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Polyphenols

Antimicrobial Phenolic Materials: From Assembly to Function

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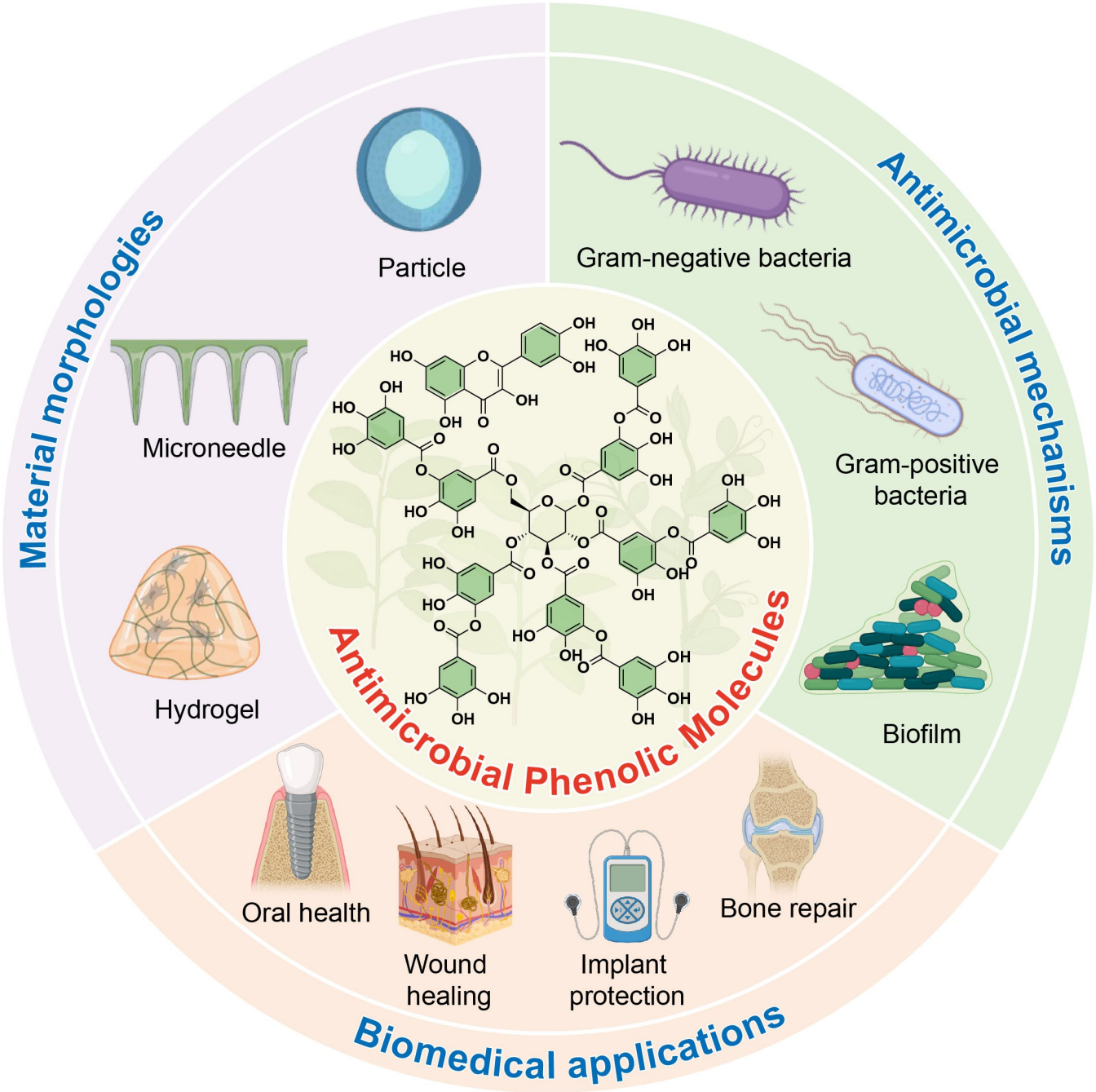

Abstract: Infectious diseases pose considerable challenges to public health, particularly with the rise of multidrug-resistant pathogens that globally cause high mortality rates. These pathogens can persist on surfaces and spread in public and healthcare settings. Advances have been made in developing antimicrobial materials to reduce the transmission of pathogens, including materials composed of naturally sourced polyphenols and their derivatives, which exhibit antimicrobial potency, broad-spectrum activity, and a lower likelihood of promoting resistance. This review provides an overview of recent advances in the fabrication of antimicrobial phenolic biomaterials, where natural phenolic compounds act as active antimicrobial agents or encapsulate other antimicrobial agents (e.g., metal ions, antimicrobial peptides, natural biopolymers). Various forms of phenolic biomaterials synthesized through these two strategies, including antimicrobial particles, capsules, hydrogels, and coatings, are summarized, with a focus on their application in wound healing, bone repair and regeneration, oral health, and antimicrobial coatings for medical devices. The potential of these advanced phenolic biomaterials provides a promising therapeutic approach for combating antimicrobial-resistant infections and reducing microbial transmission.

1. Introduction

Infectious diseases caused by microorganisms, such as bacteria and viruses, have posed significant threats to global health, resulting in high mortality rates, social disruption, and economic burden.[1] To combat bacterial infections, both natural and synthetic antibacterial drugs in various forms have been developed.[2] However, the treatment of many infectious diseases remains challenging due to the global rise in drug resistance among pathogenic microbes, often attributed to the misuse and overuse of antimicrobial drugs.[3] A 2022 report estimated that over 4.95 million deaths in 2019 were associated with bacterial antimicrobial resistance, which affected countries across all regions and income levels.[4] Another primary concern in infectious diseases is nosocomial infections, also known as healthcare-associated infections, another driver of antimicrobial resistance.[5] Microbial colonization and subsequent biofilm formation on material surfaces are responsible for over 65 % of nosocomial infections and 80 % of all microbial infections.[6] The increasing prevalence of antibiotic-resistant microbes means that surface cleaning and disinfection with bleach and alcohol are becoming increasingly ineffective. Therefore, improved and effective strategies to combat microbial infections and reduce the risk of healthcare-associated infections are urgently needed.

Various antimicrobial materials, including metal nanoparticles (NPs), metal-organic materials, peptides, and carbon materials, have been developed to combat bacterial antimicrobial resistance.[7] These materials hold promise for treating infectious diseases. However, several key challenges remain that hinder the further development and clinical application of these materials. For instance, metal NPs and metal-organic materials with synthetic ligands can exhibit high toxicity at elevated dosages, potentially causing severe side effects in patients. Additionally, the synthesis of these antimicrobials (e.g., photothermal carbon materials) often involves harsh conditions (e.g., high temperature and organic solvents), which pose a significant environmental burden.[8] Furthermore, the high costs associated with producing antimicrobial peptides and other advanced materials present additional obstacles to their commercialization and clinical translation.[9]

As an alternative, natural products–such as polyphenolic compounds and their derivatives–have attracted widespread attention in bionanotechnology owing to their potent biological activities, minimal side effects, and affordability.[10] Polyphenols are a diverse class of secondary plant metabolites containing at least one phenolic ring with one or more hydroxyl groups (Figure 1). Numerous polyphenolic compounds, such as phenolic acids, flavonoids, lignans, and tannins, are known to exhibit significant antibacterial effects, and their antimicrobial capacity and antibiofilm activity have been extensively studied.[11] Owing to their diverse structural diversity and complex mechanisms of action, polyphenols can exert synergistic effects when combined with antimicrobial peptides or polymers through covalent and noncovalent interactions.[12] However, the intrinsic properties of phenolic compounds, particularly bioactive flavonoids, including poor water solubility and instability in the gastrointestinal tract, limit their uptake and bioavailability, which impede their effectiveness as antimicrobial agents.

To address these limitations, various formulations have been explored for the delivery of polyphenols to enhance their antibacterial efficacy by improving bioavailability and providing protection against environmental degradation, as reviewed elsewhere.[13] Additionally, progress on the engineering of antimicrobial biomaterials based on the coordination between polyphenolic compounds and metal ions has been achieved, and their antimicrobial application in the biomedical sectors has been highlighted.[14] However, these strategies often do not fully leverage the structural advantages of polyphenols, including their ability to form biocompatible biomaterials through interactions with biomolecules such as proteins and peptides. Furthermore, polyphenols and their derivatives are considered as bioinspired adhesives

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that can coat a wide variety of substrates;[15] such a property is beneficial for developing antimicrobial coatings on medical devices. A comprehensive review of polyphenol-based antimicrobial materials against infectious diseases is still lacking but necessary. Therefore, generating knowledge on integrating polyphenols with other biomolecules and leveraging nanotechnology to engineer polyphenol-based antimicrobial materials are essential for developing innovative antimicrobial solutions.

In the present review, we first introduce the antimicrobial properties of polyphenols, including the classification of antimicrobial polyphenols, their antimicrobial mechanisms, and antibiofilm capacity (Section 2). Next, we highlight recent advances in the rational design and fabrication of polyphenol-functionalized antimicrobial biomaterials, including particles, hydrogels, coatings, and macroscopic materials (Section 3). Finally, we summarize progress in the biomedical application of multifunctional antimicrobial materials, specifically in wound healing, bone repair and regeneration, oral health, and as anti-infection coatings on medical devices (Section 4).

2. Antimicrobial Behavior of Polyphenols

Polyphenols have been extensively studied for their diverse biological properties and have demonstrated a range of beneficial properties, including antibacterial, anticancer, anti-inflammatory, antioxidant, and cardioprotection.[16] Owing to the versatile therapeutic effects of polyphenols and their wide availability, they are suitable biomaterials for multifunctional therapeutic applications. As antibacterials, polyphenols exhibit broad activity against Gram-positive and Gram-negative bacteria. This section focuses on the mechanism of action of polyphenols and polyphenol-functionalized materials against bacteria and bacterial biofilms.

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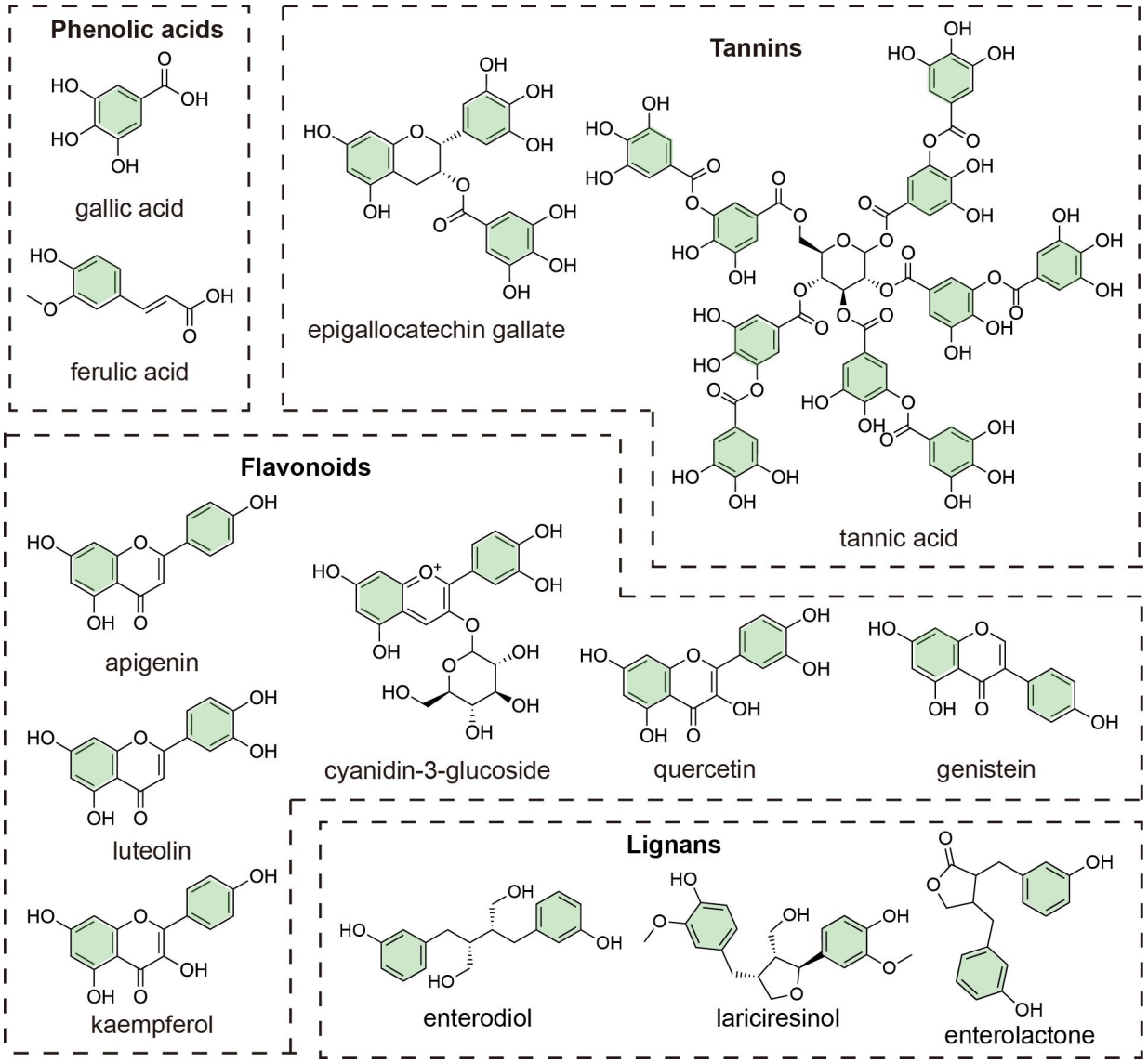

Figure 1. Chemical structures of antimicrobial polyphenols, including phenolic acids, flavonoids, tannins, and lignans.

2.1. Antimicrobial Polyphenols

Polyphenols are a large group of biologically active secondary metabolites of plants, where they play a key role against microbial pathogens and in providing protection against free radicals and toxins.[17] Traditionally, plant polyphenols have been used for oral hygiene and infection control.[18] More recently, polyphenols have gained attention in the pharmaceutical industry as antimicrobial agents and are presently incorporated into drug formulations to exploit their antimicrobial properties. The antimicrobial capacity of polyphenols can be categorized based on their chemical structures into phenolic acids, flavonoids, tannins, and lignans (Figure 1).

Phenolic acids are substances that contain a phenolic ring and an organic carboxylic acid group in their chemical structure and can exhibit broad antimicrobial properties. Examples of plant-derived phenolic acids include gallic acid and ferulic acid, both of which have demonstrated antimicrobial activity against several Gram-negative (*Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*)) and Gram-positive (*Staphylococcus aureus* (*S. aureus*) and *Listeria monocytogenes*) bacteria.[19]

Flavonoids are a vast group of polyphenolic compounds with over 9000 flavonoids identified in plants. They are structurally composed of a C6-C3-C6 carbon skeleton and with hydroxyl, methoxy, or glycosyl groups. Based on the oxidation state of the C3 segment, flavonoids are divided into various subclasses, including flavonols, flavanones, flavones, isoflavonoids, and anthocyanins. The flavonols quercetin and kaempferol display strong antibacterial activity against *S. aureus* and methicillin-resistant *S. aureus* (MRSA), with minimum inhibitory concentration (MIC) values as low as 1.95 and 7.8 $\mu g\,mL^{-1}$, respectively.[20] Hesperetin, a flavanone mainly present in citrus fruits, effectively inhibits bacterial growth, with MIC values of

125 μg mL^{-1} against *S. aureus*, 250 μg mL^{-1} against *Bacillus cereus*, and 500 μg mL^{-1} against *E. coli* and *P. aeruginosa*.[21] Flavones, such as luteolin and apigenin, have shown antibacterial activity against *S. aureus* and 11 oral bacterial strains with MIC values ranging from 31–125 and 13–50 μg mL^{-1}, respectively.[20b,22] Isoflavonoid genistein and its derivatives have shown antimicrobial activity against 8 bacterial strains, including MRSA and methicillin-sensitive *S. aureus*, with MIC values of 8–128 μg mL^{-1}.[23] Cyanidin-3-glucoside, the primary anthocyanin found in many plants, is reported to exhibit strong antibacterial activity against *S. aureus* and *E. coli*.[24]

Tannins are water-soluble polyphenols that are classified into hydrolysable and condensed tannins based on their chemical structures. Tannic acid (TA) is an important hydrolysable tannin that displays antimicrobial activity against *S. aureus*, *E. coli*, *P. aeruginosa*, and *Listeria monocytogenes*.[25] Epigallocatechin gallate (EGCG), a condensed tannin found mainly in grapes, tea, and legumes, has been shown to inhibit the growth of various Gram-positive and Gram-negative bacteria that are responsible for food spoilage.[26]

Lignans, a subclass of polyphenols abundant in flax and sesame seeds, display strong antibacterial activity associated with their phenolic hydroxyl and methoxy groups.[27] For example, dietary lignan-derived enterodiol and enterolactone (also known as mammalian lignans) have shown preventive effects against infection-related diseases, including osteoporosis and cardiovascular disease.[27b] Lariciresinol isolated from the roots of *Rubia philippinensis* was found to be effective against the foodborne pathogen *S. aureus* with MIC values of 125–250 μg mL^{-1} and has been used as a natural antimicrobial agent in the food industry.[27c]

2.2. Antimicrobial Mechanisms

The antimicrobial mechanisms of plant polyphenols have been widely explored and the proposed mechanisms include: (i) interaction with the cell wall and cell membrane (e.g., altering cell wall integrity and membrane permeability); (ii) generation of reactive oxygen species (ROS) (e.g., causing oxidative stress); (iii) inhibition of DNA replication and protein denaturation (e.g., modifying DNA topology, disrupting metabolic regulation, affecting enzymatic activity); and (iv) formation of quinoprotein (e.g., inducing a cell apoptosis cascade) (Figure 2).

The bacterial cell wall is a key component of the cellular structure that plays an essential role in maintaining cell rigidity and providing osmotic protection. Polyphenols can destroy the structural integrity of cell walls and the intracellular matrix. Galloylated catechins from green tea, such as EGCG and epicatechin gallate, have shown high affinity to cell wall components, thereby altering the cell integrity and reducing cell tolerance to low osmotic pressure and high ionic strength.[28] Flavonoids are known to cause bacterial leakage by increasing cell wall and membrane permeability, leading to the loss of intracellular content and affecting bacterial homeostasis.[29] Other polyphenols, such as curcumin and stilbenoid, have been proposed to perturb bacterial membranes enriched in negatively charged phospholipids and destabilize membrane potentials and pH gradients, both of which contribute to antibacterial activity.[30] Traditional mechanisms of antibiotics include ROS-mediated bacterial death, as excessive ROS production can lead to oxidative stress, damaging cellular components such as DNA, proteins, and lipids.[31] The generation of ROS by polyphenols has been proposed as the underlying mechanism that affects

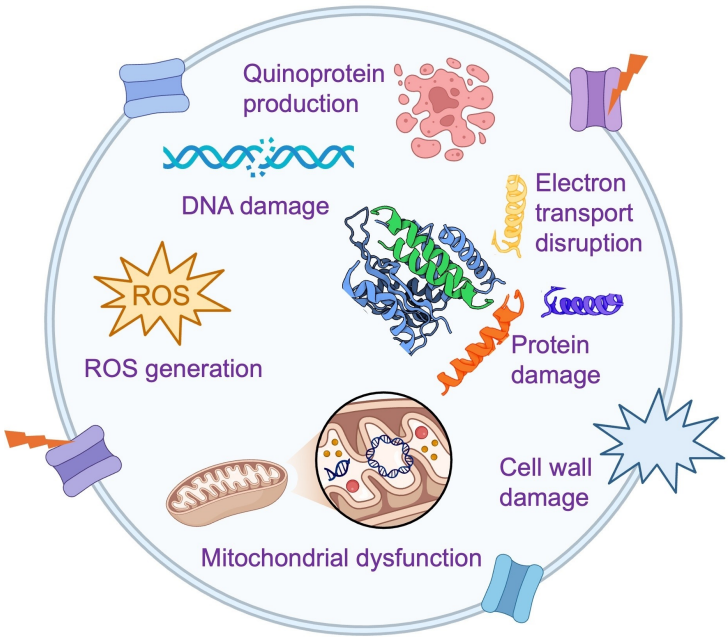

Figure 2. Schematic summarizing the primary antimicrobial mechanism of polyphenols, including DNA and protein damage, cell wall damage, mitochondrial function inhibition, ROS generation, and quinoprotein production. Created with BioRender.com.

cell wall integrity, bacterial metabolism, and iron homeostasis.[32] For example, gallic acid and kaempferol exhibit pro-oxidant effects by stimulating ROS production, resulting in the inhibitory growth of *P. aeruginosa* and *Staphylococcus epidermidis* (*S. epidermidis*).[33] The flavonoid quercetin enhances ROS production by regulating the expression of genes involved in ROS production as well as in subsequent processes.[34]

Polyphenols can also affect enzymes involved in DNA transcription and replication.[35] For example, in *E. coli*, resveratrol-*trans*-dihydrodimer has been reported to act as a strong inhibitor of DNA gyrase, an adenosine triphosphate-dependent enzyme for DNA replication; this strong inhibition effect is likely due to the binding of the phenolic compound to the adenosine triphosphate binding site of the enzyme.[36] The antibacterial activity of green tea catechin is related to several intracellular pathways, including enzyme inhibition, oxidative stress induction, and DNA damage.[37] The catechol ring of polyphenols readily oxidizes to semiquinone and benzoquinone radicals, which can interact with the bulky or high redox-potential enzymes in bacteria, leading to oxidative stress and cell apoptosis.[38] Tea catechins have been studied extensively for their antimicrobial activities, of which EGCG is the most abundant and biologically active. The antimicrobial mechanism of EGCG relies on the formation of quinoproteins (quinone-protein conjugates).[39] Studies have shown that EGCG can inhibit various enzymes, receptors, and signaling molecules owing to its strong protein-binding capacity.[39] A recent review has further proposed that exploiting polyphenol-protein interactions provides an attractive strategy to eradicate bacteria, since polyphenols have a high tendency to complex with proteins and have shown robust enzyme-inhibitory characteristics.[40]

2.3. Elimination of Bacterial Biofilms

Biofilms are microbial communities that form a self-produced matrix consisting of polysaccharides, proteins, and extracellular DNA.[41] The matrix is an intricate network that obstructs the penetration of antimicrobial agents, thereby making biofilms challenging to eradicate. The most extensively studied bacteria for biofilm formation are *S. aureus*, *P. aeruginosa*, *Streptococcus mutans* (*S. mutans*), and coagulase-negative staphylococci; these bacteria are associated with many chronic infectious diseases and medical device-associated infections.[6] Various polyphenols, such as TA, gallic acid, ellagic acids, proanthocyanidin, and tea-derived polyphenols, have shown strong biofilm formation inhibition against *S. aureus* at sub-inhibitory growth concentrations.[42] Galloyl catechins, particularly epicatechin gallate, induce the upregulation of the gene that is responsible for protection against cell wall stress and prevent biofilm formation with extensive changes in cell morphology.[43] Compounds in red wine, including quercetin, fisetin, kaempferol, apigenin, chrysin, and luteolin, effectively inhibit *S. aureus* biofilm formation and reduce *S. aureus* hemolysis, with quercetin being the most active flavonoid.[44] Although polyphenols exhibit high antibacterial and antibiofilm activities, their poor water solubility and instability in complex biological environments partially limit their biological efficiency. A recent review has described strategies for delivering natural polyphenols and phytochemicals within nanomaterials to combat and eradicate bacterial and fungal biofilms.[45] For example, the polyphenol curcumin loaded into polysaccharide NPs exerted antibacterial properties by inhibiting the activity of a tooth surface protein and reducing *S. mutans* biofilm formation in dental models.[46] TA has also been used to construct antibacterial coatings on nanoporous titanium surfaces through layer-by-layer deposition, which effectively reduced adhesion and biofilm formation of *S. aureus* on titanium implants, enhancing the antibacterial efficiency of the surfaces.[47]

3. Phenolic Antimicrobial Biomaterials

There is growing interest in the development of antimicrobial polyphenol-based materials, ranging from particles to hydrogels and macroscopic films, owing to their potent biological activities. The abundant phenolic hydroxyl groups in polyphenols enable their interaction with diverse materials or substrates through hydrogen bonding, π interactions, hydrophobic interactions, metal coordination, covalent bonding, and electrostatic interactions (Figure 3).[48a] These interactions endow phenolic materials with dynamic and customizable responsiveness to various stimuli (e.g., pH).[48] For instance, coordination bonds formed between phenolics and metal ions are sensitive to pH variations, whereas dynamic covalent bonds formed between phenolics and metalloids (e.g., boronate) can dissociate under acidic conditions or in the presence of *cis*-diols at physiological pH.[48d] Antimicrobial phenolic materials with additional functions can therefore be realized by selecting suitable formation interactions (e.g., coordination bonds for pH responsiveness) or through direct molecular modification (e.g., poly(ethylene glycol) (PEG) modification for antifouling antimicrobial coatings).[48e] This section summarizes recent advances in the design of phenolic-based materials with antimicrobial properties.

3.1. Antimicrobial Particles

Antimicrobial particles, particularly nanosized particles, are increasingly used to control bacterial infections as an alternative to antibiotics owing to their high surface-to-volume ratio and their ability to penetrate cell walls or damage membranes. Various colloidal particles, such as core-shell structures, hollow capsules, and mesoporous particles, have been fabricated from polyphenols or phenolic derivatives combined with metals, polymeric or biomolecular compounds, and their antibacterial and antibiofilm capabilities have been demonstrated.

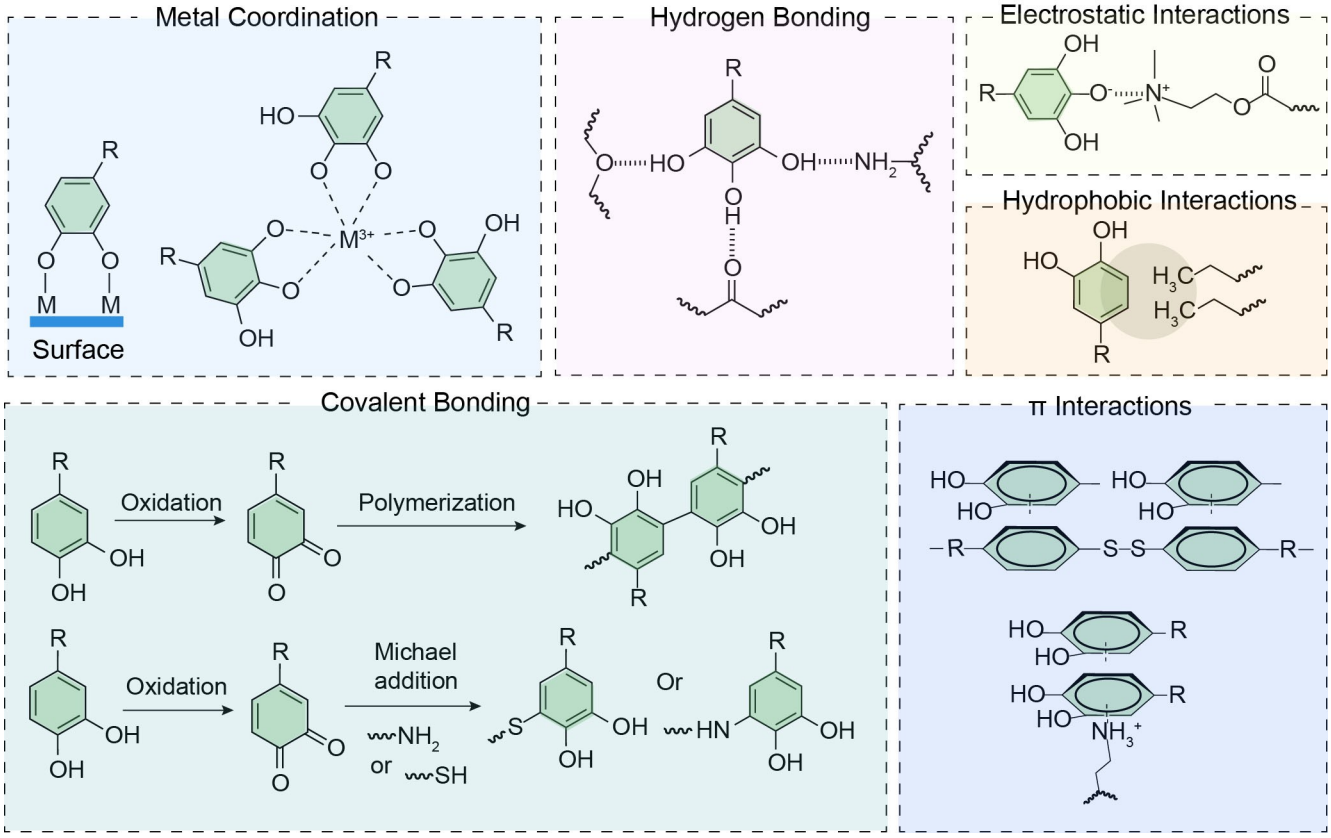

Figure 3. Various interactions between polyphenols and other components in phenolic-based antimicrobial materials.

3.1.1. Metal-Phenolic Network Particles

Polyphenols are abundant in nature and their phenolic hydroxyl groups can coordinate with various metal ions to form coordination networks–termed metal-phenolic networks (MPNs)–on a wide range of substrates (e.g., organic, inorganic, and biological entities). Owing to their physicochemical and biomedical properties, including tailorable size, high biocompatibility, tunable permeability, and pH responsiveness, MPN-based particles have been widely applied in drug delivery, bio-imaging, and cancer therapy.[49] For example, Yu et al. proposed a simple strategy for synthesizing antimicrobial MPN NPs through the one-step assembly of a seeding agent (e.g., diethyldithiocarbamate), natural polyphenols (e.g., EGCG), and metal ions (e.g., copper ions (Cu^{2+})) in aqueous solution (Figure 4a).[50] The Cu^{2+}-based MPN NPs showed high antimicrobial activity at low Cu^{2+} concentrations and negligible cytotoxicity across various models, including human cells, blood cells, zebrafish, and mice. The NPs were effective against multidrug-resistant bacteria (e.g., MRSA) by inhibiting their growth and biofilm formation, as well as destroying preformed biofilms. The antimicrobial mechanisms were identified and included bacterial cell wall disruption, ROS production, bacterial DNA deactivation, and quinoprotein formation (Figure 4b). Similarly, self-assembled tea polyphenol and magnesium NPs with antibacterial and angiogenic properties were developed to treat MRSA-infected diabetic foot wounds.[51] These NPs were formed upon the reduction of Mg^{2+} by phenolic hydroxyl groups in tea polyphenols (mainly composed of EGCG) under alkaline conditions. The NPs effectively disrupted bacterial DNA and induced ROS burst to inhibit MRSA, effectively penetrating biofilms and destroying MRSA biofilms without impacting mammalian cell viability, migration, or blood cell toxicity.

Transition metal ions, such as Cu^{2+}, silver ions (Ag^{+}), and zinc ions (Zn^{2+}), have been traditionally used for their antimicrobial properties. Huang et al. reported the fabrication of hybrid NPs formed from Zn^{2+}, ε-poly(L-lysine) (EPL), and protocatechuic aldehyde (PCA) to deliver Zn^{2+} for treating internal bacterial infections (Figure 4c).[52] The coordination between Zn^{2+} and the amino and polyphenol groups afforded NP stability in aqueous solutions and NP degradation and Zn^{2+} release in the infected microenvironment. These properties endowed the NPs with superior bactericidal ability in complex physiological environments over free Zn^{2+}, which completely lost antibacterial activity. Positively charged NPs are known to enhance bactericidal effects by disrupting bacterial membranes as the cell walls of both Gram-positive and Gram-negative bacteria are negatively charged.[53] Tobramycin (TOB), an aminoglycoside antibiotic containing phenolic hydroxyl groups, was used to design positively charged NPs through MPN assembly and Schiff base reaction (Figure 4d).[54] The TOB-loaded MPN NPs showed higher bactericidal activity than free TOB against a *P. aeruginosa* biofilm. The equivalent TOB

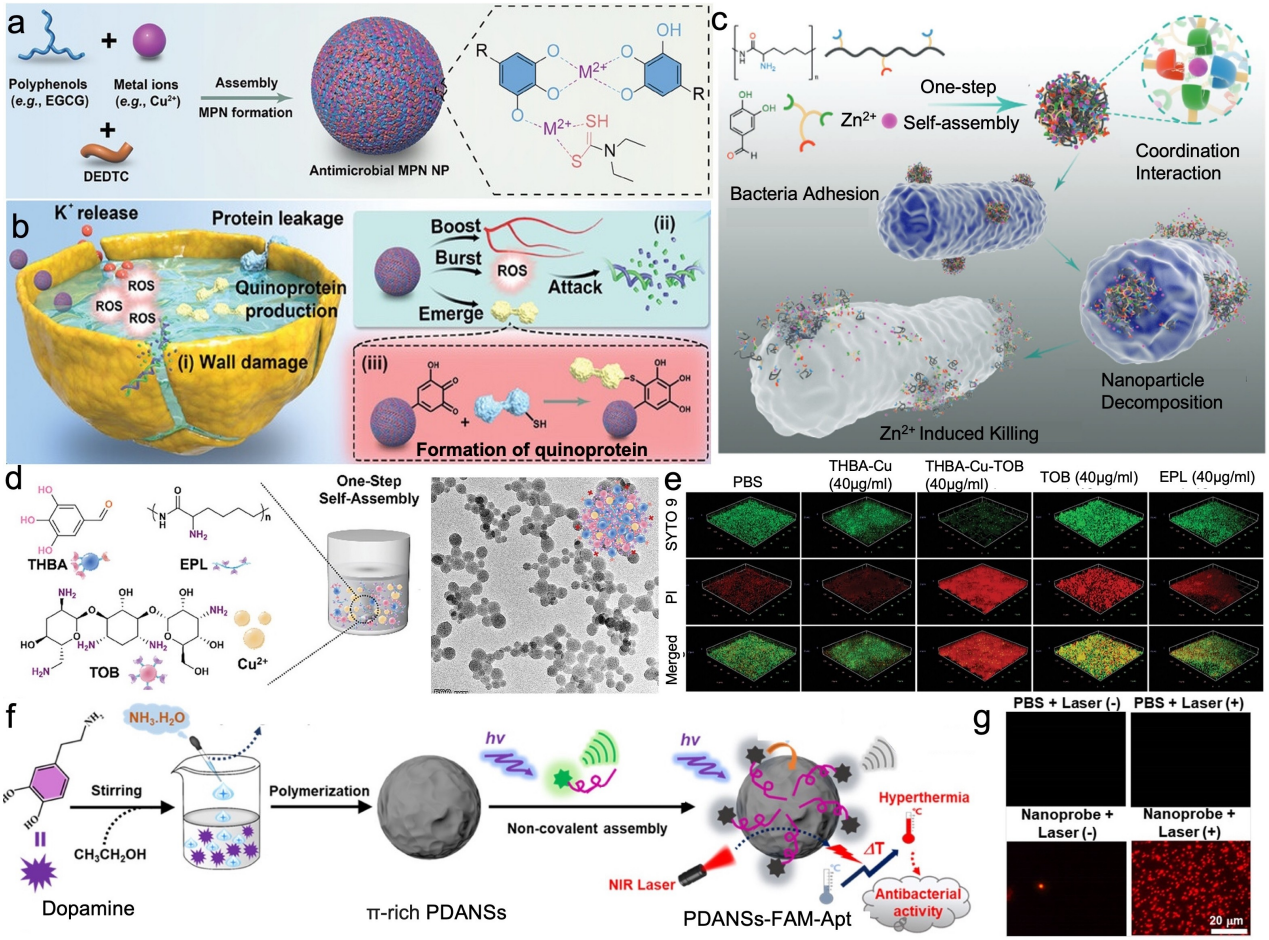

Figure 4. Schematics of (a) the synthesis of antimicrobial MPN NPs and (b) their antimicrobial modes of action. DEDTC, diethyldithiocarbamate. Adapted with permission.[50] Copyright 2023, Yu et al. (c) Illustration of the synthesis of Zn^{2+}-EPL-PCA hybrid NPs and their bactericidal mechanism. Reproduced with permission.[52] Copyright 2021 Wiley-VCH GmbH. (d) Characterization of cationic TOB-loaded MPN NPs (THBA–Cu-TOB) and (e) their biofilm formation inhibition properties, visualized by live/dead bacterial staining. PBS, Phosphate-buffered saline; THBA, 3,4,5-trihydroxybenzaldehyde. (d, e) Adapted with permission.[54] Copyright 2024, Gao et al. (f) Illustration of the assembly of nanoprobe PDA NPs (PDANSs-FAM-Apt; PDA nanospheres following incubation with fluorophore 6-carboxyfluorescein (FAM)-terminated *S. aureus*-binding aptamer (Apt)) and (g) their photothermal antibacterial activity. Adapted with permission.[57] Copyright 2020 American Chemical Society.

concentration in the NPs was only 1.6 % of the free TOB with the same sterilization efficiency. The higher performance of the NPs was mainly attributed to enhanced NP penetration into bacterial cells (Figure 4e). These positively charged MPN NPs have adjustable drug loading capacity and rapid pH responsiveness, making them a promising alternative antimicrobial for bacterial infections.

3.1.2. Polymerized Phenolic Particles

Polydopamine (PDA) is a biomimetic self-adherent polymer that readily forms through the self-polymerization of dopamine under alkaline conditions.[55] The catechol groups on PDA afford a versatile platform for adhesion with other components. Owing to the properties of PDA, such as pH responsiveness, high biocompatibility, and biodegradability, PDA-based particles have been widely used in biomedical applications, including the treatment of bacterial infections.[56] For example, Ye et al. reported an all-in-one design strategy to establish a stimuli-responsive nanoprobe based on PDA NPs for guiding precise photothermal bacterial eradication (Figure 4f).[57] The PDA NPs were synthesized via oxidative polymerization of dopamine and then incubated with a fluorophore (6-carboxyfluorescein)-terminated *S. aureus*-binding aptamer to form a nanoprobe that detected *S. aureus* at the single-cell level. The PDA NPs provided high-precision visual fluorescence imaging of living *S. aureus* and its biofilm, enabling targeted photothermal bacterial killing upon near-infrared (NIR) light irradiation (Figure 4g).[57] Polymerized phenolic particles were also fabricated by free radical copolymerization of dopamine and eugenol[58] and exhibited a high antibacterial rate of over 90 % against *E. coli*.

TA has been historically used in biomedical applications owing to its useful properties, which include antimicrobial, antioxidant, anti-allergic, antidiabetic, anticancer, and anti-inflammatory activities.[59] TA, which has a glucose core

linked to phenolic carboxylic acids via ester bonds, can self-cross-link into well-dispersed NPs and serve as a drug delivery carrier.[60] With abundant catechol groups, TA-based NPs achieved a high drug loading, similar to PDA NPs, for combination therapies targeting bacterial infections.[60] Xiao et al. reported a one-pot method to tune the polymerization of TA to fabricate well-dispersed poly-(TA) NPs with a size of 100 nm. [61] The NPs showed enhanced antibacterial effects on both Gram-positive and Gram-negative strains compared to free TA.[61] Cross-linked poly(TA) particles were prepared via cross-linking reactions between TA and biocompatible cross-linkers. The resulting NPs demonstrated strong antimicrobial effects against common bacterial strains such as *E. coli*, *S. aureus*, and *Bacillus subtilis*.[62] Furthermore, the physicochemical properties of poly(TA) particles, including size and surface charge, and the degradation of TA from poly(TA) particles were controlled by the cross-linker and the pH of the releasing media. Such poly(TA) NPs could damage the cell wall and cell membrane of bacteria to cause cell death and exert significant inhibitory and destructive effects on bacterial biofilms.[63]

3.1.3. Phenolic-Metallic Particles

Metal NPs such as silver (AgNPs) and gold NPs (AuNPs) have been widely used for antibacterial purposes owing to their high surface-to-volume ratio and strong interactions with microorganisms.[64] Phenolic compounds, such as tea polyphenols and PDA, have been used as reducing and stabilizing agents for synthesizing various particles, including metal NPs.[65] The catechol and amine groups of PDA provide active sites for reducing metal NPs, leading to metal-containing PDA NPs with high microbicidal and effective antibiofilm activity.[66] A strategy was developed to fabricate Ag-doped PDA NPs by polymerizing acrylamide with *N*,*N*-bis(acryloyl)cystamine (BA) in the presence of PDA-modified AgNPs. Transmission electron microscopy (TEM) imaging revealed the lychee-like morphology of the BA–Ag@PDA NPs with an average diameter of 238 nm (Figure 5a, b).[67] Owing to the synergistic effects of PDA and Ag^+, the NPs exhibited high antibacterial activity against both Gram-negative bacteria (e.g., *E. coli*) and Gram-positive bacteria (e.g., *S. aureus*). Yeroslavsky et al. reported a facile one-pot sonochemical method to synthesize hybrid Cu/Ag-based PDA NPs that provided oxidative conditions during sonication to polymerize dopamine into PDA NPs, which could chelate Cu^{2+} and Ag^+ for antibacterial and antibiofilm activity.[68] The resulting Cu/Ag@PDA NPs exhibited enhanced antibacterial efficiency over commercial AgNPs, while maintaining low toxicity toward NIH 3T3 mouse embryonic fibroblasts. Another PDA-based nanohybrid platform was developed to deliver the cationic peptide antibiotic colistin, achieving high antibacterial and antibiofilm activities with synergistic effects for combating bacterial infections.[69] Peng et al. developed zeolite-based imidazole framework (ZIF-8)-coated mesoporous PDA core-shell NPs and then loaded the NPs with pifithrin-μ, a natural inhibitor of the heat-shock protein essential for bacteria resistance to heat-induced damage. The mesoporous PDA NPs exhibited excellent photothermal properties, thereby realizing effective elimination of the bacterial biofilm and achieving low-temperature photothermal therapy (PTT) (~45 °C) with high antibacterial efficacy.[70] Plant extracts, such as curcumin, have also been used in the synthesis of AgNPs. The curcumin-mediated AgNPs significantly inhibited *Acinetobacter baumannii* biofilm formation with lower toxicity than the chemically synthesized alternatives.[71] The curcumin-stabilized AgNPs were further evaluated for their antimicrobial properties in vitro and in vivo–they demonstrated enhanced proliferation, migration, and collagen production in human dermal fibroblasts, as well as high biocompatibility and enhanced antibacterial effects on rats.[72] The polyphenol gallic acid has also been used as a capping agent to prepare AuNPs; the resulting NPs were stable in glucose and bovine serum albumin at different concentrations. These gallic acid-capped AuNPs exhibited low cytotoxicity in mouse embryonic fibroblast cells and showed antimicrobial effects against both *E. coli* and *S. aureus*.[73]

3.1.4. Other Phenolic-Based Particles

Phenolic compounds are also used to fabricate antimicrobial particles by combining them with biocompatible polymers or antimicrobials, such as antibacterial peptides, and antibiotics. For example, plant polyphenols were recently formulated into hexagonal column interpenetrated spheres (HCIs) through noncovalent assembly of plant-derived gallic acid with quaternary ammonium surfactants.[74] Owing to their strong hydrophobicity and adhesion, HCIs were applicable to various substrates and endowed with anti-water washing properties, thus showing high in vitro antimicrobial efficiency (>99 %) even following usage for 10 cycles. To address antibiotic resistance, a class of synthetic structurally nanoengineered antimicrobial peptide polymers (SNAPPs) was developed, which showed excellent antimicrobial activity in vivo against multidrug-resistant bacteria with low toxicity toward mammalian cells and negligible bacterial resistance.[75] SNAPPs were then immobilized into polyphenol-based capsules through two strategies: (i) complexation with TA and (ii) encapsulation within MPN coatings (Figure 5c, d).[76] The capsules demonstrated a high encapsulation of SNAPPs and displayed a sustained release of SNAPPs at pH 7.4, which maintained high antimicrobial activity with MIC values of $\approx 30\ \mu g\,mL^{-1}$ for *E. coli*. In a different study, Xiao et al. designed a biomimetic cell membrane polypeptide nanonet strategy, which involved lipid-functionalized polypeptides to modify macrophage membranes, followed by coordination with a TA-cerium complex through boronic acid-polyphenol-metal ion interactions.[77] The resulting polypeptide nanonets effectively trapped and killed bacteria, inhibited biofilm growth, neutralized lipopolysaccharides, and reduced inflammation for multifunctional antibacterial treatment (Figure 5e). Additionally, flavonoid-derived NPs were as-

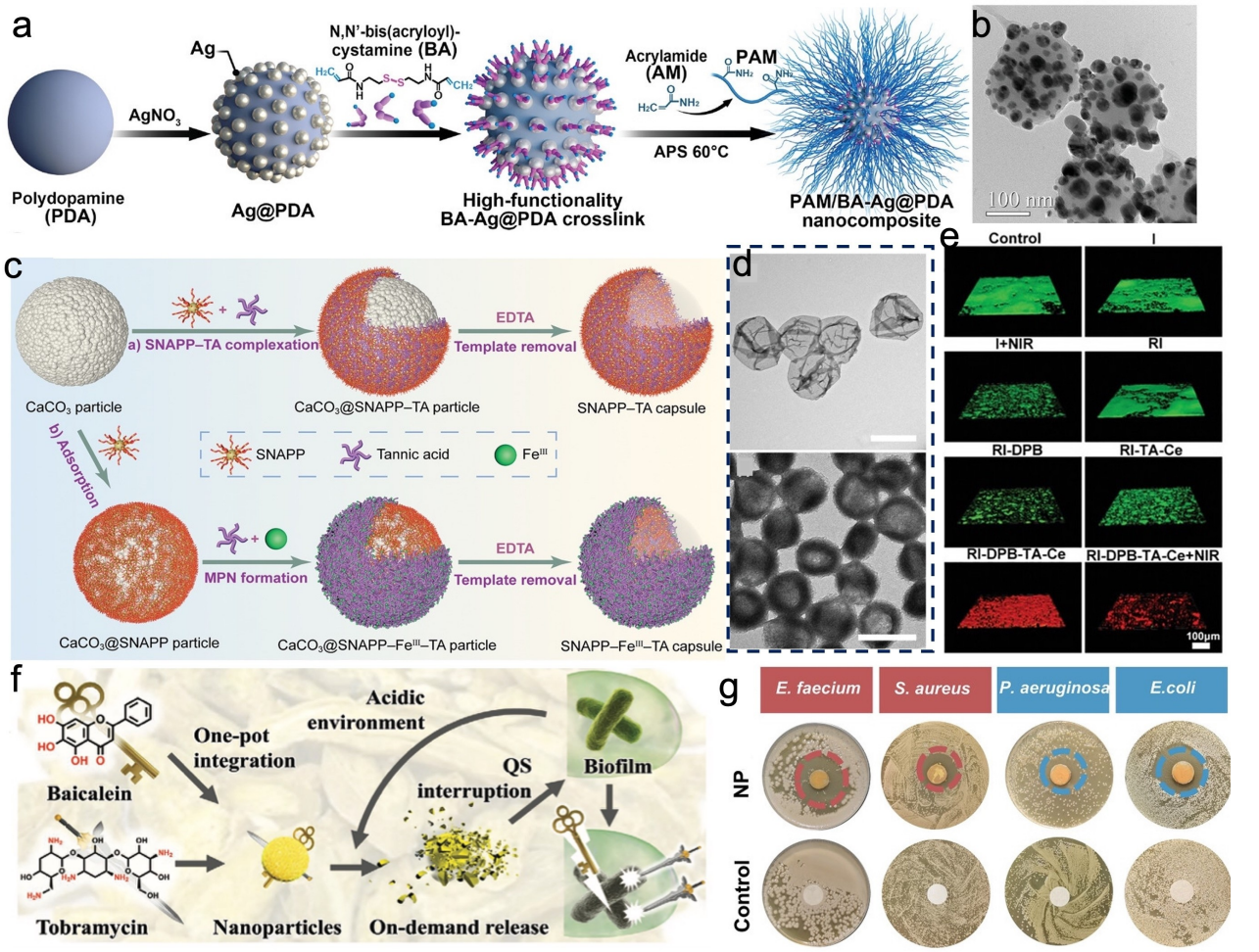

Figure 5. (a) Schematic of the polymerization of a BA–Ag@PDA nanocomposite and (b) TEM image of its morphology. Adapted with permission.[67] Copyright 2024 Shi et al. (c) Schematic of the immobilization of SNAPPs via the assembly of SNAPP-TA (complexation route) or SNAPP-Fe^{3+}-TA capsules (encapsulation route) onto sacrificial $CaCO_3$ particle templates. EDTA, ethylenediaminetetraacetic acid. (d) TEM images of SNAPP-TA and SNAPP- Fe^{3+}-TA capsules. Scale bars are 2 μm. (c, d) Adapted with permission.[76] Copyright 2021 Wiley-VCH GmBH. (e) Live/dead staining of preformed *E. coli* biofilms after different treatments. RI, macrophage membrane vesicle; RI-DPB, macrophage membrane vesicle functionalized with the liposome block polypeptide. Adapted with permission.[77] Copyright 2024 Wiley-VCH GmBH. (f) Schematic of the fabrication of antimicrobial NPs via one-pot integration of natural polyphenols and TOB and (g) antibacterial activity of the NPs against different bacteria. *E. faecium*, *Enterococcus faecium*. (f, g) Adapted with permission.[78] Copyright 2023 Wiley-VCH GmBH.

sembled through imine bonds formed between quinones in flavonoids and amino groups in TOB (Figure 5f).[78] The NPs showed high antibacterial efficiency against Gram-negative and Gram-positive bacteria (Figure 5g) and disrupted biofilms through enhanced antibiotic TOB infiltration. Chitosan, a positively charged natural polymer, approved by the U.S. Food and Drug Administration, has become a preferred candidate for antimicrobial delivery.[79] Chitosan NPs, prepared through oxidative degradation and ionic crosslinking to load the poorly soluble drug quercetin, showed excellent antibacterial activity against *E. coli*.[80] Zhao et al. developed curcumin-chitosan conjugates as antimicrobials via an esterification reaction of carboxylated chitosan with curcumin. These derivatives demonstrated good solubility, stability, free radical scavenging ability, and photodynamic antibacterial activity.[81]

3.2. Antimicrobial Hydrogels

Antimicrobial hydrogels are promising materials for wound dressings and fillers owing to their strong mucoadhesion, high biocompatibility, controlled drug release, and enhanced bioavailability.[82] Hydrogels with inherent antibacterial properties refer to a series of hydrogels composed of antibacterial components from natural polymers (e.g., polyphenols) and related derivatives. Another common strategy for designing antimicrobial hydrogels is via the loading of antibacterial agents, including metals, bioactive proteins, or naturally derived agents, into the hydrogels.[83] To date, naturally occurring phenolic compounds have been widely used to fabricate antimicrobial hydrogels owing to their strong adhesion, self-healing, good biocompatibility, and antibacterial properties.

3.2.1. Polyphenol-Metallic Hydrogels

Polyphenols are widely used as reducing agents in the synthesis of metallic NPs, and the incorporation of antibacterial metallic NPs into hydrogels is a promising strategy for wound healing applications. An injectable sodium alginate hydrogel loaded with plant polyphenol-functionalized AgNPs was developed for bacteria-infected wound healing and achieved a sustained release of Ag^+, ensuring long-term antibacterial activity and inhibition of biofilm formation.[84] Recently, a mussel-inspired TA-chelated Ag nanozyme with peroxidase (POD)-like activity was designed by in situ reduction of ultrasmall AgNPs with TA. The nanozyme catalyzed the in situ gelation of a polyacrylic acid hydrogel, endowing the hydrogel with abundant phenolic hydroxyl groups (Figure 6a) for enhanced and long-term adhesiveness.[85] The hydrogel exhibited outstanding antimicrobial activity through synergistic effects of the ROS generated from the POD-like catalytic reactions and the intrinsic bactericidal activity of Ag^+. The incorporation of metal NPs also contributed to the generation of ROS, inducing intracellular damage and providing photothermal activity to eliminate bacteria. Zhang et al. employed dopamine-modified gelatin (Gel-DA) as an enhanced biomineralizer to reduce Ag^+ in situ and subsequently generate stable AgNPs, followed by the addition of guar gum (GG) and boric acid to form a Gel-DA/GG@Ag hydrogel.[86] The hydrogel was endowed with high photothermal and synergistic AgNP-mediated bactericidal effects and exhibited remodeling, injectable, self-healing, and antioxidant properties, making it an excellent candidate for wound dressings (Figure 6b). Similarly, a biodegradable hydrogel with antibacterial and anti-inflammatory capabilities was synthesized via a facile photopolymerization process, which consisted of gelatin methacrylate as a 3D skeleton, polyphosphate as a procoagulant agent, TA as an anti-inflammatory agent and AgNPs as antibacterial agents with photothermal properties (Figure 6c).[87] The hydrogel eliminated 97.57 % of MRSA and 95.99 % of *E. coli* in vitro, mainly due to hyperthermia induced by the AgNPs and the photothermal-accelerated release of TA and Ag^+ (Figure 6d). The introduction of MPNs into antimicrobial hydrogels affords excellent antimicrobial performance and synergistic effects, resulting from the inherent antimicrobial properties of polyphenolic com-

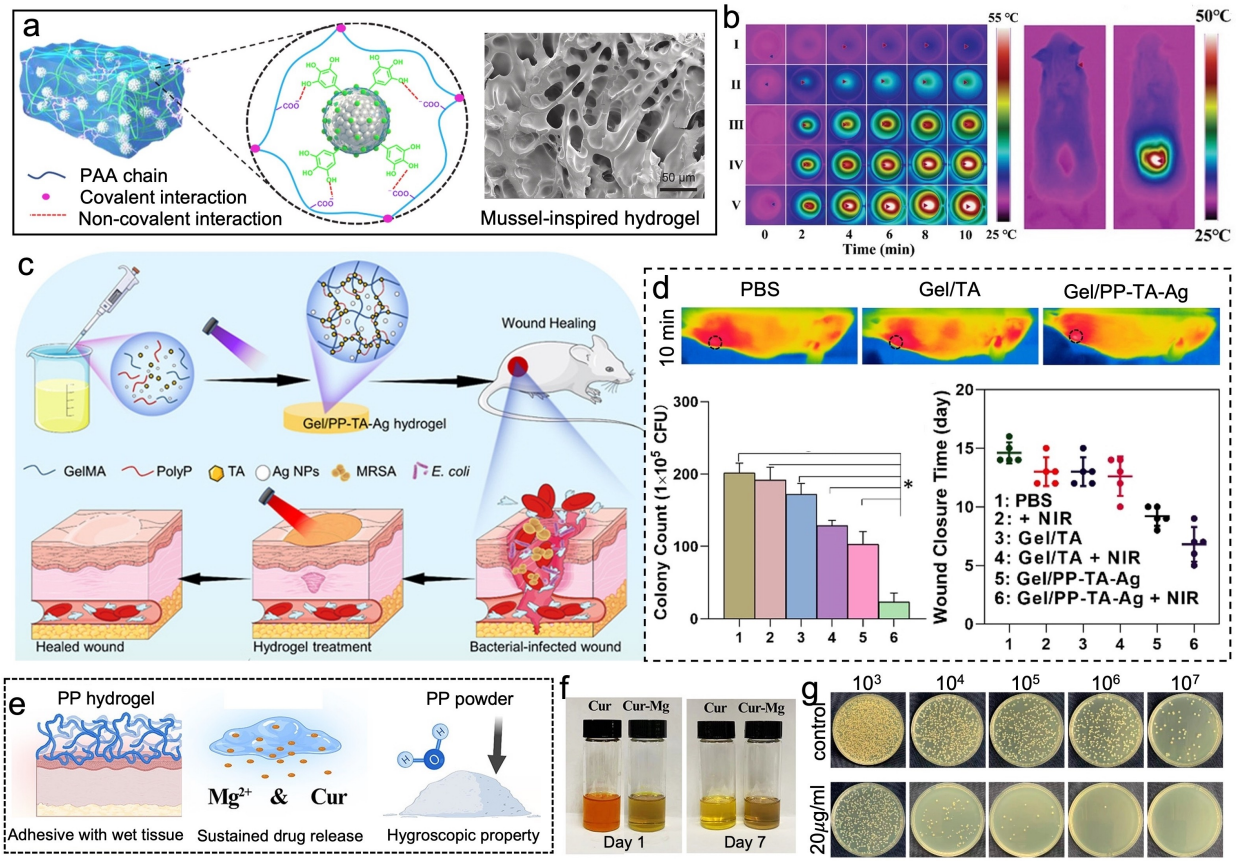

Figure 6. (a) Schematic of an ultrasmall TA–Ag nanozyme-reinforced TA–Ag-PAA hydrogel and its morphology (TEM image). PAA, polyacrylic acid. Adapted with permission.[85] Copyright 2021 Jia et al. (b) Photothermal effects of a Gel-DA/GG@Ag hydrogel. Adapted with permission.[86] Copyright 2021 Wiley-VCH GmbH. (c) Scheme of the preparation of a Gel/PP-TA–Ag hydrogel with hemostatic and antibacterial activity for wound healing. (d) Photographs of photothermal properties of hydrogels and their antibacterial activities in infected wounds. PP, Polyphosphate. (c, d) Adapted with permission.[87] Copyright 2021 Elsevier Ltd. (e) Scheme of a PP@Mg^{2+}-curcumin (Cur) hydrogel with multifunctional properties. PP, ε-poly-L-lysine (ε-PLL)/polymer poly(γ-glutamic acid) (γ-PGA). (f) Stability and (g) antimicrobial activity of curcumin-loaded MPN hydrogels. (e-g) Adapted with permission.[90] Copyright 2023 American Chemical Society.

pounds and metal ions.[88] For instance, smart hydrogels with multistimuli responsiveness and antibacterial properties were synthesized through the coordination between TA, Ti^{4+}, and other antimicrobial metal ions.[89] The metallogels exhibited pH- and H_2O_2-responsive release of Cu^{2+} and antimicrobial properties against *E. coli*, *S. aureus*, and *S. epidermidis*, and could be applied as dressings for infected wounds. Gong et al. developed an exudate-absorbing and antimicrobial hydrogel as treatment for burns; the hydrogel was composed of a hybrid ε-poly-L-lysine/poly(γ-glutamic acid) and incorporated curcumin-loaded magnesium polyphenol network particles (Figure 6e).[90] The slow and controlled release of curcumin from the hydrogel demonstrated good therapeutic efficacy for antioxidant, anti-inflammatory, and pain relief, while the structure of the magnesium polyphenol network improved the biocompatibility and stability of curcumin (Figure 6f, g).

3.2.2. Polyphenol-Polymer Hydrogels

Natural polymers, such as sodium alginate, collagen, carboxymethyl cellulose, chitosan, chitin, gelatin, and hyaluronic acid, are widely used for the preparation of hydrogels in the biomedical field because of their biocompatibility and biodegradability.[91] A hybrid hydrogel as a bioactive dressing for wound healing was formed by combining TA and cellulose nanofibrils.[92] The introduction of TA endowed the hydrogel with bioactivity, including antimicrobial and antioxidant activities, which were tailored by adjusting the dose of TA. Yang et al. reported a pH-responsive hydrogel that was fabricated using poly(vinyl alcohol)-borax and natural antibiotic resveratrol-grafted cellulose nanofibrils for bacterial-infected wound management (Figure 7a).[93] Owing to the dynamic borate ester and hydrogen bonds in the hydrogel network, the hydrogel displayed pH-responsive drug release behavior, as well as antioxidant and

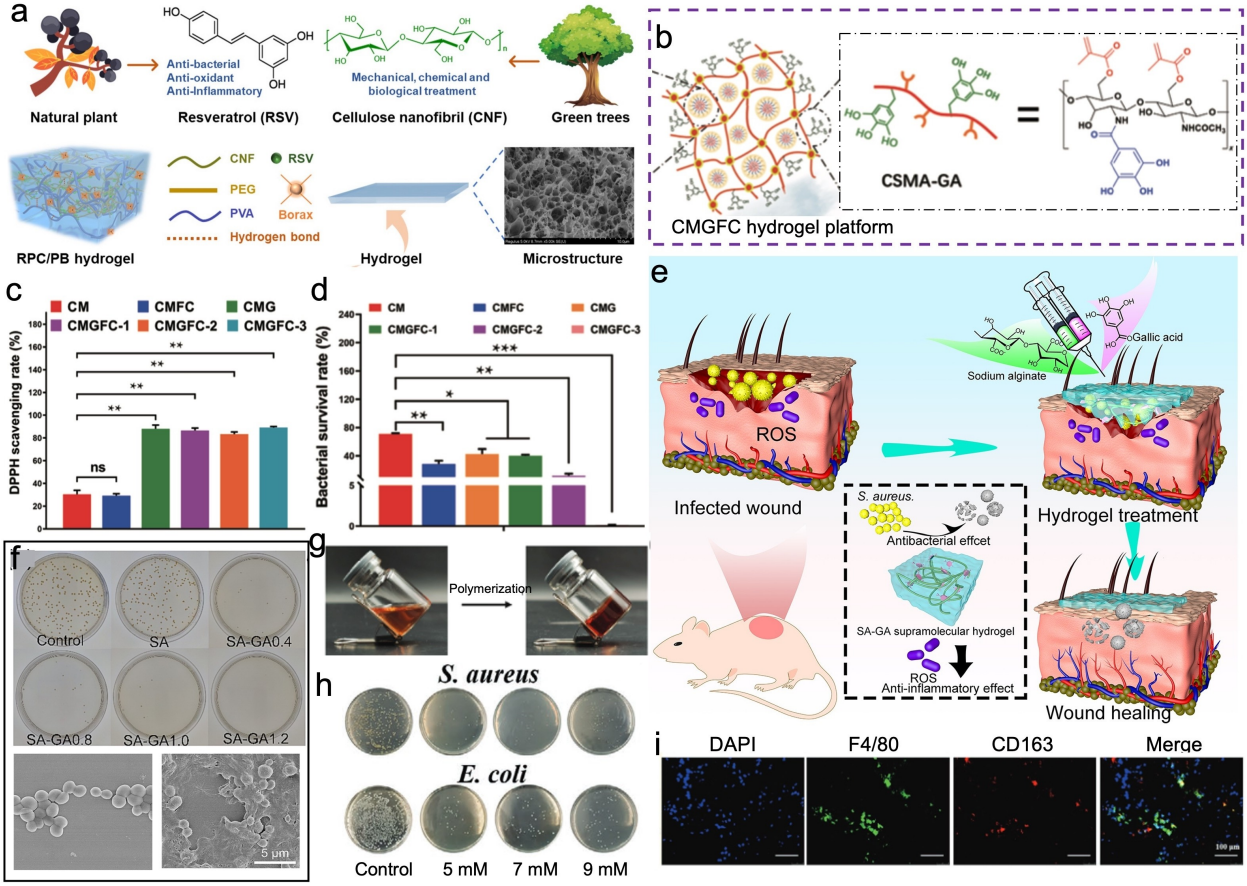

Figure 7. (a) Schematic of the preparation of a cellulose nanofibril-reinforced hydrogel. RPC/PB hydrogel, resveratrol-polyethylene glycol-cellulose/poly(vinyl alcohol)-borax hydrogel; PEG, poly(ethylene glycol); PVA, poly(vinyl alcohol). Adapted with permission.[93] Copyright 2022 Yang et al. (b) Synthesis of a polyphenol-modified chitosan hydrogel containing antibacterial NPs consisting of Pluronic F127 and chlorhexidine (CMGFC). CSMA-GA, chitosan methacrylate-gallic acid. (c) ROS scavenging and (d) antimicrobial capacity of the CMGFC hydrogels fabricated using different concentrations of Pluronic F127 and chlorhexidine. (b-d) Adapted with permission.[95] Copyright 2022 Tsinghua University Press. (e) Schematic of a polyphenol gallic acid-sodium alginate supramolecular injectable hydrogel for infected wounds. (f) Antibacterial properties of gallic acid-sodium alginate supramolecular hydrogels fabricated using different mass ratios of sodium alginate to gallic acid. GA, gallic acid; SA, sodium alginate. (e, f) Adapted with permission.[97] Copyright 2023 Elsevier B.V. (g) Morphology, (h) antimicrobial properties, and (i) inflammatory modulation effects of a polyacrylamide hydrogel fabricated using different concentrations of EGCG-3-acrylamido phenylboronic acid complex cross-linker. (g-i) Adapted with permission.[98] Copyright 2021 Wiley-VCH GmbH.

antibacterial properties from the cumulative release of the polyphenol resveratrol. Likewise, chitosan-based hydrogels are promising biomaterials for the medical and pharmaceutical industries.[94] A hybrid hydrogel platform fabricated from chitosan methacrylate and gallic acid was developed by encapsulating antibacterial NPs, consisting of amphiphilic Pluronic F127 molecules and hydrophobic chlorhexidine drug molecules (Figure 7b).[95] The hydrogel exhibited high antibacterial efficiency (99.9 %) and strong ROS scavenging ability (80 %) in vitro (Figure 7c, d). Furthermore, in vivo results confirmed that the hydrogel promoted vascularization and reduced inflammation to accelerate diabetic wound healing. Sun et al. modified chitosan to obtain quaternary ammonium-grafted chitosan for the preparation of self-healing hydrogels, resulting in enhanced antibacterial performance to promote diabetic wound healing.[96] An injectable hydrogel with antibacterial and anti-inflammatory properties was obtained using gallic acid and sodium alginate (Figure 7e).[97] The polyphenol-sodium alginate supramolecular hydrogel showed excellent antibacterial properties with a bacterial inhibition rate of 99 % against *S. aureus* (Figure 6f) and promoted infected wound healing by inhibiting bacterial infection and alleviating inflammation.

Natural bioactive compounds are emerging as potential alternatives to conventional antibiotics and incorporating natural polyphenols into antimicrobial hydrogels for wound treatment is widely applied. For example, a smart hydrogel dressing with tunable mechanical properties was developed through the copolymerization of acrylamide using EGCG-3-acrylamido phenylboronic acid complexes (Figure 7g).[98] Owing to the catechol groups and the therapeutic effect of EGCG, the resulting hydrogels showed good mechanical strength, moderate tissue adhesiveness, and exhibited antioxidation, antibacterial, anti-inflammatory, and proangiogenic effects to accelerate wound healing and facilitate dressing change (Figure 7h, i).

3.2.3. Other Polyphenol-Based Hydrogels

Bacterial cellulose is a natural biomaterial produced by few but specific microbes and bacterial cellulose-based hydrogels are attractive materials in biomedical applications, particularly in wound healing and tissue engineering owing to their excellent hydrophilicity, high purity, suitable mechanical properties, and good biocompatibility.[99] To improve antimicrobial performance, functional substances are incorporated in bacterial cellulose composites as a common strategy to form antibacterial hydrogels. A multifunctional polyphenol-functionalized bacterial cellulose hydrogel was prepared by incorporating bacterial cellulose modified with TA and EPL into a poly(vinyl alcohol) and borax matrix.[100] The hydrogel efficiently inhibited *E. coli*, *S. aureus*, and MRSA in vitro and MRSA in vivo without the use of antibiotics, owing to the synergetic effects of TA and the antimicrobial peptide. In another study, AgNP-loaded bacterial cellulose hydrogels were prepared as broad-spectrum antimicrobial hydrogels for wound dressing; the synthesis of AgNPs was achieved using a natural polyphenol curcumin.[101] This strategy was also applied to prepare biocellulose/Ag nanocomposite hydrogels that showed high antibacterial activities with 100 % bacterial reduction and significant inhibition zone against *S. aureus* and *E. coli.*[102] Naturally occurring biomolecules, such as proteins, are suitable components for preparing hydrogels because of their physicochemical properties and good biocompatibility. Lysozyme is a natural antibacterial protein, and its amine groups allow conjugation with phenolics to enable antibacterial and antioxidant biofunctionalites.[103] PEG-modified lysozyme was coupled with the polyphenol TA to form a robust biohydrogel with antibacterial and anti-inflammatory abilities for tissue patching.[104] The robustness of the hydrogel was attributed to the presence of TA, which introduced multiple noncovalent interactions, including hydrogen bonds and hydrophobic interactions into the network. Tian et al. prepared a double network hydrogel loaded with gallic acid using lysozyme amyloid fibers and chitosan as a rigid and flexible network.[105] Similarly, EGCG was added to form hybrid hydrogels in the presence of lysozyme amyloid fibrils in the nematic phase, and the hydrogels were shear-thinning and thermostable in the range of 25–90 °C without any phase transition.[106] Importantly, the hydrogels exhibited strong antibacterial activities against both Gram-negative and Gram-positive bacteria, controlled by bacterial agglomeration, without any notable cytotoxicity to human cells. Another protein-based hybrid hydrogel with antimicrobial activity was synthesized from TA and a naturally occurring protein silk fibroin.[107] The introduction of TA not only induced the gelation of silk fibroin to form a hybrid hydrogel with a short gelation time, at low gelation concentrations, and self-recovery properties, but also provided the resulting hydrogels with strong antibacterial activities.

3.3. Antimicrobial Coatings on Macroscopic Substrates

Bacterial infections from medical devices are a significant clinical challenge, and antimicrobial coatings on devices are, therefore, essential in preventing device-related infections. Owing to their universal adhesive properties, phenolic compounds represent suitable candidates for constructing these conformal coatings on diverse substrates. Additionally, polyphenol coatings can serve as platforms for immobilizing various functional cargos, including antimicrobial agents within bulk materials for diverse applications. This section presents examples of antimicrobial coatings on macroscopic substrates, including sponges, fibers, and microneedles based on phenolic compounds.

A naturally occurring polyphenol, procyanidin, with high antioxidant and antibacterial properties, was used to cross-link chitosan/gelatin sponge composites via a Schiff base reaction to fabricate polyphenol-functionalized sponges (Figure 8a).[108] The incorporated procyanidin endowed the sponge with a highly porous structure, resulting in enhanced liquid adsorption. Another series of antibacterial and antioxidant sponges based on chitosan, graphene oxide, and TA were designed; TA served as a cross-linking agent, forming connections with the deprotonated amino group on

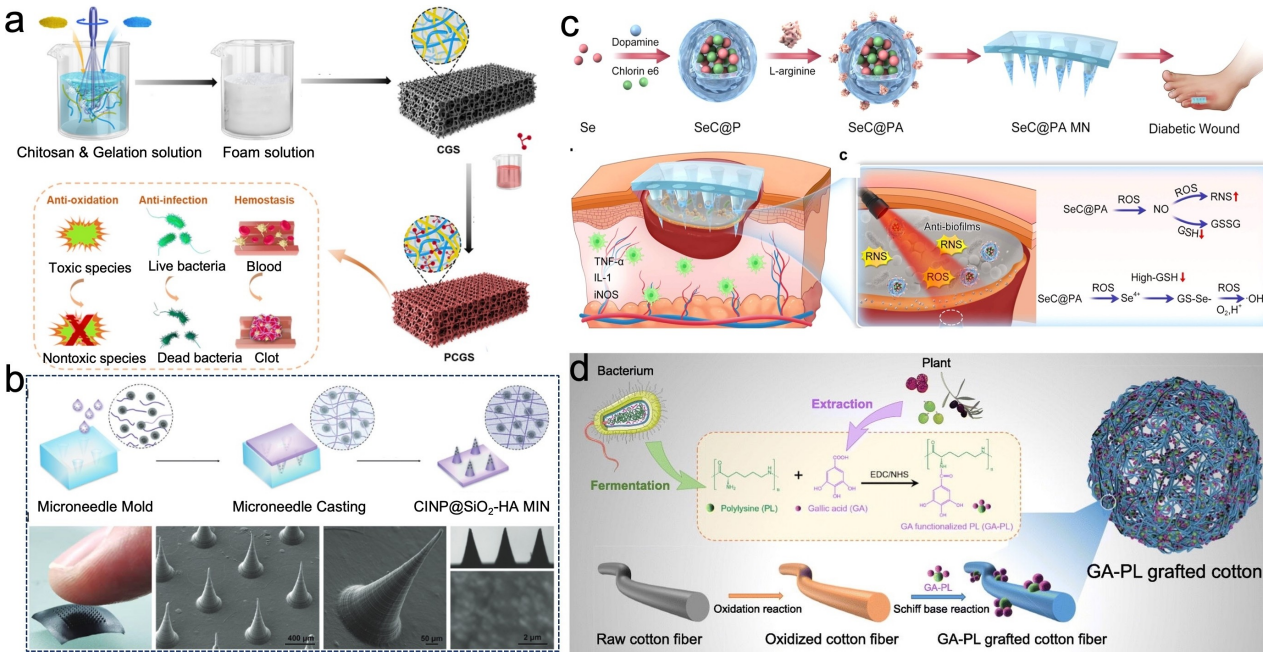

Figure 8. (a) Schematic of the preparation of chitosan/gelatin composite sponges (CGS) and polyphenol-functionalized CGS (PCGS) and their biological activities for infected wounds. Adapted with permission.[108] Copyright 2023 The Royal Society of Chemistry. (b) Schematic of the synthesis of melanin-inspired microneedles (CINP@SiO_2-HA MIN, cuttlefish ink@SiO_2-hyaluronic acid microneedle) and SEM microscopy images of their morphologies. Adapted with permission.[113] Copyright 2022 Wiley-VCH GmbH. (c) Schematics of the fabrication of multifunctional bandages (SeC@PA MIN, selenium-chlorin e6@dopamine-L-arginine microneedle) and their antimicrobial performance. Adapted with permission.[114] Copyright 2023 Yang et al. (d) Scheme of the synthesis of polyphenol (gallic acid, GA)-polypeptide (polylysine, PL)-grafted cotton fibers. Adapted with permission.[117] Copyright 2022 Elsevier B.V.

chitosan molecules through hydrogen bonding to form the sponges.[109] Additionally, a polyphenol-modified sponge was prepared using crude plant leaf extracts and cellulose, with the flavonoid quercetin grafted on cellulose as an antibacterial agent.[110] Textile materials, with their fibrous nature, are promising for medical and healthcare applications, as they can effectively hinder the spread of bacterial infections.[111]

Microneedle patches featuring miniaturized needles have emerged as promising tools for combating infections owing to their effective penetration and controlled release of bioactive molecules.[112] Melanin, a bioactive phenolic compound derived from cuttlefish ink, with strong antimicrobial and antibiofilm activities, was encapsulated with SiO_2 and then used to fabricate hyaluronic acid-based microneedles functionalized with biomineralized melanin NPs (Figure 8b).[113] The microneedles penetrated the epithelial basement membrane, inhibited *S. aureus* infection in wound beds, and released bioactive SiO_4^{4-} to stimulate skin tissue regeneration. Yang et al. developed a microneedle bandage functionalized with dopamine-coated hybrid NPs containing selenium and chlorin e6 (Figure 8c).[114] The introduction of dopamine enabled efficient loading of the photosensitizer chlorin e6 and selenium, into the microneedles, for ROS regeneration, thereby enhancing the anti-inflammatory and antibiofilm effects. Furthermore, PDA-decorated microneedles for wound healing were fabricated by preparing a core-shell hyaluronic acid microneedle patch with PDA NPs and stem cell-derived nanovesicles encapsulated in different layers of the tips.[115] A hydrogel-forming microneedle with broad-spectrum antibacterial properties was designed by introducing Fe–TA MPN composite NPs into a gelatin-based hydrogel.[116] The residual catechol groups in the MPNs were cross-linked to the glutamine residue of gelatin and the primary amino group of polylysine through enzymatic reaction to obtain the hydrogel and the microneedle patch. A cotton fiber with antibacterial and antioxidant properties was prepared using the polyphenol gallic acid and a natural polypeptide polylysine, and the complex was grafted onto cotton fibers via a condensation reaction between the carboxyl groups of gallic acid and the amino groups of polylysine (Figure 8d).[117] Jin et al. reported a strategy to modify the surface of fibers through the combined use of TA and a cationic peptide LL-37 to promote antibacterial activity; TA and LL-37 peptide interacted through hydrogen bonding, electrostatic, and hydrophobic interactions.[118] TA-coated hair fibers with long-term antimicrobial performance were fabricated by in situ reduction of AgNPs on polyamide surfaces pre-deposited with TA; the hydroxyl groups of TA enabled further covalent bonding with the carboxylic acid groups in the polyamide to form an inorganic-organic composite coating.[119]

4. Applications

Bacterial infections and surface bio-contamination present severe concerns in the biomedical field. Advances in nano-

technology have provided pathways for developing high-performing antimicrobial materials to combat complicated and severe infections. This section reviews the biomedical applications of multifunctional polyphenol-based antimicrobial materials, including wound healing, bone repair and regeneration, oral health, and anti-infection coatings for medical devices.

4.1. Wound Healing

Wound healing, a natural biological process in the human body, consists of four highly integrated and overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling or resolution.[120] Bacterial infection is a key concern during the process of wound healing and causes inflammation and tissue damage, leading to major disturbances and delays in wound repair.[121] Therefore, wound treatments that aim to mitigate bacterial infection have attracted much attention, leading to significant progress in the development of antimicrobial biomaterials for wound healing.[122] Natural-based biomaterials with excellent antimicrobial properties are suitable candidates for clinical wound healing owing to their excellent biocompatibility and biodegradability. Plant polyphenols are often combined with other components, such as chitosan, sodium alginate, agarose, and silk fibroin, to enhance their functional properties. For instance, chitosan, a natural polysaccharide with inherent antibacterial properties, was used to cross-link with TA to fabricate an injectable self-healing hydrogel.[123] The chitosan-TA hydrogel displayed rapid hemostatic capability and self-healing properties and achieved significantly faster wound healing with 92.8 % closure within 14 days, compared to the control (74.1 %) and commercial (Tegaderm) (81.6 %) treatments (Figure 9a).[123] Taking advantage of its active amino groups, chitosan was further modified with catechol and phenylboronic acid moieties to form natural-based hydrogels by cross-linking with EGCG; the resulting hydrogel achieved strong antibacterial activity via a "capture and kill" strategy (Figure 9b).[124] Similarly, sodium alginate, a hydrophilic biopolymer with abundant hydroxyl and carboxyl groups, was used to fabricate an injectable hydrogel with the polyphenol gallic acid; the hydrogel exhibited enhanced wound healing by inhibiting bacterial infection and alleviating inflammation over a 14-day period.[97] Agarose, another polysaccharide commonly employed to form hydrogels with tunable mechanical properties, was used to create a robust hydrogel dressing with TA, poly(vinyl alcohol), and polylysine.[125] The dressing demonstrated antimicrobial properties against Gram-negative and Gram-positive bacteria and suppressed scar formation in infected wounds. In another study, hydrogel scaffolds inspired by mussels were developed using chitosan, silk fibroin, and PDA-reduced graphene oxide, and the resulting scaffold exhibited excellent cytocompatibility and mechanical strength, which are suitable for wound dressing.[126] Furthermore, phenolic compounds can cross-link with stimuli-responsive polymers to form biomaterials that respond to wound environmental changes, such as pH, temperature, ROS, and glucose levels. For instance, ROS-responsive hydrogels were developed by mixing TA and ROS-responsive phenyl borate ester polymers and effectively inhibited the growth of *E. coli* and promoted wound closure in diabetic rat models (Figure 9c).[127] In response to elevated glucose levels in diabetic wounds, phenylboronic acid-modified gelatin methacryloyl and EGCG were used to design glucose-responsive hydrogels (i.e., GMPE) with reversible boronic bond networks.[128] The cumulative release amount of EGCG from the hydrogel in a glucose environment was approximately twice that in a non-glucose environment and, therefore, efficiently scavenged ROS in diabetic wound environments (Figure 9d). Additionally, phenolic compounds can chelate metal ions to promote wound healing. For example, MPN capsules containing EGCG and Cu^{2+} were incorporated into a wound dressing to provide continuous release of antimicrobial Cu^{2+} over 96 h, showing an inhibitory effect on *E. coli* and *S. aureus* and inhibiting inflammation to accelerate chronic wound healing.[129] PTT, an emerging antimicrobial therapy, employs a photothermal agent that converts NIR light into heat to eradicate bacteria by denaturing bacterial proteins at wound sites.[130] Metal-phenolic nanomaterials have been widely explored in PTT, either relying on their inherent photothermal capabilities or as carriers for the efficient encapsulation of photothermal agents. Multifunctional TA–Fe/Cu NPs with photothermal antibacterial ability for wound healing were fabricated using a self-sacrificial template method through the one-pot coordination of TA and Fe^{3+}/Cu^{2+}.[131] The hollow TA–Fe/Cu NPs exhibited robust POD-like activity, effectively eliminating excess ROS at the wound areas, and showed exceptional photothermal capabilities to capture bacteria and disrupt dense biofilms (Figure 9e). Owing to the photothermal properties of PDA,[132] a PDA-based MPN hydrogel was developed to impart photothermal activity and antibacterial activities associated with Cu^{2+}, indicating a promising dressing for infected wound healing.[133] The prepared photothermal agent CuS NPs and metal-phenolic NPs composed of TA coordinated with europium ions (Eu^{3+}) were loaded onto a supporting base and needle tips to obtain multifunctional microneedles.[134] Under NIR irradiation, the increasing temperature of the microneedle patches, due to the loaded photothermal CuS NPs, enabled the needle tips to accelerate the disassembly of metal-phenolic NPs and the release of TA and Eu^{3+} in the acidic environment, thereby achieving photothermal removal of localized bacteria (via CuS) and ROS scavenging (via Eu^{3+}-TA) at the wound site (Figure 9f).

4.2. Bone Repair and Regeneration

Bone defects caused by high-energy injuries are often accompanied with bacterial contamination, and bone tissue infection is a common orthopedic complication.[135] Bacteria that colonize bone tissue or implants induce a strong immune response and secrete acidic metabolites, reducing osteoblast activity and hindering bone defect repair.[136]

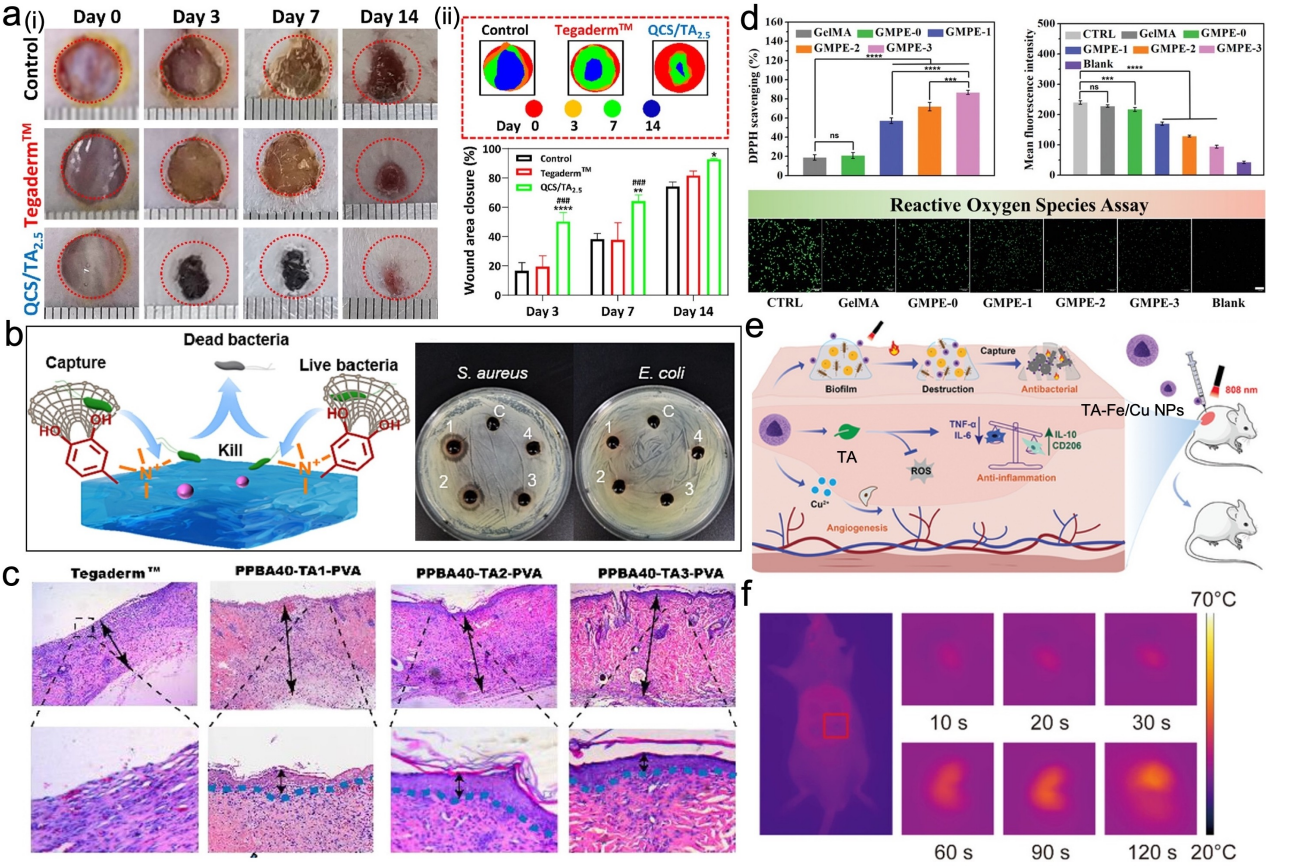

Figure 9. (a) In vivo assessment of chitosan-TA hydrogels for wound healing. (i) Photographs of wounds without treatment (control) or with hydrogel treatments (Tegaderm or QCS/TA hydrogel). QCS, quaternary ammonium chitosan. (ii) Analysis of wound area closure at different healing periods for each group. Adapted with permission.[123] Copyright 2022 American Chemical Society. (b) Schematic of antibacterial activity via a "capture and kill" strategy (left) and photographs of the inhibition zones of EGCG-chitosan hydrogel against *S. aureus* and *E. coli* (right). Adapted with permission.[124] Copyright 2022 Elsevier Ltd. (c) H&E staining of wound tissues following treatment with Tegaderm and TA-based hydrogels fabricated using different PPBA-to-TA ratios. PPBA-TA-PVA, TA-conjugated polyphosphazene phenylboronic acid (PPBA) with poly(vinyl alcohol) (PVA) hydrogel. Adapted with permission.[127] Copyright 2022 American Chemical Society. (d) ROS scavenging ability of glucose-responsive GMPE hydrogels, including quantification of 1,1-diphenyl-2-picrylhydrazine (DPPH) scavenging capacity and 2,7-dichlorofluorescein diacetate (DCFH-DA) staining to detect ROS in cells. GMPE, gelatin methacryloyl (GelMA) with 4-carboxyphenylboronic acid cross-linking EGCG hydrogel. Adapted with permission.[128] Copyright 2023 Wiley-VCH GmbH. (e) Schematic showing the impact of TA–Fe/Cu NPs on infected wound sites in diabetic mice. Adapted with permission.[131] Copyright 2024 Wiley-VCH GmbH. (f) NIR images of wounds treated with a multifunctional microneedle patch fabricated from poly(vinyl alcohol), hyaluronic acid, CuS, and TA–Eu MPN NPs. Adapted with permission.[134] Copyright 2024 American Chemical Society.

Natural polyphenols with abundant phenolic hydroxyl groups provide tissue adhesive, antioxidant, and anti-inflammatory properties and have been used to treat pathologies associated with bone resorption-like osteoporosis and rheumatoid arthritis.[137] For example, EGCG was used to assemble with a mitochondria-targeted amino acid cysteine to form EGCG-cysteine (EC) NPs for promoting osteogenic differentiation and bone tissue repair.[138] The EC NPs not only enhanced the bioavailability and osteogenic effects of EGCG but also supplied cysteine for enhanced bone regeneration (Figure 10a). Another polyphenol, PCA, was used to modify a cellulose acetate membrane for guiding bone regeneration through its immunomodulatory properties (Figure 10b).[139] The modified membrane displayed strong radical scavenging properties and reduced inflammatory response, providing a favorable immune microenvironment for osteogenesis and mineralization. Inspired by the natural structure-function relationship in bone, mineral-organic bone adhesives were developed using TA, silk fibroin, and hydroxyapatite to achieve strong water-resistant fixation and facilitate bone tissue regeneration.[140] The cross-linking between TA and silk fibroin provided a nanofibrillar structure in the hydrogel, and the coordination bonds between TA and hydroxyapatite enhanced its toughness and adhesion strength, which in turn facilitated the stable fixation of bone fracture and accelerated the bone remodeling process (Figure 10c). Additionally, tea polyphenol-hydroxyapatite hydrogels demonstrated significant anti-osteoclastic and osteogenic properties in vivo and showed early angiogenic capacities, leading to improved bone regeneration in critical-size femoral bone defects in osteoporotic rats (Figure 10d).[141] The chelating activity of

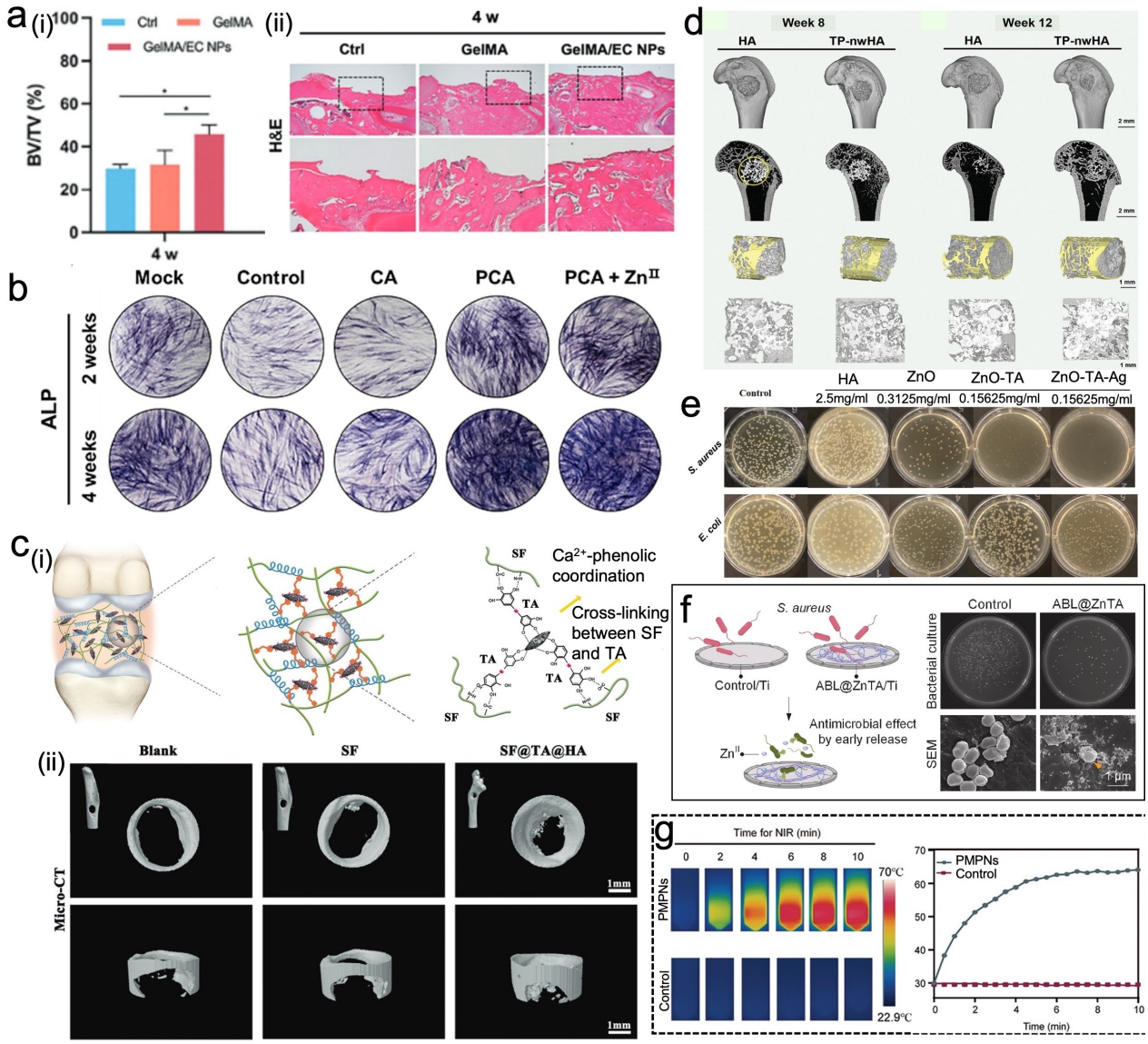

Figure 10. (a) Therapeutic efficacy of EC NPs in a rat mandibular bone defect model. (i) Micro-computed tomography (micro-CT) analysis of bone volume fraction. BV/TV, bone volume/tissue volume. (ii) H&E staining images of the mandibular bone defect at 4 weeks post-operation at low and high magnifications. Adapted with permission.[138] Copyright 2024 Wiley-VCH GmbH. (b) Alkaline phosphatase (ALP) staining of polyphenol (PCA)-modified cellulose acetate membranes in RAW264.7 cells. CA, Cellulose acetate. Adapted with permission.[139] Copyright 2023 Elsevier Ltd. (c) Assessment of mineral adhesives (silk fibroin (SF) and SF@TA@hydroxyapatite (HA) nanofibrils for bone regeneration. (i) Schematic of the proposed mechanism for achieving the high toughness of adhesives. (ii) Micro-CT images of axial and radial bone distribution in the defect sites after an 8-week implantation. Adapted with permission.[140] Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (d) Micro-CT reconstruction images and 2D sagittal images of femoral bone defect sites implanted with scaffolds at 8 and 12 weeks after implantation; scaffolds: HA (hydroxyapatite) and TP-nwHA (tea polyphenol-hydroxyapatite hydrogel). Adapted with permission.[141] Copyright 2024 Wiley-VCH GmbH. (e) Representative bacteria colony images of agar plates containing hydroxyapatite (HA), ZnO, ZnO-TA, and ZnO-TA–Ag NPs. Adapted with permission.[143] Copyright 2023 Wiley-VCH GmbH. (f) Schematic of in vitro antibacterial evaluation of coated titanium (Ti) implants (Ti-coated abaloparatide (ABL)@ZnTA) and representative images of *S. aureus* after incubation with the implants. Adapted with permission.[144] Copyright 2024 Xu et al. (g) Photothermal curves of scaffolds with 200 ppm PDA-modified EGCG–Sr complexes (PMPNs) following irradiation by a NIR laser at 808 nm and an intensity of 1.5 W cm^{-2}. Adapted with permission.[145] Copyright 2024 Wiley-VCH GmbH.

polyphenols toward metal ions plays an important role in developing functional biomaterials for bone regeneration owing to the inherent biological properties of metal ions. For instance, Mg^{2+} doping of orthopedic implants through coordination with EGCG enhanced osteogenic differentiation in human adipose-derived stem cells owing to the synergistic influence of EGCG and Mg^{2+}.[142] Similarly, a metal-phenolic composite scaffold was designed for infected bone defect repair using TA-modified zinc oxide (ZnO) loaded with AgNPs.[143] The controlled release of metal ions (Zn^{2+} and Ag^{+}) ensured sufficient antibacterial effects in promoting infected bone repair, and the synchronous release

of TA provided strong antioxidant activity for osteogenic differentiation (Figure 10e). A Zn^{2+}-phenolic (TA) network nanocoating was also developed to encapsulate the osteogenic peptide abaloparatide to prevent implant infection through immune modulation and promote osteogenesis.[144] The anti-inflammatory performance and immunomodulation of macrophage phenotype of the nanocoating enhanced bone implant integration under bacterial infection microenvironments. The phenolic-coordinated Zn^{2+} ions in this nanointerface acted as zinc finger motifs to stabilize peptide configurations through multiple molecular interactions, which enabled high bioactivity, high loading capacity, and long-term release of osteogenic peptides (Figure 10f). In addition, MPNs show promise as bone composites owing to their photothermal antimicrobial properties. A dual-functional scaffold based on EGCG–Sr complexes with PDA modification was fabricated, where the photothermal and antioxidant performances of the MPNs were enhanced by the PDA coating (Figure 10g).[145] This biomimetic scaffold with NIR stimulation significantly promoted angiogenesis and osteogenesis, effectively regulating the microenvironment and facilitating bone tissue repair.

4.3. Oral Health

Oral and periodontal diseases, such as periodontitis, are among the most prevalent diseases globally, leading to dental caries (tooth decay), tooth loss, and numerous other oral health complications.[146] According to the World Health Organization report in 2022, nearly half of the global population (i.e., 3.5 billion) suffers from untreated oral diseases, surpassing any other noncommunicable diseases.[147] Oral and periodontal diseases are often characterized by an imbalance in the oral microbiota, in which bacteria attach to salivary proteins to form complex biofilms on teeth and gingival tissues.[148] Natural polyphenols, found in many fruits and plants, have been widely used for centuries to prevent and treat oral infectious diseases, and polyphenol-based biomaterials offer a promising alternative to conventional antibiotics for treating oral and periodontal diseases.[149] For instance, green tea polyphenol EGCG has been identified as effective in treating chronic periodontitis.[150] To enhance the therapeutic effect of EGCG, a strategy for the self-assembly of EGCG NPs was developed, involving a one-step polyphenolic condensation reaction. The NPs exhibited potent ROS scavenging ability and promoted an anti-inflammatory microenvironment for efficient periodontitis therapy (Figure 11a).[151] In vivo studies further illustrated that EGCG NPs reduced the alveolar bone loss from 1347 ± 245 to 596 ± 92 μm by decreasingthe ROS level to ~50%, as well as inhibiting osteoclastic activity in a rat model of chronic periodontitis. A glucose/ROS dual-responsive EGCG release for periodontitis treatment was introduced using phenylboronic acid-functionalized oxidized sodium alginate and carboxymethyl chitosan.[152] This stimuli-responsive system displayed strong antioxidant and anti-inflammatory properties and promoted periodontal bone regeneration in diabetic rats (Figure 11b). Quercetin, a promising flavonoid for periodontal therapy, was recently incorporated into a mesoporous bioactive glass and exhibited promising effects in repairing alveolar bone defects in periodontitis and showed a concentration-dependent upregulation of the osteogenic capacity (Figure 11c).[153,154] Additionally, PDA, a natural catechol-containing biopolymer, was explored for fabricating biomaterials to treat oxidative stress-induced periodontal disease.[155] The biodegradable PDA NPs effectively scavenged multiple ROS and suppressed ROS-induced inflammation reactions, showing potential as efficient scavengers for various oral diseases (Figure 11d). Many nanomaterials with enzyme-like activities (termed nanozymes) have been widely applied in periodontitis treatment because nanozymes can produce ROS to damage bacterial cell membranes and biomacromolecules, such as DNA and proteins, eventually leading to bacterial lysis.[156] An injectable MPN-based hydrogel with antibacterial, antioxidant, anti-inflammatory, and osteogenic functions was designed through the formation of a nanozyme based on the self-assembly of Cu and TA.[157] The Cu–TA nanoenzyme exhibited broad-spectrum antibacterial properties against periodontitis bacteria and promoted tissue regeneration by enhancing anti-inflammatory factors and osteogenesis gene expression (Figure 11e). Another MPN-based nanozyme was developed using polyphenols as stabilizers and reducing agents for producing palladium (Pd) NPs, and the resulting MPN–Pd system demonstrated bactericidal effects against pathogens such as *S. mutans* and *Enterococcus faecalis* due to its oxidase-like activity.[158] Additionally, owing to its photothermal properties, MPN–Pd effectively eradicated polymicrobial biofilm in vivo, confirming the efficacy of MPN–Pd in treating oral biofilm-related infections (Figure 11f). Multifunctional MPN-based composites for periodontitis were developed by combining bone morphogenetic protein–a protein widely used for promoting bone formation–TA, and Sr^{2+} on AuNPs.[159] These composites introduced a multifunctional nanoplatform tailored for periodontitis treatment, which was attributed to the antibacterial and antioxidant properties of MPNs and the osteogenic differentiation capability of protein and AuNPs (Figure 11g). In another study, branched Au-Ag nanostructures were used to enhance the photothermal performance of MPNs by coating MPNs on dendritic Au–Ag NPs. The nanocomposites, with photothermal and anti-inflammatory properties, combined with PTT and immunotherapy exhibited excellent therapeutic effects on periodontal inflammation.[160]

4.4. Anti-Infection Coatings on Medical Devices

Healthcare-associated infections, particularly those related to medical devices and surgical tools, present severe complications that pose a threat to public health worldwide.[6,161] Surgical sutures are important medical devices that are used for closing damaged tissues and organs, and they are widely used to promote wound healing and reduce infection risk.[162] Chen et al. reported a simple method to develop antimicrobial coatings on suture (e.g.,

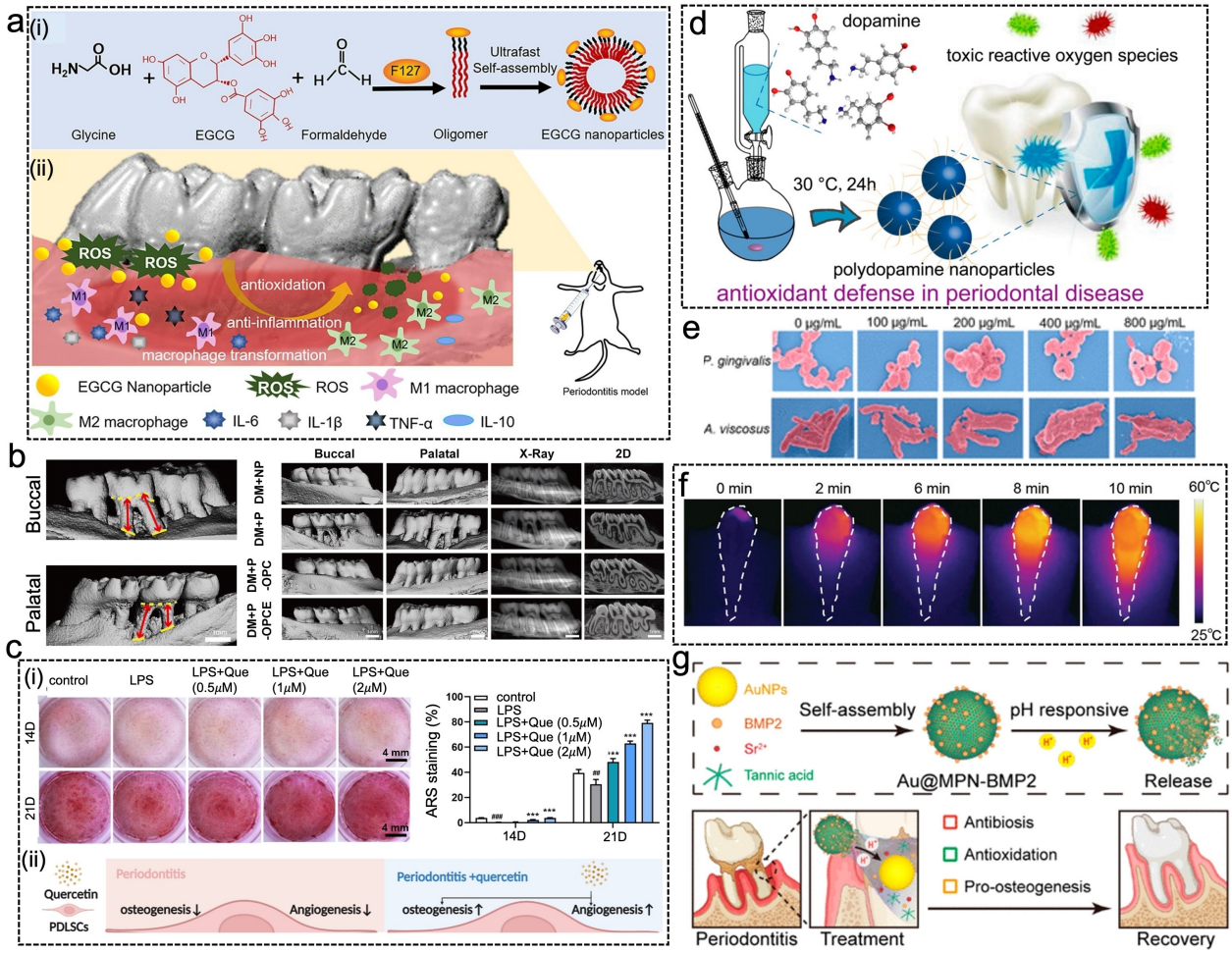

Figure 11. (a) Schematics of (i) the formation of EGCG NPs and (ii) their potential mechanism for alleviating inflammation in a periodontitis model. IL, Interleukin; TNF, tumor necrosis factor. Adapted with permission.[151] Copyright 2021 Elsevier B.V. (b) Representative 2D and 3D images of maxillary alveolar bone surrounding the maxillary second molars after different treatments. DM + NP, diabetes mellitus without periodontitis; DM + P, diabetes mellitus with periodontitis; OPC, oxidized sodium alginate-phenylboronic acid-carboxymethyl chitosan; OPCE, OPC + EGCG hydrogel. Adapted with permission.[152] Copyright 2024 The Royal Society of Chemistry. (c) Effects of quercetin (Que)-loaded mesoporous NPs in periodontitis. (i) Alizarin red S (ARS) staining and its quantitative results after incubation of Que-loaded mesoporous NPs for 14 and 21 days under periodontitis microenvironment. LPS, lipopolysaccharide. (ii) Schematic of the pharmacological mechanism of the NPs in a periodontitis microenvironment. PDLSCs, periodontal ligament stem cells. Adapted with permission.[154] Copyright 2024 Yang et al. (d) Schematic of the synthesis of PDA NPs and their use as efficient ROS scavengers in periodontal disease. Reproduced with permission.[155] Copyright 2018 American Chemical Society. (e) Scanning electron microscopy images of different types of bacteria treated with Cu-TA nanozyme at different concentrations. *P. gingivalis*, *Porphyromonas gingivalis*; *A. viscosus*, *Actinomyces viscosus*. Adapted with permission.[157] Copyright 2023 American Chemical Society. (f) Heat map of root canal during MPN–Pd nanoplatform-mediated synergistic therapy. Adapted with permission.[158] Copyright 2023 Wiley-VCH GmbH. (g) Schematic of multifunctional metal-phenolic composites for the management of periodontitis. BMP2, bone morphogenetic protein 2. Adapted with permission.[159] Copyright 2024 American Chemical Society.

Catgut suture) surfaces exploiting partial TA self-polymerization to create hybrid poly(TA)/TA mixture coatings (i.e., MPTA). The hybrid MPTA coating was successfully applied to the surfaces of commercialized poly(glycolide-*co*-lactide) (PGLA) and Catgut sutures (S_{PGLA} and S_{Catgut}), and the coated PGLA membrane exhibited superior antibacterial activity compared to the controls, which included pristine membrane and membrane treated in pH-unadjusted TA solution (Figure 12a).[163] Additionally, owing to the cross-linking of TA and chitosan/gelatin on the porous tape suture, the modified sutures (TA100) exhibited enhanced mechanical properties.[164] The modified sutures showed antibacterial performance, anti-inflammatory properties, and increased pull-out force from the tendon because of the high adhesive performance of the TA-based coating, making them suitable candidates for facilitating tissue healing (Figure 12b).[164] Adhesive coatings using dopamine or TA were also developed for needle surfaces to create self-sealing, hemostatic, and antibacterial needles. These polyphenol-derived coatings effectively retained multifunctional NPs upon needle withdrawal at the puncture to prevent bleeding during various puncture procedures (Figure 12c).[165] Biofilm-related infections, particularly those linked to implanted medical devices, such as intravascular and urinary

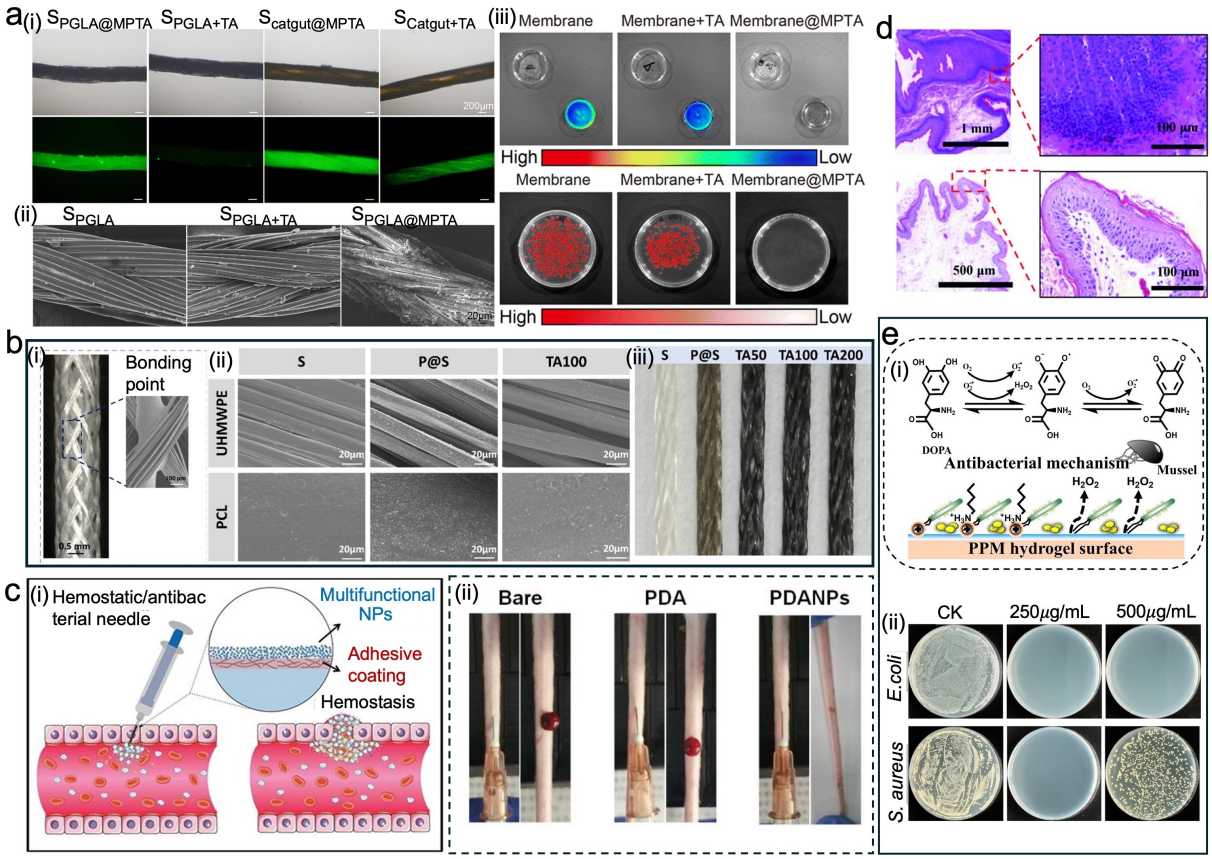

Figure 12. (a) Characterization of polyphenol coatings on sutures and their antibacterial activities on membranes. (i) Fluorescent images of sutures ($S_{PGLA+TA}$, $S_{Catgut+TA}$, $S_{PGLA@MPTA}$, $S_{Catgut@MPTA}$) bearing fluorescein isothiocyanate-labeled TA marker in green. (ii) Scanning electron microscopy images of S_{PGLA}, $S_{PGLA+TA}$, and $S_{PGLA@MPTA}$. (iii) Antibacterial activities including fluorescence characterization of bacterial cultured on membranes (poly(glycolide-*co*-lactide) membrane, Membrane + TA, Membrane@MPTA) and their agar plate spreading method results. The fluorescence represents the mCherry protein expressed by *E. coli* mBL21. Adapted with permission.[163] Copyright 2022 The Royal Society of Chemistry. (b) Characterization of PGLA sutures before and after coatings. MPTA, poly(TA)/TA hybrid coatings. (i) Morphology of the porous tape suture. (ii) Scanning electron microscopy images of the braiding yarns and melted axial yarns before and after surface modification with chitosan/gelatin-tannic acid. (iii) Color change of TA on sutures by a ferric ion-reducing test. Adapted with permission.[164] Copyright 2021 Elsevier Ltd. (c) Effects of polyphenol-assisted needles on hemostasis. (i) Illustration of hemostasis post-injection by bleed-free needles. (ii) Photographs of different uncoated and coated needles in a tail vein bleeding model, where the mice were anesthetized and punctured at the tail vein. PDANPs, PDA-coated needles further modified with ursodeoxycholic acid-polyethyleneimine NPs. Adapted with permission.[165] Copyright 2021 Elsevier B.V. (d) H&E staining of urethras of rabbits with (top panel) and without (bottom panel) TA–Cu-coated catheters 7 days post-implantation. Adapted with permission.[170] Copyright 2022 Huang et al. (e) Antibacterial property of a polyphenol-based dual network hydrogel. PPM, polyvinylpyrrolidone-polyethylene glycol acrylate-mussel protein. (i) Illustration of the antibacterial mechanism of the hydrogel. (ii) Photographs of bacterial colony distribution on agar plates following incubation with different sample coatings containing varying mussel foot protein-5 concentrations. Adapted with permission.[171] Copyright 2023 Elsevier B. V.

catheters, have attracted significant attention.[166] To combat biofilm formation, a hydrophobic TA coating was applied on the surfaces of biomedical catheters to prevent catheter-associated infections; under basic pH, the TA became partially ionized and electrostatically assembled with cationic benzalkonium chloride to form a strong hydrophobic coating on the medical catheters.[167] The modified catheters displayed excellent bactericidal activity, with more than 99 % of Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria eliminated. Mussel-inspired catechol chemistry was used to create a stable, substrate-independent coating for blood-contact catheters based on TA and 3-aminopropyltriethoxysilane, and a natural antimicrobial peptide was introduced on the TA-3-aminopropyltrieth-oxysilane coating.[168] The coated silicone rubber catheters showed long-term antibacterial performance and achieved significant reductions of $\geq$97.8 % for *S. aureus* and $\geq$96.5 % for *E. coli* adhesion even after 12 days. Yue et al. presented a biomimetic metal-catechol-(amine) surface engineering strategy to integrate therapeutic nitric oxide gas and antibacterial peptide onto catheters, mimicking the synergistic anti-infection and anticoagulant properties of natural vasculature.[169] This engineered coating maintained robust antibacterial properties even after 30 days of immersion, with an antibacterial efficiency exceeding 90 % against both *E. coli* and *S. epidermidis*. Surface modification of urinary catheters was developed using one-step coordination of TA and Cu^{2+}, and the coating exhibited high antibacterial

efficiency resulting from the synergistic antimicrobial activity of TA and Cu^{2+} (>99% of planktonic bacteria killed and biofilm coverage reduced to <1% after 24 h).[170] Additionally, the modified urinary catheters showed no significant cytotoxicity to mammalian cells, indicating improved tissue compatibility compared to unmodified catheters (Figure 12d).[170] In another study, a cross-linked hydrogel coating based on mussel protein for urinary catheters was developed, and the abundant dopamine in mussel protein not only maintained a stable coating on the surface of catheters but also exhibited enhanced antibacterial properties in vitro and in vivo (Figure 12e).[171]

5. Summary and Outlook

Polyphenols are a large class of biologically active plant products and have played an important role in combating pathogenic microorganisms. In recent years, phenolic compounds and their combination with biopolymers or other antimicrobial agents have allowed for the engineering of a wide variety of functional antimicrobial materials in various forms, including particles, capsules, coatings, and hydrogels. The enhanced antimicrobial activity, improved biocompatibility, and controlled release properties afforded by polyphenols have paved the way for applications in wound healing, bone repair and regeneration, oral health, and post-surgery infection control. Herein, we highlight research topics for advancing the development and clinical applications of phenolic antimicrobial materials (Figure 13).

Although polyphenol-functionalized biomaterials have demonstrated performance in biomedical applications, further studies are needed to fully understand their mechanism of antimicrobial action, optimize their stability and bioavailability, and evaluate their safety and efficacy in clinical settings. Most phenolic biomaterials have mainly been evaluated for antibacterial efficacy in vitro, and in vivo studies are often limited to the evaluation of biocompatibility or are performed in models that do not recapitulate clinical conditions, including trauma, comorbidities or established infections.[172] Therefore, more relevant infection models, particularly large animal models need to be developed with established infections and in the presence of a biofilm for the robust evaluation of these biomaterials in a clinical setting. The longer-term efficacy of these phenolic biomaterials is necessary and important to prevent widespread infections in patients. In particular, when considering their applications on medical implants, an extensive in vivo evaluation of the durability and stability of polyphenol-functionalized antimicrobial surfaces is needed. As the accumulation of dead bacteria on antimicrobial surfaces may promote further bacterial accumulation, reducing the antimicrobial activity over time, the development of phenolic biomaterial coatings with both antimicrobial and antifouling properties (e.g., surface PEG modification) may be a strategy to address this problem.[48e] Furthermore, introducing responsiveness into antimicrobial materials through supramolecular interactions (e.g., coordination) will be critical for the controlled release of antimicrobial components at targeted sites (e.g., bacterial-infected acidic environments or cancerous areas).[48c] Additionally, the translation of polyphenol-based antimicrobial materials from the laboratory to commercial products will require overcoming challenges related to scalability, cost-effectiveness, and regulatory approval.

Importantly, as the escalating evolution of antibiotic-resistant bacteria is a significant global health threat, it is necessary to develop alternative antimicrobial strategies for current antibiotic-based approaches to infection management. A notable advantage of phenolic biomaterials is that the diverse chemical structures of polyphenols can allow for the targeting of different bacterial proteins, ion channels, and inactivation enzymes, disrupting DNA and RNA synthesis. These nonspecific modes of action and multitargeted approaches might reduce the development of bacteria resistance, thus contributing to overcoming antimicrobial

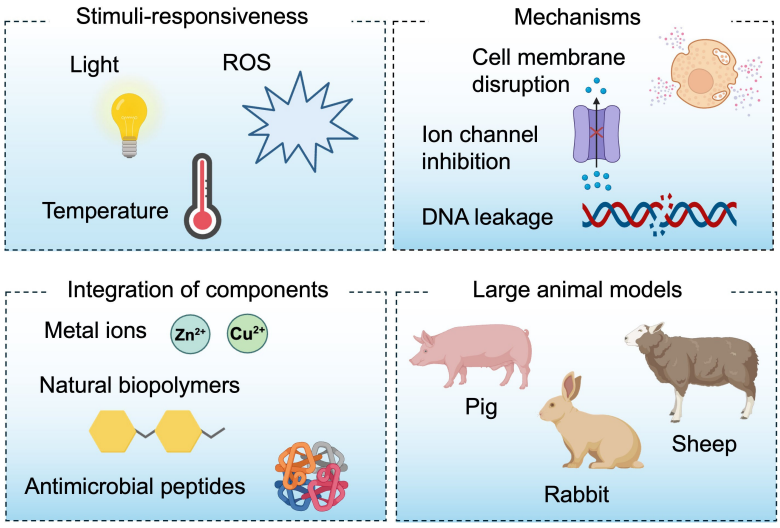

Figure 13. Examples of four future research directions for phenolic antimicrobial materials.

resistance in biomedical applications. There are over 8,000 distinct polyphenols available in nature, hence identifying suitable phenolic candidates with high biocompatibility, broad-spectrum antimicrobial activity, and scalability for cost-effective large-scale production is crucial to advancing the clinical translation of antimicrobial phenolic materials. Another aspect of polyphenol-functionalized biomaterials that may act as suitable candidates for reducing the development of resistance is their efficient synergistic effects arising from the combination of other antimicrobial components and polyphenols. The properties of polyphenols and other antimicrobial agents, such as metal ions, antimicrobial peptides, and natural biopolymers, can be combined and then mutually modified or synergistically enhance functions, potentially leading to improved performance in fighting infections. Therefore, the synergistic antimicrobial effects of polyphenols with other antimicrobial agents that could prevent or mitigate resistance to an antibiotic in clinical therapy deserve further research. Moreover, designing stimuli-responsive phenolic materials (e.g., responsive to pH, light, or temperature) in conjunction with other functional agents could enable precise antimicrobial activity at targeted sites (e.g., infected teeth) and pave the way for personalized therapies in the future.

In summary, significant progress has been made in understanding the antimicrobial mechanisms and design principles of phenolic biomaterials. We anticipate that these antimicrobial phenolic materials will play a pivotal role in combating bacterial infections, particularly those caused by antibiotic-resistant strains, and that they will show promise for biomedical applications aimed at improving human health and quality of life.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: antimicrobial applications · metal-organic materials · nanotechnology · polyphenols · supramolecular chemistry

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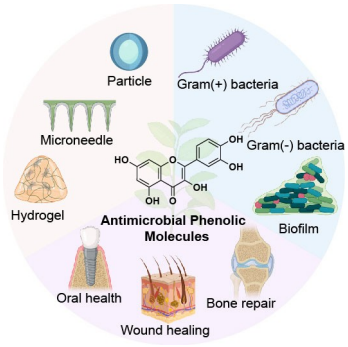
Review

Polyphenols



Natural polyphenols, primarily found in plants, can possess antimicrobial properties and have therefore been exploited widely. This review examines the antimicrobial mechanisms of polyphenols and their development into antimicrobial materials, including as particles, hydrogels, coatings and macroscopic structures. These materials hold potential for antimicrobial applications, ranging from wound healing to oral health, and offer a promising therapeutic strategy for combating and reducing the transmission of bacterial infections.