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ARTICLE

Multi-functional biomedical applications of nanoencapsulated herbal essential oils: Polymer-based encapsulation strategies and key biological properties

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Herbal essential oils (HEOs) possess broad-spectrum biological activity but their biomedical translation is limited by volatility, poor aqueous solubility, chemical instability, and compositional variability. This review critically synthesizes recent advances in polymer-based nanoencapsulation as a strategy to modulate the physicochemical and biological behavior of HEOs. Delivery platforms including polymeric nanoparticles, nanoemulsions, hydrogels/nanogels, electrospun nanofibers, and hybrid assemblies are analyzed with emphasis on structure–function relationships. Particular attention is given to how polymer selection governs mucoadhesion, degradability, release kinetics, cellular interaction, and compatibility with hydrophobic phytoconstituents. Across diverse biomedical contexts, encapsulation consistently alters exposure profiles and improves therapeutic indices relative to free oils, enhancing antimicrobial and antibiofilm performance, modulating inflammatory and oxidative pathways, promoting wound repair, and increasing selective cytotoxicity in cancer models. These effects are linked to improved physicochemical stabilization, controlled release behavior, and architecture-dependent cellular uptake mechanisms. Despite substantial progress, translational barriers remain, including limited long-term *in vivo* safety data, challenges in chemotype standardization, batch-to-batch variability, and constraints in GMP-compliant scale-up. Future development will depend on integrating rigorous quality control, scalable manufacturing technologies, and data-driven formulation design to establish clinically and industrially viable HEO-based nanotherapeutic systems.

Keywords: Controlled release; Bioavailability; Nanogels; Wound healing; Antioxidant; Anticancer; Translational challenges.

1. Introduction

Over recent decades, natural products have re-emerged as structurally diverse reservoirs of bioactive compounds that inform modern therapeutic and formulation strategies (1). Rather than replacing synthetic drugs, plant-derived molecules increasingly function as complementary or lead compounds within integrated biomedical platforms. Their renewable origin, chemical complexity, and multi-target biological activity make them particularly attractive in infection control, tissue regeneration, and advanced drug delivery systems.

Among plant-derived bioactives, herbal essential oils (HEOs) represent a distinctive and chemically complex class composed primarily of volatile terpenoid constituents (2, 3). Their multicomponent architecture enables broad-spectrum biological activity through membrane perturbation, enzyme modulation, redox regulation, and host immune interaction (4, 5). This intrinsic multifunctionality underlies their growing application in wound management, antimicrobial coatings, antiseptic systems, and adjunct therapeutic formulations. In addition, their biodegradability and renewable sourcing align with sustainability-driven biomedical innovation.

The renewed scientific and industrial interest in HEOs is driven by converging factors: rising antimicrobial resistance, demand for safer excipients, and advances in extraction technologies, analytical chemistry, and formulation science. At the same time, sustainability

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initiatives and consumer expectations for traceable, low-impact natural products encourage the adoption of HEOs when responsibly sourced (6). Their intrinsic multifunctionality also allows them to act not only as therapeutic agents but also as penetration enhancers or preservative alternatives (7). However, the popularity of "natural" ingredients necessitates rigorous safety and standardization assessment.

Despite these advantages, direct biomedical utilization of HEOs remains constrained by fundamental physicochemical and compositional limitations. Chemotype variability influenced by geographic origin, seasonal factors, and extraction conditions complicates standardization and reproducibility (8, 9). Concurrently, high volatility, oxidative susceptibility, and poor aqueous solubility reduce stability, bioavailability, and shelf life, potentially necessitating elevated doses that increase irritation or toxicity risk (2). Addressing these constraints requires formulation strategies capable of stabilizing reactive constituents while preserving biological functionality.

Encapsulation has therefore emerged as a central enabling technology for volatile phytochemicals. By entrapping HEOs within protective matrices, encapsulation mitigates environmental degradation, modulates release kinetics, improves dispersibility, and reduces exposure-associated toxicity (10-13). While microencapsulation provides partial protection, nanoencapsulation—typically operating at ≤100 nm—offers additional advantages through increased surface area, improved cellular interaction, enhanced penetration, and tunable release profiles (14-16).

Polymer-based nanocarriers are particularly attractive due to their structural versatility, biodegradability, and established biomedical relevance (4). By integrating the intrinsic bioactivity of HEOs with the controlled delivery characteristics of polymeric nanosystems, multifunctional platforms can be engineered for infection control, inflammation modulation, regenerative medicine, and targeted therapeutic delivery. Importantly, nanoencapsulation also expands potential administration routes—including topical, oral, and inhalation pathways—by enhancing mucosal adhesion, enzymatic protection, and sustained release (17, 18). Polymeric nanoparticles—whether nanospheres or nanocapsules—allow precise control over encapsulation efficiency, release behavior, and biological performance (4, 19). Numerous studies report significant improvements in HEO stability, dispersibility, and targeted release within polymeric matrices, translating into enhanced bioactivity and functional device integration (20-23).

In this review, we critically examine recent advances in polymer-based nanoencapsulation strategies for HEOs, linking formulation parameters to biological performance and translational feasibility. Beyond summarizing preparation platforms, we synthesize mechanistic insights, evaluate safety and scalability considerations, and identify the principal bottlenecks limiting clinical adoption. By integrating materials innovation with regulatory and manufacturing perspectives, this work provides a structured roadmap for advancing standardized, scalable, and clinically relevant HEO-based nanotherapeutics.

2. Overview of HEOs for biomedical applications

2.1. Definition, sources, and main bioactive components of HEOs

HEOs are chemically complex mixtures of volatile plant-derived secondary metabolites whose biological activity is largely dictated by their dominant bioactive constituents (5). Beyond their ecological function in plant defense against pathogens, herbivores, and environmental stressors, HEOs have been widely applied in pharmaceutical, cosmetic, and food systems (2). Their composition is strongly influenced by extraction methodology, with conventional techniques such as hydrodistillation and steam distillation increasingly complemented by advanced approaches including supercritical CO_2 and microwave-assisted extraction, each of which can alter yield, volatility retention, and chemical integrity (3).

Although HEO-producing species span diverse botanical families—including Lamiaceae, Rutaceae, Myrtaceae, Apiaceae, Lauraceae, Cupressaceae, Pinaceae, Zingiberaceae, and Asteraceae (24)—their biomedical relevance is governed less by taxonomy and more by chemotype. Geographic origin, genetic background, cultivation conditions, climate, and developmental stage collectively shape compositional variability (25). These oils are biosynthesized and accumulated in specialized secretory structures such as glandular trichomes, resin ducts, and oil glands (26, 27), and improper harvesting or post-harvest handling may significantly modify the resulting chemical fingerprint. Consequently, botanical source and

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processing conditions directly affect downstream formulation reproducibility.

Chemically, HEOs are dominated by terpenoids and phenylpropanoids, biosynthetically derived from isoprenoid precursors (C_5 units), which largely determine their antimicrobial, antioxidant, and anti-inflammatory behavior (28). Minor constituents—including oxygenated derivatives such as alcohols, aldehydes, ketones, and esters—often modulate overall activity through synergistic or antagonistic interactions. This multicomponent architecture underlies both the therapeutic potential and the standardization challenges associated with HEO-based biomedical systems.

2.2. Key biological properties relevant to biomedical applications

HEOs exhibit diverse biological activities that underpin their biomedical relevance. Importantly, their therapeutic versatility often arises from synergistic ("entourage") interactions among major and minor constituents, which may enhance or modulate bioactivity relative to isolated compounds (29). Rather than acting through single molecular targets, HEOs typically exert multi-pathway effects, making them particularly suitable for complex pathological conditions involving infection, oxidative stress, inflammation, and dysregulated cell proliferation (**Figure 1**).

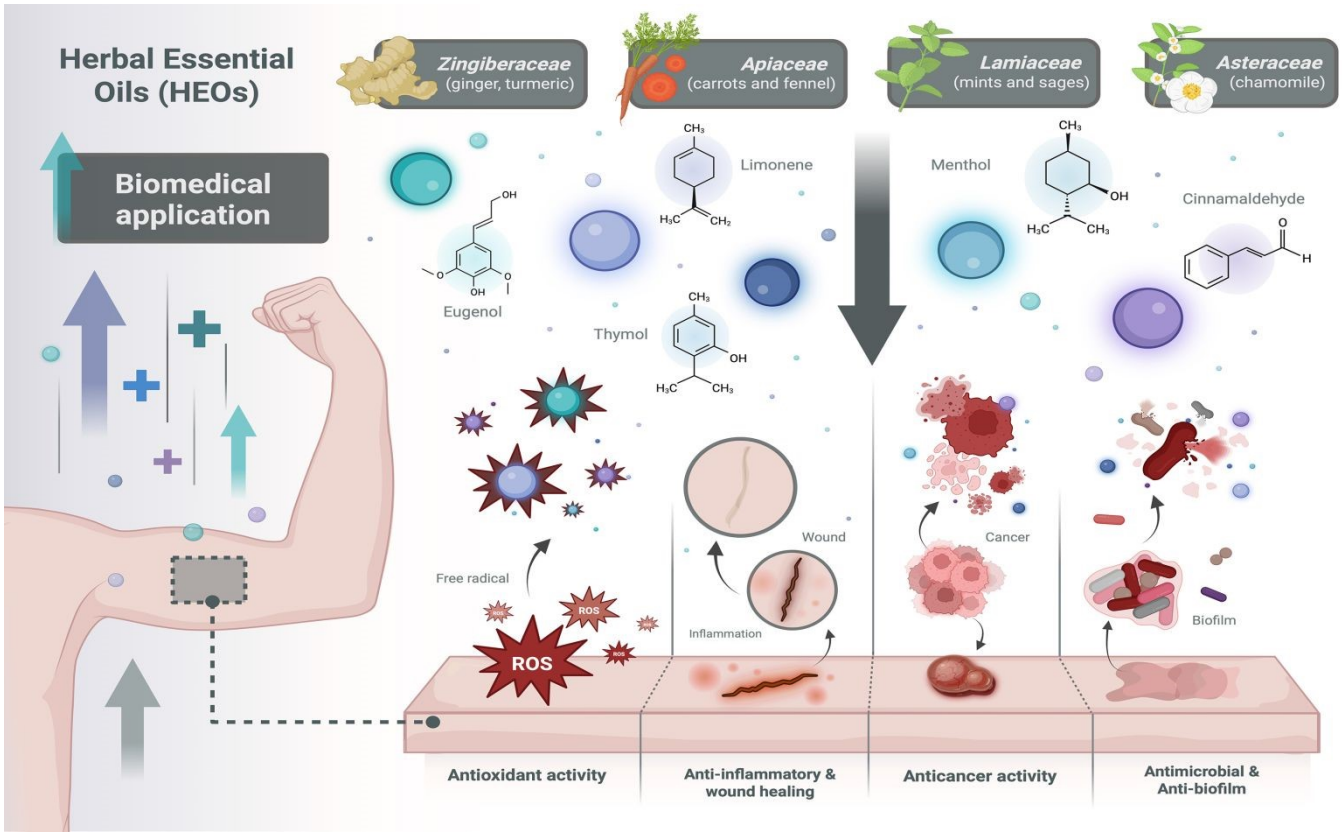

Fig. 1 Overview of HEOs for biomedical applications

2.2.1. Antimicrobial, anti-biofilm, and wound healing

The antimicrobial activity of HEOs is primarily attributed to their lipophilic constituents, which integrate into microbial membranes, disrupt lipid bilayer integrity, increase permeability, and cause leakage of intracellular contents. Additional mechanisms include interference with energy metabolism, efflux pump inhibition, and suppression of quorum sensing and biofilm formation (30-33). These membrane-targeted effects explain their broad activity against Gram-positive and Gram-negative bacteria, as well as fungi (34).

Beyond infection control, HEOs support wound healing through integrated mechanisms involving antimicrobial protection, modulation of local inflammation, and stimulation of cellular proliferation and angiogenesis. By simultaneously addressing microbial burden and inflammatory imbalance, they facilitate

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progression through the inflammatory, proliferative, and remodeling phases of healing (20, 32, 35). Such multifunctionality makes HEOs particularly attractive for incorporation into advanced wound dressings and polymeric delivery systems.

2.2.2. Antioxidant properties

The antioxidant capacity of HEOs is closely linked to their terpenoid and phenolic constituents and depends on both chemical composition and analytical methodology (36). Mechanistically, HEOs scavenge reactive oxygen species (ROS), inhibit lipid peroxidation, donate hydrogen atoms to interrupt radical chain reactions, and enhance endogenous antioxidant defenses. By mitigating oxidative damage to lipids, proteins, and nucleic acids, they may contribute to protection against aging-related disorders, inflammatory conditions, and carcinogenesis.

Numerous plant-derived HEOs have demonstrated measurable antioxidant activity *in vitro* (23, 37-42). However, biological efficacy *in vivo* is strongly influenced by stability, bioavailability, and controlled release—parameters that nanoencapsulation strategies aim to optimize.

2.2.3. Anti-inflammatory activity

Inflammation involves activation of pattern-recognition receptors and downstream signaling cascades that promote cytokine production and leukocyte recruitment (43). Central pathways—including NF-κB, MAPKs, JAK/STAT, and COX-mediated eicosanoid synthesis—amplify inflammatory signaling. HEOs attenuate these processes by suppressing pro-inflammatory mediators such as TNF-α, IL-6, COX-2, and iNOS, while reducing oxidative stress and immune cell infiltration (44, 45).

Experimental evidence supports these mechanisms across both *in vitro* and *in vivo* models. For example, nanoformulated tea tree oil has demonstrated enhanced clinical performance in inflammatory skin conditions when combined with conventional therapeutics (46). Similarly, essential oil–based hydrogel systems have been shown to regulate ROS production, angiogenesis, cytokine expression, and macrophage polarization in wound-healing models (47, 48). These findings underscore the relevance of delivery systems in amplifying anti-inflammatory efficacy.

2.2.4. Anticancer activities

HEOs exert anticancer effects through multi-target mechanisms, including inhibition of proliferation, induction of apoptosis, cell-cycle arrest, anti-angiogenesis, and suppression of metastatic signaling (49). These actions involve modulation of mitochondrial pathways, MAPK and PI3K/AKT/mTOR signaling, and transcription factors such as NF-κB and STAT3. Importantly, the multicomponent composition of HEOs enables simultaneous interference with complementary oncogenic pathways.

In addition to intrinsic cytotoxic effects, HEOs may potentiate conventional chemotherapeutics, enhancing efficacy or reducing adverse effects (23, 49). Activity has been reported across diverse cancer cell models (50-52), with synergistic interactions among constituents contributing to enhanced potency relative to isolated compounds.

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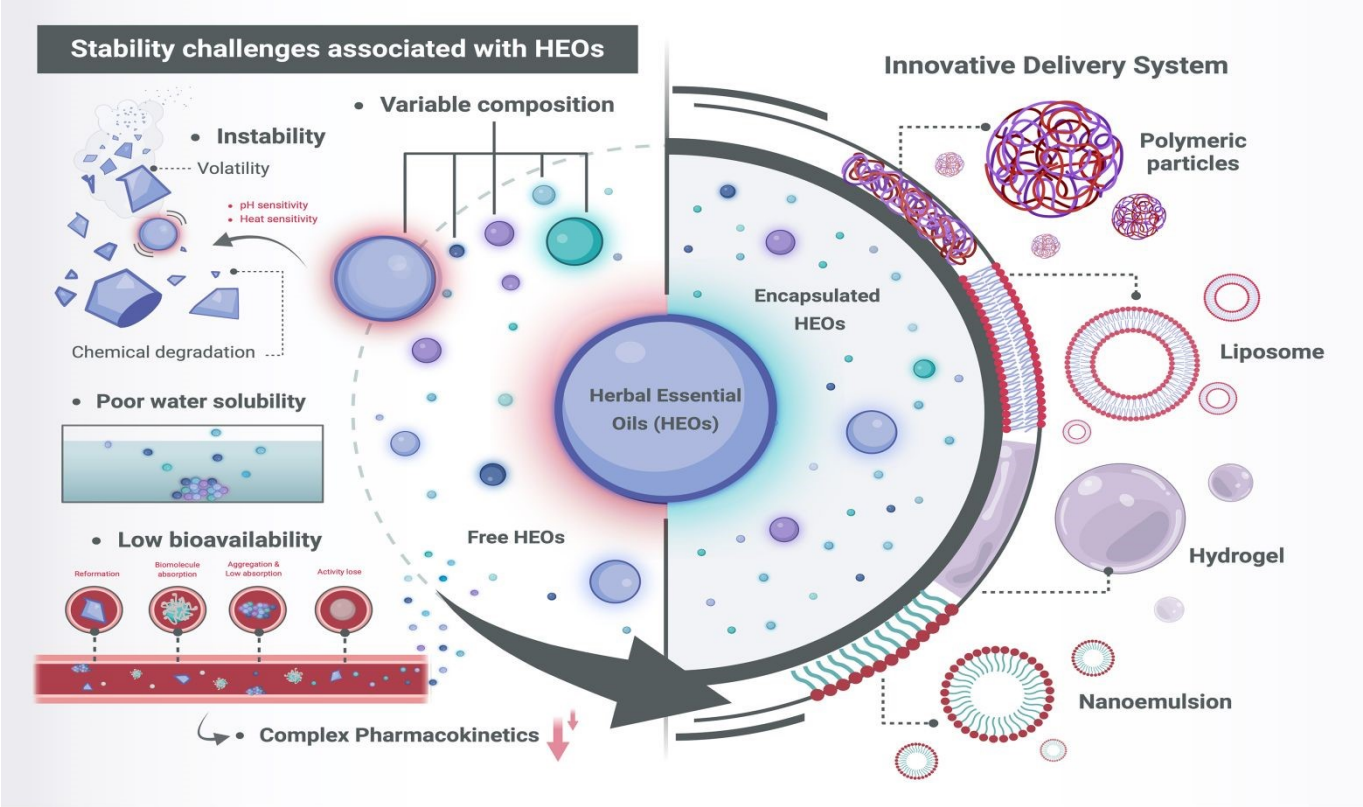

Fig. 2 Stability challenges associated with HEOs

3. Stability challenges associated with HEOs

Although HEOs demonstrate considerable pharmacological promise, their biomedical translation is fundamentally limited by interconnected physicochemical instabilities that compromise reproducibility, efficacy, and safety (**Figure 2**). These constraints arise not from a single vulnerability, but from a convergence of volatility, lipophilicity, chemical reactivity, and compositional variability.

Volatility represents one of the most immediate challenges. Many dominant constituents—particularly monoterpenes and low-molecular-weight aldehydes—exhibit high vapor pressures and readily evaporate under ambient or moderately elevated temperatures. Progressive volatilization results in quantitative loss of active components, altered chemical ratios, diminished therapeutic potency, and shortened shelf life, thereby complicating dose standardization in topical, oral, and systemic formulations (4).

Compounding this issue, the intrinsic lipophilicity of HEOs limits their dispersion in aqueous biological environments and hydrophilic pharmaceutical matrices. Poor aqueous solubility restricts bioavailability and reduces effective concentration at target tissues, often necessitating higher administered doses that may increase irritation risk.

Chemical degradation further exacerbates instability. Exposure to oxygen initiates oxidative reactions that generate peroxides and reactive intermediates, particularly in unsaturated terpenoids, phenolic compounds, and aldehydes (53). These transformations can lead to discoloration, loss of aroma, reduced biological activity, and formation of sensitizing or toxic by-products. In parallel, ultraviolet

radiation promotes photoisomerization and molecular fragmentation, while thermal stress during processing or storage may induce hydrolysis, rearrangement, or cyclization reactions that modify chemical integrity and biological performance (54). Collectively, these degradation pathways alter both safety and efficacy profiles over time.

Formulation-dependent factors such as pH also influence stability. Acidic or alkaline environments can accelerate hydrolytic reactions, modify solubility characteristics, or promote structural transformation of sensitive constituents (55). Therefore, maintaining physicochemical compatibility between HEOs and delivery matrices is critical for therapeutic reliability.

Beyond formulation parameters, upstream biological and agricultural variables significantly shape stability outcomes. Plant species, chemotype, harvested organ, and developmental stage determine baseline chemical composition, while geography, climate, and soil conditions modulate biosynthetic pathways and metabolite ratios (25). Post-harvest handling and extraction methods introduce additional variability: delayed processing may permit enzymatic conversion of volatile constituents, and high-temperature or solvent-intensive extraction can generate artifacts that deviate from native chemical profiles (56).

4. Polymer-based nanoencapsulation of HEOs

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The application of polymeric nanocarriers for HEO delivery is fundamentally driven by the need to stabilize volatile phytochemicals while enabling controlled therapeutic performance (**Figure 3**). By forming nanoscale protective reservoirs, polymer matrices shield labile constituents from oxidation, volatilization, and photodegradation, thereby improving physicochemical stability, aqueous dispersibility, and biological efficacy (57). Beyond passive protection, polymeric systems allow programmable release kinetics, enhanced tissue retention, and improved bioavailability under physiological conditions.

4.1 Natural polymers: Biofunctionality and synergy

Natural and biodegradable polymers are particularly attractive for HEO nanoencapsulation due to their intrinsic biocompatibility, biodegradability, and often mucoadhesive or bioactive properties (58). Importantly, certain natural polymers contribute complementary therapeutic effects. For example, chitosan exhibits inherent antimicrobial and hemostatic activity, while gelatin offers excellent biocompatibility and film-forming capacity (**Tables 1–2**). Such synergy enhances the overall therapeutic performance of the composite system.

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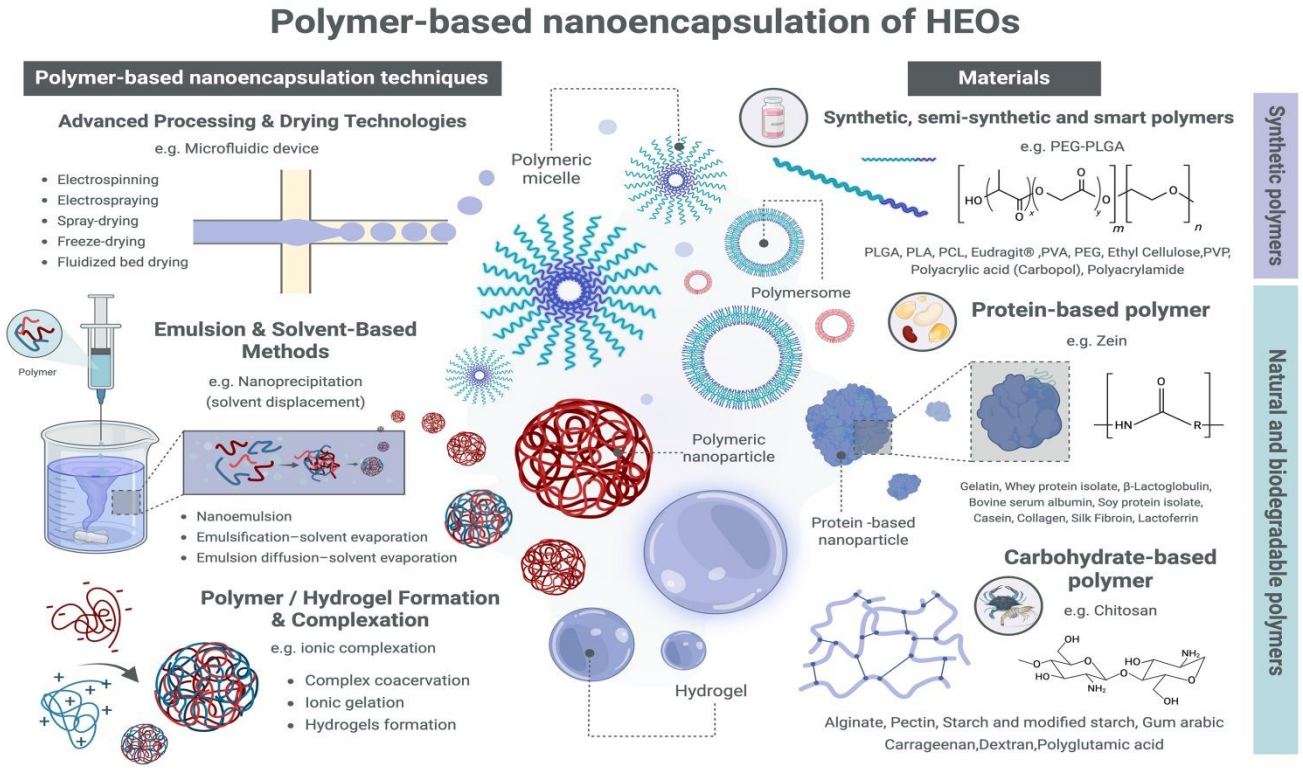

Fig. 3 Polymer-based nanoencapsulation of HEOs.

This integrative approach is exemplified by polyethylene oxide–gelatin nanofibers incorporating *Myrtus communis* L. essential oil, which demonstrated a biocompatible scaffold for antimicrobial wound management (59). In such systems, the polymer provides structural integrity and sustained release, while the encapsulated HEO delivers bioactive functionality.

4.2 Synthetic and smart polymers: Precision and scalability

Synthetic polymers—including poly(lactic-co-glycolic acid), polyethylene glycol, and polycaprolactone—offer precise control over degradation rate, mechanical strength, and release behavior, supporting reproducible large-scale manufacturing (**Table 3**). Their networks can be engineered to optimize encapsulation efficiency and diffusion kinetics while enabling stimulus-responsive behavior (57). Hybrid systems integrating natural biopolymers with synthetic polymers often achieve an optimal balance between intrinsic bioactivity and structural tunability, improving batch reproducibility and translational feasibility.

4.3 Encapsulation platforms: Functional classification

Polymer-based nanoencapsulation approaches can be conceptually classified according to their formation mechanisms rather than enumerated individually (**Table 4**). Emulsification-driven systems, including solvent evaporation and nanoemulsion methods, rely on interfacial stabilization of dispersed oil droplets within polymeric matrices. In contrast, precipitation-based techniques such as nanoprecipitation exploit polymer self-assembly during solvent exchange to entrap volatile constituents. Electrohydrodynamic

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processes, including electrospinning and electrospraying, enable fabrication of nanofibrous scaffolds or particulate carriers with high surface-area-to-volume ratios, particularly advantageous for wound-healing and topical systems. Polyelectrolyte-based strategies such as ionic gelation and complex coacervation utilize electrostatic interactions to form structured matrices capable of modulating release kinetics. Finally, post-processing stabilization techniques—including spray-drying and freeze-drying—convert colloidal nanosystems into solid-state dosage forms suitable for storage and industrial handling (60, 61).

4.4 Design-oriented selection framework

Selection of polymer type and fabrication strategy should be guided by a rational design framework that aligns the physicochemical vulnerabilities of the HEO with the structural characteristics of the carrier. Highly volatile and oxidation-sensitive oils may benefit from dense or crosslinked polymer matrices that restrict oxygen diffusion and vapor loss. Oils with poor aqueous solubility require systems that enhance dispersion while maintaining release control. Application-specific requirements further shape formulation decisions: topical wound-healing systems often prioritize film-forming or nanofibrous architectures, whereas oral or inhalable systems demand mucoadhesive or diffusion-regulated platforms (62-66). Thus, effective nanoencapsulation is not method-driven but problem-driven, integrating oil chemistry, polymer properties, and therapeutic intent into a unified formulation strategy.

Table 1 Protein-based polymers used for encapsulation of HEOs

Protein	Sources	IEP*	Key properties	Applications in encapsulation methods	Reference
Gelatin	Collagen (animal skin, bones, fish scales)	4.7–9.5 (Type A/B)	Biocompatible, biodegradable, film-forming, good emulsifier, thermoreversible gelation	Hydrogel, nanoemulsion, and electrospinning methods for encapsulating HEOs such as Litsea cubeba, oregano, Ferula assa-foetida, and Myrtus communis L. EOs	(32, 36, 59)
Whey protein isolate (WPI)	Milk (dairy by-product)	4.5–5.2	Amphiphilic, antioxidant, good emulsifier, film-forming	nanoemulsion for encapsulating HEOs such as Litsea cubeba and Cinnamomum cassia	(36)
β-Lactoglobulin (β-LG)	Whey protein (milk)	5.1–5.3	Globular protein with hydrophobic binding pockets; high affinity for lipophilic compounds	Complex coacervation and self-assembly for encapsulating HEOs such as black pepper	(67)
α-Lactalbumin (α-LA)	Milk (whey fraction)	4.2–4.5	Calcium-binding, heat-stable, and good surface-active	emulsion for encapsulating HEOs such as L-menthol and chamomile	(68, 69)
Bovine serum albumin (BSA)	Bovine blood serum	4.7–5.3	High binding affinity, antioxidant, biocompatible	complex coacervation and antisolvent precipitation methods for encapsulating HEOs such as peppermint, thymol	(70, 71)
Soy protein isolate (SPI)	Soybeans	4.5–5.0	Cost-effective, good emulsifying ability, thermal stability	Emulsion and antisolvent precipitation for encapsulating HEOs such as citrus and Litsea cubeba	(72)
Pea protein isolate (PPI)	Yellow peas	4.5–5.0	Sustainable plant protein, good emulsification and film-forming ability	antisolvent precipitation and electrospinning for encapsulating HEOs such as Hyssop and cumin	(73)

Protein	Sources	IEP*	Key properties	Applications in encapsulation methods	Reference
Zein	Corn (prolamin fraction)	6.2–6.8	Hydrophobic, film-forming, biodegradable, ethanol-soluble	electrospinning for encapsulating HEOs such as rosemary and oregano	(39, 74)
Casein	Milk	4.6–4.8	Amphiphilic, micelle-forming, excellent carrier for hydrophobic compounds	self-assembly and electrospinning systems for encapsulating HEOs such as ginger and oregano	(75, 76)
Collagen	Animal connective tissue	~9.0	Biocompatible, structural integrity, film-forming	Electrospinning and emulsion systems for encapsulating HEOs such as lemon and dill, and Palmarosa	(77, 78)
Silk Fibroin	Silkworm cocoons (*Bombyx mori*)	4.2–4.5	Biocompatible, mechanically strong, slow-degrading	Electrospinning and self-assembly systems for encapsulating HEOs such as oregano and eugenol	(79, 80)
Lactoferrin	Milk	8.0–9.0	Cationic, mucoadhesive, metal-binding, broad spectrum of antimicrobial activities	Complex coacervation and Pickering emulsion systems for encapsulating HEOs such as black pepper and clove	

*IEP: isoelectric point

Table 2. Polysaccharide-based polymers used for encapsulation of HEOs

Polysaccharide	Source	IEP*	Key properties	Use in encapsulation methods	Encapsulated HEOs	References
Chitosan	Derived from chitin (crustacean shells, fungal cell walls)	~6.3	Cationic, mucoadhesive, biocompatible, antimicrobial, film-forming	Ionic gelation, emulsification, coacervation, spray drying	Green tea, Rosmarinus officinalis	(30, 81)
Alginate	Brown algae (e.g., *Laminaria*, *Macrocystis*)	–	Anionic, biocompatible, gel-forming with Ca^{2+} ions	Ionotropic gelation, emulsion, coacervation	Satureja khuzestanica, Zingiber officinale	(82, 83)
Pectin	Citrus peel, apple pomace	–	Anionic, biodegradable, good gelling and film-forming capacity	Emulsification, complex coacervation, liposome	Lemongrass, rose	(84, 85)
Starch and modified starch	Corn, potato, tapioca	–	Good encapsulant, digestible, low cost	Spray drying, electrospinning, nanoprecipitation	Thyme, ginger	(86, 87)
Gum Arabic	Acacia tree exudate	–	emulsifier and film former, soluble in water	Emulsion, spray drying, complex coacervation, nanoprecipitation	Eucalyptus, lemongrass	(88, 89)
Carrageenan	Red seaweeds (*Kappaphycus*, *Eucheuma*)	–	Anionic, gel-forming, biocompatible	Emulsification, hydrogels	Carvacrol	(90)

Dextran	Bacterial fermentation (*Leuconostoc mesenteroides*)	–	Neutral, biocompatible	water-soluble,	Emulsion, hydrogel	Alpinia zerumbet Fructus, Eucalyptus	(91, 92)
Polyglutamic acid	Bacterial fermentation (*Bacillus* species)	-	Neutral, biodegradable, anionic	water-soluble, biocompatible,	liposome	Alpinia galanga	(93)

*IEP: isoelectric point

Table 3. Synthetic and semi-synthetic polymers used for encapsulation of HEOs

Polymer	Type	Key properties	Use in encapsulation methods		References
PLGA (Poly(lactic-co-glycolic acid))	Synthetic copolymer	Biodegradable, FDA-approved, controlled drug release	Emulsification-solvent evaporation technique	Boswellia sacra oleo gum resin, lavender	(94, 95)
PLA (Polylactic acid)	Synthetic	Biodegradable, hydrophobic, good mechanical stability	Electrospinning	Lavender, Perilla	(96, 97)
PCL (Polycaprolactone)	Synthetic	Semi-crystalline, slow degradation rate, hydrophobic	Electrospinning	Blumea balsamifera, *Mentha longifolia*	(98) (35)
Eudragit® (Methacrylate copolymer)	Semi-synthetic	pH-sensitive, tailored release profile	Spray drying, nanoprecipitation	Oregano	(99)
PVA (Polyvinyl alcohol)	Synthetic	Water-soluble, film-forming, stabilizing agent	Electrospinning	Tea tree, limonene	(100, 101)
PEG (Polyethylene glycol)	Synthetic	Hydrophilic, improves solubility and biocompatibility	Nanoliposome, Pickering emulsion/nanogel	Lemongrass, Atractylodes macrocephale	(102, 103)
Ethyl Cellulose	Semi-synthetic	Hydrophobic, film-forming, provides sustained release	Hydrogel, electrospinning	Cuminum cyminum, ginger	(76, 104)
PVP (Polyvinylpyrrolidone)	Synthetic	Amphiphilic, enhances solubility, good film former, and biocompatibility	Electrospinning	Oregano	(32)
Polyacrylic acid (Carbopol)	Synthetic	Calcium-binding, biocompatible, biodegradable, mucoadhesive properties, high water absorption capacity	Electrospinning, nanogel	Pectis brevipedunculata, Lavandula angustifolia Mill.	(105, 106)

Polyacrylamide	Synthetic	Water-soluble, biocompatible, biodegradable, gelling properties	Pickering emulsion/hydrogel	Lavender	(107)

Table 4. Summary of polymer-based nanoencapsulation techniques used for HEOs

Encapsulation technique	Principle/process description	Materials/solvents	Key features and advantages	Used for nanoencapsulation of	Ref.
Nanoemulsion	Formation of thermodynamically unstable but kinetically stable emulsions with droplet sizes in the nanometer range (20–200 nm). The EO is dispersed as fine droplets stabilized by surfactants, preventing coalescence and volatilization.	Oil phase: EOs or lipids; aqueous phase: water or buffer; surfactants: Tween, Span 80, lecithin; co-surfactants: ethanol, glycerol, propylene glycol. Polymers: chitosan, alginate, pectin, gelatin, whey protein, casein, gum arabic, Synthetic polymers: PVA, PEG	High kinetic stability, transparency, enhanced solubility and bioavailability, protection against oxidation and volatilization, suitable for thermolabile oils, and allows controlled or sustained release.	Lavender, Artemisia annua, Aniba canelilla (Kunth) Mez, Foeniculum vulgare Mill., oregano, and perilla, lemongrass, *Thymus daenensis Celak* and *Bunium persicum.*	(108-110)
Nanoprecipitation (solvent displacement)	A water-miscible organic phase (polymer + EO) is injected into an aqueous stabilizer phase; rapid solvent diffusion causes polymer precipitation and nanoparticle formation; requires polymer solubility in organic solvent and insolubility in water.	Solvents: acetone, ethanol; polymers: sodium caseinate, chitosan, whey protein isolate, poly-ϵ-caprolactone, zein; surfactants: Tween 80, PVA	Simple, low-energy, reproducible; avoids high temperature and shear; ideal for thermolabile oils.	Guava leaf, oregano, curry leaf, lemongrass	(111, 112)
Complex coacervation and ionic gelation	Electrostatic interactions between oppositely charged biopolymers (coacervation) or between a polyelectrolyte and multivalent counterion (ionic gelation) form nanocapsules.	Polymers: Gelatin, chitosan, alginate, gum Arabic, soy protein isolate, whey protein isolate; ions: sodium tripolyphosphate	Organic-solvent-free, biocompatible, and mild; ideal for heat-sensitive oils; good control of release properties.	Nepeta hormozganica, Nepeta Dschuprensis, zeylanicum, Cyperus articulatus rhizome, carvacrol, green tea, Cynometra cauliflora	(81, 113)

Encapsulation technique	Principle/process description	Materials/solvents	Key features and advantages	Used for nanoencapsulation of	Ref.
Liposomal entrapment	EO components are entrapped within phospholipid bilayers or aqueous cores of liposomes prepared via thin-film hydration, ethanol injection, or microfluidics.	Phospholipids (lecithin, phosphatidylcholine), cholesterol	Biocompatible, biodegradable, enhances solubility and bioavailability; protects from oxidation and volatilization.	Tea tree, Zhumeria majdae, lemongrass,	(102, 114)
Molecular Inclusion	Essential oil molecules form host–guest complexes within cyclodextrin cavities via non-covalent interactions (hydrophobic and van der Waals forces).	Cyclodextrins (α-, β-, γ-CD, HP-β-CD)	Solvent-free; enhances solubility, stability, and controlled release; food-grade; improves volatility control and photostability	Bergamot, rosemary, thymol, d-limonene, coriander, eugenol and cinnamaldehyde	(115, 116)
Microfluidics	Precise mixing of polymer, essential oil, and stabilizer phases within microchannels enables controlled nanoparticle formation via laminar flow and solvent diffusion.	Chitosan, alginate, hyaluronic acid, PNIPAM	Highly reproducible; continuous, scalable; offers precise control over size distribution (< 10% PDI) and morphology; low solvent use.	Frankincense, eugenol, linalool, and geraniol, mint oil	(117, 118)
Hydrogels (nanogels)	Hydrophilic polymer networks crosslinked at the nanoscale entrap EOs through electrostatic/hydrophobic interactions.	Water or buffer; polymer + EO	High water content, biocompatible, stimuli-responsive release; stable and protective.	Bunium persicum, lavender, thymus vulgaris, Syzygium aromaticum,	(108, 119)
Emulsification–solvent evaporation and emulsion diffusion–solvent evaporation	A polymer and EO are dissolved in a volatile organic solvent and emulsified in an aqueous surfactant phase (O/W); solvent evaporation induces polymer precipitation around oil droplets forming nanocapsules.	Dichloromethane, ethyl acetate; polymers (PLGA, ethyl cellulose); surfactants (PVA, Tween)	Produces uniform nanoparticles; suitable for hydrophobic oils; good encapsulation efficiency; protects against oxidation and volatilization.	Garlic, Hypericum perforatum, Boswellia sacra Oleo gum resin, lavender, Nigella sativa	(94, 95)

Encapsulation technique	Principle/process description	Materials/solvents	Key features and advantages	Used for nanoencapsulation of	Ref.
Spray-drying and freeze-drying	Emulsions containing EOs are spray-, or freeze-dried to form powders.	Polymers: maltodextrin, gum arabic, starch, whey protein	Scalable, cost-effective, and versatile; preserves volatile oils.	*Cinnamodendron dinisii*, lemon grass, *Mentha pulegium, Nepeta crispa*, oregano	(89, 120)
Electrospinning and electrospraying	A polymer–oil solution is subjected to a high-voltage field Electrospinning → nanofibers Electrospraying → nanoparticles	Soy protein isolate, pea protein isolate, gum Arabic, whey protein isolate, gelatin, gellan, poly vinyl alcohol.	Solvent-based but mild; produces dry, porous structures; suitable for thermolabile compounds.	Perilla, *Zataria multiflora*, Satureja and thyme,	(97, 121)
Fluidized bed drying	Droplets or particles containing EOs are suspended in an upward flow of moderate temperature air, creating a "fluidized" state that. It is used to dry emulsions or to apply polymer coatings onto pre-formed particles or granules containing EOs. Mostly used for microencapsulation, rarely nanoparticles.	Feed may be an emulsion or suspension containing EO and wall materials; optional coating solvents may include ethanol or water. Polymers: maltodextrin, gum arabic, modified starch, cellulose derivatives, alginate, chitosan, whey protein concentrate, zein.	Produces free-flowing, dry micro/nanoparticles; offers good retention of volatile oils; scalable and continuous; enables controlled-release coating; suitable for heat-sensitive EOs due to short drying time and efficient heat transfer.	Bitter orange	(122)

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4.5. Mechanistic basis of biological effects in polymer-encapsulated HEO systems

Polymer-based nanoencapsulation enhances the biological performance of HEOs through a multi-level mechanistic framework integrating: (i) intrinsic phytochemical bioactivity, (ii) polymer-mediated physicochemical modulation, and (iii) nano–bio interfacial interactions that govern diffusion, cellular uptake, and release kinetics. Rather than functioning as passive reservoirs, polymeric nanocarriers actively regulate structure–property–function relationships that shape therapeutic outcomes.

4.5.1. Intrinsic bioactivity of encapsulated HEOs

The fundamental biological activity of encapsulated HEOs remains rooted in their phytochemical composition. Antimicrobial effects are primarily mediated by lipophilic terpenoids that partition into microbial lipid bilayers, increasing membrane permeability, promoting leakage of intracellular contents, disrupting energy metabolism, and interfering with efflux systems (123-125).

In anticancer applications, encapsulated constituents induce mitochondrial dysfunction, excessive ROS generation, and caspase-dependent apoptosis, accompanied by modulation of BAX/BCL-2 ratios and suppression of survival signaling pathways including PI3K/AKT, mTOR, and STAT3 (126, 127).

Anti-inflammatory activity involves attenuation of cytokine cascades (TNF-α, IL-6, IL-1β), downregulation of COX-2 and iNOS, and inhibition of NF-κB–mediated transcriptional signaling (43, 128). Concurrently, antioxidant mechanisms contribute to redox homeostasis through scavenging of reactive species, suppression of lipid peroxidation, and upregulation of endogenous defense systems, thereby mitigating oxidative stress associated with chronic inflammation and impaired tissue repair (129, 130).

Encapsulation does not fundamentally alter these intrinsic mechanisms; rather, it preserves and potentiates them by stabilizing reactive constituents and optimizing local concentration profiles.

4.5.2. Polymer-mediated physicochemical regulation

Polymeric matrices actively shape biological responses by modulating surface charge, particle size, degradation dynamics, and release kinetics (131). Surface chemistry plays a particularly critical role: cationic polymers such as chitosan promote electrostatic interactions with negatively charged bacterial membranes and cancer cell surfaces, enhancing adhesion and facilitating membrane destabilization.

Release behavior—governed by diffusion-controlled (Fickian) transport or polymer degradation—maintains therapeutic concentrations while reducing burst-associated toxicity. Mucoadhesive polymers prolong local retention at mucosal or wound sites, whereas hydrogel and nanogel networks create hydrated microenvironments that support tissue regeneration and sustained diffusion (132, 133).

Electrospun nanofibrous matrices, characterized by high surface-area-to-volume ratios and tunable porosity, enable uniform bioactive distribution and enhanced surface exposure (134). Synthetic polymers such as poly(lactic-co-glycolic acid) and polycaprolactone provide predictable degradation kinetics, enabling temporal control over essential oil release and improving dosing reproducibility.

4.5.3. Nano–bio interfacial and synergistic effects

At the nanoscale, reduced particle dimensions increase surface-area-to-volume ratios and intensify diffusion gradients, facilitating deeper penetration into biofilms and tumor microenvironments (131). Positive zeta potential enhances electrostatic interactions with microbial biofilm matrices and promotes endocytic internalization by mammalian cells.

Encapsulation further preserves pharmacological integrity by protecting volatile terpenoids from oxidative and photochemical degradation. Beyond stabilization, co-encapsulation strategies enable compositional synergy, spatial co-localization of active agents, and coordinated release profiles that amplify therapeutic outcomes (135, 136).

The convergence of controlled release, enhanced permeability, polymer–cell interactions, and phytochemical synergy results in amplified antimicrobial, anti-inflammatory, wound-healing, and anticancer efficacy relative to free HEOs. Collectively, these interconnected mechanisms position polymer nanoencapsulation not merely as a protective strategy, but as an active regulator of biological performance through rational modulation of structure–property–function relationships.

5. Structure–property–function relationships in polymer-encapsulated HEO systems

The therapeutic performance of nanoencapsulated HEOs arises from quantifiable material parameters rather than solely from intrinsic phytochemical potency. Encapsulation efficiency, transport behavior, cellular uptake, and biological efficacy are governed by polymer chemistry, network architecture, interfacial characteristics, and environmental responsiveness. Establishing direct structure–property–function correlations enables predictive formulation design and advances HEO delivery from empirical optimization toward mechanism-driven materials engineering.

5.1. Polymer chemistry and encapsulation thermodynamics

At the molecular scale, encapsulation efficiency (EE) is dictated by polymer–oil thermodynamic compatibility, molecular weight (Mw), degree of deacetylation (DD) in chitosan-based systems, and crosslink density (ρx). Increasing Mw enhances chain entanglement, while higher DD increases charge density and electrostatic interactions, strengthening oil retention within the matrix. Similarly, elevated ρx reduces network free volume and limits diffusion of oil toward the particle surface during processing (137-141).

Comparative studies illustrate this dependency. Starch nanofibers achieved EE values of 99.1–99.8% for thyme oil (86), whereas zein nanofibers showed 75.23% (142). In oregano essential oil complex coacervates, hemp protein isolate–gum Arabic systems reached 57% EE (143), compared with 95% for chitosan/gum Arabic matrices (144). These differences reflect variations in polymer–terpenoid affinity, interfacial stabilization capacity, and matrix compactness. Insufficient polymer–oil compatibility promotes surface migration and accelerated initial release, ultimately reducing effective dose delivery (145).

5.2. Physicochemical properties and nano–bio interactions

Particulate-scale parameters translate molecular design into biological performance. Particle diameter governs diffusion path length and interfacial area; nanocarriers for targeted delivery commonly fall within the 10–50 nm range (146). Reduction in particle size increases surface-to-volume ratio, shortens diffusion pathways, and enhances tissue penetration. Uniformity is equally critical: a polydispersity index below 0.3 minimizes aggregation and ensures reproducible exposure kinetics.

Surface charge links colloidal stability with cellular interaction. Absolute zeta potential values of approximately ±30 mV confer electrostatic stabilization, whereas positively charged carriers enhance adhesion to negatively charged bacterial membranes and epithelial surfaces (147). This interaction facilitates endocytic uptake and increases intracellular accumulation of volatile terpenoids. Ligand functionalization, such as folate or hyaluronic acid conjugation, introduces receptor-mediated internalization pathways, enabling selective cytotoxicity in receptor-overexpressing cells and improving therapeutic index (148, 149).

5.3. Transport kinetics and quantitative modeling

Release kinetics provide the mechanistic bridge between structure and therapeutic outcome. The effective diffusion coefficient (D_{eff}) is inversely related to crosslink density and directly influenced by mesh size and matrix tortuosity. Highly crosslinked networks restrict solvent penetration and reduce D_{eff}, promoting sustained release, whereas loosely organized matrices permit rapid diffusion and early-stage release acceleration (150, 151).

Diffusion-dominated transport has been consistently reported in multiple HEO-loaded delivery systems. Application of the Korsmeyer–Peppas model ($Mt/M\infty = kt^n$) frequently yields diffusional exponent (n) values that depend heavily on the matrix geometry: the theoretical limit for ideal Fickian diffusion is n = 0.45 for cylindrical structures (e.g., nanofibers) and n = 0.43 for spherical structures (e.g., micro/nanoparticles) (152).

For example, examining the release behavior of a multi-component HEO blend (oregano, rosemary, and *Hypericum* oils) across different carrier architectures highlights this geometric dependence (153). Electrospun matrices exhibited n ≈ 0.436, which closely aligns with the ideal Fickian limit for cylindrical fibers. In stark contrast, spray-

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dried and freeze-dried particles showed markedly lower values (n 0.299 and 0.287, respectively), indicating a transition to a "pseudo-Fickian" diffusion mechanism. This substantial deviation from the spherical limit (0.43) is driven by the intrinsic physical properties of the matrices produced by these techniques. Specifically, rapid solvent evaporation during the spray-drying process often leads to early crust formation, leaving a fraction of unencapsulated core trapped at or near the particle surface (14). This physical phenomenon, combined with the inherently high size polydispersity of such particles, triggers a pronounced initial burst release that mathematically skews the overall kinetic curve and drives the n values significantly downward.

Similarly, in a cyclodextrin inclusion system encapsulating an equimolar essential oil mixture (clove, cardamom, cinnamon, and black pepper), diffusion rate constants (k_2 ≈ 0.027–0.032) substantially exceeded relaxation-associated constants ($k_1 \approx 10^{-26}$), supporting a predominantly diffusion-governed release mechanism within structurally stable matrices (154).

Importantly, systems exhibiting controlled Fickian diffusion (n ≤ 0.45) are frequently associated with reduced MIC and IC_{50} values relative to free EO formulations, as sustained exposure maintains intracellular concentrations within the therapeutic window and mitigates premature volatilization or degradation (155).

Stimuli-responsive chemistries further illustrate tunable structure–function coupling. Schiff base-linked hydrogels released 37.6% of *litsea cubeba* and cinnamon EOs at pH 7.2 but 82.1% at pH 5.5, while temperature-responsive starch carriers released 48.7% at 4 °C and only 3.5% at 25 °C within 120 min (156). These environmentally induced changes in network ionization, hydration, and permeability demonstrate how polymer chemistry governs on-demand release behavior.

5.4. Matrix degradation and gastric stability

For oral delivery systems, enzymatic resistance constitutes a critical structure–function determinant. Matrix degradation depends on pore size, chain rigidity, and isoelectric properties. In uncoated Ca–alginate hydrogels with pore diameters of 10–20 nm, rapid penetration of pepsin (hydrodynamic radius ≈ 3 nm) accelerates structural disintegration and premature EO release. The addition of a chitosan coating mitigates this vulnerability through a synergistic structural mechanism. The electrostatic complexation between cationic chitosan and anionic alginate forms a highly dense, tightly packed polyelectrolyte membrane at the particle surface. This interfacial layer significantly reduces the effective surface pore size, acting primarily as a physical barrier that sterically hinders the inward diffusion of pepsin. Furthermore, this robust electrostatic network limits polymer chain mobility and prevents excessive matrix swelling in acidic gastric conditions, thereby enhancing overall enzymatic resistance and preserving matrix integrity prior to intestinal transit (157, 158).

Protein-based matrices demonstrate similar structure-dependent behavior: compact globular conformations exhibit greater resistance to proteolysis than flexible, open networks, thereby improving gastric stability and subsequent intestinal bioavailability (158). Polymer architecture therefore directly regulates degradation kinetics, release timing, and systemic exposure.

5.5. Translation to biological outcomes

Biological efficacy—including reductions in MIC against biofilms or IC_{50} in tumor models—emerges from engineered exposure dynamics rather than intrinsic potency alone. Nanoscale dimensions enhance uptake, positive surface charge strengthens membrane interactions, and diffusion-controlled release sustains intracellular concentrations. Conversely, inadequate crosslinking or weak polymer–oil affinity leads to rapid clearance and diminished bioactivity.

By quantitatively correlating molecular parameters (Mw, DD, ρx), interfacial properties (zeta potential, particle size distribution), and transport coefficients (Deff, n, k) with biological endpoints, HEO delivery systems can be rationally engineered for predictable therapeutic performance. This integrated structure–property–function framework provides the rigorous materials science perspective necessary for advancing polymer-encapsulated essential oil systems toward translational maturity.

6. Multi-functional biomedical applications of encapsulated HEOs

6.1. Advanced antimicrobial, anti-biofilm, and wound-healing strategies

The escalation of antibiotic-resistant pathogens—including *Staphylococcus aureus (S. aureus)*, *Pseudomonas aeruginosa (P.*

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aeruginosa), *Klebsiella pneumoniae (K. pneumoniae)*, and *Candida* spp.—together with the clinical complexity of diabetic ulcers, burn wounds, and chronic dermal infections, necessitates antimicrobial systems capable of sustained activity, biofilm penetration, and tissue-compatible delivery. Nanoencapsulation addresses these requirements by stabilizing volatile phytochemicals while enabling controlled, localized exposure profiles.

Although numerous studies report superior antimicrobial and wound-healing outcomes for nanoencapsulated HEOs compared with free oils, the extent of improvement is strongly platform-dependent. Differences in carrier architecture, encapsulation efficiency, surface charge, and release kinetics directly influence membrane interaction, biofilm diffusion, and *in vivo* tissue response. Consequently, evaluating performance solely in terms of enhanced activity is insufficient; comparative analysis of nanoarchitectural features provides clearer insight into therapeutic optimization (**Figure 4**).

Distinct trends emerge across major polymeric platforms. Nanoemulsions primarily enhance antimicrobial efficacy through reduced droplet size and improved dispersion, facilitating rapid membrane penetration and short-term bactericidal action. In contrast, hydrogel and nanogel systems emphasize spatial confinement and sustained release, supporting prolonged antimicrobial exposure and improved wound microenvironment regulation—features particularly advantageous for chronic lesions. Chitosan-based nanoparticles combine controlled release with intrinsic polymer bioactivity, where electrostatic interactions with negatively charged microbial membranes amplify anti-biofilm effects beyond encapsulation alone.

These comparative distinctions highlight that antimicrobial and wound-healing enhancement is not uniform across systems but arises from specific structure–property relationships. Platform selection should therefore be guided by infection type, required duration of exposure, and translational constraints such as stability and scalability rather than by generalized reports of increased bioactivity.

6.1.1. Nanoemulsions

Nanoemulsions represent one of the most extensively investigated platforms for enhancing the antimicrobial and wound-healing performance of HEOs. Rather than the chemical identity of the oil alone, accumulated evidence indicates that therapeutic enhancement arises primarily from physicochemical restructuring at the nanoscale.

Across studies, three consistent performance trends can be identified. First, droplet size critically governs antimicrobial potency. Formulations with mean diameters below ~150 nm typically demonstrate superior bactericidal kinetics and improved biofilm penetration compared with larger droplets (>250 nm), even when EO composition remains constant. The increased surface curvature and interfacial area enhance membrane contact, facilitate terpenoid partitioning into lipid bilayers, and accelerate cytoplasmic leakage. These findings suggest that nanoemulsification enhances antimicrobial activity through geometric amplification of interfacial interactions rather than solely through increased chemical concentration.

Second, interfacial composition and surfactant–oil balance modulate release behavior and stability. Optimized surfactant systems reduce premature volatilization and oxidative degradation while preventing excessive burst release. Encapsulation efficiency and interfacial charge further influence microbial membrane affinity, particularly against Gram-negative species with robust outer membranes. The comparatively higher resistance of *P. aeruginosa* reported in several studies (40) appears linked not to insufficient EO potency, but to its efflux capacity and dense biofilm matrix, underscoring that biological barriers interact dynamically with nanoemulsion architecture.

Third, integration into secondary polymeric matrices alters therapeutic durability. While standalone nanoemulsions provide rapid antimicrobial action due to enhanced dispersion and membrane permeation, they may exhibit limited residence time in chronic wound environments. Embedding nanoemulsions within hydrogels, nanoemulgels, or composite films improves spatial retention, sustains local EO concentration, and creates moist bioactive microenvironments that support re-epithelialization and collagen remodeling. *In vivo* studies consistently report accelerated wound contraction and enhanced angiogenesis when nanoemulsions are incorporated into structured dressings rather than applied alone (20, 36).

Comparative evaluations further indicate that EO nanoemulsions often demonstrate superior antimicrobial performance relative to

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coarse emulsions and non-emulsified systems, highlighting that droplet-scale structuring—rather than encapsulation alone—is likely a primary determinant of enhanced bioactivity (40, 41, 104, 159). Emerging multi-EO nanoemulsion formulations, including binary blends of lemon and peppermint essential oils, extend this principle by leveraging compositional synergy to broaden antimicrobial spectra and, in some cases, improve anticancer activity (50). These effects are generally attributed to cooperative chemical interactions facilitated by co-localization of bioactive constituents within nanoscale droplets

Collectively, nanoemulsification enhances HEO performance through size-dependent membrane interaction, interfacial stabilization of volatile terpenoids, and adaptable integration into secondary delivery matrices. However, variability in reported MIC and IC_{50} values across studies highlights the need for standardized formulation and testing protocols to enable meaningful cross-platform comparison. Thus, the therapeutic impact of nanoemulsions should be interpreted not as universally superior, but as architecture-dependent and application-specific.

6.1.2. Hydrogels (nanogels)

Nanogels constitute a structurally distinct polymeric platform in which a crosslinked, hydrated network governs both retention and diffusion of encapsulated HEOs. Unlike nanoemulsions, where droplet mobility drives rapid membrane interaction, nanogels rely on network-controlled release kinetics and prolonged local residence. Consequently, therapeutic performance is determined less by EO composition alone and more by polymer architecture, crosslinking density, swelling behavior, and polymer–EO affinity.

Across studies, two recurring therapeutic patterns emerge. First, nanogels consistently enhance antiparasitic efficacy, particularly against Leishmania species. Carbomer-, CMC-, and thermoresponsive polymer systems stabilize volatile antiparasitic terpenoids and facilitate sustained dermal exposure. Reports of near-complete inhibition of *Leishmania major*, L. *tropica*, and L. *amazonensis* (105, 160, 161) suggest that controlled diffusion and prolonged tissue contact are critical determinants of efficacy in parasitic lesions, where continuous drug exposure is often more important than rapid concentration spikes. Thermoresponsive systems tend to induce faster initial parasite mortality due to temperature-triggered structural relaxation, whereas highly crosslinked networks favor slower yet sustained release. These differences illustrate that polymer chemistry directly modulates the balance between immediate toxicity and prolonged therapeutic exposure.

Second, in bacterial wound infections, nanogels prioritize persistence over rapid bactericidal kinetics. EO-loaded CMC, alginate, and chitosan-based systems demonstrate strong inhibition of *S. aureus* and *P. aeruginosa* (82, 104), largely attributable to enhanced retention at the application site and gradual diffusion through biofilm matrices. Compared with nanoemulsions, which often achieve faster initial membrane disruption, nanogels typically exhibit slower onset but improved local durability—an advantage in chronic or biofilm-associated infections requiring sustained antimicrobial pressure.

An additional advantage of nanogels lies in their capacity to integrate biofunctional polymers. Chitosan-based systems, for example, combine intrinsic mucoadhesive, regenerative, and antimicrobial properties with EO activity, producing synergistic effects in cutaneous leishmaniasis models when used alongside standard therapies (162). Such hybrid systems demonstrate that polymer bioactivity can complement rather than merely deliver the encapsulated oil.

However, nanogel performance remains highly formulation-dependent. Excessive crosslinking may restrict EO diffusion despite high encapsulation efficiency, while insufficient network density can compromise sustained release. Variability in gel viscosity, swelling ratios, and assay conditions contributes to wide discrepancies in reported MIC and inhibition values, complicating cross-study comparison. Additionally, large-scale reproducibility of network architecture, sterilization compatibility, and long-term storage stability remain less characterized than for nanoemulsion systems.

Overall, nanogels offer a retention-dominant delivery strategy particularly suited for chronic dermal and parasitic conditions where sustained exposure is essential. Their therapeutic superiority is not universal but indication-specific, emerging from controlled diffusion, polymer biofunctionality, and localized persistence rather than rapid membrane-targeting alone.

6.1.3. Chitosan nanoparticles

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Chitosan nanoparticles (CNPs) represent a charge-dominant delivery architecture in which therapeutic enhancement arises not only from EO encapsulation but from intrinsic polymer bioactivity. Unlike nanoemulsions (geometry-driven) or nanogels (diffusion-governed), CNP performance is strongly dictated by electrostatic interactions between protonated amine groups and negatively charged microbial membranes or biofilm matrices. Consequently, antimicrobial amplification in CNP systems typically reflects a dual mechanism: surface charge–mediated membrane destabilization coupled with controlled EO release.

Across studies, a consistent pattern emerges in which positively charged particles (<200 nm; zeta potential commonly > +25 mV) demonstrate superior antibacterial and antifungal activity compared with neutral or anionic carriers (83, 163). Enhanced inhibition of multidrug-resistant *Klebsiella pneumoniae*, as well as improved performance relative to alginate-based nanoparticles, underscores that surface charge density—rather than encapsulation efficiency alone—plays a decisive role in biological outcome. Systems with reduced zeta potential frequently exhibit diminished antimicrobial amplification despite comparable EO loading, reinforcing the central role of electrostatic adhesion and biofilm interaction.

CNPs also exhibit notable versatility across bacterial, fungal, and parasitic models. Broad-spectrum antibacterial, anticandidal, and antileishmanial activities have been reported for EO-loaded CNPs, often accompanied by reduced cytotoxicity relative to free oils (21). This improved safety profile likely arises from moderated release kinetics and spatially confined exposure. However, release behavior remains formulation-dependent: highly crosslinked particles may limit burst release but delay antimicrobial onset, whereas moderately crosslinked systems balance immediate membrane contact with sustained diffusion. Inconsistent reporting of release kinetics across studies complicates direct comparison with nanoemulsion and nanogel platforms.

In topical and wound-care applications, CNP systems benefit from chitosan's intrinsic mucoadhesive and regenerative properties. Enhanced retention on moist tissue surfaces and strong interaction with extracellular polymeric substances may improve biofilm disruption relative to low-viscosity nanoemulsions (113). Fabrication strategies—including ionic gelation, emulsion–ionic gelation, and electrospraying—further influence colloidal stability and thermal robustness, with some formulations demonstrating superior antifungal or antibacterial activity compared with free EO counterparts (37, 164). Nonetheless, aggregation under physiological ionic strength conditions remains a recurrent limitation.

From a translational perspective, CNP reproducibility presents unique challenges. Variability in molecular weight and degree of deacetylation significantly affects particle size, zeta potential, and antimicrobial potency, complicating batch-to-batch consistency. Large-scale manufacturing requires precise control of ionic gelation parameters, while potential regulatory concerns may arise from residual crosslinkers or impurities in naturally derived chitosan sources.

Overall, CNP-based EO systems derive their therapeutic distinctiveness from electrostatic amplification and polymer–EO synergy rather than nanoscale dispersion alone. Their superiority over nanoemulsions or nanogels appears context-dependent, particularly favoring biofilm-associated or surface-localized infections where charge-mediated adhesion is advantageous. Standardized comparative evaluations are necessary to determine whether this charge-driven architecture consistently translates into clinically meaningful benefit across infection models.

6.1.4. Electrospinning

Electrospinning represents a scaffold-based nanoencapsulation strategy in which HEOs are immobilized within solid polymeric nanofibers rather than dispersed as mobile droplets or nanoparticles. In contrast to nanoemulsions (geometry-driven membrane interaction) and chitosan nanoparticles (charge-mediated adhesion), electrospun systems derive therapeutic performance primarily from fiber morphology, porosity, and matrix–EO compatibility. Biological outcomes are therefore governed by structural parameters such as fiber diameter distribution, crystallinity, and core–shell architecture.

Across studies, two reproducible performance patterns emerge. First, electrospun fibers function as matrix-immobilized reservoirs that favor sustained antimicrobial exposure over rapid bactericidal onset. Restricted EO mobility within the solid matrix typically results in slower initial kinetics compared with nanoemulsions; however, the high surface-area-to-volume ratio and interconnected porosity

enable prolonged vapor-phase and contact-mediated antimicrobial activity. This reservoir-like behavior appears particularly advantageous in chronic wound environments where continuous antimicrobial pressure and recolonization prevention are more critical than immediate concentration spikes (98, 100, 165).

Second, microstructural design strongly modulates release durability and therapeutic predictability. Core–shell architectures spatially separate EO-rich domains from mechanically supportive polymer shells, reducing burst release commonly observed in blended fibers and enabling diffusion-controlled kinetics. Comparative evaluations frequently report improved stability and extended antimicrobial performance of Ajwain EO in core–shell systems relative to homogeneous blends (166). In addition to infection control, several electrospun formulations promote fibroblast adhesion, angiogenesis, and anti-inflammatory responses, reinforcing their dual function as both antimicrobial barriers and regenerative scaffolds (167).

Electrospun membranes also demonstrate efficacy against fungal and biofilm-associated infections, achieving substantial inhibition while maintaining mammalian cell compatibility (101). Unlike nanoparticle-based systems that rely on penetration into biofilm matrices, fiber-based platforms primarily exert surface-mediated and volatilization-driven effects. Although this may limit deep biofilm infiltration compared with cationic nanoparticles, it provides a stable protective interface that can prevent microbial recolonization on wound surfaces or implanted materials.

Despite these advantages, translational considerations remain significant. Uniform EO distribution within fibers can be challenging, and phase separation during spinning may compromise reproducibility. Mechanical integrity may decline at high EO loading, while large-scale electrospinning requires tight control of humidity, voltage, and flow parameters, potentially limiting industrial scalability relative to bulk nanoemulsion preparation. Standardization of fiber morphology and long-term stability under storage conditions remains insufficiently addressed.

Overall, electrospun EO-loaded nanofibers provide a structure-controlled delivery paradigm particularly suited for sustained barrier protection and regenerative wound management. Their therapeutic advantage over droplet- or particle-based systems appears context-dependent, emerging in applications where spatial confinement and prolonged surface activity outweigh the need for rapid antimicrobial penetration.

6.1.5. Alginate nanoparticles

Alginate nanoparticles (ANPs) represent an ionic network–based encapsulation strategy in which EO retention and release are governed primarily by calcium-mediated crosslinking rather than electrostatic membrane interaction. In contrast to charge-dominant chitosan systems, alginate architectures emphasize structural stability, biocompatibility, and diffusion-controlled delivery. Therapeutic performance is therefore closely linked to crosslinking density, swelling behavior, and matrix permeability (168).

Across studies, a recurring pattern indicates that antimicrobial efficacy in ANPs is strongly diffusion-dependent. Moderately crosslinked networks with higher swelling ratios tend to facilitate improved EO mobility and enhanced antibacterial activity against *E. coli*, *P. aeruginosa*, and *S. aureus* (169), whereas highly crosslinked matrices may restrict EO diffusion despite high encapsulation efficiency. These observations demonstrate that structural integrity alone does not ensure therapeutic amplification; instead, optimizing ionic network density is critical for balancing stability with bioactive availability.

Head-to-head comparisons consistently reveal that while alginate nanoparticles improve EO stability and baseline antimicrobial performance, cationic systems such as chitosan nanoparticles frequently achieve lower IC_{50} values and stronger bactericidal effects (83, 170). Mechanistically, this difference reflects surface charge: alginate particles typically exhibit neutral or negative zeta potentials, limiting direct electrostatic adhesion to negatively charged bacterial membranes. Consequently, ANP efficacy arises predominantly from controlled diffusion rather than charge-mediated membrane destabilization.

Relative to nanoemulsions, alginate nanoparticles generally display slower initial antimicrobial kinetics but enhanced structural robustness under physiological conditions. Compared with electrospun membranes, ANPs offer better adaptability to moist or mucosal environments but lack intrinsic mechanical reinforcement and barrier functionality. These distinctions suggest that alginate systems may be particularly suited for gentle mucosal delivery or

controlled dermal release applications where biocompatibility and sustained exposure are prioritized over rapid bactericidal onset.

Translational considerations further differentiate alginate platforms. Ionic crosslinking is sensitive to pH and ionic strength variations, which may influence particle stability in physiological fluids. Variability in mannuronic/guluronic acid composition can alter mechanical properties and release behavior, complicating batch-to-batch reproducibility. Additionally, precise control of calcium-mediated gelation is required to maintain uniform particle size distribution at scale.

Overall, alginate nanoparticles provide a stability-oriented and biocompatible delivery architecture in which antimicrobial performance is primarily diffusion-driven. Their therapeutic advantage appears context-dependent and may be enhanced through hybridization with cationic polymers, integrating ionic network stability with improved microbial interaction.

6.1.6. Hybrid encapsulation approaches

Hybrid encapsulation systems integrate two or more delivery architectures into hierarchical nanoassemblies, enabling sequential and spatially controlled therapeutic modulation. Unlike single-platform systems in which biological performance is governed by one dominant mechanism (e.g., charge interaction or diffusion control), hybrids combine complementary release pathways—such as nanogel-mediated diffusion embedded within electrospun structural scaffolds—thereby generating multistage kinetic profiles and enhanced mechanical stability.

Across studies, three consistent functional advantages emerge. First, hierarchical release control. Embedding EO-loaded nanogels or nanoemulsions within electrospun fibers reduces premature volatilization while introducing sequential diffusion phases: an initial release from nanoscale droplets followed by sustained liberation governed by the surrounding polymer matrix (32, 59, 171). This layered kinetic behavior appears particularly beneficial in chronic wound environments, where rapid antimicrobial onset must be followed by prolonged anti-inflammatory and regenerative support.

Second, structural–bioactive synergy. Hybrid nanofiber–nanogel constructs leverage the mechanical integrity and breathability of fibrous scaffolds alongside the high loading efficiency and hydration capacity of hydrogel domains (172). Compared with standalone nanogels, these assemblies improve spatial retention and durability; relative to fibers containing directly blended EO, pre-stabilized nanogel-in-fiber systems exhibit more predictable release profiles and reduced burst effects. Such integration enables simultaneous infection control, moisture balance, and cellular compatibility within a single platform.

Third, molecular-level stabilization through inclusion complexes. Incorporation of cyclodextrin–EO host–guest complexes into nanofibers introduces an additional encapsulation layer that enhances solubility and volatility control (173). Unlike electrostatic or diffusion-driven stabilization, inclusion complexes rely on molecular interactions that improve storage stability and homogeneous EO distribution within hydrophilic matrices. However, loading capacity may be lower than in nanoemulsion-based hybrids, potentially limiting maximal antimicrobial intensity.

Hybrid systems have demonstrated strong antimicrobial performance against drug-resistant pathogens and biofilm-associated infections, often achieving near-complete inhibition *in vitro* (35, 171). Nonetheless, the therapeutic amplification observed in these constructs appears to arise from coordinated modulation of release kinetics, spatial confinement, and matrix reinforcement rather than from additive EO concentration alone.

Despite their multifunctionality, hybrid architectures introduce significant formulation and translational complexity. Multistep fabrication processes—such as sequential nanoemulsion formation, gelation, and electrospinning—may compromise scalability and increase production cost. Interfacial incompatibility between layers can alter release behavior or mechanical stability over time, while regulatory evaluation becomes more demanding with each added structural component. Consequently, although hybrid systems frequently outperform single-platform designs *in vitro*, their clinical superiority must be validated against manufacturing feasibility and reproducibility constraints.

Overall, hybrid encapsulation strategies represent a hierarchical multi-mechanism approach best suited for complex pathological scenarios—such as chronic infected wounds or multidrug-resistant biofilm environments—where simultaneous structural support and staged antimicrobial exposure are required. Future standardized head-to-head studies are essential to determine whether the added architectural complexity translates into consistent clinical benefit.

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6.1.7. Synergistic encapsulation approach

Synergistic encapsulation strategies focus on co-delivering multiple EOs within a single nanoarchitecture to exploit phytochemical complementarity and enhance antimicrobial or antioxidant efficacy. Unlike hybrid structural systems, which combine delivery mechanisms, synergistic formulations primarily integrate chemical diversity within a shared nanocarrier. The enhanced performance observed in such systems may arise from coordinated membrane disruption, intracellular enzyme inhibition, and redox modulation occurring simultaneously at the microbial interface.

Across studies, two reproducible patterns are evident. First, nanoemulsification frequently amplifies synergistic interactions by facilitating co-localized delivery of multiple terpenoids. Reduced droplet size (<150 nm) increases interfacial area and promotes simultaneous interaction of chemically distinct EO constituents with microbial membranes (23, 174). Optimized EO ratios have demonstrated pathogen-specific improvements, indicating that synergy is context-dependent rather than universal. Distinct combinations may be required to effectively target *E. coli*, *S. aureus, E. faecalis,* or *P. aeruginosa*, reflecting differences in membrane composition and efflux capacity. These findings emphasize that rational blend design must align phytochemical profiles with microbial susceptibility patterns rather than assuming additive broad-spectrum activity.

Second, reported enhancements require careful quantitative validation. Although many blended nanoemulsions exhibit reduced MIC values and increased antioxidant capacity (175, 176), mechanistic confirmation of true synergy is inconsistently supported by fractional inhibitory concentration indices (FICI) or standardized redox assays. Variability in antioxidant methodologies (e.g., DPPH, ABTS, FRAP) further complicates cross-study comparison. Consequently, some reported improvements may reflect enhanced stability and delivery efficiency rather than verified biochemical synergy.

Overall, synergistic encapsulation represents a chemically driven optimization strategy that leverages nano-scale co-delivery to enhance antimicrobial efficiency at reduced dosages. However, rigorous interaction analyses and standardized release profiling are necessary to distinguish true synergism from additive or delivery-mediated effects.

6.2. Anti-cancer therapeutics and targeted delivery

In anticancer applications, the therapeutic performance of encapsulated HEOs is primarily governed by intracellular delivery efficiency, tumor microenvironment interaction, and controlled release behavior rather than by cytotoxic potency alone. Although numerous studies report reduced IC_{50} values and enhanced apoptosis following nanoencapsulation of HEO constituents (**Figure 4**), comparative interpretation requires consideration of nanoarchitectural parameters such as particle size distribution, surface charge, polydispersity index, and release kinetics.

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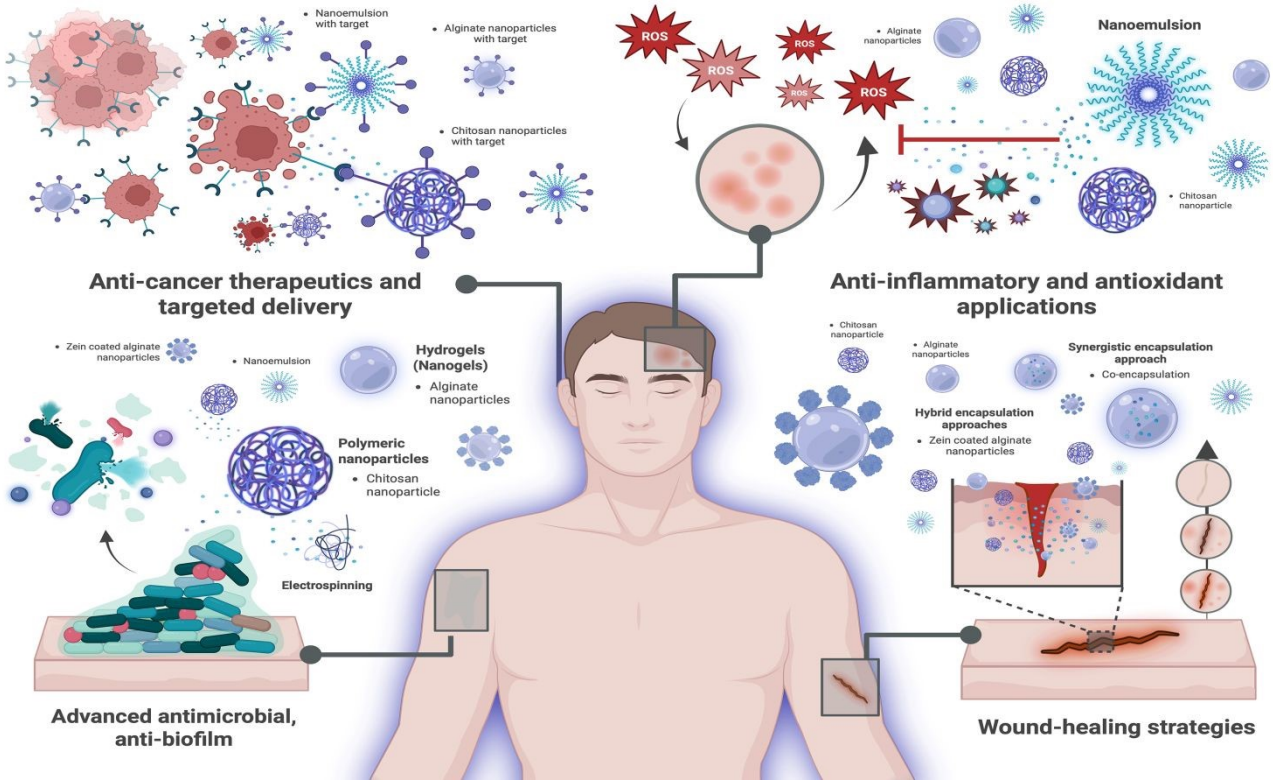

Fig. 4 Multi-functional biomedical applications of encapsulated HEOs

6.2.1. Nanoemulsions

EO-based nanoemulsions enhance anticancer activity primarily through droplet-size–dependent modulation of cellular uptake and intracellular release. In oncology applications, nanoscale droplets (<200 nm) increase interfacial surface area, promote clathrin- or caveolae-mediated endocytosis, and facilitate cytoplasmic delivery of hydrophobic terpenoids. Consequently, therapeutic enhancement arises not only from intrinsic EO bioactivity but from architecture-driven improvements in dispersion stability, bioavailability, and tumor–cell interaction.

Across reported studies, nanoemulsions consistently demonstrate lower IC_{50} values compared with free EOs; however, interpretation requires careful consideration of physicochemical parameters. For example, eugenol-loaded nanoemulsions improved cytotoxicity against MCF-7 cells while maintaining hemocompatibility (51), and *Mentha piperita* EO nanoemulsions exhibited sustained cytotoxic effects across breast cancer cell lines (22). In both cases, enhanced efficacy correlated with reduced droplet diameter and improved colloidal stability, suggesting that internalization efficiency rather than phytochemical potency alone drives performance. Nevertheless, direct cross-study comparison remains limited because particle size distribution, surfactant composition, and encapsulation efficiency are not consistently standardized.

Similar architecture-dependent enhancement is observed beyond breast cancer models. Nanoemulsified *Mentha arvensis* EO significantly increased apoptosis in anaplastic thyroid carcinoma cells

(159), while α-pinene and 2-carene nanoemulsions demonstrated improved pro-apoptotic activity and reduced IC_{50} values in melanoma and triple-negative breast cancer models, with partial *in vivo* tumor regression reported for 2-carene systems (177, 178). Although modulation of BAX/BCL-2 balance and caspase activation is frequently reported, quantitative intracellular accumulation studies are rarely performed. It therefore remains unclear whether apoptosis amplification reflects increased intracellular EO concentration or altered membrane–mitochondrial interactions mediated by nanoarchitecture.

Synergistic strategies further illustrate the delivery advantages of nanoemulsions. A clove–thyme EO nanoemulsion demonstrated stronger cytotoxicity than free oils and taxol in HepG2 and MCF-7 models, associated with caspase activation and VEGFR-2 inhibition (23). Likewise, *Teucrium polium* EO nanoemulsions enhanced oxaliplatin sensitivity in colon cancer cells, with measurable synergistic indices (179). These findings suggest that nanoemulsions may modulate oxidative stress thresholds and membrane permeability, thereby sensitizing tumor cells to chemotherapeutics. However, most synergy assessments are confined to 2D monolayer cultures, and pharmacokinetic validation *in vivo* remains limited.

Importantly, comparative evaluations across delivery architectures indicate context-dependent superiority. For example, *Cuminum cyminum* EO nanogel formulations outperformed corresponding nanoemulsions in certain cancer models due to prolonged release and sustained tumor exposure (104). This suggests that nanoemulsions may favor rapid intracellular delivery and short-term cytotoxic action, whereas gel-based matrices provide extended exposure. Head-to-head kinetic comparisons under identical tumor conditions are still scarce, preventing definitive architecture ranking.

From a translational perspective, several critical gaps persist. Many studies lack detailed reporting of encapsulation efficiency, droplet stability in serum-containing media, long-term storage behavior, and batch-to-batch reproducibility. Moreover, systemic biodistribution, reticuloendothelial system clearance, immune interaction, and tumor accumulation efficiency are infrequently quantified in animal models. Because clinical nanoemulsions must remain stable under physiological dilution and withstand large-scale manufacturing constraints, scalability of high-energy emulsification techniques and GMP-compliant reproducibility represent major barriers to translation.

Overall, EO-based nanoemulsions constitute a flexible and potent delivery platform capable of enhancing intracellular delivery, apoptosis induction, and chemotherapeutic sensitization. However, therapeutic superiority appears strongly dependent on droplet size control, physicochemical stability, and tumor model context. Rigorous integration of standardized characterization, serum stability testing, pharmacokinetic profiling, and scalable production strategies will be essential to determine whether nanoemulsions can achieve clinically meaningful performance beyond *in vitro* cytotoxicity.

6.2.2. Chitosan nanoparticles

Chitosan nanoparticles (CNPs) represent a charge-driven nanoarchitecture in which electrostatic interaction plays a central role in anticancer delivery. Owing to their intrinsic cationic surface, CNPs promote adhesion to negatively charged tumor cell membranes, facilitate endocytic uptake, and enable diffusion-controlled intracellular release. In contrast to nanoemulsions—where delivery is largely governed by droplet dispersion and passive accumulation—CNP systems combine membrane adhesion, polymer-mediated retention, and sustained release kinetics. Consequently, therapeutic performance depends not only on EO potency but critically on particle size (<200 nm), zeta potential balance, and crosslinking density.

Across diverse EO formulations, CNP encapsulation generally reduces IC_{50} values and amplifies apoptotic signaling compared with free oils. For instance, Chelidonium majus EO-loaded CNPs decreased IC_{50} values by up to twofold and significantly increased apoptosis in MCF-7 cells (52), while green tea EO nanoformulations demonstrated enhanced cytotoxicity in HepG-2, MCF-7, and HCT-116 models, with radiolabeled systems indicating improved tumor accumulation and reduced reticuloendothelial uptake *in vivo* (81). These observations suggest that surface charge uniformity and nanoscale size distribution influence systemic circulation and tumor localization, although direct comparisons with other nanoarchitectures remain limited.

Multiple monoterpene-rich EOs—including citral-containing Lippia citriodora, carvacrol, carvone, limonene, and α-pinene systems—

exhibit amplified pro-apoptotic effects following CNP encapsulation (180-182). Frequently reported mechanisms include Bax/Bcl-2 modulation, caspase activation, and oxidative-stress–mediated apoptosis. However, quantitative intracellular accumulation studies are rarely conducted. It therefore remains unclear whether apoptosis enhancement primarily reflects increased EO concentration within tumor cells or partial contribution of chitosan-induced membrane destabilization. Real-time release profiling and intracellular concentration mapping would clarify whether CNPs function solely as delivery enhancers or as synergistic bioactive participants.

Comparative studies indicate architecture-dependent differences in performance. In breast cancer models, *Zingiber officinale* EO-loaded CNPs outperformed both free EO and alginate nanoparticles (83), likely due to stronger electrostatic membrane interaction and enhanced intracellular retention rather than encapsulation efficiency alone. Compared with nanoemulsions, CNPs may exhibit slower initial release yet prolonged intracellular persistence, potentially favoring sustained apoptosis signaling over rapid cytotoxic bursts. Nonetheless, systematic head-to-head kinetic comparisons under identical tumor conditions remain scarce, preventing definitive ranking of delivery platforms.

From a translational standpoint, CNP systems face important reproducibility and standardization challenges. Variations in chitosan molecular weight and degree of deacetylation substantially influence particle size distribution, zeta potential, crosslinking efficiency, and drug release kinetics. Such variability complicates batch-to-batch consistency and GMP-compliant scale-up. Furthermore, for systems intended for systemic administration, surface chemistry strictly dictates the nanocarrier's *in vivo* fate through the dynamic formation of a protein corona. Excessive positive surface charge (characteristic of bare cationic polymers like chitosan) selectively recruits negatively charged circulating proteins, particularly opsonins such as fibrinogen, immunoglobulins, and complement factors. This specific opsonization triggers rapid recognition and clearance by the mononuclear phagocyte system (MPS). In contrast, nanocarriers with neutral or sterically hindered surfaces (e.g., via PEGylation) effectively minimize electrostatic protein adsorption, conferring a "stealth" effect that prolongs systemic circulation. Crucially, the composition of this protein corona immediately redefines the "biological identity" of the particle, directly impacting the biological properties of the encapsulated HEOs. A dense corona matrix can physically obstruct the diffusion of volatile monoterpenes, prematurely alter release kinetics, or mask surface-functionalized targeting ligands, thereby reducing the intended antibacterial or antitumoral efficacy of the HEO at the target site (183). Comprehensive pharmacokinetic, immunogenicity, and long-term toxicity studies remain limited, restricting accurate evaluation of their clinical feasibility.

Overall, CNP-based EO delivery systems offer mechanistically distinct advantages arising from charge-mediated tumor cell interaction and sustained intracellular release. However, therapeutic superiority appears context-dependent and highly sensitive to surface charge optimization and polymer standardization. Rigorous comparative studies integrating standardized physicochemical characterization, serum stability testing, and *in vivo* biodistribution analyses are necessary to determine whether CNPs consistently outperform nanoemulsion and alginate platforms in systemic anticancer therapy.

6.2.3. Alginate nanoparticles

Alginate nanoparticles (Alg-NPs) function as ionically crosslinked hydrogel matrices in which EO molecules are physically entrapped within a polysaccharide network. In contrast to cationic chitosan nanoparticles that rely on electrostatic membrane adhesion, Alg-NPs typically exhibit neutral to slightly negative surface charge, resulting in limited direct membrane interaction and reduced endocytic uptake. Their anticancer performance therefore appears to depend predominantly on diffusion-controlled, sustained EO release and microenvironment-responsive exposure rather than rapid intracellular internalization.

Across various EO systems, alginate encapsulation generally improves physicochemical stability and prolongs apoptotic signaling compared with free oils. Early studies using eugenol-rich Syzygium aromaticum and *Rosmarinus officinalis* formulations demonstrated dose-dependent apoptosis induction in melanoma and breast cancer cells, with activity influenced by EO composition and cancer type (184, 185). In some cases, α-pinene–loaded Alg-NPs exhibited stronger activity than whole-EO formulations, suggesting that alginate matrices may preferentially stabilize or release specific low-molecular-weight monoterpenes. However, most investigations do

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not quantify encapsulation efficiency of individual EO fractions, making it difficult to determine whether enhanced efficacy arises from selective component enrichment or from modified release kinetics.

More recent work highlights the relevance of tumor microenvironment conditions. Encapsulation of *Ferula gummosa* EO and β-pinene significantly lowered IC_{50} values in melanoma and triple-negative breast cancer models, with cytotoxicity intensified under hyperoxic conditions (186). This observation suggests that sustained EO release from Alg-NPs may amplify reactive oxygen species (ROS)-mediated stress when oxygen availability is elevated. Conversely, improved performance under hypoxic conditions reported for citral- or Cymbopogon citratus–loaded systems indicates that matrix-controlled release may partially overcome diffusion limitations and metabolic resistance typical of oxygen-deprived tumors (187). Together, these findings imply that Alg-NPs modulate the temporal dynamics of oxidative stress rather than directly enhancing cellular uptake.

Mechanistically, Bax/Bcl-2 modulation and mitochondrial dysfunction are frequently reported endpoints, consistent with prolonged EO exposure. Compared with CNP systems, Alg-NPs generally display slower initial cytotoxic onset but more sustained apoptotic activation, aligning with matrix-governed diffusion behavior. Relative to nanoemulsions, alginate carriers may show reduced immediate uptake efficiency yet improved colloidal and chemical stability under physiological conditions. Thus, Alg-NPs appear particularly suited for sustained local therapy or microenvironment-responsive applications rather than rapid systemic cytotoxic intervention.

Despite promising *in vitro* apoptosis data, several translational challenges remain underexplored. Alginate gelation relies on ionic crosslinking—commonly via Ca^{2+} bridges—which may destabilize under physiological ion exchange conditions, leading to premature swelling or erosion. Variability in crosslinking density significantly influences particle size, degradation rate, and EO release kinetics, yet these parameters are rarely standardized across studies. Furthermore, serum stability, protein adsorption behavior, large-scale reproducibility of gelation processes, and *in vivo* pharmacokinetics remain insufficiently characterized. Without systematic evaluation of these factors, clinical feasibility cannot be reliably assessed.

Overall, Alg-NPs provide a matrix-driven, diffusion-controlled delivery platform that enhances EO stability and enables temporally sustained apoptosis induction. Their therapeutic impact appears particularly sensitive to tumor oxygenation status and release kinetics. However, optimization of crosslinking stability, quantitative release profiling, and direct head-to-head comparisons with charge-mediated and droplet-based nanoarchitectures are essential to establish whether Alg-NPs offer a consistent translational advantage in systemic oncology applications.

6.2.4. Hydrogels (nanogels)

Hydrogel- and nanogel-based systems represent three-dimensional crosslinked polymer networks that entrap EO molecules within hydrated matrices, enabling spatial confinement and diffusion-controlled release. Unlike nanoemulsions (droplet-dispersed carriers) or chitosan nanoparticles (charge-mediated systems), hydrogels primarily function as localized depots in which therapeutic activity is governed by crosslinking density, swelling behavior, and responsiveness to external stimuli such as temperature, pH, or irradiation. Their anticancer performance therefore depends less on rapid intracellular uptake and more on sustained local exposure and stimulus-triggered release dynamics.

A notable advancement is the integration of EO-loaded hydrogels with photothermal therapy (PTT). For example, a carvacrol-loaded marine-derived hydrogel incorporating gold nanobipyramids enabled controlled EO retention while achieving efficient light-to-heat conversion under near-infrared irradiation (90). Fractionated PTT combined with carvacrol delivery produced greater tumor ablation than either modality alone, illustrating how hydrogel confinement can synchronize chemotherapeutic and photothermal effects. Mechanistically, activation of apoptotic markers such as pJNK and p53 was observed; however, quantitative release profiling during irradiation was not systematically reported. As a result, it remains unclear whether enhanced cytotoxicity was primarily temperature-driven, release-mediated, or due to synergistic ROS amplification.

Beyond multimodal systems, EO-loaded nanogels alone improve physicochemical stabilization of volatile constituents and prolong

tumor exposure. Encapsulation of *Myrtus communis* EO into nanogels increased cytotoxic potency against melanoma cells compared with the free oil (59), while *Mentha pulegium* EO formulations demonstrated differential performance between nanoemulsion and nanogel systems (188). In these comparisons, nanoemulsions produced stronger immediate cytotoxic effects—likely due to faster uptake and burst release—whereas nanogels induced more gradual apoptotic activation consistent with matrix-regulated diffusion. This kinetic distinction suggests that nanogels may be more suitable for sustained local therapy or implantable applications rather than rapid systemic tumor eradication.

Despite multifunctional potential, hydrogel-based systems present distinct translational constraints. High water content and structural heterogeneity can compromise mechanical robustness and batch reproducibility. Injectable formulations require careful optimization to ensure consistent crosslinking density and predictable degradation profiles. For nanogel systems intended for systemic circulation, avoidance of rapid clearance and maintenance of stable particle size distribution remain challenging. Moreover, large-scale sterilization procedures and long-term storage stability are rarely addressed in preclinical studies.

Collectively, hydrogel and nanogel platforms enable matrix-driven, stimulus-responsive EO delivery with particular relevance for localized or combination cancer therapies. However, their clinical translation will require rigorous standardization of release kinetics, mechanical stability, degradation behavior, and *in vivo* pharmacokinetic profiling.

6.3. Anti-inflammatory and antioxidant applications

6.3.1. Nanoemulsions

Nanoemulsion systems have emerged as versatile and highly effective platforms for enhancing the antioxidant and anti-inflammatory performance of HEOs by improving their physicochemical stability, bioaccessibility, and biological interactions (**Figure 4**). Across diverse formulations, EO-loaded nanoemulsions consistently outperform free oils, not only by mitigating oxidative stress but also by modulating inflammatory signaling pathways in both *in vitro* and *in vivo* models.

A key advantage of nanoemulsification lies in stabilizing volatile EO constituents while facilitating their penetration into biological systems. For instance, *Cuminum cyminum* EO nanoemulsions exhibit pronounced antioxidant capacity, illustrating the broader potential of nanoscale dispersion to enhance cellular protection against oxidative insults (104). Similarly, advanced carrier architectures such as the bovine serum albumin-dextran sulfate conjugate-sodium deoxycholate system for *Alpinia zerumbet* Fructus EO demonstrate how structural tailoring can significantly improve bioavailability and therapeutic efficacy (91). In diabetic models, these nanoemulsions protected endothelial cells from high-glucose-induced oxidative damage, restored vascular function, and attenuated inflammatory responses more effectively than the free EO, primarily due to prolonged systemic circulation and improved absorption.

Beyond antioxidant effects, nanoemulsions have shown robust anti-inflammatory activity while maintaining favorable biocompatibility profiles. Formulations containing *Curcuma longa* leaf EO suppressed nitric oxide production in activated macrophages without cytotoxicity (189). Likewise, carvacrol nanoemulsions exhibited sustained anti-edematogenic activity and reduced IL-1β levels with dexamethasone-like potency, highlighting the importance of optimized droplet size, low polydispersity, and colloidal stability for achieving controlled and durable therapeutic responses (190).

Interestingly, although crude *Eucalyptus camaldulensis* oil displayed stronger antioxidant activity *in vitro*, its nanoemulsified counterpart produced superior *in vivo* outcomes, including enhanced anti-inflammatory, hepatoprotective, and nephroprotective effects in CCl_4-induced models (42). Molecular docking analyses further supported these observations, revealing strong interactions between EO constituents—particularly sesquiterpenes—and key proteins involved in oxidative stress and inflammatory pathways. These findings collectively suggest that nanoemulsification not only enhances delivery but may also amplify mechanistic targeting at the molecular level.

Optimization studies further underscore the flexibility of nanoemulsions as customizable therapeutic platforms. Blended EO nanoemulsions composed of rosemary, sage, and thyme achieved synergistically enhanced antioxidant activity, while eugenol- and 2-carene-loaded nanoemulsions increased endogenous antioxidant enzyme levels, reduced inflammatory markers, and improved tissue

integrity *in vivo* (51, 174, 178). Together, these results indicate that both single-EO and multi-EO nanoemulsions can be rationally engineered to maximize therapeutic efficacy through synergistic and formulation-driven effects.

Collectively, current evidence positions EO-based nanoemulsions as powerful platforms for reinforcing antioxidant defenses and attenuating inflammatory responses via enhanced stability, improved systemic distribution, and modulation of key molecular pathways. Their consistent efficacy across experimental models underscores their promise as strong candidates for further preclinical and translational development.

6.3.2. Chitosan Nanoparticles

Chitosan nanoparticles (CNPs) have emerged as highly effective nanocarriers for HEOs in antioxidant and anti-inflammatory applications due to their intrinsic biocompatibility, mucoadhesiveness, and cationic surface properties. Beyond serving as passive carriers, CNPs actively influence bioactivity by protecting volatile phenolic and terpenoid constituents from premature oxidation while enabling controlled, diffusion-driven release. This stabilization effect underlies the enhanced free-radical scavenging performance observed for *Rosmarinus officinalis* and *Cynometra cauliflora* EO formulations, where nanoencapsulation significantly improved antioxidant capacity compared with free oils (30, 113). Targeted delivery of dominant active molecules—such as citral from *Lippia citriodora* EO—further illustrates that chitosan systems can be tailored to maximize the functional contribution of key constituents, sometimes surpassing whole-oil formulations in redox modulation efficiency (180).

Importantly, the benefits of CNPs extend beyond oxidative stabilization to immunomodulatory regulation. In chronic inflammatory models, including arthritis, EO-loaded CNPs significantly attenuated inflammatory progression. For example, geranium EO–CNP formulations reduced joint inflammation, normalized hematological indices, and suppressed major pro-inflammatory cytokines such as IL-6 and TNF-α, accompanied by histological improvement (191). These outcomes suggest that sustained EO release, combined with enhanced tissue interaction mediated by the cationic chitosan surface, contributes to prolonged therapeutic exposure and more effective cytokine modulation.

CNPs also facilitate synergistic anti-inflammatory strategies. A ternary nanoformulation combining bee pollen extract and thymol oil demonstrated pronounced anti-inflammatory and antiproliferative effects in cancer models, activating intrinsic apoptotic pathways via caspase-3, caspase-9, and p53 upregulation (192). Similarly, carvone-loaded CNPs significantly reduced arthritic severity and downregulated multiple pro-inflammatory mediators (TNF-α, IL-1β, IL-17A, IL-33), while simultaneously increasing anti-inflammatory cytokines such as IL-4 and IL-10 (193). The concurrent modulation of both pro- and anti-inflammatory signals indicates that CNP systems may promote a shift toward immune homeostasis rather than simple cytokine suppression.

Mechanistically, the enhanced bioactivity of EO-loaded CNPs likely arises from a combination of factors: improved chemical stability, increased mucosal and cellular interaction due to positive surface charge, and sustained release kinetics that extend the therapeutic window. However, the relative contribution of chitosan's intrinsic immunomodulatory properties versus EO-mediated effects is rarely quantified, representing an important area for further investigation. Overall, chitosan nanoencapsulation strengthens both antioxidant defense and inflammatory regulation through architecture-dependent stabilization and immune-interactive delivery. These properties position CNP-based EO formulations as promising candidates for managing oxidative stress–associated disorders, chronic inflammatory diseases, and inflammation-driven oncological conditions, provided that polymer characteristics and immune compatibility are carefully optimized.

6.3.3. Hydrogels (Nanogels)

Hydrogel and nanogel systems represent structurally distinct delivery platforms that enhance the anti-inflammatory and antioxidant performance of HEOs through spatial confinement, high hydration capacity, and diffusion-controlled release. Unlike droplet-based nanoemulsions or charge-mediated chitosan nanoparticles, hydrogels primarily function as localized depots, maintaining prolonged residence time at the application site while minimizing systemic dispersion. This architectural feature makes them particularly suitable for topical and tissue-repair–oriented therapies. Encapsulation within hydrogel matrices stabilizes volatile EO constituents and sustains their bioactivity under inflammatory

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conditions. Thermosensitive nanogels containing *Pectis brevipedunculata* EO demonstrated rapid edema suppression *in vivo*, suggesting that matrix-regulated release can efficiently modulate acute inflammatory responses even in infection-associated settings (105). Similarly, thymol–chitosan hydrogel formulations showed dose-dependent anti-inflammatory effects and promoted epithelial and collagen regeneration over extended treatment periods (162). These findings highlight the importance of formulation balance, as excessive EO loading may increase irritation risk, whereas optimized concentrations enable sustained therapeutic benefit.

Polyelectrolyte complex–based nanogels further illustrate the multifunctional potential of hydrogel architectures. Systems incorporating caffeic acid and eugenol within curdlan-, glucomannan-, chitosan-, or lactoferrin-based networks achieved prolonged stability and controlled release for up to 72 h (31). Enhanced antioxidant and antibacterial performance, along with reduced IC_{50} values in colorectal cancer models, indicate that such hybrid nanogels can simultaneously engage redox regulation, antimicrobial defense, and cell-signaling modulation. These effects likely arise from sustained local exposure combined with protection of phenolic constituents against premature degradation.

Improved radical-scavenging activity has also been reported for hydrogels containing *Mentha spicata* and *Myrtus communis* EOs, where nanoencapsulation increased antioxidant efficiency compared with bulk oils (59, 172). In topical applications, nanoemulsion-based gels (nanoemulgels) containing oregano EO further demonstrate how combining droplet-mediated penetration with gel-mediated retention can enhance anti-inflammatory and wound-healing outcomes (32). Reduced inflammatory cell infiltration and improved tissue remodeling observed in these systems suggest that prolonged redox stabilization contributes to a more favorable regenerative microenvironment.

Despite these advantages, hydrogel-based EO systems must address practical considerations such as viscosity optimization, long-term physicochemical stability, reproducibility of crosslinking density, and maintenance of skin compatibility during extended application. Careful balancing of release kinetics and dermal tolerance remains critical for successful translation.

Overall, EO-loaded hydrogels and nanogels provide localized, diffusion-governed platforms capable of reinforcing antioxidant defenses and modulating inflammatory cascades while supporting tissue repair. Their architecture-driven capacity for sustained exposure and multifunctional integration positions them as valuable candidates for dermatological and regenerative applications, particularly where prolonged local activity is required.

6.3.4. Electrospinning

Electrospinning represents a structurally distinct strategy for incorporating HEOs into nanofibrous matrices, enabling enhanced stability, high surface-area exposure, and controlled release within solid scaffolds. The ultrafine fiber architecture provides extensive interfacial contact between EO molecules and the surrounding environment, which can intensify antioxidant activity while maintaining localized retention. Unlike colloidal carriers, electrospun systems primarily function as surface-deployable membranes or dressings, making them particularly suitable for wound healing and regenerative applications.

Compatibility with molecular encapsulation approaches—such as cyclodextrin inclusion complexation—further strengthens electrospun platforms. Incorporation of EO–cyclodextrin complexes into nanofibers has been shown to improve hydrophilicity, moisture retention, and dermal compatibility, properties essential for cosmetic and dermatological use (194). In biodegradable polymer systems such as polylactic acid, EO incorporation into electrospun matrices enhanced antioxidant performance relative to conventional synthetic antioxidants, likely due to uniform molecular dispersion and increased surface availability within the fibrous network (96). Functional activity was influenced by both EO loading and fiber morphology, indicating that antioxidant performance is architecture-dependent rather than solely composition-driven.

Electrospun membranes can also be engineered for multifunctionality. Co-delivery of EOs with complementary bioactive compounds, such as lecithin within poly(lactic-co-glycolic acid) fibers, produced combined antimicrobial, antioxidant, and anti-inflammatory effects that exceeded simple additive interactions (195). Mechanistically, these systems modulated key redox and inflammatory pathways, including activation of Nrf2 signaling and suppression of NF-κB activity. *In vivo*, such regulation translated into reduced collagen overproduction and attenuation of fibroblast-to-myofibroblast transition, thereby limiting postoperative tissue

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adhesion. These findings highlight the ability of electrospun EO systems to shape local inflammatory microenvironments while supporting regenerative remodeling.

Despite these advantages, electrospinning-based EO delivery must address challenges related to scalability, solvent residues, fiber reproducibility, and long-term storage stability. Furthermore, release kinetics can be highly sensitive to polymer degradation rate and environmental humidity, necessitating standardized characterization for clinical translation. Overall, electrospun nanofibrous systems provide architecture-driven stabilization and localized bioactivity enhancement of EOs, particularly in topical and tissue-regenerative contexts where sustained surface exposure is desirable.

Across antimicrobial, anticancer, and anti-inflammatory applications, polymer-encapsulated HEO systems consistently demonstrate that therapeutic performance is governed less by nanoscale reduction alone and more by carrier architecture, surface functionality, and release kinetics. Colloidal systems emphasize rapid membrane interaction and systemic dispersion; charge-modulated nanoparticles influence cellular internalization and biofilm disruption; hydrogel-based matrices enable localized, diffusion-controlled exposure; and scaffold-like constructs integrate mechanical support with sustained surface bioactivity. While encapsulation generally enhances stability and efficacy relative to free oils, cross-platform superiority remains context-dependent and insufficiently standardized. Systematic comparison incorporating physicochemical characterization, mechanistic uptake studies, and *in vivo* pharmacokinetic profiling is required to determine which architectures offer reproducible advantages under clinically relevant conditions.

Table 5 integrates the principal polymer-based nanoencapsulation systems discussed in **Section 6**, correlating carrier architecture with physicochemical attributes, bioefficacy trends, scalability constraints, and translational limitations. The comparative analysis underscores that architecture-dependent performance cannot be generalized without standardized in vivo validation, pharmacokinetic profiling, and reproducible fabrication methodologies. Future research must therefore align mechanistic evaluation with scalable manufacturing strategies to enable clinically viable HEO-based formulations.

Table 5. Comparative overview of polymer-based nanoencapsulation systems for biomedical applications of essential oils

Delivery platform	Representative polymers	Typical biomedical applications	Key physicochemical features	Bioefficacy highlights	Scalability potential	Advantages	Limitations	References
Nanoemulsions	Tween-based systems; BSA–DS–SD complexes; mixed surfactant systems	Anticancer; anti-inflammatory; antioxidant; antimicrobial; hepatoprotective and nephroprotective	Droplet size ~50–200 nm; low PDI; enhanced solubility; improved systemic circulation	Enhanced cytotoxicity vs free EO; reduced IL-1β and TNF-α; improved antioxidant enzyme activity; endothelial protection in diabetic models; enhanced antimicrobial efficacy via improved membrane penetration	High (industrial homogenization feasible)	Improved bioavailability; suitable for systemic delivery; tunable formulation	Potential long-term instability; rapid clearance; limited active targeting	(42, 51, 91, 104)
Chitosan Nanoparticles (CNPs)	Chitosan–TPP ionic gelation systems; modified chitosan carriers	Anticancer; anti-inflammatory (arthritis); oxidative stress-related disorders; antimicrobial; wound healing	Positive surface charge; mucoadhesive; controlled Fickian diffusion release	Suppression of TNF-α, IL-6, IL-1β, IL-17A; activation of caspase-3, caspase-9, p53; enhanced ROS-mediated apoptosis in cancer cells; strong antibacterial activity due to electrostatic membrane interaction	Moderate (pH sensitivity; batch variability)	Immunomodulatory; sustained release; enhanced membrane interaction	pH-dependent stability; aggregation risk; scale-up reproducibility issues	(113, 180, 191, 193)
Alginate-Based Nanoparticles	Sodium alginate; ionically crosslinked alginate systems	Anticancer; antioxidant; antimicrobial	Mild encapsulation conditions; biocompatible matrix; relatively low surface charge	Enhanced cytotoxicity vs free EO; induction of apoptosis in tumor cells; increased intracellular ROS generation; improved stability of volatile components; antibacterial activity in encapsulated systems	Moderate to High (simple gelation adaptable to scale)	Gentle processing; non-toxic; stable encapsulation	Lower cellular uptake unless surface-modified; limited intrinsic targeting	(184, 185, 187, 196)
Hydrogels / Nanogels	Chitosan-based hydrogels; curdlan-, glucomannan-,	Topical anti-inflammatory; wound healing;	High water content; sustained release (up to 72	Reduced edema; enhanced re-epithelialization; decreased IC_{50} in colorectal cancer cells;	Moderate (sterilization/storage	Excellent for localized therapy; prolonged	Limited systemic applicability;	(31, 32, 59, 162)

Delivery platform	Representative polymers	Typical biomedical applications	Key physicochemical features	Bioefficacy highlights	Scalability potential	Advantages	Limitations	References
	lactoferrin-based networks; thermosensitive systems	regenerative therapy; antimicrobial	h); enhanced dermal retention	improved antioxidant capacity; sustained antibacterial activity in wound models	optimization required)	residence; regenerative support	diffusion constraints	
Electrospun Nanofibers	PLA; PLGA; biodegradable polymer blends; polymer/cyclodextrin inclusion complexes	Wound healing; anti-adhesion barriers; regenerative membranes; antimicrobial; antioxidant; anti-inflammatory	High surface-area-to-volume ratio; extracellular matrix -mimicking fibrous structure; controlled diffusion	Nrf2 activation; NF-κB suppression; reduced fibrosis; enhanced antimicrobial efficacy; improved oxidative stress modulation	Moderate (industrial electrospinning possible; solvent considerations)	Structural support + bioactivity; suitable for regenerative medicine	Solvent residue concerns; loading uniformity challenges; regulatory complexity	(96, 194, 195)

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7. Biosafety, toxicity profiles, and regulatory considerations

While nanoencapsulation may reduce the apparent acute toxicity of free HEOs under certain conditions, generalized claims regarding their "absolute safety" are not scientifically justified. The safety profile of nanoencapsulated bioactive systems depends on dose, exposure duration, release kinetics, carrier composition, and biodistribution behavior (197-200). Accordingly, comprehensive evaluation of dose-dependent cytotoxicity, *in vivo* accumulation, immunogenicity, and long-term exposure effects remains essential for responsible translational development.

7.1. Terpenoid reactivity, monoterpene toxicity, and oxidative by-products

HEOs are chemically complex mixtures dominated by monoterpenes and phenolic constituents with inherent reactivity. Although many components are classified as Generally Recognized As Safe (GRAS) at low concentrations, toxicological evidence demonstrates that excessive dosing or prolonged exposure may result in hepatotoxicity, nephrotoxicity, neurotoxicity, and hypersensitivity reactions (201-203).

Volatile terpenoids such as limonene and linalool are particularly susceptible to autoxidation under improper storage or oxidative stress, forming hydroperoxides and epoxides with increased sensitizing and cytotoxic potential (202). Encapsulation within polymeric matrices may reduce premature oxidation and limit peak exposure; however, inadequately controlled release profiles can still generate localized high concentrations.

Importantly, reductions in observed cytotoxicity in nanoformulated systems typically reflect modulation of exposure kinetics rather than chemical detoxification of reactive phytoconstituents. Therefore, defining concentration–response relationships, maximum tolerated doses, and therapeutic indices is critical to delineate pharmacologically beneficial ranges from toxicological thresholds.

7.2. Carrier-induced toxicity and polymer degradation

The biosafety of nanoencapsulated HEO systems is co-determined by carrier chemistry, residual processing agents, and degradation behavior.

Natural polymers such as chitosan are generally regarded as biocompatible and degrade into low-molecular-weight oligosaccharides (204). Nevertheless, the use of synthetic crosslinkers (e.g., glutaraldehyde) or certain copolymers may introduce cytotoxic residues if purification is incomplete. Thus, carrier safety cannot be inferred solely from polymer class but must be validated at the formulation level.

The rate of polymer breakdown relative to biological clearance pathways critically influences safety. Particles that degrade slowly may accumulate in tissues, potentially provoking localized inflammatory responses or interfering with cellular homeostasis (205). Conversely, excessively rapid degradation may cause burst release of both bioactives and degradation by-products, altering local microenvironmental conditions.

For example, poly(lactic-co-glycolic acid) (PLGA) systems degrade into lactic and glycolic acid derivatives, metabolites generally considered biocompatible; however, lactate has been shown to modulate inflammatory signaling under certain physiological contexts (131). Degradation behavior is strongly dependent on molecular weight and copolymer ratio: lower-molecular-weight PLGA degrades more rapidly, whereas higher-molecular-weight systems may persist longer and, in some models, induce transient inflammatory responses prior to complete clearance (131).

Despite encouraging short-term biocompatibility findings, systematic long-term *in vivo* studies addressing biodistribution, clearance mechanisms, and potential immunogenicity of nanoencapsulated HEO systems remain limited. Standardized chronic toxicity assessments and pharmacokinetic profiling are therefore essential to establish clinically relevant safety margins.

8. Critical challenges and future perspectives

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Despite substantial advances in polymer-based nanoencapsulation systems for HEOs, significant translational barriers continue to limit their progression from laboratory research to clinical and industrial implementation. While biosafety and *in vivo* toxicity considerations (**Section 7**) define the scientific feasibility of these systems, successful commercialization additionally depends on manufacturing scalability, compositional standardization, and regulatory clarity.

8.1. Translational challenges: Standardization, scalability, and regulatory pathways

A primary challenge in botanical nanomedicine arises from the intrinsic chemotype variability of HEOs. Variations in plant genotype, geographic origin, seasonal conditions, and extraction methodology can substantially alter terpene composition, resulting in batch-to-batch inconsistency and unpredictable encapsulation performance (206). Such variability directly affects physicochemical stability, release kinetics, and biological efficacy. Therefore, rigorous chemotyping and Gas Chromatography–Mass Spectrometry (GC–MS) fingerprinting should be implemented as mandatory pre-encapsulation quality control measures. Establishing quantitative acceptance ranges for dominant bioactive constituents is essential to ensure reproducibility and facilitate regulatory evaluation.

Manufacturing scalability presents an additional constraint. Many bench-scale encapsulation techniques rely on tightly controlled laboratory parameters, solvent systems, and mixing dynamics that do not directly translate to industrial production. For example, scale-up of batch solvent evaporation methods frequently alters hydrodynamic conditions, leading to increased particle size and broader polydispersity distributions. Continuous-flow technologies, including microfluidic nanoprecipitation platforms, offer improved reproducibility and tighter control over particle size distribution under optimized conditions (207). Similarly, industrial roll-to-roll electrospinning provides a potentially scalable route for producing EO-loaded nanofibrous membranes for wound care applications. However, solvent management, volatile terpene retention, and long-term storage stability remain critical technical barriers. Economic feasibility must also be considered, as high-purity polymers and standardized, pharmaceutically graded HEOs may substantially increase production costs.

Regulatory classification further complicates translation. Agencies such as the FDA and EMA require comprehensive physicochemical characterization, including particle size distribution, surface chemistry, degradation pathways, and stability profiles. A central regulatory ambiguity concerns product classification. Nano-functionalized matrices that primarily exert physical barrier functions may qualify as medical devices, potentially following streamlined approval pathways such as 510(k) clearance in the United States (208, 209). In contrast, systems whose therapeutic effect depends on the pharmacological activity of encapsulated HEO constituents are generally classified as drugs or combination products, requiring more extensive preclinical evaluation, clinical trials, and dual GMP compliance. The absence of harmonized regulatory frameworks specific to botanical nanotherapeutics further complicates approval processes (210, 211).

Finally, oxidative stability during storage remains a persistent concern. Volatile terpenoids are prone to compositional drift over time, potentially altering both efficacy and safety profiles. Standardized stability testing protocols and validated *in vitro–in vivo* correlation models are therefore critical components of future development strategies.

8.2. Emerging materials innovations and smart systems

Future development of HEO delivery platforms is expected to move beyond passive encapsulation toward systems capable of controlled, environment-responsive behavior. Advancing from simple protective carriers to programmable architectures may enhance therapeutic precision; however, these concepts remain largely at the experimental stage and require rigorous validation prior to clinical translation.

8.2.1. Smart, stimuli-responsive, and tumor-targeted nanosystems

Stimuli-responsive nanosystems represent a potential strategy for modulating EO release in response to localized physiological cues such as pH variation, enzymatic activity, temperature, or mechanical stress. Such responsiveness may be particularly relevant in disease-specific microenvironments, including inflamed tissues, infected wounds, or tumors, where biochemical conditions differ from healthy tissue.

Incorporating active targeting mechanisms may further improve site specificity. Surface functionalization with peptides, aptamers, or

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antibodies could facilitate receptor-mediated uptake by defined cell populations, potentially enhancing intracellular delivery while reducing systemic exposure. Nevertheless, ligand functionalization introduces additional complexity in manufacturing, stability testing, and regulatory evaluation. Consequently, future research must balance targeting precision with translational feasibility.

8.2.2. Layered hybrid assemblies

To address the intrinsic volatility and rapid diffusion of monoterpenes, hybrid architectures combining polymeric matrices with inorganic nanostructures have been proposed. Materials such as mesoporous silica, metal–organic frameworks (MOFs), or layered double hydroxides may provide structural rigidity and improved encapsulation efficiency, potentially limiting terpene evaporation during storage (212-214). Core–shell or multilayered assemblies could physically restrict diffusion while allowing controlled degradation of the polymeric component in biological environments. However, integration of inorganic nanomaterials introduces additional considerations regarding long-term biodegradability, clearance, and regulatory acceptability. Comprehensive toxicological and biodistribution studies will therefore be essential before such hybrid systems can be considered clinically viable.

8.2.3. Integration with 3D-printed biomedical constructs

The convergence of HEO nanoencapsulation with additive manufacturing technologies offers opportunities for localized and structurally customized therapeutic platforms. Incorporation of EO-loaded nanoparticles into bio-inks may enable fabrication of 3D-printed scaffolds or wound dressings capable of sustained antimicrobial or regenerative activity.

Despite this potential, significant technical challenges remain. Volatile EO components may be susceptible to degradation during high-shear mixing or thermal processing steps associated with certain 3D-printing techniques. Additionally, ensuring homogeneous nanoparticle distribution within printed constructs and preserving mechanical integrity are critical for functional reliability. Validation in clinically relevant disease models will be required to substantiate the therapeutic advantages of such integrated systems.

8.2.4. AI-assisted formulation design and standardization

The increasing availability of computational modeling and machine learning tools provides opportunities for data-driven optimization of EO nanoformulations. Predictive algorithms may assist in identifying suitable polymer–EO combinations, simulating release kinetics, and forecasting stability profiles prior to experimental synthesis (215-217). Chemometric analysis of GC–MS fingerprints could further support quality standardization by correlating compositional patterns with biological performance (218-220).

Nonetheless, the predictive reliability of such models is currently constrained by the scarcity of standardized, high-quality datasets and the intrinsic chemical variability of botanical extracts. At the current state of the art, most machine learning models in this field are limited to evaluating single-component markers (e.g., carvacrol or thymol) or simplified binary mixtures. Capturing the complex, non-linear, and synergistic interactions among the >50 minor constituents present in whole botanicals remains a profound computational challenge. While advanced deep learning architectures have the theoretical capacity to model these high-dimensional, non-linear "entourage effects," their practical execution is heavily bottlenecked by the lack of comprehensive multi-component datasets. Future progress will depend on integrating high-throughput computational screening with systematically designed experimental validation studies to bridge the gap between single-marker modeling and full-spectrum translational robustness.

9. Conclusion

HEOs possess broad biological activity, yet their therapeutic application has historically been constrained by volatility, chemical instability, limited aqueous solubility, rapid degradation, and compositional variability. The evidence synthesized in this review indicates that polymer-based nanoencapsulation can effectively mitigate many of these limitations by improving physicochemical stability, modulating release kinetics, and enhancing local or systemic bioavailability.

Across diverse delivery architectures—including polymeric nanoparticles, nanoemulsions, nanogels, electrospun fibers, and hybrid assemblies—encapsulation consistently alters the exposure profile of HEOs, thereby enhancing therapeutic indices relative to free oils. Importantly, performance is not uniform across platforms; rather, biological outcomes are strongly architecture-dependent.

Colloidal systems favor systemic dispersion and rapid cellular interaction, hydrogel-based matrices enable localized and diffusion-controlled delivery, and nanofibrous scaffolds provide surface-confined, regenerative functionality. This structure–function relationship underscores that rational carrier selection is central to optimizing therapeutic performance.

Despite these advances, substantial translational barriers remain. Long-term *in vivo* fate, biodistribution, and chronic safety data are limited, particularly for complex or hybrid systems. Botanical chemotype variability complicates standardization and regulatory evaluation, while manufacturing scalability and GMP compliance continue to challenge industrial implementation. Addressing these issues will require coordinated integration of rigorous chemotyping, standardized stability testing, scalable fabrication technologies, and systematically designed pharmacokinetic studies.

Future progress will depend less on the discovery of new essential oils and more on the refinement of delivery architecture, standardization strategies, and translational validation frameworks. Through disciplined formulation design and evidence-based regulatory alignment, polymer-encapsulated HEO systems may advance from experimental constructs toward clinically reliable therapeutic platforms.

Author contributions

Hamid Rajabi: conceptualization, methodology, investigation, writing—original draft preparation. **Utcharaporn Kamsrijai, Narudol Teerapattarakan, Sulukkana Noiprasert, Huang Zhaoxian, Marc Pignitter:** writing—review and editing**, Saroat Rawdkuen**: conceptualization, resources, visualization, writing—review and editing, supervision, project administration.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Data were not shared.

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Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.