrheic dermatitis	Skin Diseases Research Center, Iran	4 wk	5%TTO gel		23	At 4 wk: Itching% 0.64±0.34, Erythma% 0.69 + 0.7, Scaling% 0.55 + 0.2, Greasy crust % 0.0 + 0.0, Patient Sat.91.5 + 4.1
					Placebo		19	At 4 week:Itching% 2.2±1.0, Erythma% 2.2 + 1.6, Scaling% 1.9 + 0.90, Greasy crust % 1.8 + 0.3, Patient Sat.0.0 + 0.0

Ethical clearance and consent for participation

Not applicable.

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Consent for publication

Not applicable.

Data availability statement

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

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.

Declaration of Competing Interest

The authors declare no conflict of interests.

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