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Review

Antimicrobial and Regenerative Applications of Essential Oil–Loaded Hydrogels: A Mini-Review

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Abstract: Essential oils (EOs) possess broad-spectrum antimicrobial, antioxidant, anti-inflammatory, and regenerative properties; however, their therapeutic application is limited by volatility, hydrophobicity, chemical instability, and rapid loss at the target site. Hydrogel-based delivery systems have appeared as an effective strategy to overcome these drawbacks by improving EO stability, bioadhesion, retention, and controlled release. This mini-review summarizes advances reported between 2016 and 2025 in EO-loaded hydrogels for antimicrobial and wound-healing applications, with emphasis on the influence of polymeric matrices and colloidal delivery architectures on biological performance. Natural and synthetic polymers, including alginate, chitosan, collagen, gellan gum, carbomers, starch, and poly(vinyl alcohol), have been explored as carriers for EOs, while nanoemulsions, micelles, Pickering emulsions, ethosomes, and nanoparticle-based systems have been deployed to enhance solubility, stability, tissue penetration, and release control. Evidence indicates that EO-loaded hydrogels display heightened antibacterial, antifungal, and antibiofilm activity against clinically relevant pathogens, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. Beyond infection control, these systems modulate inflammatory mediators such as TNF-α and IL-6, reduce oxidative stress, and promote key regenerative processes, including fibroblast migration, angiogenesis, collagen deposition, and reepithelialization. Collectively, the findings show that therapeutic efficacy is strongly influenced by hydrogel architecture and release kinetics rather than EO concentration alone. Despite promising preclinical outcomes, substantial heterogeneity in formulations and experimental protocols, along with limited clinical data, accentuates the need for standardization, safety assessment, and translational validation to support the clinical implementation of EO-loaded hydrogels in wound management.

Keywords: essential oils; hydrogels; wound healing; antimicrobial activity; antibiofilm; inflammation; nanoemulsions; controlled release; tissue regeneration.

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1. Introduction

Essential oils (EOs) have attracted considerable attention as bioactive agents for topical therapy owing to their broad-spectrum antimicrobial, antifungal, antioxidant, anti-inflammatory, and wound-healing properties [1–4]. Major EO constituents, including carvacrol, thymol, eugenol, citronellol, geraniol, and 1,8-cineole, exert biological effects through multiple mechanisms, such as disruption of microbial membranes, inhibition of biofilm formation, modulation of inflammatory pathways, and reduction of reactive oxygen species (ROS) [1–4]. These multifunctional properties make EOs attractive for managing infected and chronic wounds, where microbial colonization, persistent inflammation, and oxidative stress impair tissue repair [1, 2].

Despite their therapeutic potential, the clinical use of free-form EOs is limited by several physicochemical challenges, including high volatility, hydrophobicity, poor aqueous solubility, chemical instability, and rapid loss at the application site [2, 5-7]. These factors reduce bioavailability and therapeutic efficacy, particularly when sustained local exposure is needed. As a result, developing delivery systems that stabilize EO constituents and control their release is now a major focus in pharmaceutical and biomedical research [6, 7].

Hydrogels have emerged as promising platforms to address these challenges. These three-dimensional crosslinked polymeric networks absorb and retain large amounts of water while maintaining structural integrity, creating a moist environment that supports tissue repair and regeneration [8–14]. Hydrogels also enhance local retention and bioadhesion, and allow control over swelling, porosity, mechanical properties, and release kinetics, all of which affect the biological performance of encapsulated compounds [8–14]. Both natural polymers, such as alginate, chitosan, gellan gum, cellulose derivatives, and pectin, and synthetic polymers, including poly (vinyl alcohol) (PVA), carbomers, and polyethylene glycol, have been studied for EO-loaded hydrogel systems [8–20].

Recent advances have expanded the functionality of EO-loaded hydrogels by incorporating colloidal and nanostructured delivery systems, such as nanoemulsions, emulgels, polymeric micelles, ethosomes, Pickering emulsions, and nanoparticle-based platforms [3, 9, 11]. These systems improve EO solubilization, protect volatile constituents from degradation, enhance tissue penetration, and enable controlled or stimuli-responsive release. Consequently, nanostructured hydrogel systems often demonstrate superior antimicrobial, antibiofilm, anti-inflammatory, and regenerative properties compared to conventional formulations [3, 9, 11].

Growing evidence indicates that the efficacy of EO-loaded hydrogels depends on both the chemical composition of the EOs and the physicochemical properties of the hydrogel matrix and delivery system architecture. Factors such as crosslinking density, swelling capacity, porosity, surface charge, rheological behavior, and release kinetics influence EO diffusion, retention, bioavailability, and interactions with microorganisms and host tissues [11–14]. Understanding the relationship between formulation design and biological activity is therefore essential for developing effective hydrogel-based therapies.

Although many studies have examined EO-loaded hydrogels for antimicrobial and regenerative applications, a gap in the literature remains due to significant heterogeneity in polymer composition, EO concentration, encapsulation strategies, and biological evaluation methods. This variability limits direct comparisons and makes it difficult to identify optimal formulations for clinical use. Additionally, the impact of hydrogel architecture and colloidal delivery systems on EO performance has not been thoroughly addressed.

Therefore, this mini-review summarizes advances in EO-loaded hydrogel systems reported from 2016 to 2025, focusing on antimicrobial, antibiofilm, anti-inflammatory, and wound-healing applications. It examines how polymeric matrices and colloidal

delivery architectures affect EO stability, bioavailability, and treatment effectiveness, and discusses current limitations, safety considerations, and future directions for clinical translation of these biomaterials.

2. Hydrogels and Their Use as Carriers for Essential Oils

Hydrogels are three-dimensional, hydrophilic polymer networks that absorb and retain large amounts of water while remaining mechanically stable and insoluble [15]. Their crosslinked polymer chains form a porous structure, allowing efficient fluid uptake, retention, and transport of bioactive compounds [15, 16]. Both natural and synthetic polymers are used in the fabrication of hydrogels, depending on the application. Synthetic polymers, such as polyvinyl alcohol, polyethylene glycol, and sodium polyacrylate, are chosen for their strength and elasticity. Natural polymers, including chitosan, alginate, gellan gum, hydroxyethyl cellulose, and pectin, are preferred for their biocompatibility and biodegradability [8, 15-20].

Studies have also investigated the antimicrobial potential of hydrogels, especially when combined with antibacterial agents. An overview of representative formulations, EOs, and their antimicrobial outcomes is presented in Table 1. It is important to note that many of these studies rely on in vitro models, which may overestimate antimicrobial performance compared with the complex in vivo wound environment. Hydrogels have demonstrated their ability to serve as effective carriers of antimicrobial compounds, allowing sustained release and localized action against bacterial pathogens [21-23]. Hydrogels are effective carriers of antimicrobial compounds because of their porous, three-dimensional structure, high water-retention capacity, bioadhesive properties, and protection of volatile EOs constituents from degradation and evaporation [6, 15, 16]. Furthermore, characteristics such as swelling capacity, crosslinking density, porosity, and polymer–oil interactions regulate diffusion and allow extended release of bioactive compounds [6, 32]. Sustained-release behavior has been reported for clove oil-loaded chitosan/oxidized pullulan hydrogels, which provided controlled release for up to 360 h [32], fibrin hydrogels containing *Litsea cubeba* EO, which maintained gradual release for up to 30 days [40], and starch-based hydrogels loaded with patchouli oil, which exhibited slower degradation and prolonged release profiles compared with classic formulations [27].

However, their effectiveness as delivery systems varies and depends on crosslinking density, polymer composition, and oil–matrix associations, which are not consistently standardized across studies.

Incorporating antimicrobial agents, such as EOs or metal ions, into hydrogel compositions enables targeted therapies for infections and improves wound management [24, 25].

Recent advances in engineering EO-loaded hydrogels have strengthened the field by integrating biomaterials, microbiology, nanotechnology, and skin healing to create multifunctional therapeutic platforms [23, 24]. As antimicrobial resistance to conventional drugs rises, developing safe, stable, and effective topical formulations is increasingly important [6].

Encapsulating EOs in hydrophilic matrices allows hydrogels to provide controlled release, prolonged adhesion, and modulation of the inflammatory microenvironment. This method addresses the limitations of free-form EOs, including volatility, chemical instability, low tissue penetration, and rapid dissipation [2, 13]. Collaboration between

polymer chemistry and phytochemistry has led to a new class of topical therapeutics [42, 43] that incorporate EO-derived bioactive compounds, such as phenolics and monoterpenes, with antimicrobial, antioxidant, healing, and immunomodulatory properties [13, 24, 44].

Research on EO-loaded hydrogels demonstrates that the hydrogel matrix actively influences the pharmacokinetic and pharmacodynamic properties of EOs by modulating diffusion, retention, and permeability of bioactive compounds [9]. Hydrogels made with different polymers can vary in hydrophilicity, crosslinking density, swelling capacity, viscosity, surface charge, and roughness, all of which affect the mobility of constituents like terpenes and phenols [21, 23, 30]. Nanostructuring methods, such as ultrasonication and high-energy emulsification, reduce oil droplets and polymeric fibers to the nanometer scale [44]. This increases surface area and enhances interactions between EO constituents and microbial membranes, enabling deeper penetration into complex microbial biofilms [37].

As a result, nanostructured systems significantly enhance antimicrobial efficacy, leading to marked reductions in minimum inhibitory and minimum bactericidal or antifungal concentrations. These findings highlight the critical role of nanoscale organization in improving the bioavailability and effectiveness of EOs oils in hydrogel-based delivery platforms [37]. This effect is particularly notable in EO-loaded hydrogels containing carvacrol, thymol, eugenol, citronellol, geraniol, and 1,8-cineole, which are known to lyse microbial cells and disrupt metabolism, thereby increasing antimicrobial activity [3, 4, 32, 45].

Table 1. Summary of essential oils incorporated into hydrogel-based systems for antimicrobial and wound-healing applications.

Hydrogel matrix type	Essential oil (common name)	Essential oil concentration (%)	Target microorganism or application	Reference
Nanoemulgel (Carbopol 940)	Coriander	50% (in nanoemulsion)	*P. aeruginosa*, *K. pneumoniae*, *S. aureus* MRSA	[21]
Bilayer mucoadhesive film (Gellan gum + Hydroxyethyl cellulose)	Clove	Up to 50%	Periodontitis (Gram-positive and Gram-negative)	[22]
Hybrid hydrogel (Alginate + PITAU)	Lavender	5%, 10%, 15%	Infected wounds (*S. aureus* and *C. albicans*)	[23]
Polymeric hydrogel (GelMA + acrylamide + AAc-NHS)	Wormwood	5–10%	Infected diabetic wounds (*S. aureus, E. coli*, MRSA)	[24]
Carboxymethyl chitosan + Carbomer 940 hydrogel	Eucalyptus, Ginger, and Cumin	5%	Burn wound healing (*S. aureus* and *E. coli*)	[25]
Carbopol hydrogel with ethosomes	Tea tree	5%	Acne therapy	[26]
Starch-based (conventional and waxy) + Carbopol hydrogel	Patchouli	3%	Wound healing (Gram-positive and Gram-negative)	[27]
Physical hydrogel (Carbomer 940 + CMC)	Eucalyptus	3%	Infected wounds (*S. aureus* biofilm)	[28]
Emulgel (Carbopol 940)	Anise	2%	Skin infections (*E. coli*)	[29]
Carbopol 940 hydrogel	Tea Tree, Rosemary, and Clove	1.5% to 2%	Gram-positive, Gram-negative, and *Candida* spp.	[30]
Methylcellulose hydrogel 10% (w/v)	Lemon balm	1% and 2%	Oral Candidiasis (*C. albicans*)	[31]
Chitosan/oxidized pullulan emulsion hydrogel	Clove	1% and 5%	Wound dressings (*S. aureus* and *E. coli*)	[32]
Lecigel® based hydrogel	Oregano	0.5% and 1%	Burn wounds (Multidrug-resistant bacteria)	[33]
Carbopol 940, Chitosan, or Alginate hydrogels	Clove and Bay Laurel	1%	Antimicrobial topical use	[34]
Collagen hydrogel	Lavender	1%	Infectious burn (*P. aeruginosa*)	[35]
Alginate + Chitosan hydrogel	Tea tree	1%	Infected wounds (*S. aureus*)	[36]
Carbopol® 940 hydrogel (3.5% w/w)	Lemongrass	1%	Acne treatment (*C. acnes*)	[37]
Carbomer-based hydrophilic hydrogel	Immortelle	0.5%	Diabetic wound repair	[38]

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Alginate/CMC and Alginate/CMC nanoparticles hydrogel	*Satureja khuzestanica*	0.25%	*S. aureus* and *P. aeruginosa*	[39]
Fibrin hydrogel	*Litsea cubeba*	0.0625–2.5%	*A. actinomycetemcomitans* and *P. gingivalis*	[40]
Topical oil application (Not applicable)	*Cinnamomum burmannii*	10–30%	Skin wound healing	[41]

Enhancing hydrogel rheological properties is equally crucial to their antifungal and antibacterial performance. Pseudoplastic formulations containing methylcellulose, such as Pluronic F-127 hydrogel or chitosan, exhibit reduced viscosity under shear. This property facilitates spreading during application. However, they regain consistency at rest, ensuring greater residence time at the target site and prolonged contact with the infected wound microenvironment [32].

Certain polymers enhance bioadhesion, prolonging the availability of EOs at concentrations above their MICs. This leads to superior efficacy against planktonic and biofilm forms [6]. The incorporation of EOs often increases the viscoelastic modulus of hydrogels. This change reinforces the network's three-dimensional integrity and stabilizes the formulation during clinical use. Such properties are decisive for the antimicrobial performance of hydrogels, especially against infections caused by *S. aureus*, *Pseudomonas aeruginosa,* and *Candida* spp. [21, 23, 30, 32].

3. Antimicrobial Activity of Hydrogels with Essential Oils

Microbial infections are among the main factors that impair tissue repair and contribute to the persistence of chronic wounds [6, 12, 13]. The increasing prevalence of antimicrobial resistance and biofilm-associated infections has stimulated the development of alternative clinical strategies [6, 21, 24]. EO-loaded hydrogels are a beneficial approach because they combine the broad-spectrum antimicrobial properties of EOs with the protective, bioadhesive, and controlled-release characteristics of hydrogel matrices [6,15,16,23]. Incorporating EOs into hydrogels improves their stability and retention at the application site while enhancing their effectiveness against a wide range of pathogenic microorganisms, including bacteria and fungi [21–25, 30–32].

3.1. Antibacterial Activity

OE-loaded hydrogels have consistently presented enhanced antibacterial activity compared with free-form EOs [21-27]. This improved performance is mainly attributed to increased stability, sustained release, and enhanced interaction between bioactive compounds and microbial cells [21-27]. However, this advantage is not uniform across all systems, indicating that antimicrobial efficacy is strongly contingent on both the polymeric matrix and the incorporation strategy. As shown in Figure 1, hydrogel-based encapsulation protects EO constituents from degradation and improves their delivery to microbial targets, thereby enhancing membrane disruption, biofilm inhibition, and overall antimicrobial activity.

EOs loaded into hydrogels generally exhibit superior antimicrobial activity compared to free-form EOs. Encapsulation within polymeric matrices (such as alginate, chitosan, Carbopol, polyvinyl alcohol (PVA), starch, and supramolecular networks, within nanostructures such as nanoemulsions, and lamellar inorganic particles layered double hydroxides (LDL) improves colloidal stability, allows controlled release, and enhances interactions with microorganisms [4–6, 21, 27, 28, 32, 5]. This approach tackles the main limitations of free-form EOs, including volatility, low solubility, and rapid degradation [23, 32]. These matrices and platforms have been shown to reduce the MIC, minimum bactericidal concentration (MBC), and minimum biofilm inhibitory/eradicating concentration for EOs, with particular relevance for resistant bacterial strains [21, 34, 39].

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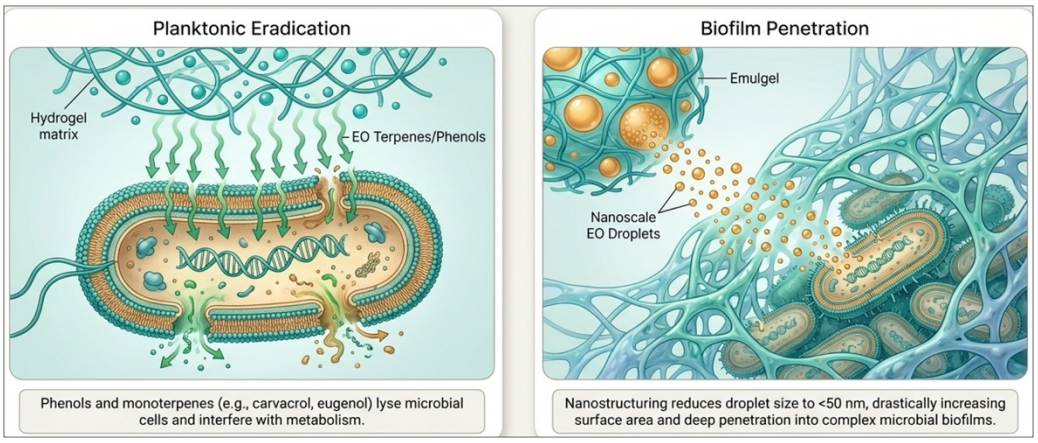

Figure 1. Schematic representation of the mechanisms responsible for the enhanced antimicrobial activity of EO-loaded hydrogels. Encapsulation in hydrogel matrices improves essential oil stability, retention, and controlled release, thereby promoting prolonged interactions with microbial cells. These effects contribute to membrane disruption, inhibition of microbial growth and biofilm formation, and enhanced antibacterial efficacy against wound-associated pathogens [21, 32, 34, 39].

Among these strategies, alginate hydrogels are widely studied because of their biocompatibility, ease of gelling, and tunable porosity. Studies incorporating oregano EO into alginate matrices have shown improved antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *P. aeruginosa* [4, 15, 16]. This effect is associated with enhanced oil retention and reduced swelling. These features favor controlled release and longer activity.

However, rapid release kinetics observed in some alginate systems may limit long-term efficacy. This suggests that additional modifications are necessary to improve performance, such as adjusting crosslinking density or hybridizing with nanostructures.

Demonstrating how matrix type and EO composition shape performance, hybrid alginate/carboxymethylcellulose (CMC) hydrogels loaded with *Satureja khuzestanica EO exhibited* shear-thinning, high incorporation of carvacrol/thymol, and 100% inhibition of *S. aureus* and *P. aeruginosa* at 1,250 μg/mL, outperforming conventional hydrogels [39]. Similarly, a hydrogel formulation containing PVA-borate, added to layered double hydroxides functionalized with alginate and loaded with thyme EO, exhibited broad, consistent zones of inhibition against *S. aureus* and *P. aeruginosa*, surpassing silver-based antimicrobial systems. Patchouli EO exhibited inhibition zones of 29 mm against *E. coli* and 26 mm against *P. aeruginosa.* When incorporated into starch-based hydrogels, particularly those formulated with waxy starch, the starch/Carbopol/glycerol system enhanced antibacterial activity by 10–20% due to increased viscosity and sustained release, indicating that waxy starch content modulates EO diffusion and retention [27]. In hydrogels containing alginate matrices loaded with oregano EO (*Origanum vulgare)*, homogeneous EO distribution increased roughness, porosity, and thermal stability, while ionic interactions between Ca^{2+} and carboxylate groups compacted the lattice [4]. Cumulatively, the hydrophobic nature of oregano EO reduced swelling, which may favor more controlled release and prolonged topical activity [4].

Chitosan-based hydrogels exhibit intrinsic antimicrobial properties owing to their cationic nature, which facilitates interaction with negatively charged microbial membranes. When combined with EO such as clove or tea tree oil, these systems show synergistic effects, resulting in reduced minimum inhibitory concentrations (MIC) and prolonged antimicrobial activity [30, 46, 47]. Despite these advantages, variations in

molecular weight and degree of deacetylation can greatly affect stability, release behavior, and bioactivity, underscoring the need for standardized formulations.

The antibacterial activity of hydrogel systems can further depend on the matrix and the type of EO used. For instance, a zein hydrogel loaded with oregano EO exhibited a high MIC against *P. aeruginosa* (400 μg/mL) but was more active in inhibiting biofilm-related parameters and Autoinducer Synthase LasI (Quorum-Sensing Protein) [48]. In contrast, hydrogel formulations containing clove EO from *Syzygium aromaticum* displayed superior performance against *S. aureus* and Gram-negative bacteria, including *Pseudomonas* spp. Oxidized chitosan/pullulan hydrogels maintained continuous antibacterial activity for 48–72 h, while systems with high-molecular-weight chitin and cyclodextrin β achieved one of the lowest MICs recorded among structural matrices (≈2.34 mg/mL) and demonstrated strong antibiofilm activity [30]. Additionally, gellan gum–based bilayer mucoadhesive films incorporating clove EO exhibited enhanced antibacterial efficacy, due to a biphasic release profile comprising an initial rapid release followed by sustained delivery [22]. These data indicate that oregano EO/zein is more appropriate for consolidated biofilms, whereas clove EO, especially when conveyed in hydrophilic matrices (chitosan, cyclodextrin, and gellan), delivers a more potent and broader antibacterial effect, with greater instant and prolonged efficacy against *S. aureus* and *Pseudomonas* spp. [22, 34, 47, 48].

Co-administration of antibiotics and EOs can synergistically broaden the spectrum and potency of the formulation [49]. A nanoemulsion formulation comprising fusidic acid with cinnamon EO, optimized using Box–Behnken design, improved rheological properties, cutaneous pH, and stability for 3 months, while extending activity to Gram-negative bacteria less sensitive to isolated fusidic acid, thus demonstrating pharmaco–EO synergism in an appropriate matrix [49]. In bilaminar films (gellan gum/hydroxyethylcellulose) loaded with moxifloxacin and clove EO, biphasic release provided a rapid initial burst followed by sustained release, augmenting inhibitory effects against *S. aureus* and *E. coli,* especially at 50% EO. This finding stresses the value of multilayer architectures in combining burst and maintenance phases [1]. The incorporation of ZnO in alginate/ovalbumin hydrogels (or "alginate/egg") loaded with lavender and eucalyptus EOs resulted in greater reductions in the order of 10^5–10^6 colony-forming units/mL (CFU) in the counts of methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*, and *E. coli*, suggesting combined mechanisms of cytoplasmic membrane damage associated with the moderate oxidative stress exerted by ZnO and physical trapping of bacteria in the matrix [1].

Fibrin hydrogels containing *Litsea cubeba EO achieved* minimum bactericidal concentrations of 1.00% against *Aggregatibacter actinomycetemcomitans* and 0.25% against *Porphyromonas gingivalis.* The hydrogels released 0.03% of EO within 24 hours and maintained release for up to 30 days. This release profile matches the requirements of the subgingival microenvironment, where sustained therapeutic presence is essential [40]. *Zanthoxylum armatum* and *Cinnamomum camphora* EOs, encapsulated in supramolecular networks of Fluorenylmethoxycarbonyl-phenylalanine (Fmoc-3F-Phe), retained antimicrobial activity for 22 hours, while free EOs lost effectiveness. This highlights the importance of π–π interactions and hydrophobic packaging in retaining activity and enabling slow release [5].

The molecular design of hydrogels significantly influences their performance. In systems composed of Carbopol and chitosan with varying molecular weights, loaded with clove leaf extracts or cyclodextrin-β-alginate containing extracts of *Verbena officinalis* and *Aloysia triphylla,* high-molecular-weight chitosan provided greater stability, improved rheology, and enhanced activity. This resulted in lower MICs and MBECs against S. aureus and E. coli [30]. The integration of cationic chitosan with clove phenols (eugenol)

was confirmed by Fourier transform infrared spectroscopy and scanning electron microscopy [30]. A chitosan-oxidized pullulan hydrogel exhibited antimicrobial and antifungal effects that depended on the clove EO dose. Its interconnected pores enabled biphasic release followed by slow diffusion for up to 15 days. This reduced the viability of *S. aureus* and *E. coli* through OE–OH/NH matrix bonds that stabilize and modulate the active ingredient [32].

Nanoemulgels and emulgels provide enhanced colloidal stability and uniformity, leading to an initial burst that quickly reduces bacterial load, followed by sustained release [29]. An emulgel containing anise EO achieved a notably low MIC against *E. coli*, likely due to interactions between monoterpenes and the FimH adhesion molecule [29]. The AF nanoemulgel with myrrh EO maintained a pH of about 6.6, appropriate viscosity, and a steady-state transdermal flux of approximately 111 μg/cm²·h. It also demonstrated antimicrobial synergy, improved spreadability, and reduced inflammation. These features are important for the clinical effectiveness of topical treatments [8].

PVA/kaolin hydrogels containing cedar EO demonstrated dose-dependent antimicrobial activity against *Bacillus cereus* and *E. coli*, as well as high antioxidant capacity. These features may help reduce tissue damage caused by reactive oxygen species and support microenvironmental recovery during infection control [2]. Controlled release can be achieved while maintaining redox and antimicrobial activity in films and membranes [4]. Antimicrobial effectiveness depended on oregano EO concentration. Oil-free alginate showed no activity, while oregano EO-loaded membranes produced significant inhibition zones against *Proteus vulgaris*, *Pasteurella multocida*, *E. coli, S. aureus,* and *Bacillus subtilis* [4].

3.2. Antifungal Activity of Hydrogels with Essential Oils

Increasing resistance to conventional antifungal drugs, combined with drawbacks such as toxicity and low tissue penetration, has spurred the development of new therapies for candidiasis and other fungal infections [10, 45]. Hydrogels that include EOs show promise due to their biocompatibility, favorable rheological properties, and controlled release of bioactive compounds [21-29]. As illustrated in Figure 2, hydrogel encapsulation enhances antifungal efficacy by promoting sustained contact between EO constituents and fungal cells. It also facilitates membrane penetration and suppresses key virulence mechanisms, including adhesion and morphogenesis.

Different incorporation matrices, such as alginate, chitosan, Carbopol, and methylcellulose, as well as thermosensitive systems such as Pluronic F127, can enhance the antifungal effects of EOs. These EOs include those from *O. vulgare, Nigella sativa, Melissa officinalis, S. aromaticum,* and *Melaleuca spp. They* may act through structural enhancement, biochemical synergy, or modulation of release kinetics [10, 31, 45].

Evidence shows that hydrogels composed of various polymeric matrices and loaded with EOs demonstrate enhanced antifungal activity against *Candida* spp. and other yeast species [45, 38]. Ultrasonic nanofabrication of quince seed mucilage hydrogels with *Nigella sativa*, *Citrus sinensis*, and *Cinnamomum verum* EOs reduced the mean fiber diameter from approximately 361 nm to 31 nm, while preserving morphology suitable for topical application and maintaining a skin-friendly pH [23]. Incorporating EOs into this nanostructure decreased the minimum inhibitory concentration (MIC) from 12.5 mg/mL for free-form oils to 3.125 mg/mL against *C. albicans* and *Malassezia furfur, indicating* a synergistic effect that enhances antifungal efficacy [45]. In comparison, alginate hydrogels with oregano EO exhibited superior colloidal stability, forming spheres approximately 3 mm in diameter with clear porosity. Methylcellulose hydrogels containing *M. officinalis EO exhibited* good viscosity and bioadhesion, but did not form uniform spheres, although they maintained a near-physiological pH [10, 31].

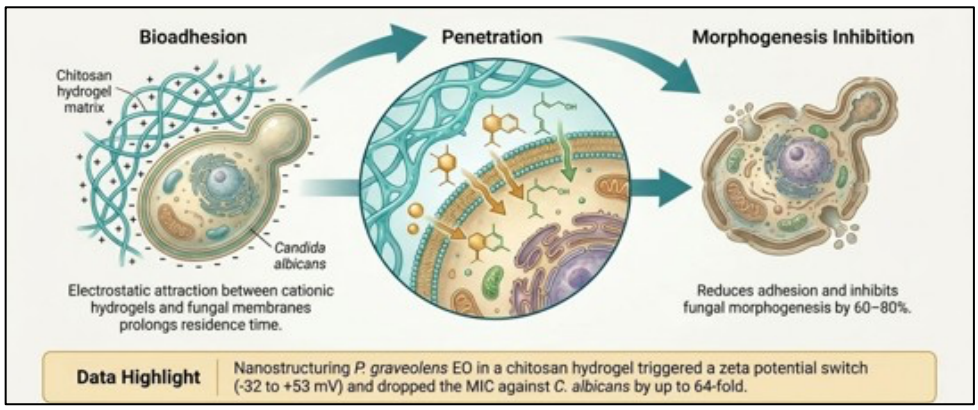

Figure 2. Proposed mechanisms underlying the enhanced antifungal activity of EO-loaded hydrogels against *Candida* spp. Cationic and bioadhesive hydrogel matrices promote prolonged retention at the target site and facilitate the diffusion of EO constituents toward fungal cells. Subsequent membrane penetration and intracellular interactions impair fungal adhesion, viability, and morphogenesis, reducing fungal persistence and biofilm-associated virulence. Nanostructured hydrogel systems may further improve these effects by improving EO bioavailability and reducing the minimum inhibitory concentration (MIC) [10, 20, 30, 31, 45].

Release kinetics of hydrogel systems show clear compromises between initial impact and sustained EO availability. This is apparent in alginate hydrogel with oregano EO, where complete phenolic release occurred within about 48 minutes. This release followed a zero-order model with a pulsatile profile and high predictability, denoting that a porous matrix allows rapid diffusion of the active ingredient [10]. In contrast, hydrogels gelled with *Pelargonium graveolens* nanoemulsions released their EOs more gradually whilst maintaining strong antifungal effects; here, the inversion of the zeta potential during gelation increases electrostatic interactions and slows diffusion rates [20]. Similarly, methylcellulose hydrogel with *M. officinalis* EO provided sustained release for up to 48 hours. This approach sustains stable tissue levels of the active ingredient rather than providing a rapid initial peak [31].

Alginate hydrogels with oregano EO achieved IC_{50} values of 0.15 mg/L for sensitive *C. albicans* and 0.20 mg/L for resistant strains, outperforming clove EO hydrogels. Although clove EO hydrogels provide biphasic release and extended antioxidant activity, their IC_{50} values were less favorable [10; 32]. Therefore, oregano EO hydrogels demonstrate stronger antifungal activity, and optimizing release rate, retention, and matrix interactions is essential to meet therapeutic objectives.

Combining EOs with synthetic antifungals often follows established formulation patterns, but significant performance improvements typically depend on the specific reference drug. For instance, a Pluronic F127-based hydrogel containing ketoconazole and 5% tea tree EO demonstrated increased viscosity and bioadhesion. It also maintained physiological pH (6.5–6.8), achieved a release rate of 540 μg/cm² over 6 hours, and a permeation rate exceeding 105 μg/cm² over 24 hours (zero-order kinetics) [9]. This formulation enhanced activity against *C. albicans*, *C. parapsilosis*, and *C. krusei*, primarily due to ketoconazole [8]. Similarly, chitosan hydrogels with 6% *Salvia officinalis* monoterpenes and 1.5% terbinafine exhibited favorable thixotropy, stability, and sustained release. Terbinafine in the dialysate reached an MIC of 2.91 μg/mL against *C. albicans*. Although synergistic effects were observed, the hydrogel's maximum efficacy is attributed to its antifungal activity [50]. In contrast, alginate hydrogels with oregano EO

maintained high activity without synthetic drugs, making them a strong reference among EO-only systems [8, 10, 50].

The architecture of the hydrogel matrix determines molecular transport, release kinetics, and interactions with microorganisms. Accordingly, the MIC of nanoemulsion-thickened chitosan hydrogels containing *Pelargonium graveolens* EO decreased by up to 64-fold, reaching 8 μg/mL against *C. albicans* and *C. glabrata* [20]. This reduction correlated with a shift in zeta potential from −32.21 to +53.43 mV, increased mucoadhesive residence time, and pseudoplastic behavior [20]. These changes enhance the diffusion of citronellol and geraniol and strengthen electrostatic attraction between the hydrogel and fungal membranes. Suflet et al. [32] introduced a double cross-linking strategy (Schiff base formation and freeze–thaw cycling) to produce oxidized chitosan–pullulan hydrogels with thick pore walls, pore sizes of 50–380 μm, water retention of 1300%–2000%, and encapsulation efficiency of 66%–95%. This system demonstrated biphasic, prolonged release (50%–60% in 7 hours, extending to 15 days), favoring sustained release over the initial burst observed in alginate-based formulations.

The composition of the hydrogel, particularly its volatile fraction, influences antifungal activity. In Carbopol 940 formulations, polymer content affects flow properties and mechanical strength, whereas the concentrations of tea tree EO and rosemary EO (*Rosmarinus officinalis*) primarily modulate antimicrobial efficacy [34]. Formulation E, containing 1% Carbopol, 2% tea tree EO, and 2% rosemary EO, demonstrated the strongest antimicrobial activity, particularly against *Candida tropicalis* [34]. Polymeric hydrogel matrices generally enhance the retention and availability of encapsulated EOs, as demonstrated in gellan gum/hydroxyethylcellulose and chitosan-based systems that exhibit sustained release profiles and prolonged antimicrobial activity [22, 32].

Micellar poloxameric systems with oregano EO, such as Pluronic F127/L31-based binary hydrogels, provide high spreadability, sensory comfort, skin-compatible pH, good consistency, and complete oil solubilization, supporting both technological effectiveness and user experience [3]. While these systems retain antimicrobial activity, their antifungal potency is moderate (MIC ≈ 2.5 μg/mL) and does not match the reduction in fungal viability seen with more rigid matrix systems [3]. In contrast, alginate hydrogels with oregano EO exhibit accelerated, near-zero-order release kinetics, achieving full release of the phenolic marker in about 48 minutes and a very low IC_{50} (0.15–0.20 mg/L) against *C. albicans. They also reduce* adhesion and fungal morphogenesis by 60%–80%. Compared to micellar systems, these hydrogels exhibit stronger antifungal efficacy due to their porous microstructure and hydrophilic interactions, which enhance the availability of the active compound [10].

Among hydrogel formulations intended for mucosal, oral, or cutaneous applications, methylcellulose hydrogels with *M. officinalis* EO (1%–2%) exhibited increased viscosity and bioadhesion while maintaining pseudoplasticity. These hydrogels achieved 92% release in 48 hours, expanded the inhibition zone diameter to 17.5 mm, and reduced *C. albicans retention on* acrylic surfaces. Notably, 2% EO eliminated all viable cells within 4 hours, whereas 1% EO required 24 hours, highlighting the importance of antifungal dose for *Candida* control [31]. Similarly, three systems containing *Bidens tripartita* EOs—a hydrogel, bigel, and oleogel—showed pH values between 6.4 and 7.2 and pseudoplastic or thixotropic profiles (hydrogel/bigel). These systems demonstrated activity against *C. albicans* and *C. tropicalis*, particularly the hydrogel, further confirming the benefits of hydrophilic matrices for diffusion and interaction with fungal targets [51].

4. Comparative Performance of Colloidal Delivery Platforms for Enhancing the Antimicrobial Efficacy of Essential Oil–Based Hydrogels

Nanostructured colloidal systems have emerged as efficient methods to enhance the solubility, stability, and bioavailability of EOs in pharmaceutical applications [52, 53]. Rather than replacing the hydrogel matrix, these systems function as dispersed or integrated components within a continuous polymeric network, permitting controlled delivery and improved biological performance. In parallel, conventional hydrogels containing EOs—such as alginate/chitosan systems loaded with *Melaleuca alternifolia* EO—have also exhibited considerable antimicrobial and anti-inflammatory activity, reinforcing their role as effective delivery platforms even in the absence of nanostructuring [36]. Their structural features, functional, and chemical characteristics, including EO concentration ranges, are summarized in Table 2.

The main characteristics of the most widely used colloidal delivery systems incorporated into EO-loaded hydrogels are summarized in Figure 3. Nanoemulsions primarily enhance antimicrobial activity through increased interfacial contact, whereas polymeric micelles improve the solubilization of hydrophobic EO constituents. Emulgels combine improved permeation with hydrogel stability, while ethosomes favor transdermal delivery through enhanced skin penetration.

Among colloidal delivery systems, polymeric micelles have been widely investigated to improve the incorporation and delivery of hydrophobic EOs. *Origanum vulgare* OE, for example, has been formulated in polymeric micelles based on Pluronic copolymers, resulting in improved stability and biological activity [3]. Likewise, *Melaleuca alternifolia* EO has been incorporated into alginate–chitosan and ethosomal hydrogels at concentrations of 1–5%, maintaining its antimicrobial activity while enhancing topical therapeutic performance and reducing microbial burden [26,36].

However, these systems mainly enhance physicochemical stability and dispersion rather than directly increasing antimicrobial efficacy [5]. Consequently, their biological performance depends on formulation variables such as polymer composition, EO concentration, and delivery architecture, which limits direct comparisons across studies [27, 34, 39, 49].

In contrast, nanoemulsion-based systems, including nanoemulgels, are widely studied for their ability to enhance interfacial contact and facilitate penetration of microbial membranes. EO concentrations in these systems range from less than 1% to 50%, depending on whether the value refers to the dispersed phase or the final formulation. For example, nanoemulgels with 50% *Coriandrum sativum* EO demonstrated strong antimicrobial activity (MIC 2.3–6.5 μg/mL) [21], while other studies found effective formulations at lower concentrations, such as 3% eucalyptus oil [2, 28], approximately 1% lavender or tea tree oil [35], and 5–10% *Artemisia absinthium* [24]. Although smaller droplet size and increased interfacial area are often linked to improved antimicrobial performance, these effects are not universal and depend on formulation stability, concentration, and experimental conditions.

Emulgels are mixed systems in which emulsified oil droplets are dispersed within a three-dimensional gel matrix, typically with EO concentrations ranging from 2% to 50%. For example, *Pimpinella anisum* EO has been incorporated at 2% into Carbopol-based emulgels [29], while *Coriandrum sativum* nanoemulgels may contain up to 50% EO in the dispersed phase, increasing bioactivity and stability [21]. Similarly, nanoemulsion-based hydrogels with 3% eucalyptus oil demonstrate the potential of gel–colloidal integrated systems for topical delivery [28]. Recent studies (Table 1) show that these integrated

systems can improve antimicrobial performance compared with conventional hydrogels, primarily due to enhanced dispersion and bioavailability of the EO phase.

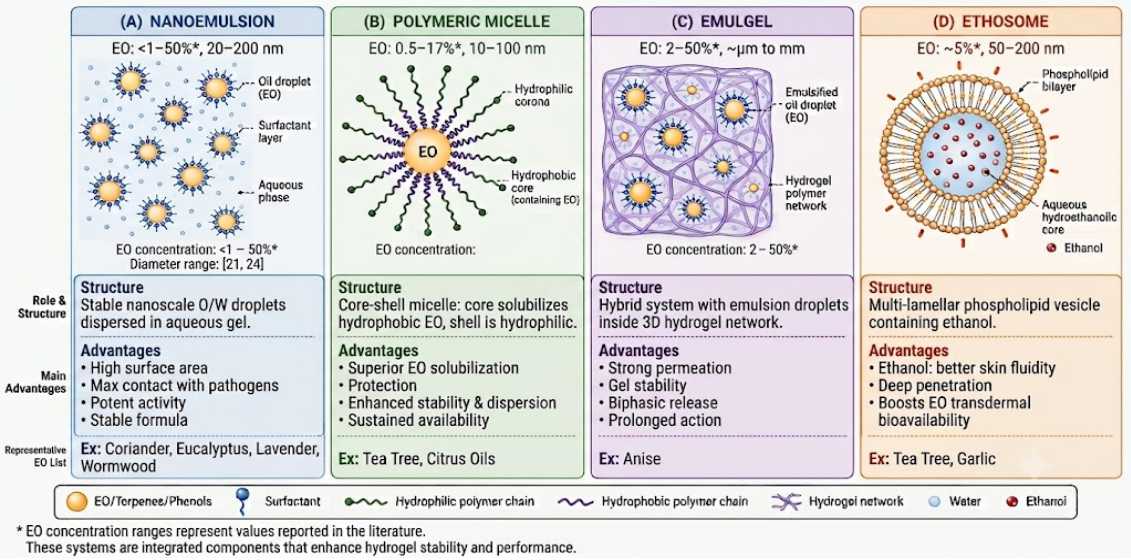

Figure 3. Comparison of colloidal delivery systems used to improve the therapeutic performance of EO-loaded hydrogels. Nanoemulsions provide a high interfacial area and enhanced antibacterial and antibiofilm activity; polymeric micelles improve the solubilization and dispersion of hydrophobic EO constituents; emulgels combine emulsion-mediated permeation with hydrogel stability and biphasic release profiles; and ethosomes promote transdermal delivery through ethanol-enhanced skin permeation. The concentration ranges shown represent values reported in representative EO-based hydrogel formulations [3, 21, 26, 29].

This hybrid architecture produces a biphasic release profile, with an initial burst followed by sustained delivery, leading to improved topical performance and prolonged therapeutic action. Polymer thickening agents, such as hydroxyethylcellulose, increase viscosity, bioadhesion, and residence time, but may also slow diffusion by increasing partitioning within the polymer network [22]. In addition, the rheological and diffusion properties of these systems are strongly influenced by polymer composition and network structure, which may modulate the release of encapsulated compounds [27, 30, 34]. These systems should be considered composite platforms that integrate colloidal and polymeric functions rather than conventional hydrogels [22, 28, 29, 32, 49, 54].

Beyond emulsified systems, ethosomal carriers—ethanol-rich phospholipid vesicles—have emerged as effective platforms to enhance the therapeutic efficacy of EOs in wound healing [26]. These systems improve transdermal permeation by ethanol-mediated disruption of the stratum corneum, making them well-suited for dermal applications [26, 55]. Recent studies show that garlic EO–loaded ethosomes exhibit significant antimicrobial and regenerative effects in both dermatophytic and bacterially infected wound models, promoting fibroblast proliferation, neovascularization, collagen deposition, and reepithelialization, with results comparable to those of standard treatments such as povidone-iodine [55]. These benefits are attributed to enhanced skin penetration and bioavailability provided by ethanol-rich vesicular systems, which allow

deeper delivery of bioactive compounds and modulate inflammatory responses and microbial load.

The stability and successful incorporation of these systems into hydrogel matrices depend on formulation design and necessitate comprehensive physicochemical characterization [34, 49, 56]. Optimized formulations can achieve effective antimicrobial and antibiofilm activity while preserving stability [21, 49]. Micellar systems are primarily employed to enhance the solubility and stability of hydrophobic EOs; however, their antimicrobial efficacy varies according to the encapsulated compounds and carrier composition [5]. Emulgels may offer a compromise between stability and antimicrobial effectiveness [29]. Ethosomal systems are generally favored for transdermal delivery due to their enhanced skin penetration capabilities [11]. Nevertheless, direct comparisons among these delivery platforms remain challenging because of substantial variability in EO concentrations and experimental methodologies across studies [39].

Recent advances in hybrid hydrogel systems indicate that antimicrobial enhancement depends more on architectural configuration and release kinetics than on EO concentration alone. Multiple studies (including those in the activity table) show that nanostructured hydrogels often outperform free EOs or conventional matrices [3, 9, 21, 32, 34, 40]. For example, pectin–starch hydrogels containing organoclay-loaded tea tree EO reduced the MIC against *S. aureus* by 50% (from 2.5 to 1.25 mg/mL), indicating synergistic antibacterial effects between the carrier system and the encapsulated EO [57]. Similarly, nanoparticle-based hydrogels and nanoemulgels provided greater bacterial inhibition than conventional hydrogels, emphasizing the importance of controlled release and reduced volatility [24, 39]. Oregano OE-based nanoemulgels have also shown strong antimicrobial and regenerative effects, promoting rapid wound closure, enhanced fibroblast migration, and reduced inflammation [58]. These findings suggest that nanostructuring and optimized delivery strategies, rather than EO concentration alone, are key to therapeutic efficacy.

In these systems, emulsion-filled hydrogels are hierarchical structures in which the hydrogel network serves as the continuous phase, and the dispersed droplets determine encapsulation efficiency, stability, and release profiles [4, 32, 37, 49]. For example, chitosan/pullulan hydrogels containing 1–5% clove EO exhibited sustained antimicrobial activity and controlled release for up to 360 hours [32], illustrating how structural design can directly influence treatment outcomes.

Preparation methods, such as ionic crosslinking and freeze–thaw processing, are critical for determining the physical integrity, porosity, and controlled-release behavior of hydrogels [4, 5, 32]. Therefore, the biological performance of EO-loaded hydrogels should be evaluated based on both compositional factors, such as EO concentration, and structural architecture, as both influence the overall effectiveness of the delivery system [2, 34, 39, 59].

Table 2. Delivery systems used to enhance the biologic efficacy of essential oil–based hydrogels.

Delivery System	Typical Hydrogel Matrix	Structural Characteristics	EO Concentration*	Role in EO Delivery	Main Advantages	Representative EO (%)	Reference
Nanoemulsions	Alginate, Carbopol, CMC	Nanometric oil droplets (O/W systems)	1–10% (final hydrogel); up to 50% in nanoemulsion phase	Solubilization and enhanced diffusion	Strong antibacterial and antibiofilm activity	Coriander (50% in NE phase), eucalyptus (3%), lavender (1%), wormwood (5–10%)	[21, 24, 28]
Polymeric micelles / Microemulsions	Poloxamers	Amphiphilic self-assembled systems	0.5–17% (v/v)	Solubilization of hydrophobic EO	Improved stability and dispersion	Tea tree (11–17%), citrus oils (~1%)	[3, 56]
Emulgel / Nanoemulgel	Carbopol 940 hydrogel	Oil-in-water emulsion dispersed within a semi-solid gel matrix	~2% (v/v)	Biphasic release profile (initial burst + sustained release) and enhanced skin retention	Improved skin permeation, high colloidal stability,	Anise (2%)	[29]
Ethosomes	Carbopol hydrogel	Ethanol-rich phospholipid vesicles	~5% (v/v)	Transdermal delivery	Enhanced skin penetration and retention	Tea tree (5%)	[26]
Emulsion-filled hydrogels	Chitosan/pullulan	Hybrid system (hydrogel + emulsion)	1–5% (w/w)	Controlled and sustained release	High stability and prolonged delivery	Clove (1–5%)	[32]

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5. Wound Healing and Anti-inflammatory Activities

Wound healing is a complicated process that can be impaired by persistent inflammation, oxidative stress, microbial infection, and poor vascularization. In this context, EO-loaded hydrogels combine antimicrobial, anti-inflammatory, and regenerative properties, creating a favorable microenvironment for tissue repair and chronic wound management [12–14].

5.1. Wound Healing

Chronic wounds, particularly those associated with diabetes, are characterized by impaired tissue repair resulting from persistent inflammation, excessive production of reactive oxygen species (ROS), insufficient angiogenesis, and disorganized collagen deposition [13, 23, 24]. In this context, several EO-loaded hydrogel formulations have been reported to accelerate wound healing by stimulating reepithelialization, increasing fibroblast proliferation, and improving extracellular matrix organization [2, 23, 24].

Advanced delivery platforms have been developed to improve the therapeutic performance of wormwood EO. Building on this need, multifunctional GelMA/HAMA hydrogels incorporating wormwood (*Artemisia* spp.) EO and black phosphorus nanosheets provide NIR-responsive controlled release while actively modulating the diabetic wound microenvironment through antibacterial, antioxidant, anti-inflammatory, and pro-angiogenic mechanisms. In this context, these materials promote ROS scavenging, M2 macrophage polarization, vascular regeneration, and collagen deposition, leading to near-complete wound closure in diabetic wound models [13]. Likewise, Pickering emulsion-based hydrogels loaded with wormwood EO exhibit broad-spectrum antibacterial and immunomodulatory activities, inducing macrophage polarization from M1 to M2 and stimulating collagen deposition and neovascularization, thereby accelerating the healing of MRSA-infected diabetic wounds [24].

Oxidative stress represents another major obstacle to effective tissue repair, especially in chronic and diabetic wounds. Accordingly, multifunctional cryogel systems based on poly(vinyl alcohol)/poly(ethylene brassylate-co-squaric acid) incorporating thymol and α-tocopherol have demonstrated promising antimicrobial and antioxidant properties [60]. These materials exhibited controlled-release behavior, broad-spectrum activity against *S. aureus*, *E. coli*, and *C. albicans*, as well as strong free-radical scavenging capacity arising from the synergistic action of both bioactive compounds. Such features highlight the potential of EO-based cryogel dressings to reduce microbial burden and oxidative stress simultaneously, two major factors that compromise wound healing [60].

Building on this concept, stimuli-responsive hydrogels have emerged as advanced platforms for site-specific and on-demand delivery of bioactive compounds. ROS- and thermo-sensitive hydrogels incorporating patchouli EO nanoemulsions improve EO stability, prolong retention at the target site, and enable controlled release in response to oxidative stress. Moreover, these systems reduce inflammatory mediators and oxidative damage while supporting tissue protection and repair, highlighting the therapeutic potential of smart EO-loaded hydrogel platforms [61]. Similarly, thermo-responsive hydrogels containing

patchouli EO undergo in situ gelation and inflammation-triggered release, improving stability and sustained delivery of the encapsulated oil [27]. These physicochemical characteristics favor fibroblast activation, cellular migration, and matrix deposition, ultimately accelerating wound closure in experimental models [27].

Nanostructured systems also play a critical role in the management of infected wounds. For instance, nanoemulsion-based hydrogels containing eucalyptus EO significantly improved reepithelialization and collagen organization in *S. aureus*-infected wounds [28]. Their effectiveness is largely attributed to the increased interfacial area and controlled diffusion provided by nanoencapsulation, which enhance tissue repair while maintaining biocompatibility. In a related delivery strategy, ethosomal carriers have emerged as promising platforms for improving the therapeutic efficacy of EOs. Garlic EO-loaded ethosomes exhibited both antimicrobial and regenerative effects in dermatophytic and bacterially infected wound models, promoting fibroblast proliferation, neovascularization, collagen deposition, and reepithelialization, with outcomes comparable to those achieved with povidone-iodine treatment [56]. These benefits are attributed to improved skin penetration and bioavailability provided by ethanol-rich vesicular systems, which facilitate deeper delivery of bioactive compounds while reducing microbial load and modulating inflammatory responses.

Advanced nanoemulsion systems incorporating oregano oil have also shown enhanced antimicrobial and regenerative activity, promoting faster wound closure, increased fibroblast migration, and reduced inflammation, particularly in diabetic wound models [57]. These therapeutic effects can be further amplified when combined with adjunctive approaches such as low-level laser therapy, which stimulates cellular metabolism, collagen synthesis, and tissue remodeling [57]. Together, these findings demonstrate that nanostructuring, controlled release, and external stimulation may contribute more substantially to therapeutic efficacy than EO concentration alone. Taken together, EO-loaded hydrogel membranes can directly enhance tissue regeneration and wound healing.

In vivo studies using gellan gum/collagen hydrogels loaded with geranium and lemongrass OEs demonstrated faster wound contraction, increased fibroblast recruitment, enhanced neovascularization, greater collagen deposition, and more advanced reepithelialization compared with control dressings [62]. These effects resulted in improved granulation tissue formation and accelerated skin repair, emphasizing the regenerative potential of multifunctional EO-based hydrogel systems [62]. Consistent with these findings, hydrogel systems based on polyvinyl alcohol and polyvinyl pyrrolidone (PVA/PVP) incorporating EOs such as fennel (*Foeniculum vulgare*), peppermint (*Mentha piperita*), pine (*Pinus sylvestris*), and thyme (*Thymus* sp.) have also shown considerable promise as wound dressings. These materials provide a moist healing environment, sustained release of bioactive compounds, and broad-spectrum antimicrobial activity [63]. In addition, they exhibit good biocompatibility and support fibroblast viability and proliferation, while encapsulation strategies improve release control and overall therapeutic effectiveness [63]. Extending this evidence to burn wounds, extracellular matrix-inspired hydrogel systems have likewise demonstrated positive effects on tissue

repair in burn wound models. Collagen-based hydrogels combined with *Lavandula officinalis* EO nanoemulsions promoted angiogenesis, fibroplasia, and organized collagen deposition, particularly in burn wounds infected with *Pseudomonas aeruginosa* [2]. Likewise, Pickering emulsion-based hydrogels containing *Artemisia* EO exhibit structural stability and sustained-release behavior, contributing to accelerated healing in infected diabetic wounds [24]. In this context, these examples further underscore the relevance of platform design to wound-specific performance.

Thermosensitive nanoemulsion-based hydrogels have further demonstrated superior wound-healing performance through controlled release and adaptive physicochemical properties. Specifically, systems incorporating *Schizonepeta annua* EO nanoemulsions accelerate wound contraction, improve epidermal regeneration, and enhance collagen organization, highlighting the central role of hydrogel architecture and release kinetics in maximizing therapeutic efficacy [64].

Overall, EO-loaded hydrogels promote wound healing through multiple complementary mechanisms, including antimicrobial activity, reduction of oxidative stress, modulation of inflammation, stimulation of fibroblast activity, enhancement of angiogenesis, and improvement of collagen organization and reepithelialization. The integration of nanoemulsions, smart delivery platforms, and stimuli-responsive materials further enhances therapeutic performance by increasing EO stability, bioavailability, and controlled release. As summarized in Figure 4, EO-loaded hydrogels support successive stages of wound repair, including infection control, fibroblast recruitment, angiogenesis, collagen deposition, tissue remodeling, and reepithelialization, ultimately accelerating wound closure and improving tissue regeneration.

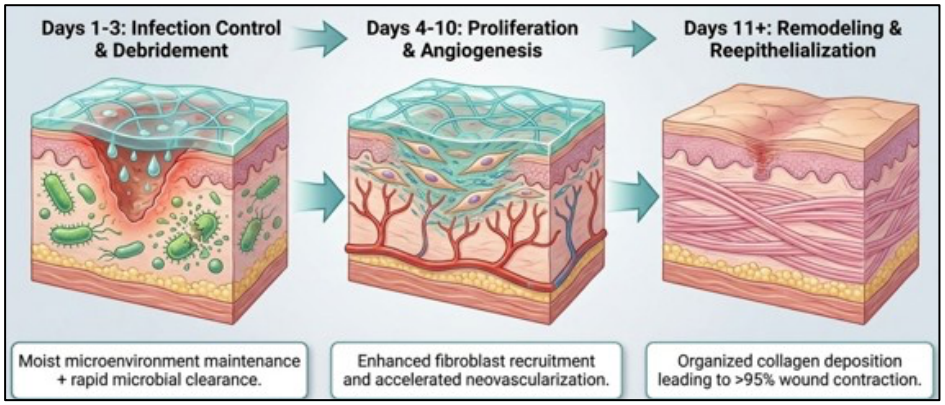

Figure 4. Proposed wound-healing mechanisms of EO-loaded hydrogels. These systems contribute to infection control, These mechanisms have been reported for selected EO-loaded hydrogel formulations and may contribute to infection control, fibroblast proliferation, angiogenesis, collagen deposition, tissue remodeling, and reepithelialization [13, 24, 28].

5.2 Anti-Inflammatory Activity

Persistent inflammation is a major barrier to wound healing, especially in chronic or infected tissues. Several EO-loaded hydrogel formulations have demonstrated anti-inflammatory activity by modulating cytokine expression, reducing oxidative stress, and regulating immune responses [23, 28]. As summarized in Figure 5, EO-based delivery systems downregulate ROS and pro-inflammatory mediators, while

stimulating growth factors and cellular responses involved in tissue regeneration.

Some studies have reported suppression of pro-inflammatory cytokines, including IL-6 and TNF-α, together with increased expression of growth factors such as TGF-β1, VEGF, and EGF. For instance, eucalyptus EO nanoemulsion-based hydrogels decreased inflammatory markers and improved tissue regeneration in infected wounds [28].

Hydrogels composed of Carbomer 940 and chitosan incorporating eucalyptus EO have also demonstrated modulation of inflammatory responses, promoting epithelial regeneration while reducing cytokine expression [1].

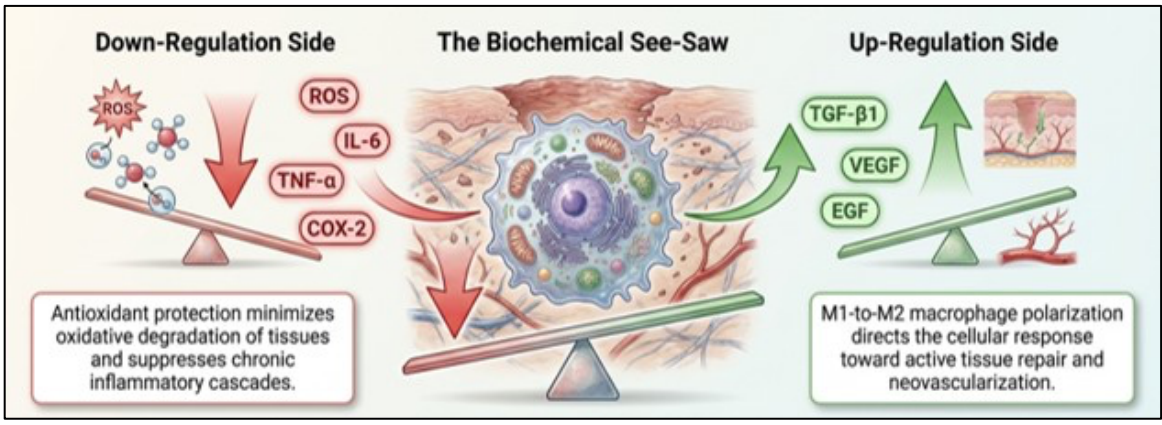

Figure 5. Schematic representation of the anti-inflammatory effects of EO-loaded hydrogels during wound healing. Representative mechanisms reported for selected EO-loaded hydrogel systems include reduction of ROS [23,66], suppression of pro-inflammatory mediators including TNF-α [28, 64, 67], IL-6 [25, 28], and COX-2 [64], modulation of growth factors associated with tissue repair, including TGF-β1, VEGF, and EGF [25, 28], and promotion of regenerative responses such as angiogenesis, reepithelialization, fibroblast migration, and extracellular matrix remodeling [25, 28, 36, 68]. Abbreviations: ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; COX-2, cyclooxygenase-2; TGF-β1, transforming growth factor-beta 1; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor.

Control of oxidative stress is an additional critical factor in the therapeutic performance of EO-loaded hydrogels. Alginate-based hydrogels associated with poly(itaconic anhydride-co-3,9-divinyl-2,4,8,10-tetraoxaspiro[5.5]undecane) (PITAU) and enriched with lavender EO significantly reduced ROS levels while maintaining structural stability and porosity [23]. This reduction in oxidative stress may also support wound healing by complementing the improved swelling capacity and exudate management reported for lyophilized alginate composites containing EOs and nanoparticles [1]. Because oxidative stress and inflammation are closely interconnected during tissue repair, these antioxidant effects may indirectly suppress inflammatory signaling. Supporting this link, nanoemulgel systems containing clove EO were shown to reduce cyclooxygenase-2 (COX-2) expression and pro-inflammatory mediators while maintaining good biocompatibility [65].

EO-loaded hydrogels also may indirectly reduce inflammation by controlling infection and biofilm formation. *Zataria multiflora* EO-containing systems, for example, showed significant antifungal activity against *C. albicans* biofilms (60–80% inhibition), reducing infection-driven

inflammation [66]. In vivo studies demonstrated that eucalyptus EO nanoemulsion hydrogels reduced wound bacterial load and downregulated pro-inflammatory mediators (IL-6 and TNF-α), while promoting growth factor expression and tissue regeneration, leading to accelerated wound closure and enhanced healing outcomes [28].

Advanced alginate-based hydrogel dressings incorporating EO-mediated nanoparticles have demonstrated multifunctional properties relevant to wound management. Alginate hydrogels containing cinnamon EO-mediated silver nanoparticles and β-carotene nanocarriers reduced intracellular ROS levels, mitigated silver-induced cytotoxicity, improved HaCaT keratinocyte viability, and maintained strong antimicrobial and antibiofilm activity [67]. Similarly, rosemary EO-loaded nanohydrogels enhanced skin permeation, preserved antioxidant activity, and suppressed inflammatory responses, including TNF-α-related pathways, highlighting the shared capacity of nanostructured EO delivery systems to modulate oxidative stress, inflammation, and tissue repair [68].

Beyond controlling inflammation, these regenerative microenvironments may also support key cellular events involved in wound healing, particularly fibroblast migration. In this context, hydrogel-based scaffolds have been shown to facilitate EO-mediated tissue repair by promoting cellular motility within a three-dimensional matrix. For instance, fibrin hydrogel scaffolds loaded with *Bursera morelensis* EO stimulated fibroblast migration and induced the formation of filopodia-like cellular projections, without affecting cell viability or proliferation [69]. These findings suggest that the EO enhances the migratory response required for wound contraction and granulation tissue development, which in turn supports collagen deposition and tissue remodeling. Altogether, these results highlight hydrogel-based delivery systems as anti-inflammatory platforms that also modulate cellular processes essential for effective wound regeneration [69].

6. Safety and Toxicity and Considerations

The safety profile of EO–loaded hydrogels is critical to their translational and clinical relevance. Although EOs oils exhibit antimicrobial, antioxidant, and anti-inflammatory activities, their direct use is often limited by dose-dependent cytotoxicity, chemical instability, and potential irritant effects. Hydrogel-based delivery systems therefore help modulate toxicity and improve safety [47, 32].

EO toxicity is strongly influenced by concentration, route of administration, and susceptibility to oxidative degradation, which can generate reactive intermediates and increase cytotoxicity. Incorporation into hydrogel matrices lessens these limitations [32]. The three-dimensional polymeric network stabilizes volatile constituents, protects them from oxidation and evaporation, and promotes the sustained release of active compounds. Compared with non-encapsulated oils, these systems improve formulation stability, reduce rapid compound loss, and prolong bioactive availability at the application site [6,10, 32, 47]. Encapsulation may also enhance the bioavailability and therapeutic performance of EOs, enabling efficacy at lower concentrations while improving delivery efficiency [5, 32, 47].

Cytotoxicity assessments consistently show favorable biocompatibility of EO-loaded hydrogels across a wide concentration range. In vitro viability assays, such as 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) and live/dead staining, show that hydrogels containing *Pimpinella anisum* (2%) or EO clove (1–5%) sustain cell viability above 75–80% in Human Adult Low-Calcium High-Temperature Keratinocytes (HaCaT), with no notable apoptosis or necrosis. Polysaccharide-based hydrogels incorporating eucalyptus, ginger, and cumin EOs also show cell viability above 92% in fibroblast models and promote cell migration and tissue repair [25]. Collectively, these findings support their safe use [29, 32].

Evidence from nanostructured systems also supports the safety advantages of encapsulation. For example, nanoemulgel formulations containing EOs, such as myrrh-based systems, show appropriate physicochemical properties, improved skin permeation, and no irritation in animal models, supporting their suitability for topical applications [68]. Taken together, these data indicate that nanostructured carriers can preserve cytocompatibility while improving biological performance.

Cytotoxicity is concentration-dependent across formulations. For instance, fibrin-based hydrogels containing *Litsea cubeba* EO (0.0625–2.5% v/v) showed approximately 73% viability in human gingival fibroblasts at low concentrations, whereas higher concentrations reduced viability, confirming a dose-dependent effect [40]. Likewise, Carbopol-based hydrogels containing EO mixtures (1.5–2%) maintained cytocompatibility within optimal ranges but showed reduced viability at higher concentrations [30]. These data point out the need for precise formulation design and EO concentration optimization to maintain efficacy and safety.

Hemocompatibility is another key parameter for biomedical applications, particularly in wound dressings. Accordingly, EO-loaded hydrogels typically exhibit hemolysis values below 5%, which is acceptable for biomaterials and reflects minimal erythrocyte membrane damage [13]. This low hemolytic activity also reflects controlled release behavior, which helps prevent rapid systemic exposure to high EO concentrations.

Beyond cytotoxicity, irritation potential and dermatological safety have been evaluated using both in vitro and in vivo models. Accordingly, nanoemulsion- and microemulsion-based hydrogels containing tea tree oil (≈5%) or lemongrass oil (≈1%) demonstrated non-irritant behavior in Hen's Egg Test–Chorioallantoic Membrane (HET-CAM) assays and histopathological analysis, showing no structural damage or inflammatory response [11, 37]. Similarly, nanoemulgel systems containing cinnamon or myrrh EOs showed no observable irritation in animal models, supporting their safety for cutaneous use [53].

Polymeric hydrogel systems also show favorable dermatological safety profiles under more complex biological conditions. For example, hydrogel formulations containing *Origanum vulgare* EO combined with biogenic nanoparticles showed good biocompatibility in ex vivo and in vivo models, with effective antimicrobial activity and no significant adverse tissue responses [33]. Likewise, alginate-based hydrogels enriched with lavender EO demonstrated excellent in vivo

biocompatibility, with no local or systemic toxicity and clear improvements in wound-healing outcomes [23].

The composition of the polymeric matrix also plays a central role in determining safety. Accordingly, natural polymers such as alginate, chitosan, gellan gum, and cellulose derivatives are regularly used due to their intrinsic biocompatibility, biodegradability, and low toxicity. In particular, chitosan-based hydrogels enhance EO encapsulation and reduce cytotoxicity through regulated release mechanisms. For example, chitosan–pullulan hydrogels loaded with clove oil (1–5%) exhibited sustained release (up to 360 h), high encapsulation efficiency, and no significant cytotoxicity [32].

Release kinetics constitute another critical factor linking efficacy and safety. Accordingly, hydrogel systems are intended to minimize burst release while offering sustained EO delivery. For instance, fibrin hydrogels containing *Litsea cubeba* EO (1% v/v) showed a very low initial release (~0.03% in the first hour), followed by sustained release over up to 30 days, which contributed to improved cellular tolerance [40]. However, excessively slow release may compromise antimicrobial activity, demonstrating the need for balanced formulation strategies [32].

Additional studies with hybrid systems further support the biocompatibility advantages of EO encapsulation. For example, PVA/kaolin hydrogels containing cedar EO demonstrated excellent hemocompatibility and high fibroblast viability, while starch-based hydrogels loaded with patchouli oil showed no evidence of cytotoxicity and maintained favorable cellular compatibility [2, 27]. These findings suggest that hydrogel matrices can mitigate the adverse effects associated with free Eos while supporting cellular responses beneficial to tissue regeneration.

Despite these advances, significant heterogeneity in EO concentrations, formulation strategies, physicochemical characteristics, and biological evaluation protocols limits direct comparisons across studies and complicates the establishment of universal safety limits [6, 23, 29, 30, 32, 40]. Moreover, most available safety data originate from in vitro studies and small-scale in vivo models, whereas comprehensive toxicological investigations, uniform safety evaluation models, and long-term clinical evaluations remain scarce [23, 25, 29, 32, 40, 68]. This fragmented evidence base highlights the need for standardized safety criteria and more robust cross-study comparisons. However, a clear gap remains in standardized, long-term, and clinically validated safety thresholds, limiting robust cross-study translation.

Overall, the available evidence suggests that EO-loaded hydrogels usually exhibit favorable safety profiles, with low cytotoxicity, acceptable hemocompatibility, minimal irritation potential, and good biological tolerance when appropriately formulated [2, 13, 23, 25, 29, 32, 40, 53, 68]. These advantages are mainly attributed to hydrogel matrices, which stabilize volatile bioactive compounds, regulate their release, and reduce direct cellular exposure to high EO concentrations [5, 6, 10, 32, 40, 47]. Therefore, hydrogel-based encapsulation should be regarded not only as a delivery strategy but also as an important platform for improving the safety profile of EO-based formulations [5, 32, 40, 47]. However, despite

these encouraging findings, standardized toxicological studies, dose–response investigations, and well-designed clinical trials are still required to define safe therapeutic ranges, clarify long-term effects, and support future regulatory approval and clinical translation [23, 25, 32, 40, 69].

7. Conclusions

Essential oil (EO)-loaded hydrogels have appeared as multifunctional therapeutic platforms capable of addressing different factors that compromise wound healing, including microbial infection, biofilm formation, persistent inflammation, oxidative stress, and impaired tissue regeneration. Available studies show that incorporating EOs into hydrogel matrices may improve the stability, bioavailability, and controlled release of volatile bioactive compounds. This may enhance antimicrobial, antifungal, anti-inflammatory, and regenerative efficacy in specific formulations.

Several EO-loaded hydrogel systems have been reported to reduce microbial burden, disrupt biofilms, modulate inflammatory mediators such as TNF-α and IL-6, decrease oxidative stress, and support tissue repair processes including fibroblast migration, angiogenesis, collagen deposition, and reepithelialization. However, these effects depend heavily on the composition of the EO, the hydrogel matrix, the delivery strategy, the release profile, and the experimental model employed.

The therapeutic performance of EO-loaded hydrogels appears to be strongly influenced by interactions between the polymeric matrix and the delivery system. Natural and synthetic polymers, including alginate, chitosan, carbomers, poly(vinyl alcohol), collagen, gellan gum, and starch-based materials, provide distinct physicochemical environments that affect bioadhesion, swelling behavior, mechanical stability, and release kinetics. Advanced delivery approaches, such as nanoemulsions, ethosomes, Pickering emulsions, micellar systems, and nanoparticle-enriched hydrogels, can further improve EO solubility, retention, penetration, and biological activity. Collectively, the available studies suggest that formulation design and release control may be more influential determinants of therapeutic performance than EO concentration alone.

Despite these promising findings, most evidence remains limited to in vitro investigations and preclinical animal studies, with substantial heterogeneity in formulation composition, EO concentration, biological assays, and outcome measures. This variation limits direct comparisons among studies and accentuates a clear research gap: the need for greater methodological standardization and more robust evidence to support clinical translation.

Future research needs to prioritize standardizing formulations, conducting mechanistic investigations, performing comprehensive safety assessments, conducting long-term toxicological evaluations, and conducting well-designed clinical studies to facilitate translation into clinical practice. Overall, the available preclinical evidence suggests that EO-loaded hydrogels constitute promising biomaterial platforms for the management of infected, chronic, and difficult-to-heal wounds. However,

further standardization, safety assessment, and clinical validation are required before their therapeutic potential can be fully established.

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Abbreviations: The following abbreviations are used in this manuscript:

AAc-NHS – N-Hydroxysuccinimide Acrylate
B. subtilis – Bacillus subtilis
C. albicans – Candida albicans
C. glabrata – Candida glabrata
C. parapsilosis – Candida parapsilosis
C. tropicalis – Candida tropicalis
Candida spp. – Candida species
Carbopol® – Crosslinked poly(acrylic acid) polymer
CFU – Colony-Forming Unit
CMC – Carboxymethylcellulose
COX-2 – Cyclooxygenase-2
E. coli – Escherichia coli
EGF – Epidermal Growth Factor
EO / EOs – Essential Oil / Essential Oils
Fmoc-3F-Phe- Fluorenylmethoxycarbonyl-phenylalanine
FTIR – Fourier Transform Infrared Spectroscopy
HaCaT – Human Adult Low-Calcium High-Temperature Keratinocytes
HET-CAM – Hen's Egg Test–Chorioallantoic Membrane
IC_{50} – Half Maximal Inhibitory Concentration
IL– Interleukin 6
IL-10 – Interleukin 10
IL-1β – Interleukin 1 Beta
IL-6 – Interleukin 6
LasI – Autoinducer Synthase LasI (Quorum-Sensing Protein)
LDH – Layered Double Hydroxides
M1 – Classically Activated Macrophage Phenotype
M2 – Alternatively Activated Macrophage Phenotype
MBC – Minimum Bactericidal Concentration
MBECs - Minimum Biofilm Eradication Concentrations
mg/mL – Milligram per milliliter
MIC – Minimum Inhibitory Concentration
MRSA – Methicillin-Resistant *Staphylococcus aureus*

MTT – 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
NF-κB – Nuclear Factor Kappa B
NIR – Near-Infrared
nm – Nanometer
O/W – Oil-in-Water
P. aeruginosa – Pseudomonas aeruginosa
PEG – Polyethylene Glycol
pH – Potential of Hydrogen
PITAU – poly(itaconic anhydride-co-3,9-divinyl-2,4,8,10-tetraoxaspiro[5.5] undecane
Pluronic F127 – Poloxamer 407
PVA – Polyvinyl Alcohol
ROS – Reactive Oxygen Species
S. aureus – Staphylococcus aureus
SDS – Sodium Dodecyl Sulfate
TGF-β /– Transforming Growth Factor Beta
TNF-α – Tumor Necrosis Factor Alpha
VEGF – Vascular Endothelial Growth Factor
VRE – Vancomycin-Resistant Enterococcus
ZnO – Zinc Oxide
μg/cm²·h – Microgram per square centimeter per hour
μg/mL – Microgram per milliliter

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