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ANIMAL MODELS OF SKIN INFECTIONS AND TREATMENT WITH ESSENTIAL OILS - REVIEW

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Abstract

Polymicrobial wound infections represent a major clinical challenge, stimulating interest in alternative therapeutic solutions such as essential oils (EOs). The aim of the study was to perform a synthesis analysis on the efficacy of EOs in the in vivo treatment of these infections, including antimicrobial mechanisms, anti-inflammatory and healing effects. Articles were identified using PubMed, Web of Science, Scopus, Science Direct and Google Scholar, published between 2014-2025 and written in English. In vivo evaluations predominantly used murine animal models, on which wounds infected with aerobic and/or anaerobic bacterial strains were induced. The results showed that EOs (lavender, oregano, thyme and clove) significantly reduce bacterial load, disrupt biofilms and enhance antibiotic efficacy. Certain EOs reduce proinflammatory cytokine levels and accelerate wound closure, an aspect confirmed by histological analyses and standardized statistical tests, thus underlining the potential of this approach as an adjuvant therapy even though limitations related to chemical composition variability, irritation risks, lack of regulation and the need for large-scale standardized studies are also highlighted. Evidence suggests a promising role for EOs in the treatment of polymicrobial infections, requiring, however, further clinical validation.

Key words: *antimicrobial, essential oils, in vivo studies, polymicrobial infections, wound healing.*

INTRODUCTION

Skin and soft tissue infections (SSTI) represent a major public health and veterinary problem, with a high incidence and significant impact on morbidity, quality of life, and treatment-related costs. These infections range from superficial, self-limiting conditions to severe disorders with systemic potential, especially when multidrug-resistant bacterial strains are involved. An important aggravating factor in SSTI pathogenesis is the ability of certain bacteria to form biofilms - organized structures that provide protection against the host immune response and markedly reduce the effectiveness of conventional antibiotics. In this context, methicillin-resistant *Staphylococcus aureus* (MRSA) stands out as one of the most problematic etiological agents, being frequently involved in both community-acquired and nosocomial infections (Yin et al., 2024; Cășaru et al., 2024).

Wound infections, in particular, are a major cause of delayed healing and local and systemic complications, especially in chronic wounds. In these settings, persistent colonization and microbial biofilm formation dramatically reduce the efficacy of antimicrobial therapy, maintain chronic inflammation, and prevent normal progression of tissue regeneration (Kennewell et al., 2019). This clinical reality highlights the need for therapeutic approaches that simultaneously target infection control, inflammation modulation, and the support of healing.

Over the last decade, scientific interest in essential oils (EOs) has grown exponentially, driven by the need to identify effective therapeutic alternatives amid the global antimicrobial resistance crisis.

The biological activity of essential oils is mainly attributed to their major bioactive components, such as carvacrol, thymol, and cinnamaldehyde. These compounds exert antibacterial effects via complex mechanisms, including bacterial membrane disruption, perturbation of ionic homeostasis, and inhibition of virulence factor expression. Unlike classical antibiotics, which

often target a single molecular site, essential oils act simultaneously on multiple cellular structures and processes, thereby reducing the probability of resistance development (Chouhan et al., 2017). Nevertheless, their direct clinical application is limited by disadvantages such as high volatility, poor water solubility, and potential irritant effects on injured tissues (Bakkali et al., 2008).

To overcome these limitations, recent research has focused on developing advanced delivery systems for essential oils to improve stability, bioavailability, and safety. Among the most studied platforms are hydrogels, nanofibers, and nanoemulsions, which enable controlled release of active compounds directly at the wound site (Lin et al., 2021; Cai et al., 2023; Mohsen et al., 2023; Shafiq et al., 2025). Validation of these systems in animal models is essential to demonstrate *in vivo* efficacy and to understand the pharmacodynamic behavior of essential oils in a living organism (Bhatia et al., 2022).

A key component in evaluating new therapeutic strategies for SSTI is the use of experimental animal models, which allow investigation of infection dynamics and healing processes in a complex biological context. Murine models are the most frequently used due to low costs, reproducibility, and the availability of genetically modified strains. They are suitable for studying infections caused by *Staphylococcus aureus*, including MRSA, and for analyzing host immune responses. These models enable assessment of EO-based topical treatments, including nanostructured formulations, under controlled conditions, providing relevant data on bacterial load reduction, inflammation modulation, and acceleration of wound healing (Yin et al., 2024; Bhatia et al., 2022; Parker, 2017).

In addition to murine models, other animal species – such as rabbits and pigs – are used to more faithfully reproduce the structure and physiology of human skin. Porcine models, in particular, are considered the gold standard in experimental dermatology due to anatomical and functional similarities to human skin, including epidermal thickness, vascularization, and scarring processes (Shiff et al., 2023; Lindblad, 2008). These models are especially relevant for translational validation of EO delivery systems and for assessing local safety, cutaneous tolerability, and therapeutic efficacy in complex infections, including those associated with bacterial biofilms (Bhatia et al., 2022; Trøstrup et al., 2013; Shiff et al., 2023; Jamin et al., 2020).

Moreover, bacteria belonging to the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* spp.) play a central role in resistant infections and are responsible for most difficult-to-treat nosocomial infections. Their capacity to develop complex resistance mechanisms means that available therapeutic options are increasingly limited, emphasizing the need for alternative infection control strategies (Arias & Murray, 2024; Preda & Popa, 2021).

In this context, essential oils – secondary metabolites of plants – represent a valuable source of bioactive compounds with high therapeutic potential. Their chemical complexity, often consisting of dozens or even hundreds of volatile constituents, provides a major advantage in preventing resistance, as it is more difficult for bacteria to evolve effective adaptive mechanisms through single-point mutations compared with synthetic single-molecule antibiotics (Scandorieiro et al., 2016; Herman & Herman, 2015).

The aim of this review is to synthesize the available *in vivo* evidence on the efficacy of essential oils and their constituents for the treatment of cutaneous infections over the period 2014-2025, with emphasis on experimental models, proposed mechanisms of action, advanced formulations, and safety. This approach allows a perspective on the translational potential of essential oils in managing cutaneous infections in both human and veterinary medicine.

MATERIALS AND METHODS

Study design and methodological framework

This work is a narrative synthesis with systematic elements, conducted using an iterative search and selection strategy in accordance with PRISMA 2020 reporting principles (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Page et al., 2021). The methodological objective was to identify, analyze, and synthesize *in vivo*

experimental studies that evaluated the efficacy of essential oils and their bioactive constituents in the treatment of cutaneous infections using animal models.

Studies published between 2014 and 2025 were analyzed, investigating topical EO-based interventions administered either as neat oils or in advanced delivery formulations (hydrogels, nanoemulsions, nanostructured lipid carriers (NLC), nanoparticles, nanofibers, or vesicular systems) applied in experimental models of infected cutaneous wounds.

Literature search strategy

Last search (all databases): 19 January 2026. Coverage period: 1 January 2014-31 December 2025. Search strategies were adapted to the syntax of each database while preserving the main concepts: (1) essential oils; (2) skin infections/infected wounds; (3) *in vivo*/animal model; (4) topical administration/formulations.

The literature search was systematically performed in the following databases: PubMed, Web of Science, Scopus, Science Direct and Google Scholar (as a supplementary source). The search covered the period from January 1, 2014, to December 31, 2025, and was restricted to original research articles published in English.

The exact search string used was: (“essential oil” OR “phytochemical”) AND (“infected wound” OR “skin infection” OR “MRSA” OR “*Pseudomonas aeruginosa*”) AND (“*in vivo*” OR “animal model” OR “mouse” OR “rat” OR “porcine”).

To ensure reproducibility, the search was performed independently by two reviewers. The Boolean operators AND/OR were applied to combine terms related to the intervention (essential oils), the condition (skin infections), and the study design (animal models). We manually screened the reference lists of all included studies and relevant reviews to identify additional records. For each database, the search was conducted across titles, abstracts, and keywords without applying initial filters for animal sex or breed to maintain a broad coverage of the preclinical evidence.

Only original articles published in peer-reviewed journals and reporting quantifiable experimental data relevant to the study objectives were considered.

Studies were included based on strict cumulative criteria to ensure relevance and comparability with the main objective focused on SSTI. Eligible studies used infected wound or cutaneous lesion models with experimentally induced or confirmed bacterial or fungal infection; non-infected wounds used solely for healing evaluation were excluded to reduce heterogeneity. Only mammalian *in vivo* studies were included, primarily in mice and rats and, where relevant, rabbits or pigs. Established experimental models were required (e.g., contaminated excisional wounds, subcutaneous abscesses, biofilm-associated wound models). Infections were induced using well-documented pathogens, predominantly *Staphylococcus aureus* (including MRSA) and *Pseudomonas aeruginosa*, as well as other clinically important bacteria or fungi. Interventions consisted of topical administration of an essential oil, a bioactive constituent, or an advanced EO-based formulation, with appropriate control groups (vehicle or standard treatments such as mupirocin or vancomycin).

For the purpose of this review, the term “essential oils” also includes major bioactive constituents when these were evaluated as isolated compounds within *in vivo* models. Eligible studies reported quantifiable outcomes including microbial burden reduction, wound closure/contracture rates, histopathology and/or inflammatory and oxidative stress markers.

Studies limited to *in vitro* or *ex vivo* investigations, non-mammalian models, reviews/meta-analyses/book chapters, or reports lacking original experimental data were excluded. Studies that did not clearly describe infection induction, EO dose/concentration, or the treatment protocol were also excluded.

Study selection was performed by two independent reviewers through screening of titles/abstracts and then full texts. The screening process was conducted independently by the two reviewers using a standardized approach based on predefined eligibility criteria. No automation tools were used during the screening process. Discrepancies were resolved by discussions until consensus. Selection followed PRISMA recommendations to ensure transparency.

Essential information extracted from eligible studies included the experimental model, wound and infection type, EO intervention, comparator,

and main reported outcomes (bacterial load reduction, wound healing progression, histological and inflammatory parameters). Data were synthesized narratively and comparatively. The search syntax was adapted to each database to account for differences in indexing and search functionalities. Detailed search strategies for each database are available upon request to ensure full reproducibility.

Risk of bias assessment

The methodological quality of the included studies was evaluated using SYRCLE's RoB tool for animal studies by two independent reviewers, with any disagreements resolved by consensus. Each study was systematically assessed across ten key domains to identify potential biases: (1) sequence generation (selection bias); (2) baseline characteristics; (3) allocation concealment; (4) random housing; (5) blinding of caregivers and investigators (performance bias); (6) random outcome selection; (7) blinding of outcome assessors (detection bias); (8) incomplete outcome data (attrition bias); (9) selective outcome reporting (reporting bias); and (10) other sources of bias. For each domain, the risk was strictly categorized as low, high, or unclear to provide a robust overview of the preclinical evidence's strength and the results were centralized to provide an overview of the robustness of the preclinical evidence.

The systematic search initially identified 55 records from electronic databases (PubMed, Web of Science, Scopus, Science Direct and Google Scholar) and manual searching. After the removal of 6 duplicates, 49 records were screened based on title and abstract. Following this initial screening, 27 records were excluded for being *in vitro*/*ex vivo* studies, using non-mammalian models, or lacking relevant original data. The full texts of the remaining 22 reports were assessed for eligibility. At this stage, 10 reports were excluded due to the absence of essential oil/active constituent interventions, lack of quantifiable outcomes, or insufficient data for comparison. Ultimately, 12 studies met all inclusion criteria and were included in the final synthesis (Figure 1).

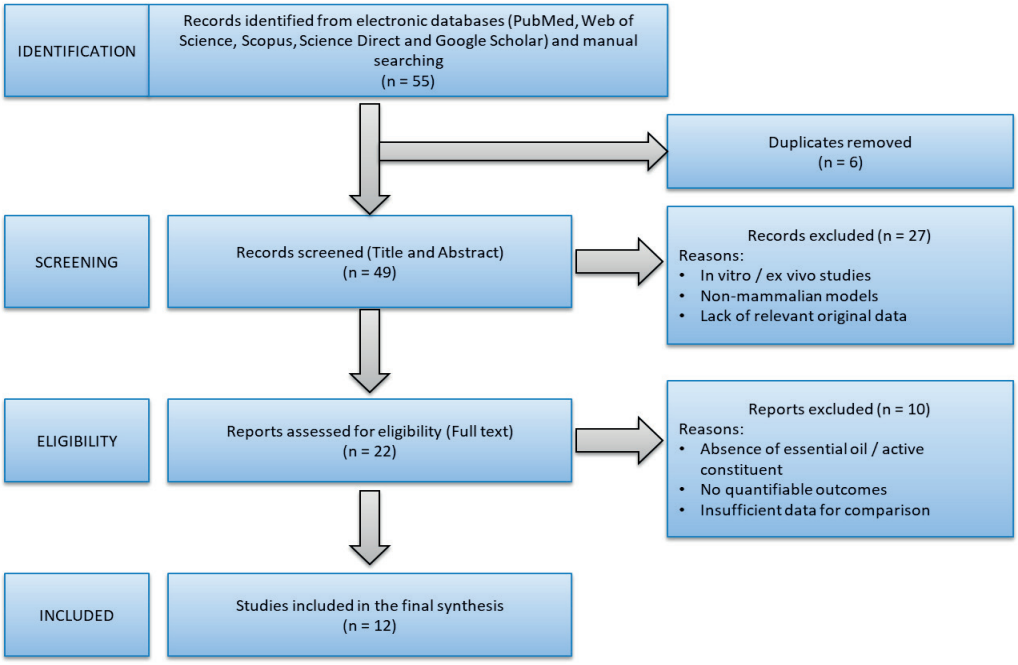


Figure 1. PRISMA flow diagram of study selection (original)

RESULTS AND DISCUSSIONS

The literature search and selection process, summarized in the PRISMA flow diagram (Figure 1), resulted in the inclusion of 12 original studies published between 2014 and 2025. These studies demonstrate a high degree of methodological diversity but converge on the significant therapeutic potential of essential oils in managing infected wounds

The analysis of the literature published over the last decade highlights a marked increase in scientific interest in using essential oils in regenerative medicine, experimental dermatology, and infected wound management. The included studies show substantial methodological diversity yet converge on consistent conclusions regarding the therapeutic potential of essential oils. The results are structured according to experimental model type, wound induction procedures, molecular mechanisms involved, antimicrobial efficacy, impact on tissue healing, pharmaceutical formulation innovations, and safety profile (Table 1).

Table 1. *In vivo* studies evaluating essential oils in cutaneous infections (selected from the bibliography).

Study	Animal model	Wound type	Infectious agent	Essential oil/ active compound	Formulation	Dose/ concentration	Main outcomes
Modarresi et al., 2019	Mouse	Infected excisional wound	*Staphylococcus aureus*	*Mentha piperita*	Topical essential oil	10 µL/day	Reduced bacterial burden; enhanced epithelialization and collagen deposition
Manzuoerha et al., 2019	Rat	MRSA-infected excisional wound	MRSA	*Anethum graveolens*	Topical ointment	2% (w/w)	Significant MRSA reduction; increased fibroblast proliferation and collagen synthesis
Farahpour et al., 2020	Rat	Infected excisional wound	*Staphylococcus aureus*	*Zataria multiflora*	Topical essential oil	1%	Anti-inflammatory effect; increased angiogenesis and collagen synthesis
Ghodrati & Farahpour, 2018	Rat	Infected wound	*Staphylococcus aureus*	*Mentha piperita*	Nanostructured lipid carriers (NLC)	0.50%	Faster wound closure and reduced bacterial load
Khezri et al., 2019	Rat	Infected wound	*Staphylococcus aureus*	*Rosmarinus officinalis*	EO encapsulated in NLC	0.50%	Increased collagen deposition; reduced inflammatory infiltrate
Nejati et al., 2015	Rat	Fungal-infected wound	*Candida albicans*	*Rosmarinus officinalis*	Topical essential oil	1%	Antifungal activity and accelerated wound healing
Ahmadi et al., 2022	Rat	Burn wound	*Pseudomonas aeruginosa*	*Zataria multiflora*	Topical essential oil	1%	Reduced burn area and bacterial load
Vila Nova et al., 2024	Rat	Infected wound	*Staphylococcus aureus*	*Melaleuca alternifolia*	Hydrocolloid gel with EO	1%	Antimicrobial and anti-inflammatory effects; faster wound closure
Teymouri et al., 2024	Rat	Infected burn wound	*Staphylococcus aureus*	*Lavandula officinalis*	Nanoemulsion gel	0.50%	Improved healing rate; reduced bacterial load; improved histology
El-Sakhawy et al., 2023	Rat	Fungal-infected wound	*Candida* spp.	*Eucalyptus globulus*	Topical essential oil	1%	Anticandidal activity; improved re-epithelialization
Alanazi et al., 2022	Rat	MRSA-infected wound	MRSA	*Syzygium aromaticum* (clove)	Topical EO ± imipenem	1%	Synergistic antibacterial activity and improved healing
Mohsen et al., 2023	Rat	Infected wound	*Staphylococcus aureus*	Thymol	Cationic nanoparticle-based hydrogel	0.30%	Reduced bacterial load and accelerated wound contraction

Risk of Bias (RoB) Analysis

The systematic application of the SYRCLE tool revealed that while 100% of the 12 studies reported low risk for selective outcome reporting, significant gaps remain in other areas. Specifically, 83% of the studies (n=10) provided

insufficient details regarding allocation concealment, leading to an unclear risk classification. Furthermore, blinding of outcome assessors was explicitly mentioned in only 25% of the reports (n=3). Most studies (approx. 70%) failed to describe random housing conditions adequately. Despite these reporting gaps, the baseline characteristics (weight, age, and strain) were consistently well-defined across 92% of the analyzed literature, providing a relatively robust foundation for the observed therapeutic efficacy of essential oils. This lack of transparency in animal experimental design underscores the need for rigorous adoption of the ARRIVE guidelines in future research

Animal models and wound induction procedures

Animal models play a crucial and indispensable role in biomedical research, especially in studying infected wounds, cutaneous lesions, and their healing mechanisms, because they allow controlled simulation of pathological conditions and investigation of therapeutic interventions in complex biological contexts. They facilitate understanding of host-pathogen interactions and of inflammatory, regenerative, and immunological processes involved in wound healing, providing essential information for the development and validation of therapeutic strategies (Lindblad, 2008). The use of different animal species is justified by distinct anatomical and physiological features that influence tissue repair mechanisms and the translational relevance of findings (Abdullahi et al., 2014).

Murine models (mouse and rat)

Most *in vivo* studies analyzed used rodents as primary biological models, representing more than 80% of investigations.

Murine models are widely used owing to broad availability of specific antibodies and advanced molecular analysis techniques. Major advantages include the possibility of robust statistical analyses and the use of genetically modified strains, such as diabetic mice, which reproduce delayed healing conditions observed clinically.

Recent literature indicates that most studies evaluating EO efficacy in cutaneous infections use mice (often BALB/c) or Wistar/Sprague–Dawley rats due to standardized skin wound induction protocols (Manzuoerha et al., 2019; Khezri et al., 2019; Teymouri et al., 2024).

A major limitation is the presence of the *panniculus carnosus*, a subcutaneous muscle layer that promotes rapid closure by contraction, a mechanism that differs from predominantly re-epithelialization-driven healing in humans. To reduce this discrepancy, many studies used silicone splints that limit contraction and force healing by granulation and re-epithelialization, increasing translational relevance (Trøstrup et al., 2013). Although murine skin shares the fundamental layers of human skin, there are profound histological, mechanical, and metabolic differences. Mouse skin is characterized by thin epidermis and dermis, a flat dermo-epidermal interface, high hair density, and accelerated regenerative cycles (Dahiya, 2009; Wong et al., 2011). Similarly, rats are classified as “loose-skin” animals due to increased elasticity and reduced adhesion to underlying structures (Abdullahi et al., 2014; Dahiya, 2009).

The porcine model

Porcine models are considered the gold standard in experimental dermatology due to remarkable similarities between porcine and human skin, including comparable epidermal and dermal thickness, collagen/elastin ratio, hair follicle density, and healing mechanisms. They are particularly valuable for evaluating skin penetration, local toxicity, and performance of dressings and topical formulations (Herman & Herman, 2015; Kopecki et al., 2017). Limitations include high costs, logistical challenges, and strict ethical requirements. Biochemically, pigs share with human collagen composition, structural proteins (e.g., keratin, fibronectin, vimentin), and immune cell profiles. A key anatomical difference is the *panniculus carnosus*, which is adherent to deep fascia and separated from adipose tissue; this promotes healing predominantly via granulation tissue formation and re-epithelialization – similar to humans – rather than contraction as in rodents (Ancuța et al., 2026; Roy et al., 2016).

Methodological considerations

Inducing cutaneous lesions in animal models is crucial in dermatological research, enabling

investigation of wound healing processes and therapeutic interventions. Various techniques have been used to create experimental skin injuries, each with distinct characteristics and implications. Skin injury models can be classified by wound type, including incisional and excisional wounds, abrasions, burns, lacerations, and open fractures (Maslova et al., 2020). Once wounds are created, infection can be induced by introducing microbial agents. Wound contamination with microorganisms is almost universal, and not all microorganisms lead to adverse effects (Kupper & Fuhlbrigge, 2004). Therefore, it is essential to evaluate the specific pathogens involved to draw clinically relevant conclusions.

Uniformity in wound creation is essential to reduce experimental variability. Controlled wound production ensures consistent size and depth, which is critical for reproducibility. Moreover, understanding immune responses to surgical interventions and factors influencing surgical site infections can inform better therapeutic strategies (Dai et al., 2011; Liu et al., 2024).

Based on the reviewed literature, three major procedures were identified:

Excisional wound model

The excisional wound model is one of the most widely used *in vivo* experimental models for evaluating cutaneous healing and is considered a reference standard in studies investigating EO capacity to accelerate re-epithelialization, stimulate tissue regeneration, and prevent or control infections in open wounds (Manzuoerha et al., 2019; Khezri et al., 2019; Teymouri et al., 2024). It allows detailed analysis of key healing stages, including inflammation, granulation tissue formation, angiogenesis, and extracellular matrix remodeling.

Methodologically, a standardized circular portion of skin (typically 4-8 mm in diameter) is surgically removed on the dorsal region. The excision is full-thickness and performed with a biopsy punch to ensure reproducibility. The wound is left open or covered with specific dressings depending on study goals, and topical treatments are applied directly for a defined period.

Using this model, Teymouri et al. (2024) demonstrated that topical Lavandula angustifolia (lavender) EO significantly accelerates wound healing by stimulating granulation tissue formation and inducing expression of transforming growth factor beta (TGF-β), a key mediator of tissue regeneration and collagen synthesis. In a similar *S. aureus*-infected excisional wound model, Modarresi et al. (2019) showed that Mentha piperita EO significantly reduces local bacterial burden and inflammatory response, facilitating transition to the proliferative phase and promoting collagen deposition.

Infected burn model

The infected burn model is relevant for studying severe cutaneous infections, as thermal injury creates a favorable environment for colonization and proliferation of opportunistic pathogens, especially *Pseudomonas aeruginosa*, a common burn pathogen known for high antimicrobial resistance. Such lesions are useful for testing oils with strong antibacterial activity.

In this model, thermal injury is induced by applying a preheated metal device (approximately 100°C) to the dorsal region for a controlled duration (4-10 seconds), followed by local inoculation with a bacterial suspension to achieve reproducible infection (Teymouri et al., 2024; Lu et al., 2022).

For example, Ahmadi et al. (2022) demonstrated in a *P. aeruginosa*-infected burn model that topical *Zataria multiflora* EO significantly reduced bacterial load and burn area, accelerated healing, and suppressed systemic inflammation, protecting animals from sepsis. These findings highlight the potential of essential oils as alternative therapeutics in burn wound infection management.

Subcutaneous abscess and biofilm model

This model is used to test the ability of advanced formulations to penetrate biological barriers (the abscess capsule or biofilm matrix) (Ding et al., 2018). The procedure involves subcutaneous injection of a bacterial suspension, most commonly *Staphylococcus aureus* or MRSA, leading to formation of a well-delimited abscess characterized by intense local inflammation and purulent accumulation (Ding et al., 2018). Alternatively, for biofilm studies, a superficial skin lesion can be maintained under an occlusive dressing to promote development of a mature biofilm before treatment initiation (Youn, 2020).

These models are particularly relevant for assessing nanostructured delivery systems. Recent studies indicate that nanoformulations – unlike unformulated Eos – can overcome the physical barriers of abscesses and bacterial biofilms (Albano et al., 2025; Lin et al., 2021). Nanoemulsions and other nanosystems loaded with phytochemicals or EOs show superior biofilm penetration and disruption, including against resistant pathogens (Albano et al., 2025; Lin et al., 2021). For example, cinnamon EO nanoemulsions exhibit significantly improved antibacterial and antibiofilm activity compared with free oil and demonstrate increased efficacy against MRSA biofilms (Kwon et al., 2021). Similarly, polymeric nanofibers or nanoparticles loaded with EOs in chronic wound models reduced bacterial burden and supported complete epidermal regeneration, underscoring their potential as alternative strategies for biofilm-associated chronic cutaneous infections (Lin et al., 2021).

Mechanisms of action of essential oils in cutaneous infections

The main mechanisms of EO action are schematized in Figure 2 and include direct antimicrobial activity, antibiofilm effects, and modulation of the wound microenvironment.

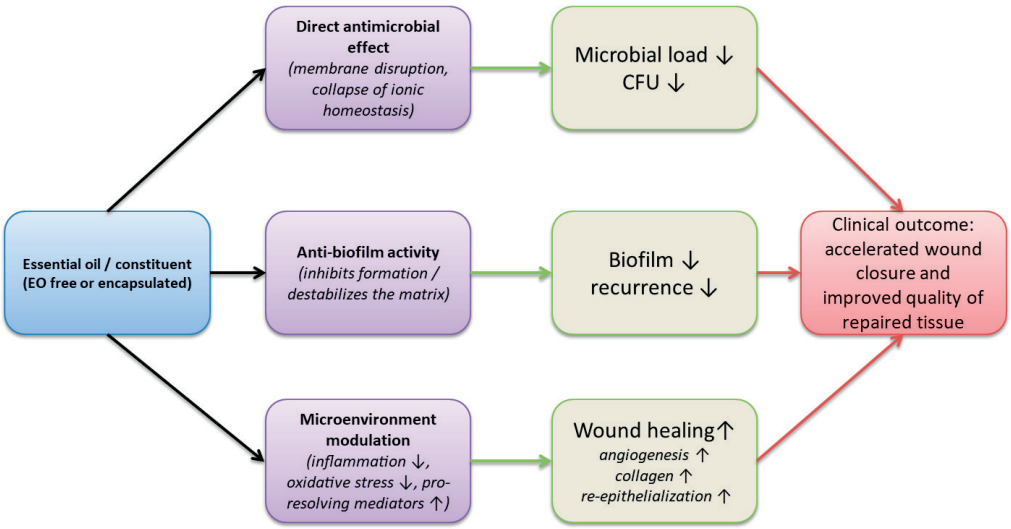


Figure 2: Mechanisms of action of essential oils in skin infections (original)

Direct antimicrobial activity: from membrane to biofilm

Although most mechanistic perspectives originate from *in vitro* studies, the *in vivo* evidence analysed supports these mechanisms indirectly through consistent reductions in bacterial load, improved wound healing, and modulation of inflammatory responses (Yin et al., 2024; Diniz et al., 2022; Manzuoerha et al., 2019).

In vivo evidence indicates that EO antimicrobial activity is central in controlling cutaneous infections, especially with antibiotic-resistant Gram-positive and Gram-negative pathogens. Unlike conventional antimicrobials targeting a single molecular site, EOs act through multifactorial mechanisms, reducing the likelihood of rapid resistance selection (Kennewell et al., 2019; Roshni & Rekha, 2024).

In vivo studies show that topical EOs or their constituents significantly reduce microbial burden quantified by CFU in wound tissue. Such effects have been reported in models infected with *S. aureus, MRSA, P. aeruginosa* (including MDR strains), carbapenem-resistant *K. pneumoniae*, and *Candida albicans* (Manzuoerha et al., 2019; Farahpour et al., 2020; Lu et al., 2022; Alturaiki et al., 2023; Nejati et al., 2015).

Mechanistically, major EO constituents (e.g., thymol, carvacrol, eugenol, linalool, terpinen-4-

ol) are lipophilic and interact directly with microbial cell membranes, increasing permeability, collapsing transmembrane potential, causing leakage of ions and essential metabolites, and ultimately cell death. *In vivo*, these mechanisms are reflected by rapid CFU reduction and limitation of infection spread into adjacent tissues.

A particularly relevant aspect is antibiofilm activity. Biofilm is a major barrier in chronic infected wounds, and several included studies indicate that EO-based formulations can reduce biofilm density and prevent re-formation (Yin et al., 2024; Kwon et al., 2021; Lin et al., 2021; Roshni & Rekha, 2024). For instance, eucalyptus oil nanoemulsions incorporated into hydrogels demonstrated antibiofilm activity associated with accelerated wound healing, suggesting that biofilm disruption directly contributes to restoration of physiological healing (Cai et al., 2023; Orchard, A., & van Vuuren, S. 2017).

Immunomodulation and control of local inflammation

Excessive and persistent inflammation is a major determinant of chronic infected wounds. In this respect, the ability of EOs to modulate local inflammation complements their direct antimicrobial activity.

Multiple *in vivo* studies reported reduced expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in EO-treated tissues, accompanied by increased anti-inflammatory and pro-resolution mediators including IL-10 and TGF-β, suggesting re-calibration of the wound inflammatory microenvironment (Modarresi et al., 2019; Farahpour et al., 2020; Cai et al., 2023).

Biologically, these changes indicate accelerated transition from the inflammatory to the proliferative phase, with a reduced and more organized inflammatory infiltrate and limited extracellular matrix destruction. This immunomodulation is particularly relevant in MRSA and *P. aeruginosa* infections where inflammation contributes significantly to delayed healing and tissue damage (Ahmadi et al., 2022; Farahpour et al., 2020).

Antioxidant activity and stimulation of tissue regeneration

Oxidative stress is recognized as a key factor in infected wound pathogenesis, being associated with damage to membranes, proteins, and DNA. Several studies show that topical EO treatment improves local antioxidant status, reflected by increased total antioxidant capacity (TAC) and decreased lipid oxidation markers such as malondialdehyde (MDA) (Farahpour et al., 2020; Seyed Ahmadi et al., 2019).

These antioxidant effects correlate with stimulation of growth factors involved in angiogenesis and regeneration, including VEGF, FGF-2, IGF-1, and EGF. Histologically, this translates into enhanced angiogenesis, more organized collagen deposition, and accelerated re-epithelialization, indicating that EOs not only control infection but actively support cutaneous regeneration (Table 2).

Table 2. Relationship between essential oil/constituent, dominant mechanism and *in vivo* therapeutic effect

EO/Constituent	Dominant mechanisms	*In vivo* effects	Supporting studies
Tea tree (Melaleuca)	Membrane disruption; immunomodulation	Antimicrobial + anti-inflammatory	Vila Nova et al., 2024
Clove (eugenol)	Antimicrobial; synergy with antibiotics	MRSA control; adjuvant potential	Alanazi et al., 2022
Cinnamon (cinnamaldehyde)	Anti-biofilm; membrane disruption; ↓ oxidative stress	↑TAC/↓MDA; biofilm inhibition	Seyed Ahmadi et al., 2019; Yin et al., 2024
Zataria multiflora	Antimicrobial + anti-inflammatory + pro-angiogenic	↓ microbial load; ↑ angiogenesis/collagen	Farahpour et al., 2020; Ahmadi et al., 2022
Thymol	Membrane effects; anti-inflammatory; delivery-dependent	Higher efficacy in advanced systems	Mohsen et al., 2023; Zohdy et al., 2025

To the best of our knowledge, this is one of the first reviews focusing specifically on *in vivo* mammalian models of infected wounds treated with essential oil-based formulations within the 2014-2025 timeframe. The evidence synthesized in this review consistently supports that essential oils and their bioactive constituents exert a dual therapeutic effect in animal models

of cutaneous infections: effective antimicrobial control, including against resistant pathogens and biofilms, and optimization of healing through reduction of persistent inflammation, limitation of oxidative stress, and stimulation of tissue regeneration. This combination is particularly relevant in infected wounds, where pathogen elimination must be accompanied by restoration of a pro-healing microenvironment to enable transition to proliferative and remodeling phases (Tong et al., 2015; Kennewell et al., 2019; Roshni & Rekha, 2024).

The included studies indicate that EOs act through pleiotropic mechanisms, including direct antimicrobial activity, antibiofilm effects, immunomodulation, and antioxidant properties, contributing synergistically to bacterial burden reduction and accelerated healing (Modarresi et al., 2019; Kennewell et al., 2019; Farahpour et al., 2020; Cai et al., 2023).

Unlike conventional antibiotics, which usually target a single molecular site, EOs and major constituents exert multi-target antimicrobial activity, predominantly via membrane perturbation, altered ionic permeability, and inhibition of virulence factors. This complex action may reduce the likelihood of rapid resistance selection (Chouhan et al., 2017; Bakkali et al., 2008; Kennewell et al., 2019).

Biofilm formation is a critical factor in chronic infected wounds and a major cause of therapeutic failure (Trøstrup et al., 2013). Advanced EO formulations (nanoemulsions, loaded hydrogels, NLC) improve penetration of active compounds into biofilm matrices, reduce bacterial density, and support accelerated re-epithelialization (Albano et al., 2025; Lin et al., 2021; Cai et al., 2023).

Excessive inflammation and oxidative stress are central drivers of delayed healing. Several included studies report that topical EOs reduce pro-inflammatory markers (TNF-α, IL-1β, IL-6) and increase pro-resolution mediators (IL-10, TGF-β), facilitating the transition from inflammation to proliferation (Modarresi et al., 2019; Farahpour et al., 2020; Cai et al., 2023).

In parallel, documented antioxidant effects (↑TAC and ↓MDA) correlate with increased keratin synthesis, organized collagen deposition, and enhanced angiogenesis, confirmed histologically by H&E and Masson staining (Farahpour et al., 2020; Seyed Ahmadi et al., 2019).

Most included studies used rodent models due to reproducibility and access to advanced molecular tools (Lindblad, 2008; Kopecki et al., 2017; Abdullahi et al., 2014; Dahiya, 2009). However, rodent healing is dominated by contraction, potentially overestimating closure speed compared with humans. Silicone splints mitigate this limitation and improve translational relevance (Wong et al., 2011).

Porcine models remain the reference standard for validating skin penetration, tolerability, and efficacy of topical formulations and are essential for translation to clinical applications (Shiff et al., 2023; Herman & Herman, 2015; Ancuța et al., 2026; Roy et al., 2016).

Limitations of unformulated EOs (volatility, instability, irritation) have been partially addressed through encapsulation into nanoemulsions, NLC, hydrogels, and polymeric nanoparticles, providing improved stability, controlled release, and better penetration into infected tissue (Herman & Herman, 2015; Cai et al., 2023; Teymouri et al., 2024; Ghodrati & Farahpour, 2018; Khezri et al., 2019).

Combined strategies pairing EOs with antibiotics or physical modalities (blue light, photodynamic therapy) have shown synergistic effects against MDR pathogens, but require rigorous safety assessment (Lu et al., 2022; Alanazi et al., 2022; Abo-Neima et al., 2023).

Interpretation is limited by heterogeneity in models, wound induction protocols, EO chemotypes, doses, vehicles, and treatment durations. Incomplete reporting of randomization, blinding, and toxicity evaluations also limits comparability and prevents robust quantitative meta-analysis (Roshni & Rekha, 2024; Page et al., 2021). Predominance of unclear risk-of-bias domains should be considered when interpreting the strength of preclinical evidence.

Future research should focus on standardizing experimental models, aligning reporting with PRISMA 2020, and directly comparing EOs to standard antimicrobials, especially in clinically relevant porcine models. Systematic exploration of EO–antibiotic combinations and long-term safety evaluation will be essential for translation toward clinical practice (Wang et al., 2022; Zohdy et al., 2025; Page et al., 2021).

CONCLUSIONS

The *in vivo* evidence synthesized in this review supports that essential oils and their major bioactive constituents are promising therapeutic candidates for managing bacterial and fungal cutaneous infections in animal models. Between 2014 and 2025, research evolved from antimicrobial screening to complex mechanistic investigations, demonstrating pleiotropic EO mechanisms combining antimicrobial and antibiofilm activity with anti-inflammatory, antioxidant, and pro-regenerative effects that support efficient transition toward proliferative wound healing phases.

Through this functional combination, EOs can overcome limitations of conventional approaches that focus exclusively on infection control by concurrently restoring the cutaneous microenvironment required for effective healing.

Murine and porcine models provide complementary insights for developing EO-based topical therapies. Rodents support rapid, reproducible, mechanistic evaluations but contraction-driven closure limits direct extrapolation. Porcine models, due to structural and functional similarity to human skin, remain critical for validating advanced formulations, local safety, and clinical potential.

Beyond relevance for human wound care, these findings have important implications for veterinary medicine, where infected wounds are frequent and challenging. EO-based nanoformulations may serve as alternative or adjunct strategies for post-surgical, traumatic, or chronic wounds in companion and farm animals. However, species-specific differences in skin structure, immune response, and healing dynamics require dedicated studies to optimize formulation composition, dosing schemes, and safety profiles across veterinary contexts.

Interpretation of this review is limited by incomplete reporting of key methodological aspects (randomization and blinding) in many included studies, leading to predominance of unclear risk-of-bias domains that should be considered when evaluating robustness and strength of available preclinical evidence.

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