Essential Oils in Veterinary Wound Management: A Review of Current Literature

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Abbreviations

AMR	**Antimicrobial resistance**
ECM	**Extracellular matrix**
EO(s)	**Essential oil(s)**
IL-1β	**Interleukin-1β**
IL-10	**Interleukin 10**
LEO	**Lavender (*Lavandula* spp.) essential oil**
MRSA	**Methicillin-resistant *Staphylococcus aureus***
NOS2	**Nitric oxide synthase**
OEO	**Oregano essential oil**
PCEO	**Java Pepper (*Piper cubeba*) essential oil**
TGF-β	**Transforming growth factor-β**
TNFα	**Tumor necrosis factor alpha**
TTEO	**Tea Tree (*Melaleuca alternifolia*) essential oil**

Abstract

Wounds are a common presenting complaint in clinical veterinary practice. Veterinarians have begun incorporating essential oils (EOs) into pet wound management protocols. This review article explores the current research and evidence for utilizing essential oils as part of a wound management plan. The literature contains many additional animal model studies, as well as review articles, human pre-clinical and clinical trials, and 1 veterinary case report. Some wounds pose special treatment challenges due to multiple factors, including underlying medical conditions, secondary infections, antimicrobial resistance (AMR), and practical/financial constraints. Successful wound management includes strategies for preventing infection by microbial pathogens. While more human and animal clinical trials are needed, the current review indicates promise for using essential oils to accelerate wound healing in veterinary practice.

Introduction

In veterinary and human medicine, wounds are a source of pain and can reduce the quality of life, while necessitating long-term, costly, and complex treatments. Wound care accounts for a considerable fraction of human health expenses as well as serious socioeconomic problems and has been called a silent epidemic (1-3). Alternatives to pharmaceutical interventions for wound care are desirable for potential cost savings, reduced incidence of adverse reactions, and as a deterrent to antibiotic resistance (1, 4-8).

Although essential oils (EOs) are well known for their antibacterial effects, few have been used commercially for this purpose (4). However, with the search for novel antimicrobial agents accelerating, there is renewed interest in exploring the role of EOs in the fight against antibiotic resistance. Many recent studies document the wound healing effects and mechanisms of action of EOs.

The aim of this review is to present recent evidence for utilizing EOs as part of a wound management plan, advantageously employing their known benefits for accelerating wound healing and preventing secondary infections.

The phases of wound healing

Skin wound healing is a multifaceted, dynamic process with several interdependent phases: hemostasis, inflammation, proliferation/migration, and restoration (1, 2, 5-10). Each phase of the wound healing process is influenced by a series of essential mediators (8, 10).

After tissue damage, hemostasis occurs immediately. Next, during the inflammatory phase, which can last up to 6 days, cytokines and growth factors such as interleukin-1β (IL-1β), platelet-derived growth factor, tumor necrosis factor-α (TNFα), and transforming growth factor-β (TGF-β) are secreted by activated macrophages (3, 6). TGF-β plays an important role in the wound healing process, specifically in the proliferation and collagen synthesis of fibroblasts, production of wound granulation tissue, and differentiation of fibroblasts to myofibroblasts in granulation tissue (3, 10).

Migration and proliferation of keratinocytes, fibroblasts, and endothelial cells follow, driven by growth factors such as hepatocyte growth factor, fibroblast growth factor, and epidermal growth factor (10). Keratinocyte migration is essential for wound re-epithelialization and skin remodeling (3, 10).

Next, extracellular matrix (ECM) biosynthesis and perfusion occur, in conjunction with angiogenesis and epithelialization. Collagen is one of the main components of the ECM and is a key player in the wound healing process. Type III collagen has been shown to increase in the early stages of the wound healing process, replaced later by type I collagen.

Finally, when restoration begins, there is a decrease in cellular accumulation and increased organization of collagen fibers (6, 10). This final stage in wound healing usually begins 3 weeks after the initial insult. In some cases, it may take up to 2 years (8). Successful wound healing results in restoration of the original structural and functional properties of damaged tissue (6).

Essential oils

Essential oils are complex, volatile oils distilled from various parts of plants. Currently, about 300 of the 3000 known EOs are used commercially. Commercial uses of EOs include pharmaceuticals, cosmetics and fragrances, personal care products, foods, and beverages (1).

The configuration, composition, volume, and interactions with pathogens all play a role in the healing potential of EOs. While the 2 to 3 primary or most abundant components of EOs may dictate their activity, up to hundreds of less prevalent minor components, some of which are present in such minute quantities that they may not even be identifiable, often play a role (4).

As plants evolved and adapted successfully to terrestrial environments, EOs have played a beneficial role as nature's smell messengers by attracting pollinators, deterring predators, and eliminating pathogens (11). In veterinary and human medicine, EOs hold promise for accelerating wound healing. They are being used both as the sole therapeutic agents for wound management and as part of a multimodal approach.

Methods

In 2021, a search for scientific studies and clinical trials utilizing EOs for animal and human wound care was conducted on PubMed, Google Scholar, and Clinicaltrials.gov databases. Search parameters included "Essential oils and wound healing" and "Essential oils and wounds." The initial search had an unrestricted time frame. However, since most relevant studies have taken place within the last 5-10 years, and prior reviews have been conducted, primary search parameters were then restricted to studies published within the past 6 years (**Table 1**).

Table 1: Summary of Literature Search Results

Database	Search Parameters	Total Studies	Studies 2015-2021
Clinicaltrials.gov	Essential Oils & Wounds/Wound Healing	10	8
Clinicaltrials.gov	Essential Oils & Bacterial Infection	2	2
Google Scholar	Essential Oils & Wounds	51,300	18,500
Google Scholar	Essential Oils & Wound Healing	85,800	17,100
Google Scholar	Essential Oils & Bacterial Infection	133,000	16,900
PubMed	Essential Oils & Wounds	642	309
PubMed	Essential Oils & Wound Healing	265	164
PubMed	Essential Oils & Bacterial Infection	736	410

In addition, a secondary search of the same 3 databases for "Essential oils and antibacterial properties" was conducted with and without the 2015-2021 date restriction. All studies were required to be available in English.

Search Results

Pubmed database searches using "Essential oils and wound healing" yielded a total of 164 results, and "Essential oils and wounds" yielded 309 results for articles published between 2015 and 2021.

Using the same search phrases, Google Scholar listed 18,500 results for "Essential oils and wound healing," and 17,100 results for "Essential oils and wounds." The Clinicaltrials.gov database yielded 8 results for these search phrases.

From the total number of references identified with these 3 databases, 61 were initially selected as relevant. The remainder were excluded based on inaccessibility, irrelevance, duplication, or no availability in English. A filter was added to restrict searches to studies published from 2015 to 2021, and references were screened a second time for relevancy. The final inclusion criteria were met by 32 references (**Table 2**) (1-3, 5-9, 11-34).

In addition, a Pubmed database search for "Essential Oils and Bacterial Infections" yielded 410 results, and a Google Scholar search returned 16,900 results. Clinicaltrials.gov listed 2 completed studies.

Of the 32 studies reviewed here, 19 (over 50%) are primarily in vivo (animal model) studies, some with an in vitro component. Additionally, there are 3 in vitro studies, 6 review studies, 1 case study, and 3 clinical trials.

Lavender essential oil (LEO, *Lavandula* spp.) was investigated the most frequently in 7 studies, followed by eucalyptus (*Eucalyptus* spp.) and tea tree (*Melaleuca alternifolia*) EOs in 3 studies each. Cinnamon (*Cinnamomun verum*), clove (*Syzygium aromaticum*), peppermint (*Mentha x piperita*), and rosemary (*Rosmarinus officinalis*) EOs are included in 2 of the studies. Almost all the studies involved the topical use of EOs as creams, emulsions, gels, or ointments, or incorporated into wound dressings. One study evaluated an EO mouth rinse and 1 utilized oral EO administration (23, 34).

Many recent in vivo animal model studies corroborate the wound healing effects of EOs. All 18 of these rabbit, rat, and mouse model studies demonstrated a significant beneficial effect of the EOs in the wound healing process.

In vivo studies—lavender EO

In 2 studies, topical application of LEO (*Lavendula aspic* or *Lavendula stoechas*) effectively enhanced wound contraction and regenerated skin tissues in rats with surgically created wounds compared with control groups. In one of these studies, on days 4, 11, and 16 wound contractions were 26.4%, 78%, and 96.3% for the LEO-treated group, and 8.5%, 64.1%, and 86.1% for a positive control group treated with a standard drug cream (Madecassol® 1%) (b) (29). Accelerated epithelial remodeling with LEO application was also observed via histopathology of skin samples (28, 29).

Two additional animal model studies in rats explored potential mechanisms of action of LEO (*Lavandula angustifolia*) in the wound healing process. One of these studies evaluated enzyme activity and gene expression. Measuring the activity of antioxidant enzymes like superoxide dismutase and glutathione peroxidase is important since they facilitate wound healing by reducing free radicals. In this study an LEO nano-emulsion cream was applied daily for 14 days to experimentally induced full-thickness wounds. Treated rats showed the highest wound contraction at multiple time points. RNA was extracted from wound samples for real-time polymerase chain reaction testing as well as superoxide dismutase and glutathione peroxidase activities. Genes for expression of TGF-ß1, type I, and type III collagen were up-regulated in all experimental treatment groups compared to untreated defects on treatment days 7 and 14 (6).

In the other study seeking to elucidate LEO's mechanisms of action in a wound healing model, a 1% LEO (*Lavandula angustifolia*) solution (in DMSO/nonionic surfactant Tween 20) (c) was applied to experimentally induced circular full-thickness skin wounds in rats every other day for 14 days. LEO promoted wound closure in the treatment group, with a significant reduction in wound area from days 4 to 10 post-treatment compared with untreated (surgery only) and control groups (treated with DMSO/Tween 20 only) ($P < 0.05$). Immunohistochemical studies showed an increase in collagen-producing fibroblasts and type III collagen production in the rat wound lesions treated with LEO. Furthermore, mRNA expression of both types I and III collagen in LEO-treated wounds was significantly increased as compared to those treated with control solution ($P < 0.01$). Finally, LEO was found to upregulate TGF-ß, which may be one of the key molecules in wound healing, promoting granulation tissue formation and wound contraction (29).

In vivo studies—rosemary EO

Rosemary EO (*Rosmarinus officinalis*) in a nanostructured lipid carrier increased rates of skin healing in mice. In one study, 2 full-thickness wounds were made on the back of each mouse. Animals were divided into 4 groups including a control and 2 treated groups (rosemary EO and rosemary EO with the lipid carrier). Treated mice had smaller wound areas than the control group ($P < 0.05$). Rosemary EO in the lipid carrier also reduced the bacterial colonization and increased vascularization, fibroblast infiltration, re-epithelialization, collagen production, and serum levels of interleukin-3 and interleukin-10 (IL-10), vascular endothelial growth factor, and stromal cell-derived factor-1α (13).

Table 2: Summary of Literature Reviewed on Essential Oils and Wound Care 2015-2021

Essential Oil(s) Common Name	Essential Oil(s) Scientific Name and/or Primary EO Constituent	Study Type	Wound Type	Intervention Dose and Route	Outcome	Reference	Antimicrobial Effect Studied?
Aceitillo	*Bursera morelensis*	Animal Model, Mouse	Incisional	25% EO	EO acted as a pro-wound healing agent; probable mechanism is promotion of fibroblast migration. Cytotoxicity almost 1000X less than doxorubicin	Salas-Oropeza (14)	No
Avishan Shirazi	*Zataria multiflora*	Animal Model, Mouse	Excisional	Topical 2%, 4% EO ointment q24h for 21 days	Accelerated wound healing process by shortening inflammatory factors and increasing proliferative phase	Farahpour (15)	No
Basil-Clove	*Ocimum gratissimum*	Animal Model, Rabbit	Excisional, Incisional	Topical 100% EO (0.2ml) q24h for 15 days	Accelerated scab formation, contraction, and granulation	Orafidiya (16)	Yes
Bay Laurel, Lavender, Pepper-Rosmarin, Plectranthus, Oregano, Sage, St John's wort, Thyme, Yellow Milfoil	*Laurus nobilis*, *Lavendula* spp., *Lippia sidoides*, *Plectranthus tenuiflorus*, *Origanum majorana & minutiflorum*, *Salviae trilobae aetheroleum*, *Hypericum perforatum*, *Thymus* spp., *Achillea biebersteineii*, Carvacrol, Thymol	Review	EOs with thymol, carvacrol	N/A	EOs act in all wound healing phases to improve tissue repair	Costa (1)	No
Cedar, Pine, Spruce	*Abies* (4 spp.), *Cedrus libani*, *Picea orientalis*	Animal Model, Rat	Excisional, Incisional	Topical 1% EO ointment q24h for 9 days (incision) or until healed (excision)	Demonstrated wound healing and anti-inflammatory activity for *Abies cilicica*, *Cedrus libani*	Tumen (17)	No
Cinnamon	*Cinnamon verum*	Animal Model, Mouse	Excisional	Topical 2%, 4% ointment	Accelerates the healing process by increasing tissue antioxidant capacity and keratin biosynthesis	Ahmadi (18)	Yes
Cinnamon, Clove, Eucalyptus, Helichrysum, Peppermint, Wintergreen	*Cinnamon verum*, *Syzygium aromaticum*, *Eucalyptus globulus*, *Helichrysum italicum*, *Mentha piperita*, *Gualtheria procumbens*	Case Study	Trauma	Topical q24h for 3 days	Enhances tissue regeneration	Fox (19)	No
Clematis	*Clematis flammula*	Animal Model, Rat	Excisional	Topical 0.012% cream (from anemonin component of EO)	Stimulated wound contraction, increased antioxidant enzyme activity; cream was non-irritating	Saidi (20)	No
Cucumis, Discoposium, Rumex	*Cucumis pustulatus, Discopodium penninervium, Rumex abyssinicus*	In vitro	Human skin ulcer (isolated bacteria in culture)	1:1:1 ratio of EOs	Reduced delayed wound healing; focused on antibacterial activity	Gadisa (21)	Yes

Essential Oil(s) Common Name	Essential Oil(s) Scientific Name and/or Primary EO Constituent	Study Type	Wound Type	Intervention Dose and Route	Outcome	Reference	Antimicrobial Effect Studied?
Dill	*Anethum graveolens*	Animal Model, Mouse	Excisional	Topical 2%, 4% ointment q24h for 16 days	Significantly reduced the inflammatory phase and accelerated re-epithelialization, angiogenesis, fibroblast and collagen deposition	Manzoureh (22)	Yes
Eucalyptus	*Eucalyptus* spp.	Animal Model, Rat	Excisional	Oral EO administration 25 mg/kg q24h for 24 days	EO nanoemulsion showed significant wound healing potential and collagen level enhancement	Alam (23)	No
Eucalyptus, Rosemary	*Eucalyptus globulus*, *Rosemarinus officinalis*	Animal Model, Rat + In vitro	Burn	Topical EO in lipid (olive oil) carrier daily for 18 days	Promoted excellent healing, with good re-epithelialization and stratum corneum formation	Saporito (24)	Yes
Geranium, Mooshkorok	*Oliveria decumbens*, *Pelargonium graveolens*	Animal Model, Rat	Excisional	Topical Cream, 1% each EO	Cream with both EOs had the best tissue repair efficacy in rats w/diabetic foot ulcers	Mahboubi (25)	No
Helichrysum, Lemongrass, Lavender, Myrrh, Patchouli	*Helichrysum italicum*, *Cymbopogon* spp., *Lavandula* spp., *Pogostemon* spp., *Commiphora*	Clinical Trial	Hypertrophic scars	Topical 5.4% EO	Combination of EOs works synergistically to reduce scars	Rahman (26)	No
Java pepper	*Piper cubeba*	Animal Model, Rat	Excisional	Topical EO cream	Increased wound healing and contraction	Alminderej (27)	Yes
Lavender	*Lavandula aspic*	Animal Model, Rat	Excisional	Topical 4% EO ointment	Stimulated wound contraction, increased antioxidant enzyme activity, regenerated skin tissues	Ben Djemaa (28)	No
Lavender	*Lavandula angustifolia*	Animal Model, Rat	Excisional	Topical 2% EO, 2% Licorice extract nanoemulsion	Highest wound contraction, increase in expression of TGF-β1, Type I and type III collagen genes	Kazemi (6)	No
Lavender	*Lavandula angustifolia*	Animal Model, Rat	Excisional	Topical 1% EO every other day for 14 days	Promoted wound healing, promoted collagen synthesis and fibroblast differentiation by up-regulation of TGF-β	Mori (29)	No
Lavender	*Lavandula stoechas*	Animal Model, Rat + In vitro	Excisional	Topical 0.5% cream	Decreased inflammation, increased tissue perfusion, proliferation and re-epithelialization	Boukhatem (30)	No
Lavender	*Lavandula* spp.	Review	Lavender EO (20 studies)	N/A	Accelerated wound healing, increased collagen expression, enhanced activity of proteins involved in tissue remodeling	Samuelson (31)	No
Lavender, Tea Tree	*Melaleuca alternifolia*, *Hypericum perforatum*, *Lavandula angustifolia*, *Origanum vulgare*	Review	EOs in wound dressings	N/A	Many studies show promising results	Negut (8)	Yes
Lavender, Thyme	*Lavendula* spp, Thymol	Clinical Trial, Single-Blinded, Randomized	Incision (Episiotomy)	Topical 2% EO solution (jojoba oil base)	Reduced erythema, edema, and ecchymosis	Marzouk (32)	No
Oregano	*Origanum vulgare*	In vitro	Human keratatinocytes	25 µg/ml	EOs inhibit pro-inflammatory damage from interferon-γ, histamine	Avola (3)	No
Peppermint	*Mentha piperita*	Animal Model, Mouse	Excisional	Topical 2, 4, 8% EO ointment	Wound area significantly declined in EO treated mice	Modarresi (9)	Yes
Pepper-Rosmarin	*Lippia sidoides*	Clinical Trial	Equine oral wounds	EO mouth rinse (~0.5%) every other day for 14 days	Induced intense fibroblast proliferation, intense angiogenesis, complete epithelial recovery	Alancar-Araripe (34)	No

Table 2: Summary of Literature Reviewed on Essential Oils and Wound Care 2015-2021							
Rosemary	*Rosmarinus officinalis*	Animal Model, Mouse + In vitro	Excisional, infected wounds	Topical EO gel (0.5 grams) in nanostructured lipid carrier q24h for 14 days	Promoted wound healing by reducing tissue edema, increasing fibroblast infiltration, collagen deposition, neovascularization, and re-epithelialization	Khezri (13)	Yes
Sage	*Salvia officinalis*	Animal Model, Mouse	Excisional, infected wounds	Topical 2%, 4% EO ointment q24h for 14 days	Promoted the healing process by shortening the inflammatory phase and stimulating cellular proliferation	Farapour (33)	Yes
Tea Tree	*Melaleuca alternifolia* mixture - see endnote a	Clinical Trial	Excisional or Incisional (biopsy, oral mucosal)	Topical EO (bioadhesive) gel q8h for 7 days	Surgical sites had re-epithelialization w/o suture; no adverse events	Scotti (12)	Yes
Tea Tree	*Melaleuca alternifolia*	Review	Tea Tree EO	N/A	Plays a role in wound healing and modulation of the immune response	Low (7)	Yes
Thyme	*Thymol* (from *Thymus lippia*)	In vitro	Macrophages	Electrospun anti-inflammatory patch	Expressed efficacy against inflammation and holds great promise for wound healing	Garcia-Salinas (5)	No
N/A	*Abies, Blumea, Cedrus, Croton, Cymbopogon, Eucalyptus, Lavandula, Origanum, Pinus, Plectranthus, Rosmarinus, Salvia*	Review	EOs in a polymer matrix	N/A	EO-biopolymer dressings or scaffolds may enhance wound healing, especially in chronic wounds	Pérez-Recalde (2)	No
N/A	N/A	Review	Biological activity and mechanisms	N/A	Documents antimicrobial, antioxidant, anti-inflammatory, and anticancer activities of EO (in vivo/in vitro)	Sharifi-Rad (11)	Yes

In vivo studies—additional

Highlights from additional in vivo studies include evidence of cinnamon EO (*Cinnamon verum*) accelerating wound healing in a mouse model by shortening the inflammatory phase due to its antioxidant properties, EOs of geranium (*Pelargonium graveloens*) and oliveria (*Oliveria decumbens*) causing a reduction in diabetic foot ulcers, and EOs from a Mexican tree (*Bursera morelensis*) hastening scar repair (14, 18, 25).

In many cases, compelling new scientific evidence validates the intuitive wisdom of ancient traditions. Java pepper essential oil (*Piper cubeba*) (PCEO) is a perfect example. In 2021, Alminderej et al. demonstrated the rapid cutaneous wound healing properties of PCEO in rats with experimentally induced excisional wounds. Wounds treated with PCEO showed faster healing dynamics with signs of re-epithelization after 10 days and total contraction after 13 days compared to slower healing with greater inflammation in the control group (n=16, $P < 0.05$). All control group wounds showed scarring, and some remained open after 13 days (27).

A study validating ancient traditional wisdom from Turkish folk medicine examined the in vivo wound healing activity of EOs from 6 species of pine cones (*Abies cilicica* subsp. *cilicicai*, *Abies nordmanniana* subsp. *bornmulleriana*, *Abies nordmanniana* subsp. *equi-trojani*, *Abies nordmanniana* subsp. *nordmanniana*, *Cedrus libani*, and *Picea orientalis*). In linear incision and circular excision experimental wound models in rats, wound healing potential of pine cone EOs (1% in a base ointment containing glycol stearate, propylene glycol, and liquid paraffin) was comparatively assessed with a reference wound healing and scar prevention ointment (Madecassol®) (b) and the base ointment alone. Wounds were treated once daily for 9 days for the incision model and until healed in the excision model. For the linear incision wound model, only 1 of the 6 pine cone EO species (*Abies nordmanniana* subsp. *bornmulleriana*) was found to be highly effective. In the excision wound model, 3 of the 6 pine cone EO species (*Abies cilicica* subsp. *cilicica*, *Abies nordmanniana* subsp. *bornmulleriana*, and *Cedrus libani*) were found to have wound-healing potential.

Subsequent histopathology was also performed, with re-epithelization in the epidermis and fibroblast proliferation, neovascularization, and collagen deposition in the dermis used to score the degree of epidermal or dermal remodeling. Results indicated remodeling, especially re-epithelization, with 5 of the 6 EO groups

(*Cedrus libani*, *Abies cilicica* subsp. *cilicica*, *Abies nordmanniana* subsp. *bornmulleriana*, and *Abies nordmanniana* subsp. *nordmanniana*) and particularly in the *Abies nordmanniana* subsp. *equi-trojani* ointment-treated groups as well as in the reference (Madecassol®) group, while 1 of the EO groups (*Picea orientalis*), base ointment, and negative control groups exhibited delayed wound healing (17).

In vitro studies

In vitro studies have confirmed the potent anti-inflammatory activity of some EOs and their components and explored mechanisms of action. Oregano EO (OEO) (*Origanum vulgare*) facilitated wound healing in a human keratinocyte cell model (3). Anti-inflammatory activity was proven by reduced levels of reactive oxygen species and oxidative stress in cells pre-treated with OEO. The monoterpene components, comprising about 61% of the OEO, are described as powerful inhibitors of the pro-inflammatory cytokines IL-1β, interleukin-6, and (TNFα). Treatment with OEO reduced the gene and protein expression of pro-inflammatory mediators like inducible nitric oxide synthase (NOS2), intracellular adhesion molecule-1, and cyclo-oxygenase-2 (3). Results of this study supported the hypothesis that OEO helps preserve ECM remodeling and tissue healing, likely due to reduced ECM disruption by inhibition of the breakdown of matrix collagens, proteoglycans, and glycoproteins (3).

Another in vitro study using murine macrophages evaluated the anti-inflammatory properties of EO components including carvacrol and thymol. Macrophages are pivotal immune cells that play a key role in the initial inflammatory stages of wound healing. To recognize foreign patterns, macrophages express toll-like receptors on their surface that activate the inflammatory process. Toll-like receptor stimulation results in activation and nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells and mitogen-activated protein kinase. Both signaling pathways involve activating protein-1 and the downstream transcription of pro-inflammatory genes, such as IL-1β. This cytokine is synthesized in the early stages of inflammation, triggering subsequent signals which activate interleukin-6, IL-10, NOS2, cyclo-oxygenase-2, and others. As the inflammatory response ensues, these signals recruit other effector cells to the wound and begin a progression from inflammation to tissue repair and regeneration (5).

Macrophages exposed to nanofiber patches loaded with EO components were evaluated for pro- and anti-inflammatory genes. Specifically, the expression of IL-1β, NOS2 (pro-inflammatory), and IL-10 (anti-inflammatory) was analyzed. The thymol-loaded patch demonstrated the highest anti-inflammatory effect for all genes tested. Furthermore, when compared to dexamethasone, thymol exhibited a similar ability to modulate the expression of IL-1β and NOS2, demonstrating its potential as a natural anti-inflammatory compound (5).

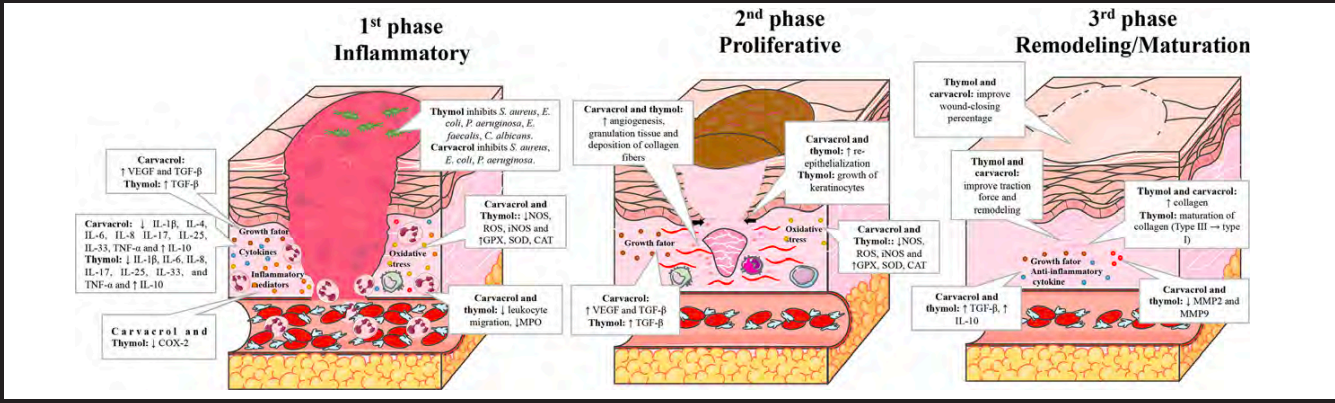
Review studies

Preclinical studies have documented anti-inflammatory, antimicrobial, and antioxidant activities of essential oils in several cell and animal models and have elucidated their mechanism of action and pharmacological targets. Human clinical trials (2008-2016) using citrus (*Citrus* spp.), eucalyptus (*Eucalyptus* spp.), and peppermint (*Mentha x piperita*) EOs are included in this general review. In addition, a few studies included have shown that the application of LEO post-episiotomy may enhance wound healing. Although not solely restricted to wound care, this review provides an excellent database for the broad scope of EO research and corroborates traditional EO healing methodologies such as Ayurvedic medicine and Traditional Korean medicine with modern scientific evidence (11).

A review of LEO for wound healing based on human clinical trials, animal trials, in vitro studies, and previously conducted reviews suggests a potential therapeutic benefit of LEO in wound healing. Faster wound healing, increased collagen expression, and enhanced tissue remodeling protein activity were described in wounds treated with LEO (31).

A systematic review of EOs containing thymol, carvacrol, or these individual EO components examined evidence for their therapeutic potential, specifically with respect to developing biotechnological products for wound healing. Ten articles on the healing capacity of thymol or thymol-containing EOs were included, while 3 articles on carvacrol or carvacrol-containing essential EOs were included. The excision wound model was the most commonly used experimental model. The EOs and EO components were able to modulate the production of nitric oxide and pro-inflammatory cytokines TNFα and IL-1β. **Figure 1** illustrates carvacrol and thymol's specific actions and biochemical pathways targeted during each phase of wound repair (1). Histological analysis demonstrated that they stimulated re-epithelialization, angiogenesis, granulation tissue formation, and collagenization. Thyme (*Thymus vulgaris*) EO, which contains approximately 55% thymol and 9% carvacrol, inhibited the growth of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. The authors conclude that these EOs and EO components can improve tissue repair and are thus strong

Figure 1.



Effects of Carvacrol, Thymol, and essential oils containing such monoterpenes on wound healing (1). License granted by Oxford University Press and Copyright Clearance Center on August 10, 2021

candidates for the development of new wound treatment products. Skin irritation as a side effect was only reported when EOs were used at very high concentrations (50% or greater) and was less pronounced at lower (12%) concentrations (1).

Tea tree essential oil (TTEO) (*Melaleuca alternifolia*) has potent anti-inflammatory, antibacterial, antifungal, antiviral, anti-inflammatory, and antioxidant properties. Like many essential oils, TTEO is comprised of over 100 different chemical components. A review of several clinical studies shows that the water-soluble components of TTEO, especially terpinen-4-ol, are important in regulating inflammation during wound healing by suppressing monocyte production of superoxide ions and inflammatory-inducing mediators including TNFα, IL-1β, interleukin-8, IL-10, and prostaglandin E2. This limits the production of other inflammatory cytokines and reduces oxidative damage to cells, enhancing wound healing (7).

A 2018 review examined the evidence for the therapeutic use of EOs in experimental wounds and the possibility of combining them with biopolymers commonly used in skin regeneration. Treatments with EOs including cedar (*Cedrus libani*), lavender (*Lavandula* spp.), lemongrass (*Cymbopogon nardus*), eucalyptus (*Eucalyptus* spp.), oregano (*Origanum vulgare*), pine (*Pinus* spp.), rosemary (*Rosmarinus officinalis*), and sage (*Salvia triloba*) have shown positive results in rodent wounds with faster closure rates, better collagen deposition, and/or enhanced fibroblast proliferation (2). These EO-biopolymer dressings or scaffolds have promise for wound therapy, especially for chronic wounds (2).

Another review that included TTEO reported positive results for helping to resolve wounds in nursing home residents, with 14 of 16 of the infected wounds resolving within 4 weeks. While this review focuses on incorporating EOs into nanoparticle platforms for wound dressings, it also lends support for the use of LEO and OEO in wound healing (8).

Case study

A veterinary case study involved a 1-year-old female-spayed domestic shorthair cat with severe, multifocal traumatic injury to the mandible, gingivae, and surrounding soft tissues. She was given a very poor to grave prognosis. This case report described how the wounds were managed with a combination of antibiotics and EOs. Numerous EOs were applied topically as part of the wound care protocol, which included a cleanser and blend containing cinnamon (*Cinnamomun* spp.), clove (*Syzygium aromaticum*), eucalyptus (*Eucalyptus* spp.), lemon (*Citrus limon*), and rosemary (*Rosmarinus officinalis*), as well as a second blend containing clove (*Syzygium aromaticum*), helichrysum (*Helichrysum* spp.), peppermint (*Mentha x piperita*), and wintergreen (*Gualtheria* spp.). Fourteen days after the initial presentation, healthy granulation tissue was visualized. Clinical evaluation at that time revealed the absence of tissue necrosis or infection. A complete recovery was reported (19).

Clinical trials

One human pilot study, the first stage of a Phase II clinical trial, reported the effectiveness of a bioadhesive gel (a) containing EOs to promote wound healing and prevent postoperative pain and infection. In 10 patients undergoing oral mucosal biopsies (14 biopsy sites), the procedure was followed by application of a gel containing myrrh (*Commiphora myrrha*), peppermint (*Mentha x piperita*), tea tree (*Melaleuca alternifolia*), and thyme (*Thymus vulgaris*) EOs (12). The EO-based bioadhesive gel reduced inflammation and promoted wound healing. None of the patients enrolled in the study reported adverse events from the gel. The conclusion was that this product may represent a promising alternative to the use of sutures and chlorhexidine (12).

A placebo-controlled, single-blinded, randomized clinical trial involving 60 primiparous women demonstrated that a combination of lavender (*Lavandula officinalis*) EO and thymol was highly effective, suitable, and safe for episiotomy wound care. The 2% lavender-thymol in a jojoba oil base was added

to 4 liters of warm tap water and used to clean the perineum twice daily for 7 days. Data showed a significant reduction in inflammation and discharge for the lavender-thymol treated group compared with a placebo-treated group (less redness, P = 0.032; less edema, P = 0.027; less discharge, P = 0.016). There were no reported side effects (32).

Based on previous research, a combination of helichrysum (*Helichrysum italicum*), lavender (*Lavandula* spp.), lemongrass (*Cymbopogon* spp.), patchouli (*Pogostemon cablin*), and myrrh (*Commiphora* spp.) had demonstrated possible effectiveness for healing hypertrophic scars, which can occur when the wound healing process has been disrupted. It is believed that hypertrophic scarring results from a disturbance with fibroblast proliferation and/or collagen synthesis and degradation. Test subjects had a total of 37 scars, which were self-treated with the EO blend (1.67% helichrysum, 1% lavender, 1.3% lemongrass, 0.6% patchouli, and 0.83% myrrh in a vegetable oil base) twice daily for 6 months. Subjects reported significant scar size reduction using a scar assessment scale for evaluation (P < 0.01) (26).

One additional study that deserves mention is an equine clinical trial published in 2014 (34). Data from this study confirm the benefit of pepper-rosmarin EO (*Lippia sidoides*, a tropical flowering plant in the same family as verbena) for healing wounds experimentally induced in the oral mucosa of 16 horses. A mouth rinse containing the EO was applied to the wound area every 48 hours for 14 days. The EO-treated tissue showed induction of intense fibroblast proliferation and angiogenesis leading to complete epithelial healing by day 14. The control group showed only moderate angiogenesis and epithelial tissue healing (P = 0.02 for angiogenesis and re-epithelization) (34).

Essential oils and antimicrobial resistance (AMR)

Bacteria generally develop resistance to new antibiotics within about 5 years (2). According to one widely quoted review, by the year 2050, AMR may result in 10 million deaths per year worldwide, replacing cancer as the leading cause of death (35). This projection may predict an extreme scenario, and its underlying assumptions have been challenged. Nevertheless, AMR is a real threat, and although the exact toll on our animal companions is currently unknown, it does pose highly significant concerns.

Wound colonizing bacteria can compromise the healing process and increase patient morbidity and mortality. Antimicrobial agents play a vital part in tissue regeneration, helping to prevent these secondary bacterial infections (29). However, antibiotic overuse and misuse are the most common cause of AMR. Concerns about the abundant use of antibiotics in the medical field and in industries like agriculture and aquaculture to promote growth and reduce disease prompt a search for new, cost-effective alternatives (4).

Resistance to penicillin appeared in the 1940s, and rapidly over 50% of staphylococcal strains were resistant. Numerous strains of *S aureus* became multidrug resistant (4). Methicillin-resistant *S aureus* (MRSA) is becoming so common in hospitals in the United States that it accounts for approximately 60% of clinical *S aureus* strains isolated from intensive care units (36). Limited therapeutic options necessitate new strategies, especially those that minimize or eliminate the risk of resistance. Not only do many EOs inherently exhibit anti-bacterial properties, but their molecular complexity is a deterrent to the development of AMR (8).

EOs directly inhibit the growth of microbial pathogens (33). Their cytotoxic effects center on disrupting the structure of bacterial cell membranes, leading to permeabilization. Consequently, membrane potential, efflux pump activity, respiratory activity, and additional cellular functions are compromised (4, 33).

Numerous EOs display potent action against gram-positive and gram-negative bacteria. Of 53 EOs screened, all exhibited activity against pathogenic bacteria such as *Bacillus subtilis, E coli, P aeruginosa,* and *S aureus*. Effective antimicrobial properties against *E coli* were displayed by EOs of bay laurel (*Laurus* spp.), cinnamon (*Cinnamomum* spp.), clove (*Syzygium* spp.), lemon myrtle (*Backhousia* spp.), lemongrass (*Cymbopogon* spp.), oregano (*Origanum* spp.), rosewood (*Aniba* spp.), tea tree (*Melaleuca* spp.), and thyme (*Thymus* spp.) in concentrations as low as 0.02% (4).

Clove and cinnamon provide 2 specific examples of EOs with recent evidence validating their traditional antimicrobial use (4). Clove EO has been used by indigenous peoples in Madagascar and the Spice Islands to kill bacteria, especially the tuberculosis bacillus. As common ingredients in toothpaste, mouthwash, EO blends, and cleaning products, clove (*Syzygium aromaticum*) and cinnamon (*Cinnamonum verum*) EOs are widely recognized for their bactericidal effects against *S aureus* (4, 37-39).

An in vitro study examined the combined effect of EOs mekmeko (*Rumex abyssinicus*, a flowering perennial), gurkor melon (*Cucumis pustulatus*, in the cucumber family), and *Discopodium penninervium* (a flowering shrub)

on wound colonizing bacteria extracted from multidrug-resistant isolates of skin ulcers. These 3 EOs originate from traditional medicinal plants in the highlands of tropical Africa. Farming communities in these areas lack access to modern pharmaceuticals and depend on traditional medicinal plants to treat many human and animal maladies. Interestingly, these EOs were selected based on traditional knowledge gleaned from healers regarding their treatment of skin wounds and infections such as gonorrhea, bacterial pneumonia, and syphilis (21). The majority of bacteria isolated from wounds were resistant to 2 or more antibiotics. Gram-positive bacteria (including MRSA and vancomycin-resistant enterococci) were resistant to amikacin, amoxicillin, ampicillin, cefotaxime, and cefoxitin. Gram-negative bacteria (including extended-spectrum beta-lactamase-producing *E coli* and *P aeruginosa*) were unexpectedly resistant to penicillin and third-generation cephalosporin antibiotics. The EOs had broad bactericidal activities, inhibiting the growth of *Enterococcus faecalis*, *E coli*, *K pneumoniae*, *P aeruginosa*, and *S aureus* (20). The effectiveness of the EOs varied with the concentration and type of bacterial species. Combinations of 2 EOs in a 1:1 ratio had more potent antibacterial effects (on *E coli*, *K pneumoniae*, *P aeruginosa*, and MRSA) than currently available antibiotics. Furthermore, there was a strong synergistic antibacterial effect between *R abyssinicus* and *D penninervium* EOs, specifically on MRSA and *P aeruginosa* (20).

Table 2 indicates which (of the reviewed) wound healing studies also evaluated the EOs' antimicrobial effects. An increasing number of studies in experimentally induced infections document the antimicrobial properties of EOs (7, 9, 15, 21, 22, 33).

A recent trend is the incorporation of nanofibers, biomimetic scaffolding materials, (produced from hyaluronic acid, chitosan, silk fibroin, and other materials) into matrices for wound management. These innovative nanoengineered fibers integrate the ideal attributes of a wound dressing due to their protective effect against infection and external trauma and their ability to promote cell adhesion, differentiation, and proliferation with potential anti-scarring effects. They mimic the dermal ECM with a large surface-to-volume ratio, interconnected porosity, flexibility, and a mechanical framework to support cell regeneration. Biopolymers also provide biological cues for the crucial processes of cell adhesion and migration in tissue regeneration (39). Moreover, the ability of these nanofibers to incorporate and control the local delivery of EOs into the wound milieu for preventing infection and accelerating

cell regeneration is widely expanding their adaptability to various wound applications. The inclusion of EOs presents a functional strategy to discourage microbial invasion of the wound while concurrently reducing the AMR issue (8, 39).

Another novel use of nanotechnology was demonstrated in an excisional wound rat model using an oral nanoemulsion formulation of eucalyptus EO. Nanoemulsions enhance oral absorption and the therapeutic efficacy of drugs. Rats in the EO treatment group received 25 mg/kg oral eucalyptus nanoemulsion daily for 24 days, in comparison with a control group receiving the same oral solution without EOs and a second treatment group receiving 25 mg/kg oral gentamycin for the same period. Wound healing parameters, including collagen levels, were comparable in the EO oral nanoemulsion and gentamycin groups compared with the control groups. Histopathological examinations of the nanoemulsion-treated rats did not reveal signs of inflammatory cells, suggesting the nanoemulsion was safe and nontoxic to animals (22).

The most commonly utilized EOs in recent wound healing studies include eucalyptus, lavender, oregano, tea tree, and thyme. Research within the past 5-10 years, coupled with a greater awareness of the practical utility of essential oils in the clinical setting, lends compelling evidence for the incorporation of EOs in animal wound management.

Safety Considerations

As with any treatment modality, education is vital with essential oils (38). EOs work best when veterinary practitioners understand what they are, how they work, and how to utilize them for animal patients. In addition, it is advised to be familiar with potential adverse events and to establish safety guidelines for essential oil use (40, 41). To remain safe when using EOs with pets, most adverse reactions can be prevented by avoiding ingestion, using dilutions for topical applications, and safeguarding proper storage (4, 42).

Skin reactions are the most common types of adverse reactions to essential oils, but these are individual reactions, do not happen the first time of use, and are dependent on gender (women being more sensitive than men) and concentration. When using OEO, there is a moderate risk of skin sensitization, and a dermal maximum of 1.1% has been recommended (41).

Conclusion

EOs have been utilized widely to treat wounds, inflammation, rheumatic joints, skin lesions, bleeding, leprosy, cystitis, burns, syphilis, fungal infections, and pharyngitis (4). Mechanisms of action for EOs and their individual chemical constituents are rapidly being elucidated. Their anti-inflammatory, regenerative, and anti-microbial properties make EOs strong candidates for the development of veterinary and human biotechnological products for managing skin damage, tissue repair, and wound healing (3).

Although current studies show great promise, continued research is warranted. Additional veterinary case studies and clinical trials are needed to increase practitioner familiarity with EOs and confidence in including EOs in wound healing protocols. Nevertheless, as the search for antibiotic alternatives evolves and the evidence substantiating many EO's antimicrobial activity mounts, serious consideration should be given to their use as safe and effective wound care options.

Endnotes

a. Hobagel Plus®, HOBAMA S.r.l. Milano, Italy. The gel contained *Melaleuca aternifolia* L leaf oil, *Leptospermum scoparium* branch/leaf oil, ammonium glycyrrhizate, *Thymus vulgaris* oil, menthol, *Mentha piperita* oil, eucalyptol, anethole, *Commiphora myrrha* oil, bisabolol, tocopheryl acetate, allantoin, cetylpyridinium chloride, hydrogen peroxide, sodium hyaluronate hydrolyzed, sodium hyaluronate and triclosan as active ingredients, and calcium/sodium PVM/MA copolymer, paraffinum liquidum, petrolatum, cellulose gum, and polyvinylpyrrolidone as excipients.

b. Madecassol®, Dongkook Pharmaceutical, Seoul, Korea. Dosage form: ointment. Ingredients: *Centella asiatica* 10mg in 1g, neomycin sulfate 3.5mg in 1g labeler: I World Pharmaceutical Co., Ltd. NDC Code: 73442-0004

c. Tween®20, Croda International, PLC, Snaith, England. A nonionic detergent.

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