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Menthol as a Novel Therapeutic Strategy for Enhanced Wound Healing

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Abstract:

Menthol is a natural compound derived from mint plants, has emerged as a promising therapeutic agent for wound healing due to its multimodal biological activities. This review synthesizes current evidence on menthol's mechanisms of action, including its antimicrobial properties against pathogens like Staphylococcus aureus and Methicillin-Resistant Staphylococcus aureus, its ability to modulate inflammation by suppressing pro-inflammatory cytokines (Tumor Necrosis Factor-alpha, Interleukin-6), and its role in promoting tissue regeneration through enhanced microcirculation and anti-edema effects. Clinical applications demonstrate its efficacy in accelerating wound closure, particularly in formulations combined with zinc oxide nanoparticles or silver ions for chronic wounds. Additionally, menthol exhibits protective effects in liver and gastrointestinal injury models by reducing inflammatory markers (e.g., Hypoxia-Inducible Factor 1-alpha, Vascular Endothelial Growth Factor) and preserving tissue integrity. Despite its potential, challenges such as optimal dosing and delivery systems remain. Future research should focus on clinical trials and novel derivatives (e.g., amino acid menthyl esters) to expand its therapeutic applications.

Keywords: Menthol; Wound healing; Antimicrobial; Anti-inflammatory; Biofilm inhibition.

1. Introduction

In recent years, hiking, mountaineering, and similar outdoor activities have gained immense popularity. However, with the increasing participation in these sports, the incidence of related injuries has also risen significantly. For instance, a study spanning from 2013 to 2022 reported a total of 2,543 mountain biking (MTB)-related cases in US emergency departments, with a national estimate of 109,558 injuries. Notably, MTB-related injuries exhibited a marked increase during this period (P = .009), including a sharp 64% rise between 2019 and 2020 [1].

In this context, the exploration of effective treatments for sports-related injuries becomes imperative. Menthol, a naturally occurring compound, has demonstrated significant potential in wound healing. Specifically, research indicates that 0.5% menthol cream

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accelerates healing by modulating inflammatory responses. During the inflammatory phase (3 days), it reduces the mRNA expression of pro-inflammatory cytokines. In the proliferative phase (7 days), menthol enhances the activity of antioxidant enzymes (Superoxide Dismutase,Glutathione Reductase and Glutathione Peroxidase) and increases glutathione (GSH) levels, while further suppressing inflammatory cytokines and promoting cellular proliferation via elevated Ki-67 expression. By the remodeling phase (14 days), menthol not only continues to suppress inflammation but also upregulates the anti-inflammatory cytokine IL-10 and its mRNA expression [2].

Moreover, menthol exhibits notable antimicrobial properties. Studies have shown that ND-menthol particles effectively inhibit biofilm formation in both Gram-positive (e.g., Staphylococcus aureus) and Gram-negative (e.g., Escherichia coli) bacteria, outperforming conventional antibiotics like ampicillin [3]. These findings suggest that menthol not only aids in wound repair but also mitigates bacterial colonization, thereby reducing the risk of infection.

Given these promising properties, our study aims to evaluate the efficacy of menthol in treating sports-related injuries under controlled conditions. The research will commence with observational tests on injured mice, comparing menthol-treated subjects with those recovering naturally. Subsequently, we will extend the study to human volunteers through a controlled experiment to validate the findings and draw definitive conclusions.

2. Mechanisms of Action of Menthol in Wound Healing

2.1 Antimicrobial Activities Against Wound Pathogens

Menthol demonstrates significant and potent antimicrobial properties, rendering it effective against a diverse array of pathogens commonly implicated in wound infections [4,5]. The primary mechanism underlying its antimicrobial efficacy involves the disruption of bacterial cell membranes. As a lipophilic compound, menthol integrates into the lipid bilayer of microbial membranes, disrupting membrane integrity and increasing membrane fluidity and permeability. This action culminates in the leakage of intracellular contents, cell lysis, and eventual death of the microorganisms [6]. Empirical studies have consistently shown that menthol exhibits robust activity against prevalent wound pathogens, including Staphylococcus aureus, Pseudomonas aeruginosa, and critically, antibiotic-resistant strains such as Methicillin-Resistant Staphylococcus aureus. For instance, minimum inhibitory concentration assays reveal that menthol effectively inhibits the growth of these bacteria at concentrations that are clinically achievable through topical formulations. Time-kill kinetic studies further support its bactericidal effects, showing a significant reduction in bacterial viability within a few hours of exposure.

Beyond its direct bactericidal and bacteriostatic effects, menthol plays a crucial role in inhibiting biofilm formation. Biofilms represent a major pathological feature in chronic wound infections, characterized by structured communities of bacteria encased in an extracellular polymeric matrix. This matrix confers heightened resistance to conventional antibiotics and host immune defenses. Menthol interferes with the quorum-sensing pathways essential for biofilm development and destabilizes the extracellular matrix structure. It downregulates the expression of genes involved in adhesion and exopolysaccharide production, critical steps in biofilm establishment. By preventing biofilm formation and disrupting pre-established biofilms, menthol significantly enhances the susceptibility of embedded bacteria to other antimicrobial agents, thereby markedly improving wound healing outcomes in chronic and infected wounds [7]. This anti-biofilm activity is particularly valuable in the context of multidrug-resistant infections, where conventional therapies often fail.

Furthermore, menthol functions as a selective agonist of the Transient Receptor Potential Melastatin 8 (TRPM8) receptor channels, which are expressed on sensory nerve endings. Upon topical application, menthol activation of TRPM8 induces a pronounced cooling sensation. This effect is not merely sensory; it provides immediate and effective analgesic relief by modulating nociceptive signaling pathways. The reduction in pain perception is particularly beneficial in the management of burn wounds and traumatic injuries, enhancing patient comfort and compliance with treatment regimens. Recent studies also suggest that TRPM8 activation may indirectly influence local inflammatory mediators, adding another layer to its therapeutic profile. Additionally, this cooling effect can help reduce the burning sensation often associated with wound inflammation, providing immediate symptomatic relief while the compound exerts its therapeutic effects at the cellular level.

2.2 Modulation of Inflammatory Responses

Inflammation is an indispensable yet double-edged process in wound healing. While acute inflammation is essential for the initial clearance of pathogens and debris, excessive or protracted inflammatory responses can impede healing, cause collateral tissue damage, and contribute to the development of chronic wounds. Menthol

exerts sophisticated modulatory effects on the inflammatory phase of wound healing through multiple pathways. It significantly suppresses the production and release of key pro-inflammatory cytokines, most notably Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6). This suppression occurs at the transcriptional level, as evidenced by reduced messenger RNA expression of these cytokines in menthol-treated wound models [8]. The consequent reduction in cytokine signaling leads to decreased recruitment and infiltration of neutrophils to the wound site, mitigating oxidative stress and tissue damage caused by reactive oxygen species and neutrophil-derived proteases. This creates a more balanced and favorable microenvironment conducive to progression into the proliferative phase of healing.

At the cellular level, menthol has been shown to influence macrophage polarization, promoting a shift from the pro-inflammatory M1 phenotype towards the anti-inflammatory and pro-healing M2 phenotype. This transition is crucial for the resolution of inflammation and the initiation of tissue repair processes. M2 macrophages produce anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta, which further dampen inflammation and stimulate fibroblast proliferation and collagen synthesis. The ability of menthol to modulate macrophage polarization represents a sophisticated mechanism through which it coordinates the transition from the inflammatory to the proliferative phase of wound healing [9].

Emerging research has begun to elucidate novel anti-inflammatory pathways activated by menthol and its synthetic derivatives. Specifically, certain advanced menthol derivatives, such as valine menthyl ester (MV) and isoleucine menthyl ester (MI), have been shown to act as potent agonists of Liver X Receptors (LCRs). LXRs are nuclear receptor proteins that play pivotal roles in regulating lipid metabolism and cholesterol homeostasis, and they are increasingly recognized for their involvement in the resolution of inflammation. Activation of LXRs by these menthol esters leads to the transrepression of pro-inflammatory gene networks and promotes the expression of anti-inflammatory mediators. Importantly, this LXR activation pathway operates independently of the well-characterized TRPM8 channel mechanism, revealing a previously underappreciated complexity in menthol‘s anti-inflammatory actions. This discovery substantially expands the potential therapeutic applications of menthol, particularly for managing chronic inflammatory wound conditions such as diabetic ulcers and venous leg ulcers, where dysregulated inflammation is a central pathological feature.

3. Menthol Applications

3.1 Promotion of Tissue Regeneration and Repair

Menthol actively promotes tissue regeneration through several interconnected and synergistic mechanisms that operate across different phases of the healing process. During the very early haemostatic phase following injury, menthol induces vasoconstriction in the superficial microvasculature through its action on smooth muscle cells. This action is crucial for controlling bleeding and minimizing initial blood loss in acute wounds, thereby establishing a stable foundation for subsequent healing stages. The vasoconstrictive effect is followed by a period of enhanced vasodilation, which facilitates the delivery of immune cells and nutrients to the wound site [10].

As the healing process transitions into the proliferative phase, menthol‘s vasoactive properties shift towards enhancing microcirculation around the wound periphery. This improvement in local blood flow optimizes the delivery of oxygen and essential nutrients to the highly metabolically active regenerating tissues, while simultaneously facilitating the removal of metabolic waste products. The increased perfusion also supports the metabolic demands of proliferating cells, including fibroblasts, keratinocytes, and endothelial cells, all of which are essential for successful wound closure.

A particularly valuable property of menthol in this context is its significant anti-edema effect. Edema, or tissue swelling, is a common sequelae of inflammation that can cause mechanical pressure, compromise microcirculation, and lead to localized tissue hypoxia. By reducing vascular permeability and promoting fluid resorption through enhancement of lymphatic drainage, menthol effectively mitigates edema formation. This reduction in swelling alleviates tissue hypoxia, prevents secondary ischemic damage, and supports a faster and more organized recovery process. The anti-edema effect is particularly beneficial in the management of burns and traumatic wounds, where significant fluid accumulation can complicate the healing process.

At the molecular level, clinical and preclinical studies have demonstrated that menthol can downregulate key markers associated with tissue damage and impaired healing. Notably, it reduces the expression of hypoxia-inducible factor-1 alpha (HIF-1α), a key regulator of cellular responses to hypoxia which, when overexpressed, can contribute to excessive and aberrant angiogenesis [11]. Menthol also modulates the levels of vascular endothelial growth factor (VEGF), guiding a more controlled and effective angiogenic response. The compound appears to

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optimize the spatial and temporal expression of VEGF, ensuring the formation of functional and mature blood vessels rather than the leaky, immature vessels often seen in chronic wounds.

Furthermore, menthol application has been linked to increased proliferation of fibroblasts and keratinocytes, elevated synthesis of collagen Type I and III, and enhanced epithelialization rates, as quantified by markers like Ki-67. These effects collectively promote the restoration of functional tissue architecture and strength in the regenerated skin. Menthol also influences the remodeling phase of wound healing by modulating the activity of matrix metalloproteinases and their tissue inhibitors. This regulation ensures balanced extracellular matrix degradation and synthesis, preventing either excessive scarring or weak wound strength. The compound appears to promote the formation of well-organized collagen bundles with improved tensile strength, ultimately leading to better cosmetic and functional outcomes [12].

In summary, the mechanisms through which menthol facilitates wound healing are multidimensional, encompassing direct antimicrobial action, sophisticated immunomodulation, and proactive support of tissue regeneration. Its ability to target multiple pathological aspects of wound healing simultaneously makes it a promising candidate for inclusion in advanced wound care strategies. The compound influences virtually every phase of the healing process, from initial haemostasis and inflammation through proliferation and final remodeling. Future research aimed at optimizing delivery systems, such as nanoparticle encapsulation or hydrogel integration, to ensure sustained and localized release of menthol will be crucial for translating its full therapeutic potential into clinical practice, particularly for complex and hard-to-heal wounds. Additionally, more studies are needed to establish optimal dosing regimens and to explore potential synergies with other wound healing agents, which could further enhance its therapeutic efficacy and application scope in various wound types and healing stages.

3.2 Clinical Applications

The therapeutic potential of menthol has been substantiated across a spectrum of clinical contexts. For instance, a bilayer hydrogel patch incorporating peppermint essential oil—abundant in menthol—in combination with zinc oxide nanoparticles, has been shown to significantly expedite wound closure in animal models. This composite formulation not only attenuated inflammatory responses but also augmented collagen synthesis and facilitated the restoration of native skin architecture within a 14-day treatment period.

In the domain of chronic wound management, a patented therapeutic solution comprising low-concentration silver ions, menthol, and glycerol has demonstrated superior efficacy compared to traditional silver-based wound dressings. The synergistic interaction between menthol and silver enables a reduction in silver content below cytotoxic levels, while concurrently amplifying antibacterial and anti-biofilm activities. This advancement holds particular promise for the treatment of diabetic ulcers and pressure injuries, effectively addressing prevalent limitations such as local tissue toxicity and antimicrobial resistance.

Notably, the therapeutic benefits of menthol extend beyond cutaneous wound repair. Preemptive administration of menthol markedly ameliorated Campylobacter jejuni-induced enterocolitis in murine models, achieved through reduction of bacterial colonization and suppression of mucosal inflammatory responses. Importantly, these beneficial effects were accomplished without perturbation of commens gut microbiota—a distinct advantage over conventional antibiotic regimens.

Clinical formulations increasingly capitalize on the synergistic potential of menthol with other bioactive compounds to enhance therapeutic outcomes. A representative study involving a bilayer hydrogel patch enriched with peppermint oil and zinc oxide nanoparticles reported accelerated wound healing in rat models, underscored by diminished inflammation, enhanced collagen deposition, and architectural restoration of skin within two weeks. Complementary thermal imaging analyses corroborated the formulation's cooling effect, contributing to improved patient comfort. Similarly, a patented wound solution blending low-dose silver ions, menthol, and glycerol exhibited enhanced performance relative to conventional silver dressings, effectively mitigating issues of cytotoxicity and microbial resistance while maintaining robust antimicrobial efficacy.

Further expanding its therapeutic repertoire, menthol administration significantly reduced the infiltration of inflammatory cells in liver tissues of mice exposed to diethylnitrosamine. It also suppressed the upregulation of multiple biomarkers, including alpha-fetoprotein, programmed cell death 6, HIF-1α, and VEGF, with sustained protective effects observed over a six-month period. Menthol treatment also attenuated diethylnitrosamine-induced histopathological alterations in hepatic architecture, underscoring its hepatoprotective potential.

The scope of menthol's regenerative properties further encompasses gastrointestinal wound healing. Prophylactic treatment with menthol alleviated Campylobacter jejuni-induced enterocolitis in murine models through mechanisms involving reduced bacterial load, suppression of mucosal inflammation, decreased nitric oxide secretion,

and diminished immune cell infiltration—all without adversely affecting resident microbiota.

4. Discussion and Future Directions

Menthol has evolved considerably from its historical use as a palliative agent, now emerging as a scientifically grounded component within advanced wound management protocols. Its pleiotropic actions—encompassing antimicrobial, anti-inflammatory, analgesic, and tissue-regenerative effects—collectively endorse its utility as a versatile therapeutic candidate.

Nevertheless, several challenges warrant further investigation. Foremost among these are the optimization of delivery mechanisms to achieve controlled release kinetics and the determination of dosing parameters that maximize efficacy while minimizing potential irritancy. Subsequent research should aim to establish evidence-based dosing guidelines to facilitate clinical translation.

Innovative menthol derivatives, including amino acid-conjugated menthyl esters such as MV and MI, exhibit enhanced anti-inflammatory and metabolic activities. These novel compounds hold promise for managing wound complications associated with metabolic disorders—such as obesity—via inhibition of adipogenesis and modulation of metabolic parameters. It is noteworthy, however, that topical menthol application may influence thermoregulatory processes; while it enhances thermal perception and athletic performance in hot environments, it concurrently reduces sweat production—a factor requiring careful consideration in specific patient populations.

Future research efforts should prioritize large-scale, randomized controlled trials evaluating the efficacy of menthol across diverse wound etiologies and patient demographics. Exploration of novel formulation strategies—including nano-encapsulation, biomaterial-based delivery systems, and combination therapies—may further expand menthol's applicability in regenerative medicine and dermatology.

5. Conclusion

In summary, this review has systematically elucidated the multifaceted therapeutic potential of menthol in wound healing, emphasizing its broad-spectrum antimicrobial, anti-inflammatory, and tissue-regenerative activities. Specifically, menthol disrupts bacterial cell membranes and inhibits biofilm formation, demonstrating efficacy against prevalent wound pathogens, including methicillin-resistant Staphylococcus aureus. Furthermore, it modulates key pro-inflammatory cytokines, including TNF-α and IL-6, and facilitates macrophage polarization toward the pro-regenerative M2 phenotype, thereby fostering an immunomodulatory microenvironment conducive to tissue repair. Additionally, menthol enhances microvascular circulation, attenuates edema, and regulates critical molecular mediators such as VEGF and HIF-1α, collectively promoting angiogenesis, collagen deposition, and re-epithelialization throughout the wound healing cascade.

These mechanistic insights carry notable implications for the management of sports-related injuries, an area of growing concern as highlighted in the introduction. The increasing incidence of such injuries necessitates effective treatment strategies that synergistically address infection control, pain management, and accelerated recovery. Menthol emerges as a promising non-antibiotic candidate, capable of mitigating microbial colonization while providing analgesic effects through TRPM8 receptor activation. Its incorporation into composite formulations—such as those combining zinc oxide nanoparticles or silver ions—further underscores its applicability in advanced wound dressings, potentially overcoming limitations associated with conventional treatments, including antibiotic resistance and impaired healing in chronic wounds.

Nevertheless, several limitations should be acknowledged. The current body of evidence predominantly relies on preclinical models, and clinical validation in human cohorts, particularly among athletic populations, remains scarce. Moreover, parameters such as optimal dosing, long-term safety profiles, and formulation compatibility across varied wound etiologies necessitate further elucidation.

Prospective research efforts should prioritize rigorously designed clinical trials to establish evidence-based application guidelines and explore potential synergies with adjunctive therapeutic agents. Innovations in delivery platforms—such as nanoencapsulation technologies and biomaterial-based hydrogels—hold promise for enhancing the stability and controlled release of menthol. Additionally, investigation into synthetic menthol derivatives, including amino acid-conjugated esters such as MV and MI, may uncover novel mechanisms of action and expand therapeutic applications to metabolic and complex chronic wounds. Ultimately, menthol-based interventions represent a advancing frontier in precision wound care, offering viable strategies to improve healing outcomes across both clinical and sports medicine settings.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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