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Nanotechnology-Based Formulations of Propolis Bioactives for Modern Natural Product Therapy: A Narrative Literature Review

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ABSTRACT

Propolis contains phenolic acids, flavonoids, and other bioactive metabolites with antimicrobial, anti-inflammatory, antioxidant, wound-healing, and anticancer activities. However, their therapeutic application is limited by poor aqueous solubility, physicochemical instability, and low bioavailability. This narrative review summarizes recent advances in nanotechnology-based formulations developed to improve the delivery of propolis extracts and identified bioactive compounds. A structured search of Scopus, ScienceDirect, and PubMed identified studies published between 2022 and 2026, with the final search completed on 31 July 2026. Of 333 records retrieved, 25 studies met the eligibility criteria. Reported nanocarriers included nanoemulsions, polymeric and chitosan nanoparticles, lipid nanoparticles, niosomes, nanovesicles, micelles, dendrimers, protein- and starch-based nanoparticles, metal–organic frameworks, and injectable hydrogels, with particle sizes ranging from 8.87 to 488.28 nm. These systems generally enhanced solubility, bioaccessibility, controlled release, and biological efficacy in antimicrobial, wound-healing, anticancer, anti-inflammatory, periodontal, and cardiovascular models. Nevertheless, evidence remains preclinical and methodologically heterogeneous. Future studies should emphasize standardized chemical and nanocarrier characterization, pharmacokinetics, long-term safety, and clinical validation. Unlike previous reviews, this study systematically links identified propolis bioactives with specific nanocarriers, providing a framework for the rational development of clinically translatable propolis nanomedicines.

Keywords: nanoemulsion; nanoformulation; nanoparticles; natural product therapy; propolis.

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Introduction

Propolis is attractive as a natural therapeutic material because its phenolic acids, flavonoids, and related secondary metabolites support a broad range of antimicrobial, anti-inflammatory, antioxidant, wound-healing, and anticancer activities. Its principal limitation is the same chemical complexity that underlies these effects: the composition of propolis varies with botanical and geographical origin and with extraction conditions, making standardization difficult. The recent primary literature illustrates this diversity, including p-hydroxybenzoic acid, pinocembrin, and quercetin in ethanolic propolis extract [1], vestitol, formononetin, and biochanin A in Brazilian red propolis [2], and artepillin C and baccarin in Brazilian green propolis [3]. In addition, several important propolis constituents are poorly water-soluble or show limited dispersion and absorption, which can restrict reproducible pharmaceutical performance [4–7].

Nanotechnology-based delivery systems have therefore been investigated to improve the pharmaceutical performance of propolis extracts and isolated propolis-associated bioactives. Recent studies have explored a wide range of nanoformulation platforms, including nanoemulsions, polymeric nanoparticles, lipid-based systems,

micelles, and other nanocarriers. These systems may improve aqueous dispersion, encapsulation, bioaccessibility, and controlled or sustained delivery, although their performance depends on carrier composition, preparation method, particle characteristics, and the chemical form of the active material [4–8].

Previous reviews have established that propolis and nanopropolis are already active areas of research. Kustiawan et al. reviewed propolis nanoformulations published from 2013 to 2023 and discussed active compounds, formulation classes, design concepts, mechanisms, and translational challenges [8]. Other recent narrative reviews have focused more narrowly on propolis bioactives in bone homeostasis [9], in vitro antimicrobial activity [10], or preventive and therapeutic applications in dentistry [11]. These contributions are important, but they address different scopes and do not provide the same article-level linkage between experimentally identified propolis bioactives, nanocharacterization data, and biological outcomes across multiple therapeutic areas.

Accordingly, the research gap addressed in this review is not the absence of literature on propolis or nanopropolis. Among the recent reviews identified, none applied the same article-level framework used here to simultaneously evaluate experimentally identified propolis bioactives, nanocharacterization parameters, and biological outcomes across multiple therapeutic areas [8–11]. This narrative review therefore aimed to synthesize original studies published from 2022 to 2026 on nanoformulations of propolis extracts and explicitly identified propolis-associated bioactives. Its novelty lies in integrating recent chemical profiling, particle or droplet characteristics, encapsulation or loading performance, release behavior, and reported pharmacological activity while distinguishing whole-extract formulations from purified bioactive systems. This approach is intended to clarify which formulation-related advantages are experimentally supported, where evidence remains heterogeneous, and which gaps must be addressed before clinical translation.

METHODS

Literature Search and Study Identification

Preliminary literature exploration was conducted from March 2026, followed by final structured searches of Scopus, ScienceDirect, and PubMed on 31 July 2026. Scopus was searched using propolis AND (nanoformulation* OR nanoparticle* OR nanoemulsion*) in the article title, abstract, and keywords, with filters for 2022–2026, article, journal, English, and open access. ScienceDirect used the equivalent propolis and nanoformulation/nanoparticle/nanoemulsion terms with filters for 2022–2026, research articles, and open access; English language was screened manually. PubMed used propolis[Title/Abstract] AND (nanoformulation*[Title/Abstract] OR nanoparticle*[Title/Abstract] OR nanoemulsion*[Title/Abstract]) with filters for 2022–2026, free full text, English, and exclusion of preprints. The initial searches retrieved 3,630 records, and 435 remained after database filters were applied.

Eligibility, study selection, and data synthesis

Original English-language studies published from 2022 to 2026 were eligible when they investigated a propolis extract or a bioactive explicitly identified as a propolis constituent, incorporated the active material into a nanotechnology-based formulation, experimentally identified or quantified propolis bioactives or secondary metabolites, reported particle or droplet size plus at least one additional nanocharacterization parameter, and evaluated a biological or therapeutic outcome. Duplicates were removed before title/abstract and full-text screening. Numerical values were extracted only when explicitly reported; missing data were not inferred. Because the included studies differed substantially in formulation type, assay, dose, organism, cell line, and animal model, the findings were synthesized narratively. Study selection was documented using a PRISMA 2020-style flow diagram [12].

RESULT AND DISCUSSION

After database filtering, 435 records were retained. Removal of 102 duplicates left 333 records for title and abstract screening. A total of 286 records were excluded

at this stage, and 47 reports were sought for full-text retrieval. Two Scopus reports were unavailable, leaving 45 full texts for eligibility assessment. Twenty reports were excluded after full-text review, and 25 studies fulfilled all criteria. Fifteen included studies originated from the Scopus screening set and ten from the ScienceDirect screening set; PubMed did not contribute an additional unique study after deduplication and full-text assessment, as depicted in **Figure 1**.

The included literature comprised three studies published in 2022, seven in 2023, eight in 2024, four in

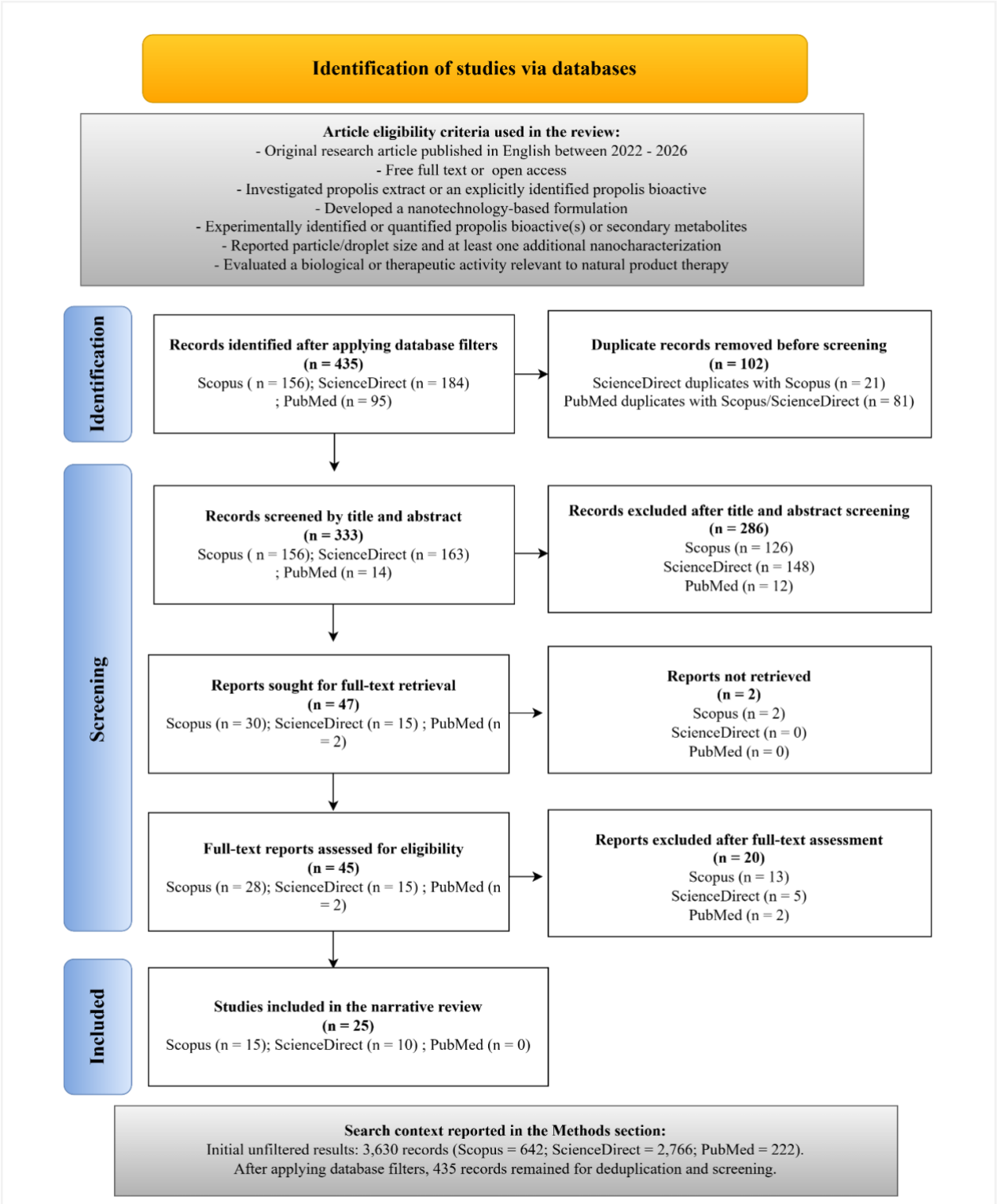

Figure 1. PRISMA flow diagram of study identification, screening, eligibility assessment, and inclusion.

2025, and three in 2026. Fourteen studies investigated propolis extracts, whereas eleven investigated purified propolis-associated bioactives. The purified-compound studies focused principally on CAPE, chrysin, and galangin. All efficacy evidence was preclinical, consisting of physicochemical studies, in vitro assays, and animal models. No human clinical efficacy study met the eligibility criteria.

Propolis is a resinous substance produced naturally by bees from plant exudates mixed with enzymes, wax, and pollen. Its color can range from yellow and green to red and dark brown depending on the plant source and collection season, while its composition and biological properties vary with botanical source and environmental conditions [11].

The extract-based studies demonstrated substantial chemical heterogeneity. Alarjani et al. [1] quantified 18 phenolic acids and 12 flavonoids, with p-hydroxybenzoic acid, pinocembrin, and quercetin among the major compounds. Justino et al. [2] used vestitol, formononetin, and biochanin A as biomarkers of Brazilian red propolis, while Silveira et al. [3] used artepillin C and baccarin as markers of Brazilian green propolis. Elsamman et al. [13] qualitatively detected chlorogenic acid and apigenin. Vaseghi et al. [14] reported a broader chromatographic profile that included catechin, epicatechin, quercetin, vitexin, diosmin, resveratrol, cinnamic acid, salicylic acid, and hydroxybenzoic acid. The principal propolis bioactives, nanoformulations, nanocharacterization, and outcomes are organized by therapeutic focus in **Tables 1-5**.

Other studies quantified total phenolic and/or total flavonoid content rather than individual markers [4,15–19]. Kazemi et al. [20] identified pinostrobin chalcone, galangin, tectochrysin, and naringenin, whereas Dimmito et al. [21] identified caffeic acid, ferulic acid, quercetin, CAPE, chrysin, and galangin and quantified total phenolics and flavonoids. These differences confirm that propolis nanoformulations are chemically distinct; future studies should report origin, extraction conditions, chemical fingerprints, and quantitative markers.

Across the 25 included studies, the nanoformulation strategies could be grouped into nanoemulsions and nanoemulgels; polymeric and chitosan-based nanoparticles or nanocapsules; solid lipid nanoparticles, nanostructured lipid carriers, and polymeric nanovesicles; niosomes, micelles, and dendrimers; protein- and starch-based nanoparticles; ZIF-8 or ZnO-based nanoparticles; and nanoparticle-loaded hydrogels. **Figure 2** summarizes these formulation platforms together with the principal pharmacological activities reported in the included studies. Because no human clinical efficacy study met the eligibility criteria, these outcomes are described as pharmacological rather than clinical activities.

The formulations covered a broad size range. The smallest reported system was the pH-shifted bovine serum albumin-galangin nanoparticle at 8.87 nm [22], whereas selected chitosan-tripolyphosphate propolis nanoparticles reached 488.28 nm [17]. Red propolis polymeric nanocapsules showed a particle size of 177.8 nm and a low polydispersity index of 0.06 [2]. In contrast, chrysin-loaded phenylboronic acid-functionalized zinc oxide nanoparticles showed a hydrodynamic diameter above 400 nm and a relatively broad size distribution [23]. These findings indicate that the label nanoformulation encompassed systems with markedly different dispersion quality and hydrodynamic behavior.

Surface charge was also formulation-dependent. Negative values were common for nanoemulsions, lipid nanoparticles, polymeric nanocapsules, niosomes, and nanovesicles, including -37.4 mV for the Iranian propolis nanoemulsion [20] and -31.5 mV for the propolis nanostructured lipid carrier [15]. Chitosan-based systems generally showed positive zeta potentials, reaching +48.20 mV in propolis-loaded chitosan-tripolyphosphate nanoparticles [17] and up to +77.02 mV in chrysin-loaded chitosan nanoparticles [24]. Direct comparisons remain difficult because some studies reported exact numerical values, while others described only a change in surface charge or provided morphology without a complete colloidal dataset.

Encapsulation efficiency was frequently high but not uniform. Biochanin A, vestitol, and formononetin showed encapsulation efficiencies above 97% in Brazilian red propolis nanocapsules [2]. Artepillin C and

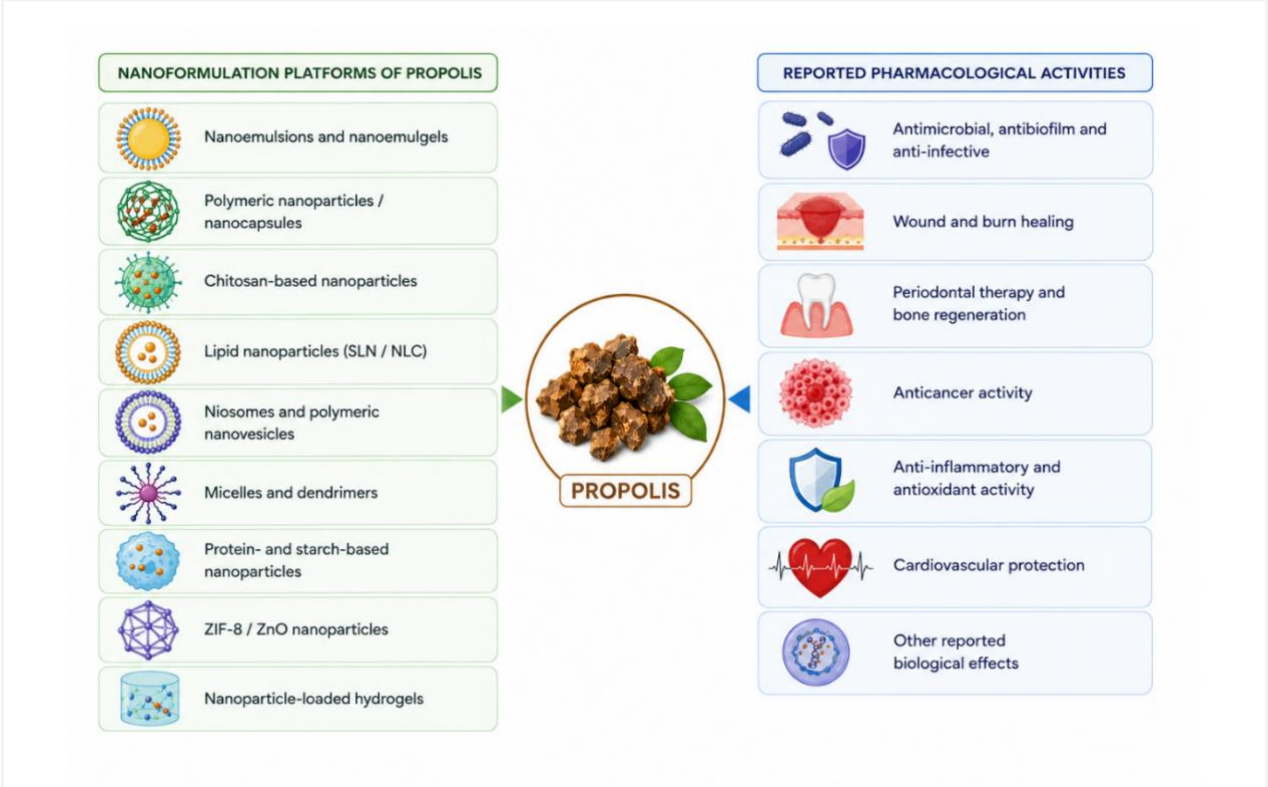

Figure 2. Nanoformulation platforms of propolis and their reported pharmacological activities in the included studies.

baccarin were encapsulated at 99.9% and 98.7%, respectively [3], and the chrysin nanoemulsion achieved 99.19% encapsulation [5]. By comparison, chitosan-tripolyphosphate propolis nanoparticles showed 23.94-41.19% encapsulation [17], and chrysin nanomicelles showed 37.06% [6]. The choice of carrier, preparation method, matrix affinity, and analytical marker therefore strongly influenced loading performance.

Differences between microscopy and dynamic light scattering also require careful interpretation. The propolis-hyaluronic acid-vitamin K nanoemulsion showed a 10.35 nm Z-average by dynamic light scattering but an 80-180 nm mesh-like structure by transmission electron microscopy [13]. Chrysin-loaded zinc oxide nanoparticles measured approximately 25-30 nm by transmission electron microscopy but 415.1 nm hydrodynamically [23]. Such discrepancies may reflect hydration layers, aggregation, sample preparation, or differences between the measured physical dimensions and hydrodynamic behavior. Accordingly, claims of nanoscale performance should be supported by complementary characterization methods.

Nanoformulated propolis showed broad antimicrobial activity. Chitosan nanoemulsions containing ethanolic propolis extract inhibited Gram-positive and Gram-negative bacteria, including methicillin-resistant Staphylococcus aureus, and also suppressed toxigenic fungi and mycotoxin production [1]. Propolis-loaded nanostructured lipid carriers exhibited stronger antibacterial and antifungal activity than the crude extract [15]. Chitosan nanoparticles containing ethanol- or methylal-extracted propolis produced minimum inhibitory concentrations of 2-230 micrograms/mL and reduced Escherichia coli biofilm bacteria by 98-100% at 300 micrograms/mL for the methylal-extracted system [14].

Targeted and combination strategies were also investigated. Aptamer-modified PEGylated niosomes carrying ethanolic propolis extract accumulated on the Mycobacterium tuberculosis cell wall, inhibited bacterial growth at a lower dose than the non-functionalized formulation, and maintained more than 80% viability in alveolar macrophages [16]. Iranian propolis nanoemulsion reduced the minimum inhibitory concentration against multidrug-resistant Pseudomonas aeruginosa to 3.2-15 mg/mL, compared with 25-50 mg/mL for the unformulated extract, and produced synergistic or additive effects with ciprofloxacin

depending on the isolate [20].

The most pronounced potency gain was reported for propolis-loaded solid lipid nanoparticles against clarithromycin-resistant Helicobacter pylori. The optimized system produced minimum inhibitory and bactericidal concentrations of 0.06 and 0.25 micrograms/mL, respectively, compared with 32 and 64 micrograms/mL for free propolis extract [21]. However, activity was not universal because the same formulation was inactive against Fusobacterium nucleatum and

Table 1. Propolis nanoformulations evaluated primarily for antimicrobial, antibiofilm, and anti-infective applications.

Propolis bioactive(s)/secondary metabolites	Nanoformulation	Nanocharacterization	Reported biological or therapeutic activity	Reference
p-Hydroxybenzoic acid, pinocembrin, quercetin (among 18 phenolic acids and 12 flavonoids)	EEP-loaded chitosan nanoemulsion	• Particle size 71.16 ± 5.21 - 112.34 ± 7.36 nm. • PDI 0.26 ± 0.02 - 0.39 ± 0.03. • zeta potential - 27.87 ± 0.62 to - 23.89 ± 1.05 mV.	Antibacterial activity against Gram-positive and Gram-negative bacteria, including MRSA, plus antifungal and anti-mycotoxigenic activity. At 200 ng/mL, Fusarium culmorum was completely inhibited; zearalenone was undetected at 150–200 ng/mL; Aspergillus parasiticus inhibition reached 47.18% at 200 ng/mL.	[1]
Catechin, epicatechin, quercetin, vitexin, diosmin, resveratrol, cinnamic acid, salicylic acid, hydroxybenzoic acid.	Ethanol- and methylal-extracted propolis encapsulated in chitosan nanoparticles (PE-CH and PM-CH).	• Spherical nanoparticles, Particle size 360–420 nm. • PDI 0.105–0.166. • zeta potential ~+30 to +48 mV. • encapsulation efficiency ~90–92%. FTIR confirmed propolis incorporation.	Antibacterial and antibiofilm activity; MIC 2–230 µg/mL and MBC 3–346 µg/mL. PM-CH reduced E. coli biofilm bacteria by 98–100% at 300 µg/mL. DPPH inhibition: 43% PM-CH and 36% PE-CH. IC_{50} was ~60–160 µg/mL in normal cells and ~20 µg/mL in MCF-7 cells.	[14]
Total phenolics	Ethanolic propolis extract-loaded PEGylated niosomes surface-functionalized with an Ag85A aptamer (Apt-PEGNio/EEP) for targeted Mycobacterium tuberculosis delivery.	1. Before aptamer conjugation: • Particle size 176.14 ± 13.88 nm. • PDI 0.21 ± 0.04, • zeta potential −21.86 ± 0.36 mV. • entrapment efficiency 80.38 ± 7.58%. 2. After conjugation: • 198.30 ± 5.02 nm, • PDI 0.36 ± 0.02. • zeta potential −19.55 ± 2.27 mV. • STEM showed relatively uniform spheres; >60% release after 48 h.	Free EEP inhibited M. tuberculosis dose-dependently (IC_{50} equivalent to 30 µg/mL GAE). Apt-PEGNio/EEP accumulated on the M. tuberculosis cell wall and significantly inhibited the bacterium at a lower dose than non-functionalized niosomes; macrophage viability remained >80% after 24 h.	[16]
Pinostrobin chalcone, galangin, tectochrysin, naringenin	Iranian propolis nanoemulsion prepared by high-energy emulsification and ultrasonication.	1. FE-SEM showed nearly spherical particles. • DLS size 161.4 nm. • zeta potential −37.4 mV.	More active than unformulated propolis against multidrug-resistant Pseudomonas aeruginosa: MIC 3.2–15 mg/mL versus 25–50 mg/mL. It reduced bacterial growth and biofilm metabolic activity; combination with ciprofloxacin was synergistic in the sensitive strain and one MDR isolate and mainly additive in other resistant isolates.	[20]
Caffeic acid, ferulic acid, quercetin, CAPE, chrysin, galangin	Propolis ethanolic extract-loaded solid lipid nanoparticles (PEE-SLNs); PEE-SLN10 was the optimized formulation.	1. PEE-SLN10: • Particle size 161.71 ± 3.35 nm. • PDI 0.14 ± 0.05. • zeta potential −23.13 ± 0.15 mV. • entrapment efficiency 86.08% using chrysin as marker. • TEM showed nearly spherical particles; biphasic chrysin release, thermal/storage stability, and improved chrysin permeability were reported.	Enhanced activity against clarithromycin-resistant Helicobacter pylori (MIC/MBC 0.06/0.25 µg/mL vs 32/64 µg/mL for free extract). No activity against Fusobacterium nucleatum or Clostridioides difficile up to 128 µg/mL. It reduced superoxide-anion production and caused no Galleria mellonella mortality over four days.	[21]

Abbreviations: CAPE, caffeic acid phenethyl ester; EEP, ethanolic extract of propolis; EE, encapsulation efficiency; MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; MRSA, methicillin-resistant Staphylococcus aureus; PDI, polydispersity index.

Clostridioides difficile at concentrations up to 128 micrograms/mL. Shahab-Navaei and Asoodeh [18] also reported antibacterial activity of propolis solid lipid nanoparticles against Escherichia coli, Staphylococcus aureus, Bacillus subtilis, and Pseudomonas aeruginosa. Collectively, these studies support formulation-dependent enhancement but also demonstrate that bacterial susceptibility remains organism-specific. The formulations classified primarily under antimicrobial, antibiofilm, and anti-infective applications are summarized in **Table 1**.

Four studies evaluated topical tissue repair. CAPE-loaded PEG-PLGA nanoparticles incorporated into hydroxypropyl methylcellulose hydrogel produced approximately 97% wound contraction on day 14 in diabetic rats and enhanced collagen deposition, antioxidant defense, anti-inflammatory responses, proliferation, and angiogenesis [25]. A propolis nanostructured lipid carrier gel achieved 56.97% wound healing on day 7 and 90.03% on day 14 in rabbit full-thickness wounds [15].

A propolis, tea tree oil, and jojoba oil nanoemulgel reduced nitric oxide and interleukin-1 beta, increased superoxide dismutase activity, reduced malondialdehyde and tumor necrosis factor alpha, and promoted collagen deposition and re-epithelialization

Table 2. Propolis nanoformulations evaluated for wound healing and burn repair.

Propolis bioactive(s)/secondary metabolites	Nanoformulation	Nanocharacterization	Reported biological or therapeutic activity	Reference
Caffeic acid phenethyl ester (CAPE)	CAPE-loaded PEG–PLGA nanoparticles incorporated into an HPMC hydrogel for topical application.	• Particle size 198 ± 7.3 nm. • PDI 0.43 ± 0.04. • CAPE loading 81.73 ± 5.1%. Release: 77.8 ± 7.9% at 24 h and 98.6 ± 10.7% at 48 h.	In diabetic rats, the formulation accelerated wound healing and produced ~97% wound contraction on day 14, with enhanced collagen deposition and antioxidant, anti-inflammatory, pro-collagen, proliferative, and angiogenic effects.	[25]
Total phenolics and total flavonoids	Propolis-loaded nanostructured lipid carriers incorporated into a Carbopol gel.	• Particle size 41.64 ± 0.85 nm. • PDI 0.290. • zeta potential −31.5 ± 6.87 mV. • entrapment efficiency 83.29 ± 0.47%; drug loading 3.97 ± 0.02%. • SEM showed uniform elliptical particles; TEM confirmed nanoscale morphology.	Antioxidant, antibacterial, antifungal, and wound-healing activities. DPPH inhibition was 65.47%; antimicrobial activity was stronger than crude extract. Rabbit wounds showed 56.97% healing on day 7 and 90.03% on day 14.	[15]
Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl; 5-hydroxy-7-methoxyflavanone; 4H-1-benzopyran-4-one, 5-hydroxy-7-methoxy-2-phenyl; hexadecanoic acid; octadecanoic acid; benzene ethanol.	Propolis-loaded oil-in-water nanoemulsion with tea tree and jojoba oils, incorporated into Carbopol 940 hydrogel as a nanoemulgel.	1. Optimized 5% propolis F-PN2: • droplet size 187.8 ± 3.29 nm; PDI 0.214 ± 0.019. • zeta potential −28.6 ± 1.91 mV. • TEM showed spherical, evenly distributed droplets of approximately 18–34 nm.	Antioxidant, anti-inflammatory, cytocompatibility, and wound-healing effects. NO and IL-1β decreased by ~35% and 40%; in vivo treatment accelerated wound closure, increased SOD, reduced MDA and TNF-α, and enhanced collagen deposition and re-epithelialization.	[26]
Chlorogenic acid, apigenin	Oil-in-water nanoemulsion containing propolis, hyaluronic acid, and vitamin K, prepared by emulsification–solvent technique and probe ultrasonication.	• TEM: mesh-like structure, 80–180 nm. • mean 118.1 nm. • DLS: Z-average 10.35 ± 1.719 nm. • PDI 0.226. • zeta potential −21.6 ± 6.22 mV. FTIR was also used.	Antioxidant and antimicrobial activity against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus; enhanced fibroblast migration. In rat second-degree burns, wound contraction reached 98.13% on day 14 with improved epithelialization, collagen deposition, fibrous tissue, and angiogenesis.	[13]

Abbreviations: CAPE, caffeic acid phenethyl ester; DLS, dynamic light scattering; EE, encapsulation efficiency; HPMC, hydroxypropyl methylcellulose; PDI, polydispersity index; SEM, scanning electron microscopy; TEM, transmission electron microscopy.

Table 3. Propolis nanoformulations evaluated for periodontal therapy and bone regeneration.

Propolis bioactive(s)/secondary metabolites	Nanoformulation	Nanocharacterization	Reported biological or therapeutic activity	Reference
Artepillin C, baccarin	Green propolis-loaded lipid nanoparticles used locally as an adjunct to scaling and root planing in experimental periodontitis.	• Average diameter 144.8 nm. • PDI 0.28. • zeta potential −24.6 mV. • TEM confirmed nanosized lipid particles. • Encapsulation efficiency: artepillin C 99.9%, baccarin 98.7%.	Improved periodontal tissue repair. Total bone tissue reached 81.8 ± 1.9% in VEH-SRP-GPlnp; in zoledronate-treated rats, non-vital bone decreased to 17.8 ± 5.4%, with TNF-α and IL-1β immunolabeling reduced to 8.5 ± 1.3 and 7.6 ± 1.6.	[3]
Caffeic acid phenethyl ester (CAPE), chrysin	Injectable ROS-responsive CC-B-CAPE@CY-NPs hydrogel containing chrysin-loaded PLGA nanoparticles.	• Blank and chrysin-loaded nanoparticles were 224.63–262.81 nm, negatively charged, spherical, and uniformly dispersed. • TEM, FTIR, XRD, NMR, SEM, and release analysis were used. • CAPE and chrysin release was quantified by HPLC.	Scavenged ROS, reduced M1 macrophage polarization and NF-κB signaling, and increased alkaline phosphatase and osteogenic protein expression. In rat periodontitis, it reduced inflammation and alveolar bone loss and promoted bone regeneration.	[27]
Caffeic acid phenethyl ester (CAPE)	Phenylboronic acid-modified carboxymethyl chitosan injectable hydrogel containing CAPE-loaded ZIF-8 nanoparticles.	• Hydrodynamic diameter increased from 182.83 nm (unloaded ZIF-8) to 333.9 nm after CAPE loading. • loading efficiency 28.93%. TEM/SEM showed uniform dodecahedral particles. • CAPE incorporation was confirmed by FTIR, UV–Vis, XRD, XPS, elemental mapping, and porosity analysis. • zeta potential increased but the exact value was not stated.	Targeted antibacterial/antibiofilm activity against Porphyromonas gingivalis, ROS scavenging, reduced inflammation, restored mitochondrial function, and promoted mesenchymal stem-cell osteogenic differentiation. In rat periodontitis, it reduced inflammation and alveolar bone defects and restored bone height.	[28]

Abbreviations: CAPE, caffeic acid phenethyl ester; PDI, polydispersity index; PLGA, poly(lactic-co-glycolic acid); ROS, reactive oxygen species; TEM, transmission electron microscopy; ZIF-8, zeolitic imidazolate framework-8.

[26]. A propolis, hyaluronic acid, and vitamin K nanoemulsion produced 98.13% wound contraction by day 14 in a rat second-degree burn model and improved epithelialization, angiogenesis, and fibrous tissue formation [13]. Although these outcomes are promising, differences in animal species, wound models, formulation composition, dosing, and comparators prevent direct ranking of the platforms. The wound-healing and burn-repair formulations are summarized in **Table 2**.

Three studies combined local nanoformulation with periodontal tissue repair. Green propolis-loaded lipid nanoparticles used as an adjunct to scaling and root planing improved periodontal repair in ovariectomized rats and reduced non-vital bone and inflammatory immunolabeling in zoledronate-treated rats [3]. In a reactive oxygen species-responsive hydrogel, CAPE provided anti-inflammatory activity while chrysin-loaded poly(lactic-co-glycolic acid) nanoparticles promoted osteogenesis. The system reduced macrophage M1 polarization and nuclear factor kappa B signaling, activated osteogenic pathways, and restored alveolar bone in experimental periodontitis [27].

A more recent dual-mode hydrogel incorporated CAPE-loaded zeolitic imidazolate framework-8 nanoparticles and phenylboronic acid-mediated targeting. The formulation enhanced antibacterial activity against Porphyromonas gingivalis, scavenged reactive oxygen species, restored mitochondrial function in mesenchymal stem cells through the SIRT1/p-AMPK/PGC-1alpha pathway, promoted osteogenic differentiation, and reduced alveolar bone defects in rats [28]. These studies illustrate a transition from simple local delivery toward multifunctional systems that simultaneously address infection, inflammation, oxidative stress, and bone regeneration. The periodontal

and bone-regeneration formulations are summarized in **Table 3**.

Nanotechnology-based anticancer studies included whole propolis extracts and purified bioactives. Brazilian red propolis polymeric nanocapsules showed greater activity than the free extract against OVCAR-3 ovarian cancer cells in two-dimensional monolayers and three-dimensional spheroids [2]. Propolis-loaded chitosan nanoparticles showed approximately 20 micrograms/mL half-maximal inhibitory concentrations in MCF-7 cancer cells, compared with approximately 60-160 micrograms/mL in normal cells [14]. Propolis solid lipid nanoparticles showed time-dependent cytotoxicity against A549 lung cancer cells while not significantly reducing human dermal fibroblast viability under the tested conditions [19].

For purified chrysin, stearic acid-modified Pluronic F68 nanomicelles enhanced A549 cellular uptake, apoptosis, and growth inhibition and increased the plasma area under the concentration-time curve approximately 5.6-fold compared with chrysin suspension [6]. Fucose-functionalized generation-four polyamidoamine dendrimers increased chrysin solubility and uptake in A549 cells and produced half-maximal inhibitory concentrations of 1.5 micrograms/mL after 24 hours and 0.7 micrograms/mL after 48 hours, while the unloaded carrier was reported as non-cytotoxic [29]. Phenylboronic acid-functionalized zinc oxide nanoparticles enabled pH-responsive chrysin release and promoted oxidative stress-mediated apoptosis, cell-cycle arrest, and inhibition of migration and invasion in A549 cells, with no significant cytotoxicity reported in normal L132 lung epithelial cells [23].

CAPE delivery was evaluated in a prostate cancer xenograft model. A single injection of a CAPE-loaded self-healing micellar hydrogel provided sustained release for approximately two weeks. Biweekly administration enhanced tumor-growth suppression 2.7-fold compared with weekly free CAPE and modulated Ki67, cyclin B1, nuclear factor kappa B p65, P21Cip1, and P27Kip1 [7]. These results show that nanocarriers can alter exposure and dosing frequency, but the evidence remains limited to cell and animal models. The anticancer nanoformulations are summarized together in **Table 4**; purified propolis-associated bioactives such as chrysin and CAPE are identified separately within the table to distinguish them from whole-extract formulations.

Antioxidant and anti-inflammatory effects were reported in several formulation platforms. Propolis-loaded chitosan–hyaluronic acid nanoparticles increased aqueous solubility and retained DPPH radical-scavenging activity [4], while propolis-loaded chitosan–tripolyphosphate nanoparticles showed DPPH activity that increased with propolis loading [17]. A chrysin nanoemulsion increased simulated gastrointestinal bioaccessibility by approximately fourfold and reduced lipopolysaccharide-induced reactive oxygen species, interleukin-6, and prostaglandin E2 in RAW264.7 macrophages [5]. Bovine serum albumin–galangin nanoparticles reduced intracellular reactive oxygen species and pro-inflammatory cytokines, with the pH-shifted system showing greater uptake and anti-inflammatory effects [22]. Chrysin-loaded starch nanoparticles also retained DPPH/ABTS antioxidant activity during simulated gastrointestinal digestion [30]. These results support nanoencapsulation as a means of improving delivery while preserving or enhancing antioxidant and anti-inflammatory responses, although most evidence remains biochemical or cell-based.

A cardiovascular application was reported for propolis-loaded PLA–PEG–PLA nanovesicles. In isoproterenol-induced heart-failure rats, the formulation improved ejection fraction and fractional shortening, reduced brain natriuretic peptide, galectin-3, interleukin-1 beta, interleukin-6, and interleukin-17, increased interleukin-10, and upregulated AMPK and SIRT1 [19]. Ragab et al. [24] reported that chrysin-loaded chitosan nanoparticles inhibited mitochondrial complex II activities in normal mouse liver preparations and normal human fibroblasts; this finding is better interpreted as a biological and potential safety signal than as direct evidence of selective anticancer efficacy. Antioxidant, anti-inflammatory, cardiovascular, and other biological outcomes are summarized in **Table 5**.

The current evidence has several limitations. First, propolis extracts were not chemically equivalent across studies. Differences in geographic source, extraction

Table 4. Propolis extract and purified propolis-associated bioactive nanoformulations evaluated for anticancer activity.

Propolis bioactive(s)/secondary metabolites	Nanoformulation	Nanocharacterization	Reported biological or therapeutic activity	Reference
Vestitol, formononetin, biochanin A	Brazilian red propolis extract-loaded PLA polymeric nanocapsules with a tributyrin core and Poloxamer P407.	• DLS: 177.8 ± 3.3 nm. • PDI 0.06 ± 0.03. • zeta potential -7.7 ± 0.3 mV. • TEM: spherical core-shell nanocapsules, 188.6 ± 12.7 nm. • Encapsulation efficiency: biochanin A 97.56 ± 2.57%, vestitol 99.67 ± 0.07%, formononetin 99.7 ± 0.32%. • stable for 90 days.	Greater activity than free propolis extract against OVCAR-3 ovarian cancer cells in both 2D monolayer and 3D spheroid models.	[2]
Salicylic acid, total phenolics, total flavonoids	Optimized propolis solid lipid nanoparticles prepared by hot homogenization and ultrasonication using Tween 20.	• DLS: 71.97 ± 5 nm; • PDI 0.14. • zeta potential −10 ± 3 mV. • TEM: nearly spherical, 57.55 ± 15 nm. • XRD indicated an amorphous structure. • UV–Vis/FTIR retained phenolic- and flavonoid-associated characteristics.	Antioxidant activity (DPPH and ABTS IC_{50} ~0.028 mg/mL) and antibacterial activity against E. coli, S. aureus, B. subtilis, and P. aeruginosa (MIC 0.5, 0.25, 0.125, and 1 mg/mL). A549 IC_{50} decreased from 0.0451 ± 0.0065 to 0.0102 ± 0.0012 mg/mL from 24 to 72 h; human dermal fibroblast viability was not significantly reduced.	[18]
Chrysin (purified propolis-associated bioactive)	Chrysin-loaded stearic acid-modified Pluronic F68 nanomicelles.	• Particle size 142.73 ± 7.56 nm. • PDI 0.259 ± 0.114; • zeta potential −15.7 ± 4.72 mV. • maximum encapsulation efficiency 37.06 ± 0.62%. • drug loading 11%. • TEM showed spherical particles. • NMR, DSC, and XRD indicated amorphous chrysin incorporation.	Enhanced A549 cellular uptake, reduced viability, increased apoptosis, and reduced colony formation more than free chrysin. Oral administration produced ~5.6-fold higher plasma AUC than chrysin suspension.	[6]
Caffeic acid phenethyl ester (CAPE) (purified propolis-associated bioactive)	CAPE-loaded Pluronic micelles incorporated into an injectable self-healing chitosan–Pluronic hydrogel.	• Micellar nanostructures ~20 nm. • DLS assessed size/PDI, but exact PDI was not stated. • Micelles remained colloidally stable for 30 days. • CAPE release after 14 days was 44.6 ± 2.1% at pH 7 and 53.9 ± 3.1% at pH 4.	A single administration sustained CAPE release for ~2 weeks. In PC-3 prostate cancer xenografts, biweekly treatment enhanced tumor-growth suppression 2.7-fold versus weekly free CAPE and modulated Ki67, cyclin B1, NF-κB p65, phospho-MEK/RB, P21Cip1, and P27Kip1.	[7]
Chrysin (purified propolis-associated bioactive)	Chrysin-loaded fucose-functionalized generation-four polyamidoamine dendrimers.	• TEM: spherical particles, 17.84 ± 4.57 nm. • zeta potential +21.0 ± 1.5 mV. • chrysin loading ~46.9%. • encapsulation efficiency 63.1 ± 0.6%. • FTIR/NMR confirmed interactions. • XRD/DSC indicated amorphous chrysin.	Increased aqueous solubility, sustained release, and A549 uptake. IC_{50} was 1.5 ± 0.3 μg/mL at 24 h and 0.7 ± 0.3 μg/mL at 48 h; apoptosis increased and colony formation decreased. Unloaded fucosylated dendrimers were reported non-cytotoxic.	[29]

Chrysin (purified propolis-associated bioactive)	Chrysin-loaded phenylboronic acid-functionalized zinc oxide nanoparticles.	TEM diameter ~25–30 nm. hydrodynamic diameter 415.1 nm. zeta potential −17.36 mV. During 14-day stability testing, size was 428.56–436.46 nm with PDI 0.674–0.691. Drug loading 30.56%; entrapment efficiency 44.00%. At 48 h, chrysin release was ~59% at pH 5.0, ~14% at pH 6.0, and 9% at pH 7.4.	Enhanced A549 uptake and dose-dependent cytotoxicity without significant toxicity in normal L132 cells. It increased ROS, reduced mitochondrial membrane potential, induced intrinsic apoptosis and G0/G1 arrest, and inhibited migration/invasion by reducing MMP-2 and vascular endothelial cadherin.	[23]

Abbreviations: Purified propolis-associated bioactives are identified explicitly to distinguish them from whole-extract formulations. Abbreviations: CAPE, caffeic acid phenethyl ester; DLS, dynamic light scattering; EE, encapsulation efficiency; PDI, polydispersity index; TEM, transmission electron microscopy.

solvent, marker selection, and reporting of total phenolic or flavonoid content limit cross-study comparison. Second, nanocharacterization was inconsistent. Some studies reported complete particle size, polydispersity, zeta potential, morphology, and encapsulation data, whereas others omitted exact numerical values or showed substantial differences between microscopy and hydrodynamic measurements. Third, outcome methods varied widely, from chemical antioxidant assays and in vitro digestion to cell culture, bacterial models, and different animal disease models.

Most importantly, all included evidence was preclinical. Improved activity relative to a free extract or free compound does not by itself establish human efficacy, safety, dose equivalence, or biodistribution. Future studies should use chemically standardized propolis, predefined critical quality attributes, validated analytical methods, appropriate free-drug and blank-carrier controls, and physiologically relevant release media. Pharmacokinetic and biodistribution studies should precede well-designed toxicology and clinical evaluation. Whole-extract formulations and purified-bioactive formulations should also be interpreted separately because they differ in chemical complexity, mechanism, and regulatory requirements.

In our view, the future development of propolis as a modern natural product will depend on a shift from proof-of-concept nanoformulation toward standardized, mechanism-driven, and clinically translatable nanomedicine. Nanotechnology offers an opportunity to transform chemically complex propolis extracts from conventional natural preparations into more reproducible pharmaceutical products by improving solubility, stability, bioaccessibility, tissue exposure, and controlled delivery. Future research should therefore prioritize chemically standardized propolis preparations with defined botanical origin, extraction procedures, chemical fingerprints, and quantitative marker compounds, followed by the rational selection of nanocarriers according to the intended route of administration and therapeutic target.

The emerging use of surface-functionalized, stimuli-responsive, and multifunctional nanocarriers is particularly promising for achieving site-specific delivery and combining antimicrobial, anti-inflammatory, antioxidant, and regenerative effects within a single therapeutic platform. However, technological sophistication should be accompanied by rigorous assessment of pharmacokinetics, biodistribution, nanocarrier-related toxicity, stability, scalability, and manufacturing reproducibility. An important future direction is also the development of standardized quality attributes and comparative benchmarks that enable meaningful comparison between whole-propolis and purified-bioactive formulations.

Table 5. Nanoformulations evaluated for antioxidant, anti-inflammatory, cardiovascular, and other biological outcomes.

Propolis bioactive(s)/secondary metabolites	Nanoformulation	Nanocharacterization	Reported biological or therapeutic activity	Reference
Total flavonoids	Propolis extract-loaded chitosan/hyaluronic acid nanoparticles prepared by ionic gelation; selected formulation used a 4:7 chitosan:hyaluronic acid ratio and 1:2 core:wall ratio.	• Particle size 357.5 ± 14.1–378.3 ± 6.1 nm. • PDI 0.173 ± 0.019-0.424 ± 0.059. • zeta potential +21.0 ± 0.7 to +29.6 ± 1.7 mV. • entrapment efficiency 85.8 ± 0.3–91.2 ± 0.5%. • SEM showed smooth, glass-like structures.	Improved aqueous solubility (2.43-fold) and retained DPPH antioxidant activity; no cellular or in vivo therapeutic assay was performed.	[4]
Total phenolics	Propolis extract-loaded chitosan–tripolyphosphate nanoparticles prepared by ionic gelation.	• Particle size 350.000 ± 4.910–488.280 ± 4.291 nm. • PDI 0.305 ± 0.010–0.482 ± 0.022. • zeta potential +39.340 ± 0.814 to +48.200 ± 0.208 mV. • encapsulation efficiency 23.937-41.192%; pH 3.9-4.8.	DPPH antioxidant activity of ~0.0030–0.0072 mmol TE/mL, increasing with the amount of propolis incorporated.	[17]
Chrysin	Octenyl succinic anhydride-modified starch-stabilized chrysin oil-in-water nanoemulsion.	• Droplet size 82.10 ± 0.58 nm. • PDI 0.24 ± 0.02. • zeta potential −0.68 ± 0.14 mV. • encapsulation efficiency 99.19 ± 0.07%. • drug loading 0.0093 ± 0.00001%. • Physically stable for 30 days.	Increased chrysin bioaccessibility ~4-fold and enhanced membrane permeability. Anti-inflammatory activity was stronger than free chrysin, reducing LPS-induced ROS, IL-6, and PGE2 in RAW264.7 macrophages.	[5]
Galangin	Bovine serum albumin–galangin nanoparticles prepared by ethanol desolvation and pH-shifting.	• Ethanol desolvation: 58.95 nm, PDI 0.277. • pH shifting: 8.87 nm, PDI 0.199. • Both had >70% encapsulation efficiency at 50 μM galangin; pH shifting gave higher loading. • Morphology, zeta potential, FTIR, XRD, CD, fluorescence, and molecular interactions were evaluated.	Both scavenged free radicals/intracellular ROS and protected RAW264.7 cells from H_2O_2 injury, reduced LDH and IL-6, IL-1β, TNF-α, and IFN-γ, and increased IL-10. pH-shifted nanoparticles showed greater uptake and anti-inflammatory effects.	[22]
Chrysin	Chrysin-loaded self-assembled nanoparticles from debranched quinoa, maize, and waxy maize starches.	• Quinoa: 226.1 ± 0.02 nm, PDI 0.23 ± 0.030, zeta -18.32 ± 0.09 mV, EE 79.12 ± 0.11%, loading 25.20 ± 0.13%. • Maize: 234.7 ± 0.25 nm, PDI 0.28 ± 0.020, zeta −17.70 ± 0.12 mV, EE 74.27 ± 0.13%, loading 22.42 ± 0.07%. • Waxy maize: 230.3 ± 0.07 nm, PDI 0.34 ± 0.011, zeta −16.21 ± 0.04 mV, EE 77.42 ± 0.07%, loading 23.77 ± 0.06%. • HPLC confirmed chrysin.	Sustained chrysin release during simulated gastrointestinal digestion with retained DPPH/ABTS antioxidant activity; no disease model was evaluated.	[30]
Total phenolics and total flavonoids	Propolis-loaded PLA–PEG–PLA triblock copolymer nanovesicles prepared by thin-film hydration.	• TEM: spherical nanovesicles, 23-53 nm. • DLS confirmed nanoscale distribution, but exact mean DLS size and PDI were not reported. • Zeta potential -26.6 mV.	In isoproterenol-induced heart-failure rats, oral nanovesicles improved ejection fraction and fractional shortening by 26.75% and 19%, reduced BNP, galectin-3, IL-1β, IL-6, and IL-17, increased IL-10, and upregulated AMPK/SIRT1; effects were generally stronger than free propolis.	[19]

Chrysin	Chrysin-loaded chitosan nanoparticles prepared by ionic gelation.	Spherical particles; TEM size 49.7 ± 3.02 nm and SEM size 30–42 nm. Zeta potential +35.5 to +77.02 mV; encapsulation efficiency 92.63 ± 1.30%; ~90% chrysin released within 18 h. UV, FTIR, and XRD confirmed incorporation.	Inhibited mitochondrial complex II succinate dehydrogenase and ubiquinone oxidoreductase. IC_{50} values were 12.2 µg/mL in adult mouse liver mitochondrial preparations and 156 µg/mL in normal human fibroblasts.	[24]

Abbreviations: AUC, area under the concentration-time curve; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EE, encapsulation efficiency; PDI, polydispersity index; ROS, reactive oxygen species; TEM, transmission electron microscopy.

Table 6. Propolis nanoformulations evaluated for periodontal therapy and bone regeneration.

Nanotechnology platform	Principal advantage	Formulation-related benefit for propolis	Representative therapeutic potential
Nanoemulsion/nanoemulgel	Improved dispersion and bioaccessibility	Suitable for poorly water-soluble propolis constituents and topical delivery	Antimicrobial, wound healing
Polymeric nanoparticles/nanocapsules	High encapsulation and controlled release	Protection and sustained delivery of propolis bioactives	Anticancer, systemic delivery
Chitosan nanoparticles	Mucoadhesion and positive surface charge	Potential for local interaction with biological surfaces	Antimicrobial, mucosal delivery
SLN	Lipid compatibility and protection of lipophilic compounds	Improved stability and biological activity	Antimicrobial, gastrointestinal
NLC	Improved lipid loading and topical performance	Enhanced skin delivery and retention	Wound healing, dermatological
Niosomes	Flexible vesicular carrier and surface functionalization	Potential for targeted delivery	Targeted antimicrobial
Micelles	Solubilization of poorly water-soluble compounds	Improved exposure and sustained release	Oral and anticancer delivery
Dendrimers	Highly tunable surface functionality	Enhanced cellular uptake and targeting	Targeted anticancer
Protein/starch nanoparticles	Biocompatibility and gastrointestinal protection	Preservation of bioactivity	Oral delivery
Metal/MOF nanoparticles	Stimuli-responsive and functionalizable platform	Targeted and controlled delivery	Anticancer, periodontal
Nanoparticle-loaded hydrogels	Local retention + controlled nanoparticle delivery	Multifunctional local therapy	Wound healing, periodontal regeneration

Ultimately, the most promising propolis nanoformulations should progress through a translational pathway encompassing scalable manufacturing, comprehensive preclinical safety and efficacy studies, regulatory assessment, and well-designed clinical trials. Such an approach could position nanotechnology-enabled propolis not merely as an improved natural extract, but as a standardized and

evidence-based natural product platform with potential for modern pharmaceutical applications.

"Overall, the reviewed evidence demonstrates that the advantages of propolis nanoformulations are platform-dependent, with different nanocarriers offering specific benefits such as improved solubility and bioaccessibility, enhanced encapsulation, controlled release, targeted delivery, or prolonged local retention. These complementary advantages and their prospective therapeutic applications are summarized in **Table 6**.

CONCLUSION

Nanotechnology-based formulations have substantially expanded the pharmaceutical potential of propolis and its associated bioactives by addressing key limitations related to aqueous solubility, physicochemical stability, bioaccessibility, controlled release, and biological exposure. Across the 25 studies included in this review, nanoemulsions, polymeric and chitosan nanoparticles, lipid-based systems, niosomes, nanovesicles, micelles, dendrimers, protein- and starch-based nanoparticles, metal–organic frameworks, and nanoparticle-loaded hydrogels demonstrated formulation-dependent advantages across antimicrobial, wound-healing, periodontal, anticancer, anti-inflammatory, antioxidant, and cardiovascular applications. Their respective advantages and prospective applications are summarized in **Table 6**.

Importantly, the current evidence indicates that the future value of propolis nanotechnology will depend not simply on increasing formulation complexity, but on achieving a rational relationship between standardized propolis chemistry, nanocarrier characteristics, route of administration, biological target, and therapeutic outcome. The major challenge remains the transition from heterogeneous preclinical proof-of-concept studies to reproducible and clinically translatable pharmaceutical products. Therefore, future research should prioritize chemical standardization, predefined critical quality attributes, scalable manufacturing, comparative pharmacokinetic and biodistribution studies, long-term safety assessment, and appropriately designed clinical trials. With these translational requirements addressed, nanotechnology has the potential to transform propolis from a chemically variable natural extract into a more standardized, targeted, and evidence-based platform for modern natural product therapy.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation

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