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CURCUMIN (DIFERULOYLMETHANE) AS A MULTIFUNCTIONAL ANTISEPTIC AGENT IN TOPICAL OINTMENT FORMULATIONS

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ABSTRACT

Diferuloylmethane, commonly known as curcumin, is the principal bioactive diarylheptanoid isolated from the rhizome of Curcuma longa. Beyond its long-recognized culinary and traditional medicinal use, curcumin has attracted sustained pharmaceutical interest as a topical antiseptic and wound-healing agent owing to its combined antioxidant, anti-inflammatory, antibacterial, antifungal, and pro-regenerative properties. This review synthesizes current evidence on the chemistry, pharmacology, and formulation science underlying the use of curcumin in ointments intended for cuts, burns, wounds, and infected lesions. The molecular basis of its multi-target activity, comparative antimicrobial potency against common wound pathogens, evidence from preclinical and clinical wound and burn studies, and the physicochemical barriers that limit its direct topical use are examined. Particular attention is given to nanotechnology-enabled delivery platforms — Nano emulsions, liposomes, solid lipid nanoparticles, hydrogels, and nanofibers — that have been developed to overcome curcumin's poor aqueous solubility and photodegradation and to enable its incorporation into stable, effective topical ointments. The review concludes

by outlining translational gaps and future research directions needed to move curcumin-based antiseptic ointments from bench formulations toward validated clinical products.

KEYWORDS: Diferuloylmethane; Curcumin in; topical antiseptic; wound healing; burn management; ointment formulation.

1. INTRODUCTION

Wound healing is a tightly orchestrated biological cascade comprising haemostasis, inflammation, proliferation, and tissue remodelling. While acute wounds such as clean cuts generally progress through this sequence in a predictable manner, burns and contaminated or chronic wounds are frequently complicated by persistent inflammation, microbial colonization, and delayed closure, presenting a substantial clinical burden.[1,3] Effective topical management of such injuries requires an agent capable of simultaneously controlling microbial load, limiting excessive inflammation, and actively supporting tissue regeneration.

Curcumin, chemically designated diferuloylmethane (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, C21H20O6), is the major curcuminoid of turmeric and has been investigated for a remarkably wide range of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and wound-healing effects.[34,36] Its structural motif of two feruloyl aromatic rings linked by an α,β-unsaturated β-diketone bridge underlies both its biological reactivity and several of the physicochemical limitations that complicate its pharmaceutical use.[35,37]

This review is organized to first describe the chemistry of diferuloylmethane and its behaviour in different formulation environments, followed by an examination of the specific mechanisms by which it exerts antiseptic and regenerative effects relevant to cuts, burns, and infected wounds. The comparative antimicrobial potency of curcumin against pathogens commonly implicated in wound infection is summarized, along with the evidence from preclinical and clinical studies of curcumin-based topical preparations. Finally, the review addresses the principal formulation challenge for any curcumin ointment— its poor aqueous solubility and susceptibility to degradation — and surveys the nanotechnology-based strategies being used to address it.

2. CHEMISTRY OF DIFERULOYLMETHANE

Diferuloylmethane is a symmetric diarylheptanoid: two ortho-methoxylated phenolic rings connected through a seven-carbon chain containing a central β-diketone moiety, with

unsaturation giving the molecule its characteristic yellow-orange colour and reactivity.[34,37] The compound has a molecular weight of 368.38 g/mol and a melting point in the range of 176–183 °C, and it exhibits pH-dependent keto–enol tautomerism: the keto form predominates in acidic and neutral solution, while the enol tautomer becomes the dominant species under alkaline conditions (Figure 1).[34,37]

Figure 1. Keto-Enol Tautomers of Diferuloylmethane (Curcumin)

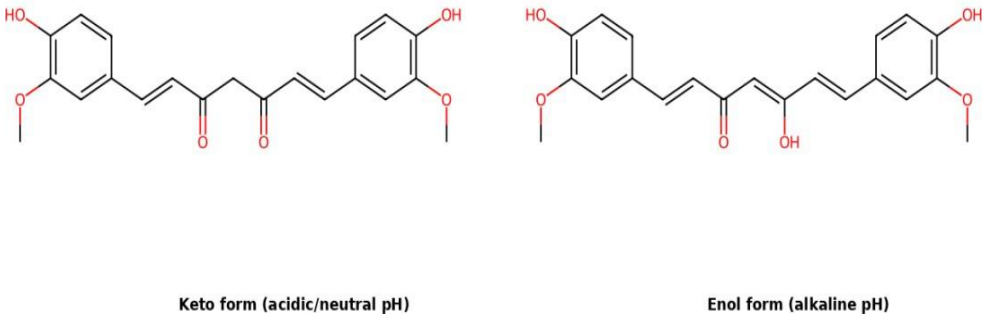

Fig. 1: Keto and enol tautomers of diferuloylmethane.

Commercial curcumin extracts are typically a mixture of three related curcuminoids — curcumin, demethoxycurcumin, and bisdemethoxycurcumin — that differ in the number of methoxy substituents on the aromatic rings and show differential biological potency.[37] The two phenolic hydroxyl groups and the reactive β-diketone are largely responsible for curcumin's antioxidant capacity, its participation in Michael addition reactions with nucleophilic biomolecules, and its susceptibility to hydrolytic and oxidative degradation, particularly above neutral pH where its aqueous half-life has been reported to fall below 30 minutes.[38] Curcumin is essentially insoluble in water at physiological pH but dissolves readily in ethanol, DMSO, and other organic solvents,[36] a solubility profile that has direct consequences for how it must be incorporated into an aqueous or semi-solid ointment base.

3. Pharmacological Basis of Antiseptic and Wound-Healing Activity

The therapeutic rationale for using curcumin in wound and burn ointments rests on several convergent mechanisms rather than a single mode of action (Figure 2). These mechanisms map closely onto the successive phases of wound healing and onto the requirements of infection control.

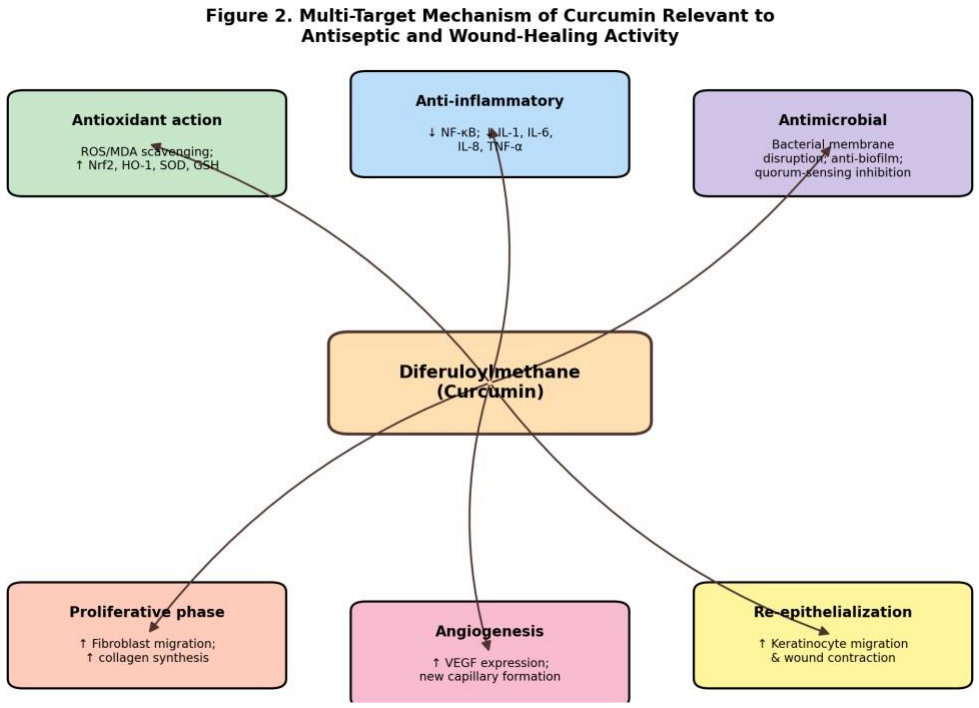

Fig. 2: Principal mechanisms of antiseptic and wound-healing activity of curcumin.

3.1 Antioxidant Activity

Oxidative stress generated by excess reactive oxygen species (ROS) at the wound site delays healing by damaging cellular membranes and proteins. Curcumin has been shown in a murine skin-wound model to lower ROS and malondialdehyde (MDA) levels while upregulating Nrf2, haem oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione (GSH), collectively restoring redox balance and accelerating healing rates relative to controls.[4]

3.2 Anti-Inflammatory Activity

Curcumin down-regulates the NF-κB signalling pathway and reduces the output of pro-inflammatory cytokines including interleukin (IL)-1, IL-6, IL-8, and tumour necrosis factor-alpha (TNF-α).[1] By tempering an excessive or prolonged inflammatory phase, curcumin helps a wound transition more efficiently into the proliferative phase, which is of particular relevance in chronic and infected wounds where inflammation often becomes self-perpetuating.

3.3 Antimicrobial and Antibiofilm Activity

Curcumin exerts direct antibacterial effects through disruption of the bacterial cell membrane and, in some Gram-positive species, through interference with the FtsZ protein required for bacterial cell division.[11,14] Against Pseudomonas aeruginosa, curcumin has additionally been reported to impair virulence factor expression, quorum sensing, and biofilm initiation.[11]

These actions are strain- and species dependent, and the available susceptibility data (Table 1, Figure 3) show considerable variability, with some multidrug-resistant isolates requiring markedly higher concentrations for inhibition.[10]

3.4 Proliferative and Remodelling Effects

Beyond controlling inflammation and microbial load, curcumin actively supports the proliferative phase of healing. It has been associated with increased fibroblast migration and collagen fibre synthesis,[4,6] enhanced vascular endothelial growth factor (VEGF) expression supporting angiogenesis,[4,7] and accelerated keratinocyte migration that promotes re-epithelialization and wound contraction.[7,31]

4. Antibacterial and Antibiofilm Activity Against Wound Pathogens

A substantial body of in vitro work has characterized curcumin's minimum inhibitory concentrations (MICs) against pathogens typically implicated in cuts, burns, and secondarily infected wounds, most notably Staphylococcus aureus (including methicillin-resistant strains, MRSA), Pseudomonas aeruginosa, Enterococcus faecalis, and Klebsiella pneumonia.[10,12,14,16,17] Table 1 and Figure 3 summarize representative MIC values compiled from two independent susceptibility studies.

Table 1: Representative minimum inhibitory concentration (MIC) values of curcumin against selected wound- and skin-associated pathogens.

Organism / strain	Reported MIC	Source
Streptococcus pyogenes (median)	31.25 µg/mL	[10]
MRSA / MLSB-phenotype staphylococci (mean)	46 µg/mL	[12]
Gram-positive cocci overall (mean)	92 µg/mL	[12]
Methicillin-sensitive S. aureus / Acinetobacter lwoffii	250 µg/mL	[10]
Susceptible P. aeruginosa / E. faecalis strains	62.5 µg/mL	[10]
Gram-negative bacilli overall (mean)	600 µg/mL	[12]
Klebsiella pneumoniae (mean)	1040 µg/mL	[12]
Multidrug-resistant strains (S. aureus, E. coli, P. mirabilis)	≥ 2000 µg/mL	[10]

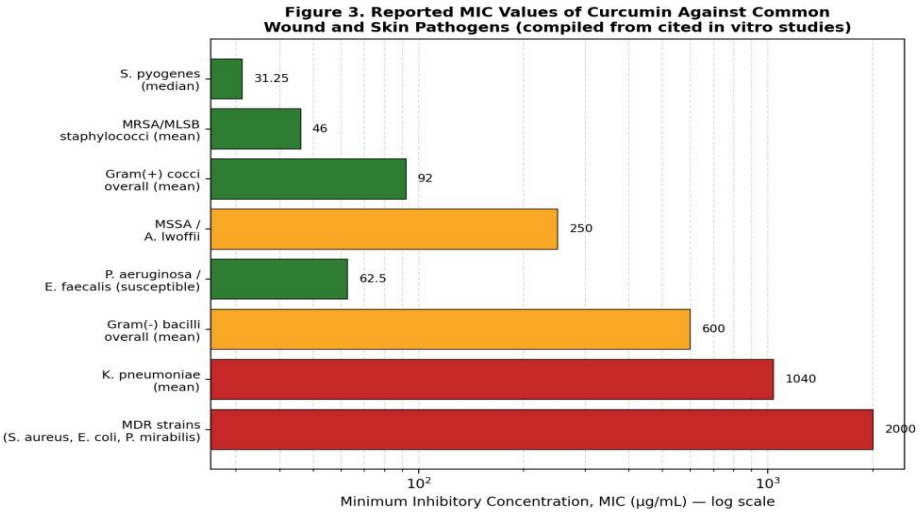

Fig. 3: Comparative MIC values of curcumin against selected wound pathogens.

Gram-positive cocci are generally more susceptible to curcumin than Gram-negative bacilli, and susceptibility does not appear to correlate with conventional antibiotic-resistance phenotypes: MRSA and MLSB-resistant staphylococci showed MICs comparable to susceptible strains in one study,[12] suggesting curcumin's membrane-disrupting mechanism operates independently of the resistance determinants that confer insensitivity to beta-lactams and macrolides. However, a considerable proportion of multidrug-resistant clinical isolates showed poor sensitivity, with MICs at or above 2000 µg/mL,[10] underscoring that curcumin alone is unlikely to match the potency of dedicated antibiotics against all pathogens and is better positioned as an adjunct or as a component of a combination or nanoparticle-enhanced formulation. Indeed, curcumin-capped silver nanoparticles have been reported to achieve considerably lower MICs (approximately 14 µg/mL) against both MRSA and P. aeruginosa than free curcumin, illustrating the potentiating effect of nanoformulation on antimicrobial activity.[9]

Mechanistic studies indicate that curcumin also reduces biofilm viability: exposure of MRSA biofilms to curcumin caused loss of membrane integrity and DNA fragmentation consistent with a bactericidal, membrane-targeted mode of biofilm disruption,[16] while curcuminoid-intercalated layered double hydroxide nanohybrids achieved a 50% biofilm-inhibitory concentration within three hours against P. aeruginosa, S. aureus, and E. faecalis biofilms.[10]

5. Antifungal Activity Relevant to Infected Wounds

Chronic and moist wounds, including burns, are also susceptible to fungal colonization, principally by Candida species. Curcumin possesses intrinsic antifungal activity, though this

is generally weaker than its antibacterial potency when used alone.[48] Nanoformulation markedly improves this activity: curcuminnanoparticle suspensions have shown antifungal efficacy against oral candidiasis comparable to the standard antifungal nystatin in an animal model, albeit with a slower onset of action.[46] and curcumin-loaded nano-emulgels have demonstrated dose-dependent antifungal effects against Aspergillus species in addition to antibacterial activity, where free curcumin alone showed only limited antifungal effect.[48] Combination hydrogels pairing curcumin with conventional azole antifungals such as voriconazole have also been developed specifically for topical treatment of Candida albicans infection.[41] reflecting a broader trend of using curcumin as a synergistic partner rather than a stand-alone antifungal ointment design.

6. Application in Burn Wound Management

Burns present a distinct clinical challenge because of their propensity for both excessive inflammation and secondary bacterial colonization, most often by S. aureus and P. aeruginosa. Silver sulfadiazine (SSD) has for decades been the standard topical agent for burn care, but its established antimicrobial efficacy is offset by reported cytotoxicity to keratinocytes and fibroblasts, which can delay epithelialization and wound closure.[19,24] This limitation has motivated interest in natural antimicrobial alternatives, including curcumin-based preparations.

In an animal model, curcumin loaded onto polyethylene glycol-modified chitosan-gelatin nanoparticles and incorporated into an ointment was compared against a carrier-only ointment, plain saline, and 1% silver sulfadiazine ointment in a rat burn-wound model, with wound size and markers of cell apoptosis and survival assessed over a three-week period.[26] A separate randomized open-label clinical study compared a curcumin-, amla-, and green-tea-containing biodegradable dressing (VELVERT) against silver sulfadiazine in the management of second-degree burn wounds in humans, evaluating safety and healing efficacy relative to the silver-based standard of care.[19] An earlier observational study additionally reported that a simple curcumin ointment (0.5% curcumin in white petroleum jelly) reduced malodour in over 90% of patients with fungating wounds, indicating symptomatic as well as reparative benefit.[30] Collectively, these findings position curcumin-based ointments as a plausible low-cytotoxicity alternative or adjunct to SSD, though the evidence summary literature notes that robust human trial data specifically for full-thickness burns remain limited.[30] Table 2 summarizes the comparative profile of curcumin ointments against SSD

based on the cited evidence.

Table 2: Qualitative comparison of curcumin-based topical preparations and silver sulfadiazine (SSD) for burn and wound management.

Attribute	Curcumin-based ointment	Silver sulfadiazine (SSD)
Antimicrobial spectrum	Broad-spectrum Gram(+)/Gram(-) and antifungal action; variable potency across strains[10,12,17]	Broad-spectrum, well-established clinical antimicrobial[21,24]
Cytotoxicity to healing tissue	Generally reported as low with good tolerability[30]	Cytotoxicity to keratinocytes/fibroblasts reported to delay epithelialization[19]
Anti-inflammatory action	Intrinsic NF-κB and cytokine-modulating activity[1,4]	Minimal direct anti-inflammatory action
Wound odour/exudate control	Odour reduction reported in fungating wounds (>90% of patients)[30]	Not a primary indication
Formulation stability	Photolabile; poor aqueous solubility; needs advanced carriers.[33–37]	Chemically stable in conventional cream base
Clinical evidence base	Growing but still limited randomized trial data (19 trials identified as of 2025)[2]	Extensive, decades of clinical use.[22,24]

7. Clinical Evidence in Wound Healing

A 2025 PRISMA-ScR-guided scoping review searched PubMed, Scopus, Web of Science, and Cochrane Library from 2000 to May 2025 and identified 920 initial records, of which 19 clinical trials on topical or systemic curcumin formulations for human wound healing met inclusion criteria, 14 of them randomized controlled trials.[2] This relatively small but growing evidence base spans applications including surgical wounds, burns, diabetic ulcers, and fungating malignant wounds, and covers curcumin formulations ranging from simple ointments to nanocapsule and microemulgel preparations.[2,30] In a related topical application, a double-blind randomized placebo trial in older adults with knee osteoarthritis found that a 5% curcumin ointment produced a significantly greater reduction in pain intensity than a Vaseline placebo ointment over six weeks, supporting the transdermal bioactivity and tolerability of curcumin ointments even outside the wound-care context.[28] Despite these encouraging signals, reviewers consistently note that trial numbers remain small, formulations are heterogeneous, and standardized, adequately powered trials specifically addressing infected wounds and burns are still needed.[2,30]

8. Formulation Challenges for Topical Ointments

Translating curcumin's favourable pharmacological profile into an effective, stable ointment is constrained chiefly by three physicochemical properties: very low aqueous solubility, rapid degradation at neutral-to-alkaline pH, and susceptibility to photodegradation.[33,35,38] Curcumin has been classified as a Biopharmaceutics Classification System (BCS) Class IV compound, indicating both poor solubility and poor permeability.[35] and its aqueous half-life above neutral pH has been reported at under 30 minutes, yielding breakdown products such as ferulic acid and vanillin.[38] For a topical ointment, this translates into limited and inconsistent skin penetration, visible discoloration and loss of potency on storage, and the need for careful selection of base, pH, and antioxidant excipients.

These limitations have driven a shift away from simple petrolatum- or paraffin-based curcumin ointments toward advanced, nanotechnology-enabled delivery platforms designed specifically to protect curcumin from degradation while enhancing its solubility and skin penetration (Figure 4).

Figure 4. Formulation Strategies to Overcome the Physicochemical Limitations of Curcumin for Topical Ointment Development

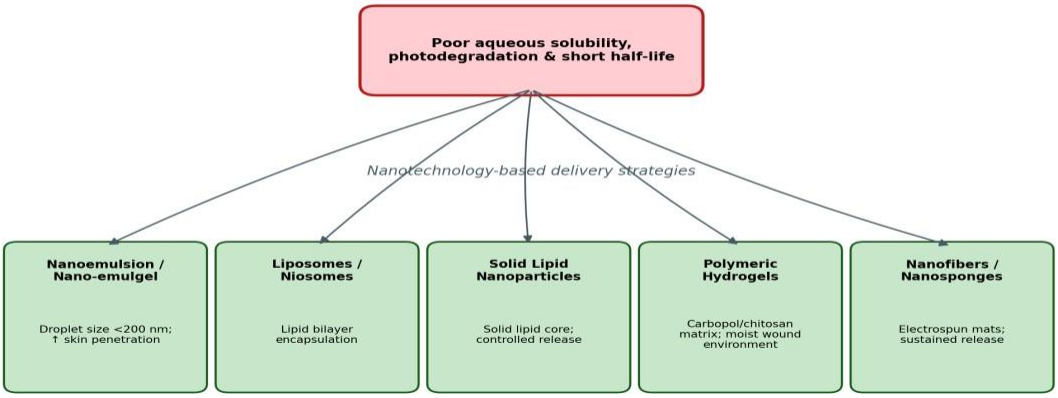

Figure 4: Nanotechnology-based strategies for topical curcumin delivery.

9. Advanced Delivery Systems for Curcumin Ointments

9.1 Nanoemulsions and Nano-emulgels

Nanoemulsion and nano-emulgel systems reduce the oil droplet size carrying curcumin to below 200 nm, improving both aqueous dispersibility and skin permeation. A quality-by-design-optimized curcumin nano-emulgel demonstrated markedly stronger antimicrobial activity than free curcumin against Staphylococcus aureus and Salmonella, together with antifungal activity against Aspergillus species that free curcumin lacked, while showing lower cytotoxicity than pure curcumin in an MTT viability assay.[48]

9.2 Liposomes, Niosomes, and Solid Lipid Nanoparticles

Lipid-based carriers encapsulate curcumin within a bilayer or solid lipid matrix, protecting it from hydrolytic and oxidative degradation while enabling controlled release. Such nanocarriers have been explored extensively to improve curcumin's solubility, stability, and targeted delivery relative to the free compound.[33,36]

9.3 Polymeric Hydrogels and Biopolymer Nanoparticles

Hydrogel-based dressings incorporating curcumin, often combined with biopolymers such as chitosan and gelatin, provide a moist wound-healing environment while sustaining local curcumin release. Curcumin-polyethylene glycol loaded onto chitosan-gelatin nanoparticles and incorporated into an ointment base has been evaluated head-to-head against both a carrier-only vehicle and silver sulfadiazine ointment in a burn-wound animal model,[26] while nanosponge-loaded hydrogels have been developed for combined curcumin-antifungal topical delivery against Candida albicans.[41]

9.4 Nanofibers and Nanosponges

Electrospun nanofibrous mats loaded with curcumin, sometimes in combination with a co-active antimicrobial such as tetracycline, have been fabricated using coaxial electrospinning and layered fibre architectures that protect curcumin from photodegradation while maintaining an antibacterial barrier at the wound surface for extended periods, in one case up to ten days.[1] Curcumin-loaded cellulose nanofibre aerogels and antibacterial-coated surgical sutures represent further examples of this fibre- and scaffold-based delivery approach for chronic wound care.[1]

10. Safety, Tolerability, and Formulation Stability Considerations

Across the cited clinical and preclinical studies, topical curcumin preparations are generally described as well tolerated, with the osteoarthritis ointment trial reporting no significant adverse events over six weeks of twice-daily application.[28] and the wound-management evidence summary describing turmeric and curcumin preparations as generally well tolerated on skin.[30] Nonetheless, curcumin's intense yellow-orange pigmentation can stain skin, clothing, and dressings, which has practical implications for patient acceptability and product design. From a manufacturing standpoint, formulators must address curcumin's photolability and pH-dependent degradation through appropriate packaging (opaque or light-protective containers), pH buffering close to neutral, and inclusion of antioxidant excipients, in addition to selecting a nanocarrier or emulsification strategy suited to the intended ointment base and

shelf-life target.[35,38]

11. FUTURE DIRECTIONS

Several translational gaps remain before curcumin-based antiseptic ointments can be positioned as validated alternatives to standard agents such as silver sulfadiazine or povidone-iodine. First, larger and more standardized randomized controlled trials are needed specifically in burn and infected-wound populations, since the existing clinical evidence base, while growing, remains limited to 19 identified trials as of mid-2025 and is heterogeneous in formulation and outcome measures.[2] Second, given the pronounced strain-dependent variability in curcumin's antimicrobial potency, combination approaches — pairing curcumin with conventional antibiotics, antifungals, or metal nanoparticles — warrant continued investigation, as several of the cited studies indicate synergistic rather than purely additive benefit.[9,41] Third, scalable and cost-stable manufacturing routes for curcumin nanoemulsions, hydrogels, and nanofibre dressings will need to be established to support consistent, shelf-stable ointment products suitable for institutional and household use. Finally, structural analogues such as bisdemethoxycurcumin and demethoxycurcumin, which have shown differential potency in specific wound contexts such as diabetic ulcers,[4] merit further systematic comparison against the parent compound to identify optimal actives for future topical antiseptic formulations.

12. CONCLUSION

Diferuloylmethane brings together antioxidant, anti-inflammatory, antimicrobial, and pro-regenerative activity in a single natural molecule, making it a mechanistically well-supported candidate for topical ointments intended for cuts, burns, wounds, and infected lesions.

Its principal limitation is not pharmacological but physicochemical: poor aqueous solubility and photochemical instability restrict the performance of simple curcumin ointments and have driven the development of nanoemulsion, liposomal, hydrogel, and nanofibre-based delivery platforms that substantially enhance its topical efficacy. While preclinical evidence is extensive and increasingly mechanistic, the clinical trial base specific to infected wounds and burns remains comparatively small. Continued formulation innovation paired with larger, well-designed clinical trials will determine whether curcumin-based ointments can move from a promising adjunct therapy to an established component of first-line wound and burn care.

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