

Review

Propolis-Functionalized Biomaterials for Wound Healing: A Systematic Review with Emphasis on Polysaccharide-Based Platforms

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Abstract

Wound healing is a complex process, and propolis, a natural resin with antimicrobial, anti-inflammatory, and antioxidant properties, emerges as a promising candidate for its treatment. This systematic review analyzed 26 studies on propolis-functionalized biomaterials. Great diversity was observed in materials and incorporation techniques, including direct blending, surface coating, and nanoencapsulation. Mostly based on polysaccharides like chitosan, pectin, and bacterial cellulose, these formulations showed biocompatibility, biodegradability, and promoted inflammation reduction and tissue repair. In vitro assays confirmed high biocompatibility (>80% cell viability) and antimicrobial activity, while in vivo studies validated regenerative benefits. Despite their potential, marked heterogeneity in propolis composition (intrinsically variable due to its botanical and geographical origin, and processing methods), coupled with diverse concentrations used and the lack of standardization in assessment methods and results reporting, significantly limits cross-study comparability and reproducibility. Overcoming these challenges requires promoting greater standardization in extraction, characterization, and evaluation protocols, including chemical fingerprinting and more detailed and consistent reporting of findings. Despite these limitations, propolis–polysaccharide systems hold strong clinical potential, with further standardization and well-designed preclinical studies being essential for their effective translation, especially in chronic wound management.

Keywords: propolis; bee glue; biomaterials; polysaccharides; wound healing; wound therapy; regenerative medicine



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1. Introduction

The skin, as the largest organ of the human body, plays a vital role in maintaining physiological balance by serving as a dynamic barrier that protects against continuous physical, chemical, and biological aggressions [1]. When this barrier is compromised, whether by trauma, burns, surgical procedures, or chronic illnesses, the risk of infection increases significantly, healing processes are delayed, and the likelihood of serious complications rises, often leading to a diminished quality of life for the patient [2]. Both acute and chronic skin wounds represent a growing global public health concern, with a high prevalence and

considerable impact on healthcare systems. In developed countries, the incidence of chronic wounds ranges from 1% to 2% of the population at any given time, a rate that continues to rise due to population aging and the increasing prevalence of lifestyle-related diseases [3]. Among these, pressure ulcers are particularly common, with a global prevalence of 12.8% and a hospital incidence of 8.4% [4]. Additionally, venous ulcers affect approximately 1% of individuals aged 18 to 64 years worldwide [5] further underscoring the global burden of chronic wounds.

The wound healing cascade is a multi-stage biological event that progresses through four interdependent and overlapping stages: hemostasis, where rapid vasoconstriction and clot formation occurs to prevent blood loss; inflammation, where immune cells including neutrophils and macrophages clear pathogens and debris; proliferation that includes migration of fibroblasts, angiogenesis, deposition of an extracellular matrix and re-epithelialization; and remodeling when the collagen is reorganized to restore tissue strength and function [6]. Nevertheless, a variety of conditions, such as diabetes, ischemia, and chronic infections, can disrupt these phases, resulting in chronic, non-healing wounds that pose an important clinical burden [7].

Although numerous developments have been made in wound management, selecting an appropriate dressing remains one of the most persistent challenges, particularly for skin wounds and burn injuries. An ideal dressing should strike a thoughtful balance between therapeutic effectiveness, patient safety, and economic feasibility [8]. It should be biocompatible and biodegradable, and allow adequate water vapor transmission to maintain a moist environment that promotes continuous tissue regeneration throughout all stages of healing. Additionally, the dressing should conform gently to the wound bed without adhering to the tissue, while also serving as an effective barrier against microbial contamination, mechanical stress, and thermal fluctuations [9].

Advanced wound dressings, also known as high-tech dressings, have been developed to overcome the limitations of conventional materials. These interactive products can modulate the wound microenvironment by controlling moisture, temperature and pH to promote healing processes, such as granulation and re-epithelialization, and prevent infection. As a multifunctional design, they promote tissue regeneration, attenuate inflammation and play a role in accelerating wound healing [10]. Some of the most studied biomaterials include hydrogels, electrospun nanofibers, polymeric membranes, and modified biocellulose. So, depending on the origin or the substrate, they can be classified into natural, synthetic, or hybrid biomaterials. All these can be modified or functionalized by conjugating additional compounds to improve their therapeutic efficacy [11].

Propolis, often referred to as “bee glue,” is a resinous material collected by honeybees (*Apis mellifera* L.) from plant exudates, which they blend with beeswax, salivary enzymes, and pollen (Figure 1). Within the beehive, propolis plays an essential role in maintaining colony hygiene by sealing small openings, reinforcing structural integrity, and even embalming intruders to prevent microbial proliferation [12]. Its chemical complexity is remarkable and highly variable, as it is influenced by factors such as the botanical source, geographical region, climate conditions, bee species, and methods of collection and processing. On average, propolis is composed of more than 300 distinct compounds, including approximately 50% plant resins, 30% waxes, 10% essential oils, 5% pollen, and 5% other organic substances [13]. This intricate and dynamic composition underlies the wide range of biological activities attributed to propolis, which have garnered increasing interest in biomedical research. It is primarily composed of flavonoids, phenolic acids, terpenoids, aldehydes and amino acids which are responsible for its documented antimicrobial [14–16], anti-inflammatory [17,18], antioxidant [19,20], antifungal [21,22], antiviral [23,24], antiprotazoan [25], antitumor [26,27] and wound healing [28,29] properties.

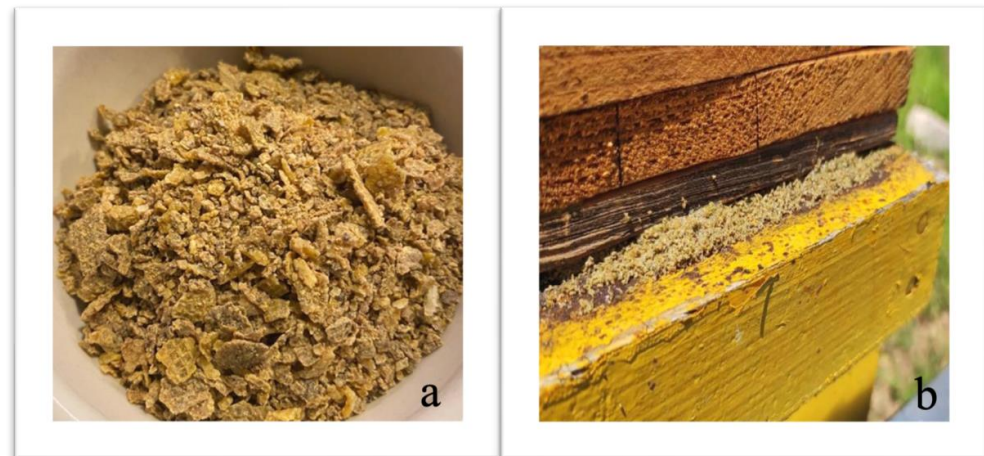


Figure 1. Propolis samples. (a) Raw propolis harvested using the mesh technique. (b) Propolis inside a beehive. Photographs courtesy of Apiarios del Cielo, Chihuahua, Mexico.

According to several studies, the incorporation of propolis in dressings based on biopolymers, such as chitosan, pectin and biocellulose, can favor cell adhesion, stimulate fibroblast proliferation, and promote the regeneration of damaged tissue, in addition to providing an antimicrobial barrier to pathogenic bacteria and yeasts frequently involved in wound infections [30].

Although significant progress has been made in the development of propolis-enriched biomaterials, the current literature reveals inconsistencies regarding the effectiveness of the various incorporation strategies and the underlying mechanisms responsible for their bioactivity in wound healing. In light of these gaps, this systematic review aims to summarize state-of-the-art approaches for the development of propolis-based dressings and to assess their impact on the wound healing process.

2. Materials and Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor and transparency in the selection and analysis of the relevant scientific literature.

2.1. Search Strategy

An extensive search was conducted in the PubMed database using the following set of keywords with Boolean operators: “propolis” AND “biomaterials” AND “wound healing”. No time restrictions were applied to ensure the inclusion of all relevant studies.

2.2. Inclusion Criteria

The inclusion criteria considered studies that evaluated the use of propolis in biomaterials developed for wound healing, described their synthesis and characterization, and assessed their effects in *in vitro* or *in vivo* models. Only articles published in English were included. Additionally, studies that tested multiple components independently, where propolis was evaluated as a separate variable, were also considered provided that the specific effects of propolis could be clearly distinguished.

2.3. Exclusion Criteria

Studies unrelated to wound healing and review articles were excluded. Likewise, studies that did not use propolis, or that used it without incorporating it into a biomaterial, were not considered. Articles in which propolis was combined with other components in a way that prevented independent evaluation of its effects were also excluded. Furthermore,

clinical studies involving human participants were not included. Finally, articles for which full-text access was not possible, despite documented retrieval efforts, were excluded, in accordance with PRISMA 2020 guidelines. The specific reasons for exclusion and the number of studies excluded for each criterion are detailed in Figure 2 to enhance methodological transparency.

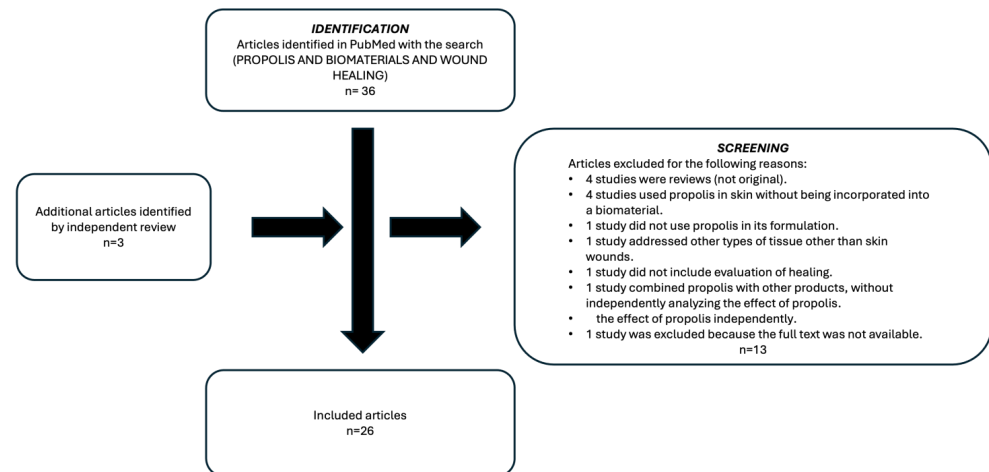


Figure 2. Flow diagram illustrating the article search strategy and the screening steps used to determine the inclusion or exclusion of studies in the systematic review. Figure created by the authors.

2.4. Study Selection Process

The selection of articles was carried out in sequential stages. The screening followed a three-phase process: phase one involved reviewing titles and abstracts for relevance and alignment with the inclusion criteria; phase two focused on the removal of studies that did not meet eligibility requirements. Subsequently, during the full-text evaluation phase, each article was assessed in detail based on the predefined criteria. Two independent reviewers conducted the selection and assessment of the studies. No discrepancies were identified that required the intervention of a third reviewer.

2.5. Data Extraction and Analysis

Data extracted from each included study included bibliographic information (author, year, country), the base material of the biomaterial, its physical form, and the type and concentration of propolis used. Additionally, chemical and morphological characterization, mechanical and thermal properties, degradation behavior, fluid interactions, and biological properties assessed through both in vitro and in vivo models were recorded. In studies involving authors from multiple countries, the country of the corresponding author was considered. All extracted information was organized into comparative tables to facilitate analysis and synthesis.

2.6. Methodological Quality Assessment

To assess the methodological quality of preclinical studies included in this review, an evaluation tool was specifically adapted based primarily on the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments).

The instrument covered three domains: biomaterial synthesis and characterization, biological evaluation, and overall study design and reporting. Each item was scored on a three-point scale (0–2), and total scores classified studies as high (27–32), moderate (20–26), or low quality (0–19), providing a systematic and reproducible basis for evaluating the reliability of the included evidence.

2.7. Analysis of the Results

The results were structured in comparative tables and graphical representations to facilitate interpretation and strengthen the discussion of the findings.

2.8. Use of Generative Artificial Intelligence

The authors used ChatGPT (OpenAI, GPT-4) during the preparation of this manuscript to support the translation of the content, as well as the editing and enhancement of the clarity and coherence of the text. All materials were thoroughly reviewed and validated by the authors, who take full responsibility for the final version of the manuscript.

3. Results

This systematic review was based on a PubMed search using the terms “propolis AND biomaterials AND wound healing”, which initially yielded 36 articles that met the preliminary inclusion criteria. After applying the defined inclusion and exclusion criteria, 13 studies were excluded. In addition, 3 relevant studies identified independently by the reviewers and meeting the eligibility criteria were included. As a result, a total of 26 studies were analyzed in the final review [31–56] (Figure 2). The results of the methodological quality assessment showed that 92.3% of the included preclinical studies were rated as high quality, while 7.7% were rated as moderate quality. Importantly, none of the studies were excluded based on methodological quality, as all met the minimum criteria for inclusion. This distribution reflects a generally strong adherence to methodological standards across the selected studies.

The year 2024 accounted for the highest number of publications, with a total of 8 articles, followed by 2019, which contributed 7 studies. Geographically, the country with the greatest number of contributions was Iran, with 11 publications, followed by Brazil (7) and Egypt (3). Other countries with individual contributions included Turkey (2), and Saudi Arabia, India, and Thailand (1 each), suggesting a strong regional research emphasis in the Middle East and South America (Table 1).

A wide variety of biomaterials was observed across the included studies. Natural based biomaterials were the most frequently employed, even when slight chemical modifications were applied to enhance their functional properties. Hybrid biomaterials, composed of both natural and synthetic components, were the second most used category. In contrast, purely synthetic biomaterials were the least frequently reported (Figure 3). Bacterial cellulose, natural rubber latex, and polycaprolactone were among the most frequently used base materials. These were often combined with other natural or synthetic polymers such as chitosan, gelatin, polyurethane, pectin, or hyaluronic acid, and fabricated into various forms including electrospun nanofibers, hydrogels, aerogels, films, and bilayer wound dressings. These formulations enabled efficient incorporation of propolis and provided suitable properties for topical application. Among the various strategies for incorporating propolis, direct incorporation into the formulation mixture was the most frequently reported method. Table 1 summarizes the general characteristics of the included studies, arranged in chronological order from the most recent to the oldest. It provides information on the country of origin, the base material used, the physical form of the biomaterial, and the type and concentration of propolis employed.

The most frequently employed form of propolis was the ethanolic extract (EEP), although some studies used aqueous extracts or standardized commercial formulations such as EPP-AF[®]. Among the studies that reported specific concentrations, values ranged from 0.5% to 30%, with common ranges between 2% and 10% (Table 1).

Table 1. General characteristics of the included studies: origin, biomaterial composition, physical form, and type and concentration of propolis used.

Reference	Country	Base Biomaterial	Biomaterial Form	Type and Concentration of Propolis
[31]	Turkey	Methacrylated pullulan (PULMAN)	Photocurable hydrogel-type film	Ethanollic propolis extract (Turkey), used at 0.5%, 0.1%, and 2% (<i>w/w</i> of solid polymer)
[32]	Saudi Arabia	Microcrystalline cellulose and chitosan (CS)	Electrospun nanofibers mats	Propolis powder (from northern Tunisia), incorporated at 2% <i>w/v</i> into polymer solution.
[33]	Brazil	Polyacrylamide and methylcellulose hydrogel	Hydrogel	Propolis extract (from Brazil) incorporated at 1.0% and 2.5% <i>w/v</i> .
[34]	Iran	Dialdehyde xanthan gum and soy protein isolate	Crosslinked self-healing nanocomposite film	Ethanollic extract of propolis (Mashhad, Iran), 1 wt% and 3 <i>w/w</i> %
[35]	Iran	Bilayer scaffold consisting of 3D-printed PCL coated with propolis and electrospun PVA/CS/PCL nanofibers loaded with diltiazem hydrochloride.	Bilayer membrane: 3D-printed scaffold with electrospun nanofiber overlay.	Ethanollic propolis extract (from hives in Isfahan, Iran) applied as a coating in 30% ethanol (no exact concentration on scaffold reported).
[36]	Iran	Poly(lactic-co-glycolic acid) (PLGA)	Nanoparticles	Ethanollic extract of propolis (exact concentration not specified.)
[37]	Iran	Silica–oxidized silk fibroin–chitosan–propolis (silica–SFO–CS–PP) scaffold.	3D-printed aerogel scaffold	Propolis extracted with ethanol (EEP) and methylal (EMP), including EEP-CS and EMP-CS nanoparticle forms. Specific mass concentration not reported.
[38]	Egypt	Marine collagen–chitosan gel functionalized with zinc oxide nanoparticles (ZnO–NPs) and propolis.	Bioactive gel	Raw propolis from Mansoura (Egypt), used at 0.25 g (PP2) and 0.5 g (PP1) in ZnO–NPs synthesis; final gel concentrations 1.67% and 3.3% <i>w/v</i> .
[39]	India	Polyvinyl alcohol (PVA)	Hydrogel	Indian propolis extract; 4 g incorporated into hydrogel (concentration not expressed as % <i>w/w</i>).
[40]	Thailand	Quaternized chitosan (QCS) and pectin	Hydrogel film	Green propolis (Chiang Mai, Thailand), 0.5% <i>w/v</i>
[41]	Brazil	Polycaprolactone (PCL)	Electrospun nanomats (fiber, beaded fiber, beads only)	Ethanollic extract of Brazilian green propolis (Apis Flora, São Paulo, Brazil); 15% <i>v/v</i> added to polymer solution.
[42]	Iran	Polycaprolactone (PCL), Chitosan (CS), and Polyurethane (PU) coated with ethanollic extract of propolis (EEP).	Electrospun fibrous sublayer + PU foam top layer = bilayer wound dressing (BWD).)	Ethanollic extract of propolis (EEP) from Isfahan, Iran; concentration not specified.

Table 1. Cont.

Reference	Country	Base Biomaterial	Biomaterial Form	Type and Concentration of Propolis
[43]	Turkey	Polyvinyl alcohol (PVA) and chitosan crosslinked with genipin.	Membranes (PVA/C, PVA/C-P1, PVA/C-P2)	Ethanol extract of propolis from Istanbul, Turkey; 0.25% and 0.50% <i>v/v</i> .
[44]	Iran	Polyurethane (PU) foam with nanolignin (NL), coated with ethanolic extract of propolis (EEP).	Porous coated foam	Ethanol extract of propolis from Shahr-e Kord (Iran); used as coating (exact concentration not specified).
[45]	Egypt	Deacetylated cellulose acetate nanofibers loaded with chitosan/propolis nanoparticles.	Electrospun nanofibers	Ethanol extract of propolis (Egypt); 10 mg used in nanoparticle formulation.
[46]	Iran	Cellulose acetate (CA) and polycaprolactone (PCL).	Electrospun nanofibrous	Ethanol extract of propolis from Khansar, Iran. Concentration not explicitly quantified.
[47]	Brazil	Natural rubber (<i>Hevea brasiliensis</i>) and aqueous extract of propolis.	Membrane (cast film).	Aqueous extract of propolis from <i>Scaptotrigona polysticta</i> , Brazil; 10% <i>w/w</i> relative to natural rubber.
[48]	Egypt	Polyvinyl alcohol, chitosan, and honey	Electrospun nanofibers	Aqueous extract of propolis (PP), loaded at 10% <i>w/w</i> in the HPCS nanofiber matrix.
[49]	Brazil	Natural rubber latex (NRL)	Cast membranes	Three types: green, red, and poplar propolis; incorporated as ethanol extract (1 mL of extract in 3 mL of NRL).
[50]	Iran	Cornstarch blended with hyaluronic acid (HA) and ethanol extract of propolis (EEP)	Solvent-cast film	Ethanol extract of propolis from Isfahan, Iran; used at 0.25%, 0.5%, and 1% <i>w/w</i> .
[51]	Brazil	Bacterial cellulose (BC)	Membrane (BC/PP membrane)	Propolis EPP-AF [®] soft extract in self-microemulsifying formulation (SMEF); final amount in BC/PP membrane: 5 mg/cm ² (dry matter), with 84.25 µg/cm ² of <i>p</i> -coumaric acid and 306.25 µg/cm ² of artemillin C.
[52]	Brazil	Bacterial cellulose (BC)	Membrane	Brazilian green propolis standardized extract (EPP-AF); incorporated via ethanol solutions at 1.2%, 2.4%, and 3.6% <i>w/v</i> .
[53]	Brazil	Bacterial cellulose	Membrane impregnated with extracts	Red propolis from Northeastern Brazil; ethyl acetate and butanol extracts at 1% (<i>w/v</i>) concentration.

Table 1. Cont.

Reference	Country	Base Biomaterial	Biomaterial Form	Type and Concentration of Propolis
[54]	Iran	Polyurethane (PU), coated with water extract of propolis (WEP).	Porous foam wound	Water extract of propolis (WEP) from Isfahan, Iran; used at 10%, 20%, and 30% <i>v/v</i> .
[55]	Iran	Polyurethane (PU) and hyaluronic acid (HA), enriched with ethanolic extract of propolis (EEP).	Electrospun nanofibers	Ethanolic extract of propolis (EEP) from Isfahan, Iran; used at 0.5%, 1%, and 2% <i>w/w</i> .
[56]	Iran	Polyurethane (PU) membrane with ethanolic extract of propolis (EEP) and electrospun Polycaprolactone/Gelatin (PCL/Gel) nanofibers.	Bilayer wound dressing (PU/EEP membrane as top layer, PCL/Gel scaffold as sublayer).	Iranian ethanolic extract of propolis; 0.5% <i>w/w</i> in PU layer.

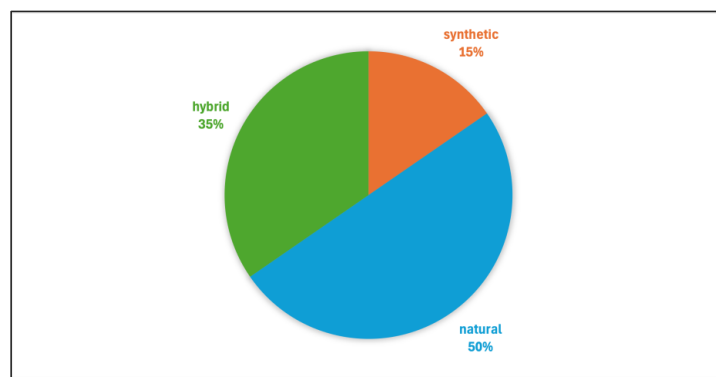


Figure 3. Classification of biomaterials and methods of propolis incorporation. Distribution of the biomaterials included in the review based on their origin: natural, hybrid, and synthetic. Materials classified as natural were those derived from plant, animal, or microbial sources, even when chemically modified, provided their biological origin remained predominant. Figure created by the authors.

Regarding chemical and morphological analyses, most studies used techniques such as FTIR, SEM, and, in some cases, NMR, TEM, XRD, or GC-MS to confirm the incorporation of propolis and the homogeneous structure of the biomaterial. For example, Bal-Öztürk et al. confirmed the homogeneous dispersion of propolis using FTIR and NMR [31], while Sharaf et al. [45] employed FTIR, SEM, and TEM to validate the formation of nanofibers and nanoparticles.

In terms of mechanical properties, values for tensile strength and elongation varied significantly. Materials with high elasticity, such as that reported by Bal-Öztürk et al. [31] (848% elongation), contrasted with others like that of Phonrachom et al. [40], which exhibited higher strength (33.96 MPa), reflecting the diversity in formulations and compositions used. With respect to thermal stability, studies employing thermal analyses (mainly TGA and DSC) reported major degradation events ranging from 225 °C to over 575 °C, depending on the system. For instance, the aerogels developed by Vaseghi et al. [37] showed high thermal stability, with degradation beginning at 358 °C.

Degradation behavior was evaluated in media such as PBS or under enzymatic conditions. Some materials, such as that reported by Mehdikhani et al. [35], showed up to 68.75% weight loss in only three days, while others like those described by Eskandarinia et al. [56] presented 78% enzymatic degradation over 14 days. Finally, in terms of fluid interaction, swelling capacity, and propolis release, several studies reported high water absorption and controlled release profiles. For instance, Ferreira et al. [33] reported water absorption up to 1541%, while Barud et al. [52] documented a release of up to 60.2% of p-coumaric acid at 24 h. These findings, compiled in Table 2, provide an essential comparative overview of the most relevant physicochemical characteristics of propolis-functionalized biomaterials, which are fundamental for assessing their applicability in the biomedical field.

The main biological results of the studies included in Table 3 provide evidence of the beneficial properties of propolis-functionalized biomaterials for wound healing and infection control. In *in vitro* models, most studies reported high cell viability, antimicrobial activity, especially against *Staphylococcus aureus* and *Escherichia coli* and antioxidant capacity as determined by DPPH assays [31,34,46]. Cell adhesion and proliferation, as well as scratch assays showing wound closure capacity, were also frequently documented [35,40].

Table 2. Physicochemical and functional characterization of propolis-based biomaterials for wound healing.

Reference	Chemical and Morphological Analysis	Mechanical Properties	Thermal Properties	Degradation Behavior	Fluid Interaction, Swelling, Propolis Release, and Vapor Transmission	Main Findings
[31]	FTIR and NMR confirmed chemical structure; homogeneous dispersion with propolis.	Modulus 2.55 MPa, strength 2.48 MPa, elongation 848%.	TGA/DSC showed stability, degradation ~225 °C.	50–60% weight loss in PBS over 2 weeks.	Swelling decreased with propolis; release equilibrium at 24 h.	Good mechanical, thermal and fluid properties; homogeneous structure.
[32]	FTIR and SEM confirmed crosslinking and uniform fiber formation.	Strength 7.42–8.27 MPa, modulus 174.61–199.08 MPa.	Not reported	Not reported	Swelling 436–438%; WVP 1698–1735 g/m ² /day.	Hydrophilic scaffold; good fiber morphology and moisture transmission.
[33]	XRD confirmed amorphous structure; porosity increased with 2.5% propolis.	Not reported	Not reported	Not reported	Swelling up to 1541%; high solubility at 2.5%.	Excellent fluid interaction; high swelling and porosity.
[34]	FTIR, XRD, SEM and EDX confirmed chemical bonding and uniform structure.	Strength 16.9 MPa, elongation 14.2%; improved with HNTs.	TGA: three stages; higher residue with HNTs.	24% loss with 7% HNTs in 10 days.	Increased swelling with PP; no release data.	Good mechanical and thermal behavior; tunable degradation and swelling.
[35]	FTIR and SEM confirmed hydrogen bonding; uniform nanofiber distribution.	Strength 2.05–4.86 MPa, modulus 3.35–6.58 MPa.	Not reported.	Up to 68.75% loss in 3 days; pH dependent.	Swelling ~496%; DTZ release controlled in bilayer.	Balanced mechanical and degradation profile; pH-responsive system.
[36]	FTIR, TEM and FE-SEM showed spherical nanoparticles and propolis inclusion.	Not reported	Not reported	Not reported	Not reported	Nanoparticles with confirmed structure; no performance data.
[37]	FTIR, SEM and UV–Vis confirmed interactions and hierarchical structure.	Not reported	Degradation above 575 °C; improved stability.	Varied by formulation over 6 days.	Good swelling; release studied at pH 2 and 7.	High thermal stability; functional swelling and release.
[38]	XRD, TEM and DLS confirmed nanoparticle morphology and propolis loading.	Not reported	Not reported.	Not reported	Not reported	Confirmed nanostructure; no release data.
[39]	FTIR and DSC confirmed uniform dispersion and molecular interaction.	Strength 198.18 g; comparable to povidone-iodine.	DSC showed absence of propolis peaks, indicating dispersion.	Not reported	Biphasic release: 40% in 40 min, sustained 4 h.	Stable hydrogel with good mechanical strength and release profile.
[40]	FTIR and SEM confirmed smooth, homogeneous surfaces with good compatibility.	Strength 33.96 MPa, modulus 20.21 MPa; elongation decreased.	Not reported	Higher degradation in QCS/Pec than QCS.	Swelling ~600%; 64% release in 48 h.	Robust mechanical performance; good release and antioxidant profile.
[41]	FTIR and SEM confirmed morphology and phytochemicals; GPC showed polymer degradation.	Not reported	DSC: dual melting peaks; TGA: single degradation ~383–404 °C.	Not reported	Burst release in 30 min; equilibrium at 2 h.	Controlled release and thermal behavior; propolis stability confirmed.
[42]	SEM and FTIR confirmed successful incorporation of functional groups.	Strength ~6 MPa; elongation ~350%.	Not reported	28-day weight loss ranged 3–28%.	Swelling varied; contact angle ~58°.	Enhanced hydrophilicity and swelling; validated incorporation.

Table 2. Cont.

Reference	Chemical and Morphological Analysis	Mechanical Properties	Thermal Properties	Degradation Behavior	Fluid Interaction, Swelling, Propolis Release, and Vapor Transmission	Main Findings
[43]	FTIR, SEM, and XRD confirmed propolis crosslinking and reduced crystallinity.	Strength 12.72 MPa; elongation 58.68%.	Not reported	Weight loss increased over 9 days.	WVTR 75.16–106.15 g/m ² /day; angle ~45°.	Improved mechanical performance; good degradation and hydrophilicity.
[44]	FTIR, SEM and DLS confirmed chemical interactions and nanostructure.	Strength ~0.91 MPa; elongation ~73–96%.	Not reported	Not reported	Absorption ~267%; angle ~50°.	Meets tensile requirements; good hydrophilicity and absorption.
[45]	FTIR, SEM and TEM confirmed deacetylation and nanofiber formation.	Not reported	DSC: 325 °C exothermic peak confirms incorporation.	Slow dissolution over 7 days.	36.2% at 48 h; 51.6% at 264 h.	Stable nanofibers; slow release and reduced dissolution.
[46]	FTIR and SEM confirmed propolis coating; smooth nanofibers observed.	Not reported	Not reported	Not reported	Absorption 400%; treated mats fully hydrophilic.	Hydrophilic nanofibers; high water retention.
[47]	Microscopy showed propolis modified surface and porosity.	Not reported	Not reported	Not reported	Angle decreased to ~65°, more wettability.	Wettability improved with propolis.
[48]	FTIR and SEM confirmed stable incorporation of propolis.	Not reported	Not reported	Not reported	Not reported.	Stable matrix; data lacking for behavior.
[49]	UHPLC and FTIR confirmed classification and no new bonds.	Strength increased with red and poplar propolis.	Not reported	Not reported	Release: Green 54.2%, Red 41.5%, Poplar 49.0%.	Safe profiles; different release by propolis type.
[50]	FTIR, SEM and GC-MS confirmed bioactive compound integration.	Strength decreased with EEP; elongation increased.	Not reported	Hydrolytic: 31% in 1 week; enzymatic: 87% in 24 h.	EEP release up to 74% in 48 h.	Bioactive integration; sustained degradation and release.
[51]	HPLC and laser diffraction confirmed compound incorporation and droplet size.	Not reported	Not reported	Not reported	90% p-coumaric acid, 24% artemillin C in 48 h.	Efficient compound release over time.
[52]	SEM, XRD, FTIR and TGA confirmed surface and thermal changes.	Not reported	TGA: extended degradation up to 450 °C.	Not reported	24 h: p-coumaric 60.2%, isosakuranetin 53.9%.	Effective delivery of bioactive compounds.
[53]	HRMS and UFLC confirmed flavonoid quantification.	Not reported	Not reported	Not reported	Progressive decline of compound over 14 days.	High flavonoid content; release data confirms activity.
[54]	FTIR and SEM confirmed coating; pore structure remained unchanged.	Strength 2.99 MPa; elongation 434%.	Not reported	Not reported	Uptake decreased with WEP; angle 35.53°.	High hydrophilicity; mechanical compromise with WEP.
[55]	FTIR and SEM confirmed porous fibers; porosity > 80%.	Strength decreased with EEP; elongation increased.	Reduced stability with EEP; onset 300–460 °C.	Not reported	Sustained release over 48 h; 43% total.	Thermally stable; effective propolis release and absorption.
[56]	FTIR, SEM and GC-MS confirmed EEP incorporation and nanofiber formation.	Strength ~5.8 MPa; elongation ~340%.	TGA: lower temp with EEP; mass loss from gelatin moisture.	Enzymatic: 78% loss in 14 days.	Hydrophilic sublayer; release up to 48 h.	Good hydrophilicity and sustained release in bilayers.

Table 3. In vitro and in vivo biological evaluations propolis-containing biomaterials for wound healing applications.

Reference	Technique Used	Antibacterial Assay Results	MTT Assay	In Vivo Biological Properties
[31]	Agar disk diffusion	<i>S. aureus</i> ATCC 25923: 20.6–26.2 mm with propolis, compared 23.1 mm. <i>E. coli</i> ATCC 25923: 10.5–13.7 mm with propolis compared 11.3 mm without propolis.	NIH/3T3 fibroblasts. Viability: 93.73%, 90.47%, 81.74%, 61.04% for increasing PRO; $p < 0.05$. Biocompatible; dose-dependent cytotoxicity; optimal at 90.47%	Not reported
[32]	Agar disk diffusion	<i>M. luteus</i> : 15.0–25.8 mm with propolis, compared to 25.8 mm without propolis. <i>S. aureus</i> : 14.0–19.3 mm with propolis, compared to 23.8 mm without propolis. <i>E. coli</i> : 11.0–15.2 mm with propolis, compared to 18.0 mm without propolis. <i>P. aeruginosa</i> : 12.0–17.5 mm with propolis, compared to 20.0 mm without propolis	HepG2 (human hepatocellular carcinoma), fibroblasts. Improved metabolic activity over 24–72 h; 70/30 CA/CS blend $> 90/10$; $p < 0.05$. No cytotoxicity; excellent biocompatibility; improved fibroblast activity due to propolis	Not reported
[33]	Microdilution in plates	<i>S. aureus</i> : 93–97% with propolis; ~100% with standard drug. <i>P. aeruginosa</i> : >80 –100% with propolis; ~90% with propolis hydrogel; 100% only at high drug concentrations. <i>E. coli</i> : ~80–90% with propolis extract; no inhibition with hydrogels; >90 % only at high drug concentrations	Not reported	Not reported
[34]	Agar disk diffusion	The activity was more potent against <i>Staphylococcus aureus</i> than against <i>Escherichia coli</i> . It does not provide specific numerical values (in millimeters) for the diameter of these inhibition zones	NIH3T3 fibroblasts. All samples promoted proliferation; no dead cells. High cytocompatibility; synergistic effect of PP and HNTs.	Not reported
[35]	Well diffusion and Kirby–Bauer	<i>S. aureus</i> . Propolis: 10–17 mm (well); membrane 2–15 mm (Kirby–Bauer)	L929 fibroblasts. >80 % viability (P1/P2); 99.89% for PCP-10; <30 % for PCP-12. Safe up to 10% DTZ; hydrophilic scaffolds promote attachment.	Wistar rats; full-thickness skin defect. 95.3% closure at 14 days (vs 75.3% control); reduced IL-1 β , TNF- α ; enhanced collagen, granulation, and epidermis formation
[36]	Not reported	Not reported	Not reported	Rats; 20 mm full-thickness wound. EEPNPs enhanced angiogenesis, fibroblast growth, and contraction; reduced inflammation and infection
[37]	Agar disk diffusion	Post-printed modified scaffolds reached up to 2.5 cm against <i>E. coli</i> and 1.5 cm against <i>S. aureus</i> , while pre-printed scaffolds showed no obvious bactericidal properties or ZOI.	L929 fibroblasts. Viability: up to 120% (SFO-PM-CH); PE scaffold toxic at high propolis. Optimal at 200 $\mu\text{g/mL}$; post-printing modification improved performance	Not reported
[38]	Agar disk diffusion	The gel loaded with 5% PP1/ZnO-NPs showed inhibition zones of 9 ± 0.08 mm (<i>E. coli</i>), 10 ± 0.84 mm (<i>S. typhimurium</i>), 10 ± 1.05 mm (<i>S. mutans</i>), and 7 ± 0.05 mm (<i>C. albicans</i>). The 10% PP1/ZnO-NPs gel was the most effective overall, with inhibition zones of 26 ± 2.31 mm (<i>E. coli</i>), 25 ± 2.73 mm (<i>S. typhimurium</i>), 20 ± 1.99 mm (<i>S. mutans</i>), and 12 ± 0.91 mm (<i>C. albicans</i>). In comparison, gels with 5% PP2/ZnO-NPs produced inhibition zones of 14 ± 1.42 mm, 15 ± 1.88 mm, 16 ± 1.76 mm, and 8 ± 0.07 mm for the same microorganisms, respectively. The 10% PP2/ZnO-NPs gel showed increased activity, with inhibition zones of 21 ± 1.51 mm (<i>E. coli</i>), 19 ± 1.92 mm (<i>S. typhimurium</i>), 19 ± 1.79 mm (<i>S. mutans</i>), and 10 ± 1.01 mm (<i>C. albicans</i>).	Not reported	Sprague-Dawley rats; 2×2 cm ² full-thickness incision. G6 group had 94.31% contraction by day 14; high collagen, capillaries, low inflammation

Table 3. Cont.

Reference	Technique Used	Antibacterial Assay Results	MTT Assay	In Vivo Biological Properties
[39]	Not reported	Not reported	Not reported	Wistar rats; burn, excision, incision models. Propolis hydrogel showed 91.45% contraction by day 21 (excision); enhanced tensile strength and collagen formation.
[40]	Surface antibacterial assay (CFU/mL)	Pec, QCS, propolis-loaded Pec, and propolis-loaded QCS films demonstrated complete growth inhibition for all three tested bacteria (<i>S. aureus</i> , <i>S. epidermidis</i> , <i>S. pyogenes</i>), as no colonies were detected (ND)	L929 fibroblasts. >70% viability for all hydrogels. Non-toxic; suitable for wound dressing	Not reported
[41]	Not reported	Not reported	Not reported	Not reported
[42]	Agar disk diffusion	<i>S. aureus</i> PU (0 mm), PCL2:1CS-PU (0 mm), PU/EEP (4.65 ± 0.44 mm), and BWD (0.53 ± 0.19 mm). <i>E. coli</i> PU (0 mm), PCL2:1CS-PU (0.58 ± 0.19 mm), PU/EEP (1.32 ± 0.39 mm), and BWD (1.54 ± 0.41 mm)	L929 fibroblasts. No significant viability difference PCL/CS vs. BWD; PCL/CS > PU/EEP. Good biocompatibility; PCL/CS mat enhanced viability	Wistar rats; 11 mm punch wound. BWD nearly healed by day 15; better dermis, hair follicles, and sebaceous glands
[43]	Not reported	Not reported	MEF (mouse embryonic fibroblasts). Proliferation with PVA/C-P2: 176%, 775%, 853% at 24, 72, 120 h. Enhanced proliferation; good cytocompatibility; suitable for wound healing.	Not reported
[44]	Agar disk diffusion	<i>S. aureus</i> , (PU-NL/WEP): 10.5 ± 0.7 mm, (PU-NL/EEP): 11.2 ± 0.6 mm. Against <i>E. coli</i> , PU-NL/WEP: 4.3 ± 0.3 mm, and PU-NL/EEP films: 7.2 ± 0.4 mm.	L929 fibroblasts. All samples biocompatible; PU-NL/EEP highest viability EEP non-toxic; supports fibroblast growth	Wistar rats; 11 mm dorsal excision. PU-NL/EEP wounds nearly closed by day 10; better epidermis and dermis vs. control; $p < 0.05$
[45]	Not reported	Not reported	HFB4 fibroblasts. IC50: 116 µg/mL (NPs), 137.5 µg/mL (free); 89.46% viability at 25 µg/mL. Safe below 25 µg/mL; no cytotoxicity at tested dose	Mice; 2 × 2 cm ² burn wound. NFMTs reduced wound size by day 21; induced regeneration of epidermis, follicles, glands
[46]	Minimum Inhibitory Concentration (MIC) Assay.	The MIC against <i>Staphylococcus aureus</i> was 270 µg/mL. The MIC against <i>Staphylococcus epidermidis</i> was 340 µg/mL. Furthermore, the MIC against <i>Escherichia coli</i> was 900 µg/mL, and against <i>Pseudomonas aeruginosa</i> , it was 1200 µg/mL	Not reported	Not reported
[47]	Not reported	Not reported	Not reported	Wistar rats; second-degree burns. NRP60 group had 60.18% lesion retraction at day 10 vs. 19.46% control; enhanced collagen, epithelium, and angiogenesis
[48]	Viable cell count technique (Log CFU)	HPCS-Pr nanofibers demonstrated enhanced antibacterial activity against <i>S. aureus</i> and MRSA compared to the commercial Aquacel Ag dressing ¹ . However, they exhibited “nearly no” antibacterial activity against <i>E. coli</i> and multidrug-resistant (MDR) <i>P. aeruginosa</i>	Human fibroblasts. Lower proliferation in HPCS-Pr vs. HPCS-BV and Aquacel Ag. Biocompatible despite reduced proliferation	Mice; 9 mm dorsal wound. HPCS-Pr had superior closure vs. Aquacel Ag; strong collagen deposition and early granulation
[49]	Minimum Inhibitory Concentration (MIC) Assay.	MIC: red propolis (78 µg/mL), poplar propolis (312.5 µg/mL), green propolis (1250 µg/mL)	3T3 fibroblasts. Red propolis eluate: 104.13% (30%), 91.64% (50%); green toxic at 50–100%. Concentration-dependent toxicity; red propolis best performance	Not reported

Table 3. Cont.

Reference	Technique Used	Antibacterial Assay Results	MTT Assay	In Vivo Biological Properties
[50]	Agar disk diffusion	<i>S. aureus</i> ATCC 25923: 0.93–4.68 mm with propolis, 0 mm without propolis <i>E. coli</i> ATCC 25922: 1.21–4.33 mm with propolis, 0 mm without propolis <i>S. epidermidis</i> ATCC 25925: 1.02–2.92 mm with propolis, 0 mm without propolis <i>P. aeruginosa</i> ATCC 27853: 0 mm in all formulations	L929 fibroblasts. EEP > 0.5% reduced proliferation at 7 days; 0.5% EEP optimal. CS/HA/0.5%EEP most biocompatible; higher EEP reduced cell growth	Wistar rats; 12 mm excised skin. CS/HA/0.5%EEP accelerated healing by day 14; induced fibroblast proliferation and HA synthesis
[51]	Agar disk diffusion	<i>S. aureus</i> (22.3–23.7 mm), <i>K. pneumoniae</i> (23.0–25.0 mm), <i>P. aeruginosa</i> (14.7–16.7 mm), and <i>E. coli</i> (16.7 mm) over 0–24 hours. Notably, the zone for <i>S. epidermidis</i> significantly increased from 21.7 ± 1.2 mm at 0 h to 40.0 ± 0.0 mm after 24 h	Not reported	Wistar rats; 1.5 cm full-thickness wounds. BC/PP group nearly healed by day 14; reduced neutrophil infiltration; no difference in angiogenesis vs. BC
[52]	Agar disk diffusion	<i>Staphylococcus aureus</i> ATCC 25923: 8.0–10.0 mm with propolis; resistant with BC without propolis. <i>Staphylococcus aureus</i> ATCC 43,300 (MRSA): 7.0–9.0 mm with propolis; resistant without propolis. <i>Staphylococcus epidermidis</i> ATCC 14990: 7.0–9.0 mm with propolis; resistant without propolis	Not reported	Rattus Norvegicus; 6 mm circular incisions. All wounds fully repaired by 30 days; no significant difference among groups; confirmed by histology.
[53]	Not reported	Not reported	Not reported	Diabetic mice; 10 mm dorsal wound. Red propolis groups had better healing by day 14; increased MPO and cytokine activity at day 7
[54]	Agar disk diffusion	<i>S. aureus</i> (0.93–3.89 mm) and <i>E. coli</i> (1.21–3.55 mm) showed increasing inhibition with higher propolis concentration. No antimicrobial activity was observed against <i>S. epidermidis</i> or <i>P. aeruginosa</i> in any of the formulations.	L929 fibroblasts. All WEP dressings > 100% viability on day 7; $p < 0.05$. Propolis enhanced proliferation; no cytotoxicity	Wistar rats; 11 mm excised skin. PU/30WEP group had best contraction (5.68%) at day 15 vs. 20.97% control; improved dermis and follicles
[55]	Agar disk diffusion	<i>Staphylococcus aureus</i> (ATCC 25923): 0.35–5.63 mm. <i>Escherichia coli</i> (ATCC 25922): 0.43–3.18 mm	L929 fibroblasts. Highest viability in PU-HA; 2% EEP reduced viability on day 7. All samples biocompatible; optimal EEP concentration needed	Wistar rats; 11 mm dorsal wound. PU-HA/1%EEP showed complete closure by day 21; superior dermis and collagen development
[56]	Agar disk diffusion	<i>Staphylococcus aureus</i> (ATCC 25923): 5.4 ± 0.3 mm. <i>Escherichia coli</i> (ATCC 25922): 1.9 ± 0.4 mm. <i>Staphylococcus epidermidis</i> (ATCC 25925): 1.0 ± 0.2 mm. <i>Pseudomonas aeruginosa</i> (ATCC 27853): 0 mm (resistant strain). <i>Klebsiella pneumoniae</i> (ATCC 27553): 0 mm (resistant strain)	L929 fibroblasts. No toxicity; higher proliferation in PCL/Gel vs. PU/EEP after day 4. Good biocompatibility; PCL/Gel enhanced proliferation	Wistar rats; 11 mm punch biopsy. Wound area 2.6% by day 15 in PU/EEP-PCL/Gel vs. 17.9% control; enhanced collagen, dermis, and hair follicle formation

Regarding *in vivo* models, several studies demonstrated effective wound healing, enhanced tissue regeneration, and histological improvement in rodent models [45,48,56]. Inflammatory cytokine modulation and angiogenesis were confirmed in some models through immunohistochemistry or gene expression analysis [35,36]. Although some studies lacked *in vivo* data, the overall trend supports the biomedical potential of propolis-containing scaffolds, films, and hydrogels across various experimental models.

4. Discussion

In recent years, research on propolis-functionalized biomaterials has progressed significantly, as evidenced by the growing number of publications analyzed in this review. Iran and Brazil stand out as leading countries in scientific production in this field, with 11 and 7 studies, respectively. This prominence can be attributed to factors such as the biodiversity of apicultural flora, the tradition of beekeeping, and the empirical knowledge of propolis in traditional medicine [57]. Iran produces approximately 211 tons of propolis annually, rich in flavonoids and phenolic acids [58–61], while Brazil is renowned for its red propolis, characterized by its high content of triterpenes and flavonoids, exporting up to 75% to Japan [62–65]. This review was limited to studies published in English and indexed in PubMed, due to practical constraints and the predominant use of English in biomedical literature. While this approach ensured consistency in evaluation, it may have excluded relevant findings from non-English-speaking regions. This limitation is recognized, and future systematic reviews should consider incorporating a broader linguistic and regional spectrum to improve global representativeness and inclusivity.

Significant heterogeneity was observed regarding the form and origin of the biomaterials, as well as the techniques employed for propolis incorporation (Table 1). Biomaterials of natural origin were the most frequently utilized, a finding that aligns with previous reports highlighting their extensive application in biomedical fields. Materials such as chitosan [66,67], xanthan gum [68,69], soy protein [70–72], cellulose (bacterial or plant-derived) [70–72], and natural rubber [73,74] have been widely explored, given that, in general, they are biodegradable or bioabsorbable and highly biocompatible. Additionally, certain natural biomaterials, such as chitosan, exhibit intrinsic antimicrobial properties [75]. Natural proteins and polysaccharides have garnered significant interest owing to their structural resemblance to macromolecules naturally recognized by the human body, thereby facilitating the biomimicry of the extracellular matrix (ECM), a key factor in supporting tissue regeneration [76].

In efforts to achieve an optimal balance between mechanical performance and bioactivity, hybrid formulations such as chitosan–PCL [42] or PU–gelatin [56] composites are increasingly explored. These systems integrate natural and synthetic polymers, often reinforced with inorganic additives like zinc oxide or carbon nanotubes [77,78]. Zinc oxide nanoparticles (ZnO-NPs), in particular, are widely recognized for their biocompatibility, low toxicity, chemical stability, and multifunctional biological properties, including antimicrobial, anti-inflammatory, and antioxidant activity [79,80]. For instance, Zayed et al. incorporated *in situ* synthesized zinc oxide nanoparticles (ZnO-NPs) into a collagen–chitosan gel, not only to enhance the antimicrobial and antioxidant properties of the material, but also to improve its mechanical characteristics, thereby demonstrating the multifunctional role of inorganic reinforcements in wound healing applications [38].

Furthermore, synthetic polymers such as PVA, PLGA, PU and PCL are extensively utilized owing to their exceptional versatility, biodegradability, and tunable physicochemical properties. These materials are particularly advantageous in applications demanding precise control over degradation kinetics and mechanical performance. Their high availability, ease of processing, adsorption capacity, and functionalization potential have facilitated

their widespread use across biomedical and industrial sectors, notably in drug delivery systems, wound dressings, and scaffolding for tissue engineering [76,81].

Regarding the incorporation methods, the direct addition of propolis prior to polymerization was the most commonly employed strategy. This technique offers multiple advantages, such as uniform distribution of the active agent within the polymer matrix, high resistance to polymer processing conditions, no adverse effects on the material's properties, and a slow and controlled release of the bioactive compound, thereby preventing an initial burst release [82]. For instance, Ferreira et al. highlight that pre-polymerization incorporation of bioactive substances into polylactic acid (PLA) matrices promotes uniform dispersion and enables better control over the release profile, which is essential in biomedical and food packaging applications [83].

However, despite these benefits, the direct incorporation of propolis into polymeric matrices also presents significant technical challenges. One of the main issues is the incompatibility between the solvent of the propolis extract and the polymer solution, which can lead to aggregation and non-uniform distribution of the bioactive compound. Such irregularities negatively impact the physical integrity, antimicrobial activity, and functional reproducibility of the biomaterial. Olewnik-Kruszkowska et al. reported these effects in polylactide films, where the formation of aggregates and loss of homogeneity compromised the material's stability [84].

Various strategies have been employed to functionalize biomaterials with propolis. Post-fabrication coating effectively concentrates the bioactive agent on the surface of the material, enhancing its antimicrobial and anti-inflammatory activity. El-Ghoul et al. (2024) demonstrated that increasing the surface content of propolis significantly improves antimicrobial and antibiofilm performance [32].

Encapsulation has emerged as a novel method to protect propolis bioactive compounds from environmental degradation (light, temperature, oxygen) while enabling controlled release [85,86]. Specifically, chitosan-based nanoparticle encapsulation has proven effective in stabilizing propolis, achieving sustained release, and enhancing the structural and therapeutic properties of the biomaterial [45].

In the context of 3D bioprinting, propolis can be incorporated either before printing (pre-printing), by mixing it into the bio-ink to ensure homogeneous distribution, or after printing (post-printing), to enhance antimicrobial and antioxidant properties on the scaffold surface [37,87]. Although this combined approach provides flexibility, it requires careful optimization to prevent compound degradation and ensure proper adhesion. Lastly, impregnation or immersion has been used with highly porous materials such as bacterial cellulose. This simple and cost-effective method allows propolis to penetrate or adsorb onto the scaffold, facilitating sustained release. However, limitations include heterogeneous distribution, reduced release control compared to encapsulation, and potential compound loss in highly permeable matrices.

Overall, the choice of biomaterial type is linked to strength, degradation and tissue compatibility requirements, while the propolis incorporation strategy directly impacts bioactive agent distribution, release kinetics, and antimicrobial and antioxidant efficacy. Many studies combine multiple techniques to maximize the functionality of dressings, highlighting the search for versatile solutions that balance mechanical properties, biocompatibility and therapeutic activity. This broad spectrum of approaches confirms the growing interest in propolis in tissue engineering and regenerative medicine, taking advantage of its benefits in wound healing, and reflects the experimental versatility in its incorporation into diverse biomaterial systems.

A common trend among the reviewed studies was the use of ethanolic extracts of propolis, although the geographical origin of these extracts varied widely, which could

influence their chemical composition and, consequently, the concentration required to achieve an optimal therapeutic effect [88]. The concentrations of propolis applied ranged mainly between 0.5% and 2.5% (*w/v* or *w/w*), a range consistently observed in films, hydrogels, and membranes. This interval appears sufficient to confer antimicrobial and antioxidant properties without compromising the structural characteristics of the biomaterials. However, some studies explored significantly higher concentrations, up to 10% or more, particularly in immersion or impregnation coatings [48,54] suggesting that higher concentrations may be necessary in surface incorporation methods to compensate for lower retention or faster release of the bioactive agent. Similarly, studies employing techniques such as electrospinning or emulsion for nanoparticle formation often did not specify the exact final concentration of propolis in the biomaterial, complicating direct comparisons.

In certain cases, propolis was integrated into more complex architectures, such as ZnO nanostructures, reaching concentrations of 5% and 10% (*w/w*), possibly to enhance synergistic effects [38]. It is also important to note that the choice of concentration may be influenced by the form of propolis used and the incorporation technique employed. This broad variability highlights the need to standardize incorporation methodologies and to optimize concentrations based on the type of biomaterial, the processing method, and the intended clinical application.

The comprehensive characterization of propolis-functionalized biomaterials is crucial for understanding their performance in wound healing applications [89,90]. In terms of structural and chemical characterization (Table 2), most studies report that spectroscopic techniques, including FTIR, ATR-FTIR, and XRD, confirm the successful incorporation of propolis into polymeric matrices, in the majority of cases through physical interactions that preserve the original structure of the polymer. However, in certain cases, the appearance of new peaks (e.g., at approximately 1707 or 1714 cm^{-1}), suggested the occurrence of chemical modifications, such as the formation of methacrylated pullulan [31,91] or crosslinking reactions [32], specifically esterification and amidation processes between cellulose and chitosan [92,93].

Propolis has been shown to enhance porosity in hydrogel-based wound dressings, as reported by authors such as Ferreira et al. [33], Vasegui et al. [37], and Pahlevannehan et al. [44]. This increased porosity is a highly advantageous feature, as it facilitates oxygen diffusion, fluid absorption, and cellular adhesion, critical factors for effective tissue regeneration. The porous architecture supports the attachment and proliferation of fibroblasts and keratinocytes, thereby promoting extracellular matrix formation. Moreover, enhanced oxygenation through interconnected pores stimulates angiogenesis and expedites the wound healing process [94]. It also tended to reduce fiber diameters [35,46] and facilitated homogeneous dispersion within the polymer matrix, although at higher concentrations, some studies noted aggregation effects [43].

The incorporation of propolis into biomaterials often improves flexibility and elongation, while its effect on tensile strength varies depending on the matrix. Studies like those by Bal-Ozturk et al. [31] and Jaberifard et al. [34] showed increased strength and modulus, especially when combined with chitosan or halloysite nanotubes. In contrast, propolis acted as a plasticizer in other formulations slightly reducing tensile strength but significantly enhancing stretchability, which is beneficial for wound dressings [40]. Overall, propolis contributes to mechanical adaptability, offering a balance between strength and flexibility, making it a suitable component in dressings that must conform to tissue and withstand physiological movement.

Thermal characterizations will provide general information on stability, shrinkage, expansion, effect of sterilization methods, insulation and storage [95]. Limited thermal analyses (TGA, DSC) showed that propolis may enhance or slightly reduce thermal stability

depending on the matrix, often increasing residue at high temperatures when combined with materials like hydroxyapatite or lignin [44,55]. DSC data revealed molecular dispersion of propolis and variable effects on crystallinity [41,43]. Overall, propolis affects the thermal profile and structural organization even without forming new bonds [42,52].

Propolis incorporation enhances the hydrophilicity, swelling capacity, and fluid management of wound dressings. Most systems showed increased water absorption and lower contact angles, improving cell adhesion and moist wound environments. Maintaining appropriate WVTR/WVP values is essential to prevent both excessive dehydration and fluid accumulation, conditions that can negatively impact wound healing. In the reviewed studies, propolis-functionalized biomaterials, including electrospun membranes, hydrogels, and 3D-printed scaffolds, demonstrated WVTR/WVP values ranging from approximately 75 to 4212 g/m²·day. This wide range encompasses the values considered optimal for wound healing and highlights the adaptability of these systems. The findings suggest that propolis-based materials, especially those formulated with polysaccharide or PCL matrices, can be effectively tailored to regulate moisture according to wound type and healing phase. Additionally, several studies reported that degradation of the materials occurred more rapidly under acidic conditions, which may further influence their behavior in inflamed or infected wound environments [96].

Among the reviewed studies, only the article by [51] explicitly reported the application of kinetic models to describe propolis release, providing correlation coefficients (R) for each model. In this study, the release kinetics of p-coumaric acid (a hydrophilic compound) and artemisin C (a lipophilic compound) from bacterial cellulose membranes (BC/PP) were evaluated using a Franz diffusion cell. The linear portions of the release profiles were fitted to zero-order, Higuchi, and first-order kinetic models. The correlation coefficients obtained were as follows: for p-coumaric acid—zero-order (R = 0.9839), Higuchi (R = 0.9812), and first-order (R = 0.8776); and for artemisin C—zero-order (R = 0.9947), Higuchi (R = 0.9915), and first-order (R = 0.9421). These findings indicate that both compounds followed a zero-order release pattern, suggesting a sustained and controlled release behavior. Although the zero-order model showed the best fit, the high correlation values for the Higuchi model also point to a diffusion-controlled mechanism. Furthermore, the study observed a biphasic release profile, with an initial burst followed by a slower, prolonged release phase—especially for artemisin C, which showed sustained release for more than seven days, typical of lipophilic molecules. Overall, these properties support faster healing, improved tissue regeneration, and make propolis-based biomaterials highly effective for wound care applications.

A central aspect of this analysis has undoubtedly been the characterization of the physicochemical and morphological properties of these biomaterials, including the contact angle and porous structure. These properties are essential, as appropriate porosity enhances oxygen diffusion, fluid absorption, and cell adhesion—all critical factors for effective tissue regeneration. Similarly, hydrophilicity, swelling capacity, and fluid management are key to maintaining an optimal moist wound environment, which promotes cell adhesion and healing. In addition, the flexibility and elongation of the biomaterials, often improved by the incorporation of propolis, are crucial for dressings to conform to the tissue and withstand physiological movement.

Furthermore, the stability of propolis within the biomaterial matrix and its controlled release are vital aspects for ensuring therapeutic efficacy. Incorporation strategies, such as nanoencapsulation and direct addition before polymerization, aim to protect the bioactive compounds of propolis from environmental degradation (light, temperature, oxygen) and allow for sustained and controlled release. For example, a biphasic release profile has been observed, with an initial rapid release followed by a slower, prolonged phase—a

key feature for maintaining long-term therapeutic effects. Thermal analyses (TGA, DSC) have provided insights into the stability of these biomaterials, indicating that propolis may influence thermal stability and structural organization without necessarily forming new bonds.

As summarized in Table 3, the studies demonstrate strong evidence for the biological properties (in vitro and in vivo) of propolis-derived biomaterials. These properties are attributed to its complex chemical composition, rich in polyphenols, flavonoids, and other bioactive compounds [13]. Among the diverse methodologies employed, the most frequently reported evaluations included antimicrobial activity assays, MTT cytotoxicity assays, and in vivo wound healing models.

Any laboratory-produced or modified biomaterial may pose potential side effects, which are influenced by factors such as its composition, processing and modification methods, sterilization, and implantation site [97]. The MTT assay is an internationally validated test for cell viability. In the reviewed literature, most formulations incorporating propolis, including scaffolds, films, and hydrogels, showed viability rates above 80–90% when tested on fibroblast lines such as NIH/3T3, L929, or human fibroblasts (e.g., HFB4), indicating low cytotoxicity and high compatibility with host tissues. Some materials even demonstrated enhanced proliferative responses, with values reaching up to 120% viability or proliferation rates as high as 853% in specific formulations. For instance, Bal-Öztürk et al. [31] reported 93.73% viability with the PULMAMid-10-PRO1 scaffold, while Zayed et al. [38] observed over 90% viability with propolis and ZnO nanoparticles in L929 cells. These findings reinforce the safety profile of propolis in regenerative applications. Despite these encouraging outcomes, a dose-dependent cytotoxic effect was consistently reported. While optimal concentrations promoted cell growth, excessive amounts of propolis led to reduced viability in several cases (e.g., >0.5% EEP or $\geq 10\%$ propolis). These findings underscore the critical importance of optimizing propolis concentrations in scaffold design to ensure safety and efficacy. According to ISO 10993-5 guidelines, materials with cell viability $\geq 70\%$ are considered non-cytotoxic, further supporting the suitability of most of these formulations [98]. In summary, the MTT assay has served as a robust indicator of the cytocompatibility of propolis-based biomaterials, providing foundational support for their advancement into in vivo studies and future clinical translation. On the other hand, studies highlight and suggest the importance of evaluating the cytotoxicity in animal models due to the discrepancies and inconsistencies between cytotoxicity in cultures and biocompatibility in animal models.

Regarding antimicrobial activity, the agar diffusion technique was predominantly used to assess the ability of propolis and its compounds to inhibit microbial growth. Propolis demonstrated notable efficacy against Gram-positive bacteria, such as *Staphylococcus aureus*, with inhibition zones ranging from 0.35 mm to 26.2 mm, and even reaching 40.0 mm in the case of *S. epidermidis* after 24 h. Other Gram-positive pathogens, such as *Micrococcus luteus* and *Streptococcus mutans*, were also susceptible. Against Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, the activity varied, with inhibition zones ranging from 0.43 mm to 26 mm for *E. coli*, although *P. aeruginosa* often exhibited resistance or lower susceptibility in some formulations. Antimicrobial efficacy also depended on concentration and formulation, as shown by gels containing 10% PP1/ZnO-NPs, which produced the largest inhibition zones. In microdilution or MIC assays, propolis inhibited *S. aureus* (MIC of 270 $\mu\text{g/mL}$) and *E. coli* (MIC of 900 $\mu\text{g/mL}$), with red propolis being more potent (78 $\mu\text{g/mL}$) than other varieties. In addition, *Candida albicans* also showed sensitivity to propolis, with inhibition zones up to 12 mm in specific gel formulations.

Propolis exhibits multifaceted antibacterial mechanisms, acting both directly on microorganisms and indirectly through host immune modulation. One primary mechanism is the disruption of bacterial membrane integrity and permeability, which impairs essential functions such as ATP production and nutrient transport, ultimately compromising bacterial viability and biofilm formation [99,100]. Interestingly, several studies showed selectivity, where propolis inhibited Gram-positive bacteria more effectively than Gram-negative. The greater effectiveness of propolis against Gram-positive bacteria, compared to Gram-negative strains, may be attributed to the presence of hydrolytic enzymes in the outer membrane of Gram-negative bacteria. These enzymes can degrade or inactivate the bioactive compounds present in propolis, thereby reducing its antimicrobial efficacy [100].

Additionally, flavonoids present in propolis, such as quercetin, apigenin, and kaempferol interfere with nucleic acid synthesis by targeting bacterial enzymes like DNA gyrase and topoisomerase II [101,102]. Cinnamic acid, another component, has been shown to inhibit ATPase activity and bacterial division [103]. Propolis also contributes to protein synthesis inhibition, often by acting on bacterial ribosomes or blocking RNA polymerase activity, which explains its synergistic effects with antibiotics like chloramphenicol and β -lactams [104,105]. These synergistic actions not only increase antibacterial efficacy but also reduce bacterial resistance [106,107].

At the anti-inflammatory level, the propolis exerts its action by modulating inflammation toward a regulatory balance and an anti-inflammatory environment. Its mechanisms of action include the inhibition and downregulation of key signaling pathways such as TLR4 (Toll-like receptors), MyD88, IRAK4, and TRIF [108]. It also reduces the expression of NLRP inflammasomes (such as NLRP1 and NLRP3) [109] and the transcription factor NF- κ B, which are central to the inflammatory response [110–112]. Additionally, propolis decreases the production and expression of key pro-inflammatory cytokines, including IL-1 β , IL-6, IFN- γ , and TNF- α [109,113]. It has also been observed to reduce the migration of immune cells such as macrophages and neutrophils, possibly through the downregulation of chemokines CXCL9 and CXCL10 [114]. In this context, propolis has been observed to induce an initially intense inflammatory response that rapidly subsides, thus promoting significantly faster healing. These mechanisms suggest a favorable profile in terms of the host's immune response, helping to prevent a chronic inflammatory reaction that could delay the healing process.

Finally, propolis can damage bacterial membranes via hydrophobic interactions, alter membrane proteins, and cause potassium ion leakage, leading to cellular collapse [115,116]. Some studies also highlight propolis's ability to reduce biofilm formation, especially through flavonoids like quercetin-3-glucoside and tectochrysin [117,118].

Antioxidant capacity of propolis has been widely assessed through assays such as DPPH. Studies by Phonrachom et al. [40] and Khoshnevisan et al. [46], among others, have demonstrated its potential to counteract oxidative stress, especially in the context of skin injuries. This effect is primarily attributed to its rich content of flavonoids, phenolic acids, vitamins, and trace elements, which enable it to neutralize free radicals and protect cellular structures from oxidative damage, particularly in severely burned tissue [119,120]. Additionally, propolis has been shown to stimulate antioxidant enzymes, reduce inflammatory mediators such as TNF- α and PGE2, and promote tissue regeneration [121–123]. Notably, reactive oxygen species generated by propolis can traverse cell membranes through aquaporin channels (AQP3), facilitating cell migration and enhancing wound repair processes [124].

In vivo studies also support the regenerative properties of propolis. Research by Mehdikhani et al. [35] and Zayed et al. [38] demonstrated significant improvements in wound contraction, angiogenesis, and collagen deposition in animal models. Furthermore,

Yang et al. [29] reported that propolis modulates the inflammatory response and accelerates re-epithelialization, which may explain the beneficial effects observed in these studies.

Mast cells are key regulators in all wound healing phases, promoting inflammation, angiogenesis, and tissue remodeling [125]. However, their excessive activity is linked to pathological scarring [126,127]. Blocking mast cell activation has been shown to reduce inflammation and scar formation without compromising the mechanical integrity of the regenerated tissue [128]. Propolis has demonstrated a significant ability to modulate mast cell activity. Topical application of propolis reduces mast cell counts in inflamed tissue, accelerating wound healing. This is attributed to active compounds such as caffeic acid phenethyl ester (CAPE), chrysin, and kaempferol [129–131]. CAPE inhibits histamine release and cytokine production in wound tissue [130]. Chrysin downregulates pro-inflammatory cytokines (TNF- α , IL-1 β , IL-4, IL-6) via NF- κ B and caspase-1 pathways and also suppresses calcium influx in activated mast cells [132,133]. Kaempferol similarly inhibits mast cell degranulation and cytokine release [132]. In summary, by modulating mast cell behavior and associated inflammatory mediators, propolis contributes not only to reduced inflammation and oxidative stress but also supports tissue regeneration and minimizes fibrosis.

The use of propolis in different types of wounds has been explored in the *in vivo* studies reviewed, which include models of full-thickness wounds, burns, and excisional wounds in rodents. These studies consistently confirm regenerative benefits such as improved healing, increased angiogenesis, enhanced collagen deposition, and better histological outcomes. Despite this versatility and promising evidence, the effective translation of these biomaterials into clinical practice, especially for the management of chronic wounds, remains a significant challenge.

The biological activity of propolis is strongly influenced by its chemical composition, which varies with geographical origin and botanical source. A study analyzing 13 European poplar-type propolis samples found substantial differences in total polyphenol content, antioxidant activity, and the profile of 18 polyphenolic compounds, with galangin being exclusive to Polish samples. These variations also affected antimicrobial activity against intestinal bacteria, highlighting that compositional differences can impact both efficacy and safety [134]. These findings emphasize the importance of detailed phytochemical characterization and standardization to ensure consistent therapeutic outcomes with propolis-based biomaterials.

Building on this compositional foundation, propolis-functionalized wound dressings offer remarkable potential due to their high biocompatibility, with cell viability frequently exceeding 80–90% in *in vitro* studies, and well-documented antimicrobial, antioxidant, and regenerative properties. Among the various biomaterials employed, most dressings use polysaccharide-based matrices, such as chitosan, bacterial cellulose, or pectin, which provide a biocompatible and biodegradable platform for wound healing. The incorporation of propolis into these substrates enhances biological performance by promoting effective antimicrobial action against common wound pathogens, improved tissue regeneration in *in vivo* models, and increased cell proliferation. Additionally, propolis can improve key physicochemical properties of the dressings, including hydrophilicity, swelling capacity, porosity, and the controlled release of bioactive compounds.

To achieve these therapeutic effects, several incorporation strategies have been explored, such as direct addition, post-coating, and nanoencapsulation, to ensure homogeneous distribution and controlled release of propolis within these biomaterials. Combined with the intrinsic advantages of polysaccharides, this synergy positions propolis-based wound dressings as promising candidates for next-generation therapies. Advanced fabrication methods, including electrospinning, hydrogel casting, and 3D printing, further expand the design possibilities and functional precision of these systems.

However, despite these advances, scalability and standardization still face significant challenges. The primary limitation is the intrinsic variability of propolis, whose complex chemical profile is shaped by its botanical source, geographical origin, and processing methods. This variability hinders reproducibility and complicates the comparison of outcomes across studies. Moreover, inconsistencies in extraction methods, evaluation protocols, and potential incompatibilities between propolis solvents and polymeric solutions can affect the uniformity, stability, and safety of the final materials.

To address these challenges and advance toward effective clinical translation, several key measures should be prioritized. First, it is essential to optimize propolis concentrations in formulations to achieve an appropriate balance between therapeutic efficacy and safety, as excessive doses may cause cytotoxic effects. Second, standardizing extraction methods and evaluation protocols for both propolis and the resulting biomaterials, along with implementing chemical fingerprinting, is crucial to ensure consistent batch characterization and reproducibility. Third, it is equally important to design and conduct robust, well-controlled preclinical *in vivo* studies that address more complex wound models, such as chronic wounds, and that allow for the direct comparison of the therapeutic performance of different propolis incorporation strategies (such as direct addition, coating, and nanoencapsulation) in standardized models, with the aim of identifying the optimal methods for clinical applications. This will enable a comprehensive assessment of long-term therapeutic efficacy, biocompatibility, and the modulation of the biological response, while also accounting for the discrepancies often observed between *in vitro* and *in vivo* results. Finally, the development of tailored engineering strategies for propolis incorporation will help achieve uniform distribution, bioactive stability, and controlled release profiles, while minimizing potential solvent incompatibilities with polymeric solutions. In addition to these methodological aspects, future research should strengthen the representativeness and diversity of the evidence to ensure robust and reliable conclusions applicable across different contexts. Together, these efforts will enhance the reliability and translational potential of propolis-functionalized biomaterials in advanced wound care.

5. Conclusions

Propolis-functionalized biomaterials represent a promising frontier in wound healing and regenerative medicine due to their broad-spectrum antimicrobial activity, antioxidant potential, and high biocompatibility. This review highlights the versatility of natural and synthetic matrices, particularly those based on polysaccharides, for the effective incorporation of propolis through diverse strategies such as direct addition, post-coating, and nanoencapsulation. Despite variations in composition, formulation, and evaluation methods, most studies report enhanced wound healing performance and controlled release profiles. However, challenges remain regarding standardization, propolis variability, and clinical translation. In addition, the geographical and linguistic concentration of the available studies may limit the generalizability of current findings. Future research should aim to optimize concentrations, standardize extraction and evaluation protocols, and further explore *in vivo* efficacy, including direct comparisons between formulation strategies, to support regulatory approval and the scalability of these multifunctional systems.

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Abbreviations

AF	Apoptotic Factor
AQP3	Aquaporin 3
ARRIVE	Animal Research: Reporting of In Vivo Experiments
ATP	Adenosine Triphosphate
ATR	Attenuated Total Reflectance
BC	Bacterial Cellulose
BWD	Bilayer Wound Dressing
CA	Cellulose Acetate
CAM	Chorioallantoic Membrane
CAPE	Caffeic Acid Phenethyl Ester
CS	Chitosan
DLS	Dynamic Light Scattering
DNA	Deoxyribonucleic Acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DSC	Differential Scanning Calorimetry
DTZ	Diltiazem
ECM	Extracellular Matrix
EDX	Energy-Dispersive X-ray Spectroscopy
EEP	Ethanollic Extract of Propolis
EPP	Standardized Extract of Propolis
FE-SEM	Field Emission Scanning Electron Microscopy
FTIR	Fourier Transform Infrared Spectroscopy
GC-MS	Gas Chromatography–Mass Spectrometry
GPC	Gel Permeation Chromatography
GPT	Glutamate Pyruvate Transaminase
HA	Hyaluronic Acid
HFB4	Human Fibroblasts
HNT	Halloysite Nanotubes
HPLC	High-Performance Liquid Chromatography
HPCS	Hydroxypropyl Chitosan
HRMS	High-Resolution Mass Spectrometry
IL	Interleukin
MEF	Mouse Embryonic Fibroblasts
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-Resistant Staphylococcus aureus
MS	Mass Spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

MyD88	Myeloid Differentiation Primary Response 88
NF	Nanofibers
NF- κ B	Nuclear Factor kappa-B
NIH	National Institutes of Health
NL	Nanolignin
NLRP	NOD-, LRR-, and Pyrin Domain-Containing Protein (Inflammasome Family)
NMR	Nuclear Magnetic Resonance
NPs	Nanoparticles
NRL	Natural Rubber Latex
PP	Propolis
PCL	Polycaprolactone
PEC	Pectin
PLGA	Poly(lactic-co-glycolic acid)
EMP	Propolis Extracted with Methylal
PMN	Polymorphonuclear Cells
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PU	Polyurethane
PULMA	Methacrylated Pullulan
PVA	Polyvinyl Alcohol
QCS	Quaternized Chitosan
RNA	Ribonucleic Acid
SEM	Scanning Electron Microscopy
SFO	Silk Fibroin Oxidized
SPI	Soy Protein Isolate
TAC	Total Antioxidant Capacity
TEM	Transmission Electron Microscopy
TGA	Thermogravimetric Analysis
TLR4	Toll-Like Receptor 4
TNF- α	Tumor Necrosis Factor alpha
TRIF	TIR-domain-containing Adapter-Inducing Interferon- β
UHPLC	Ultra-High-Performance Liquid Chromatography
UV-Vis	Ultraviolet-Visible Spectroscopy
WEP	Water Extract of Propolis
WVP	Water Vapor Permeability
WVTR	Water Vapor Transmission Rate
XRD	X-ray Diffraction
ZnO-NPs	Zinc Oxide Nanoparticles

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