



Research progress of polyphenols in nanoformulations for antibacterial application

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ABSTRACT

Infectious disease is one of the top 10 causes of death worldwide, especially in low-income countries. The extensive use of antibiotics has led to an increase in antibiotic resistance, which poses a critical threat to human health globally. Natural products such as polyphenolic compounds and their derivatives have been shown the positive therapeutic effects in antibacterial therapy. However, the inherent physicochemical properties of polyphenolic compounds and their derivatives limit their pharmaceutical effects, such as short half-lives, chemical instability, low bioavailability, and poor water solubility. Nanoformulations have shown promising advantages in improving antibacterial activity by controlling the release of drugs and enhancing the bioavailability of polyphenols. In this review, we listed the classification and antibacterial mechanisms of the polyphenolic compounds. More importantly, the nanoformulations for the delivery of polyphenols as the antibacterial agent were summarized, including different types of nanoparticles (NPs) such as polymer-based NPs, metal-based NPs, lipid-based NPs, and nanoscaffolds such as nanogels, nanofibers, and nanoemulsions. At the same time, we also presented the potential biological applications of the nano-system to enhance the antibacterial ability of polyphenols, aiming to provide a new therapeutic perspective for the antibiotic-free treatment of infectious diseases.

In recent research, polyphenolic compounds have been proved to have potential antibacterial activity. Nanoformulations can overcome the shortcomings of polyphenols such as the low-water solution, ease to degraded and oxidized.

1. Introduction

According to the statistics and forecast of the World Health Organization (WHO), the annual mortality of infectious diseases caused by drug resistance exceeds 700,000 all over the world, and the number will be up to 10 million by 2050 without better treatment [1]. However, the excessive and long-term use of conventional antibiotics has increased the occurrence of drug resistance, which has gradually led to increased mortality and healthcare costs. WHO listed multi-drug resistant (MDR) bacteria as one of the top ten hazards for the health of humans in 2019 [2,3]. Due to the emergence of new resistance mechanisms, the development of new antibiotics is much slower than the emergence of

resistant bacteria. Therefore, it is a severe problem to develop new non-antibiotic antibacterial agents to provide a new option for the treatment of infectious diseases.

Over the past decades, natural products have raised hopes for the treatment of infectious diseases due to their promising antibacterial activity. Among these natural compounds, more than 49% of them have been approved by the U.S. Food and Drug Administration (FDA) and regulatory agencies in other regions to treat bacterial infections [3]. Polyphenolic compounds are widely present in vegetables, flowers, stems, and seeds [2]. They play an important role in the growth of plants of their radiation and microbial resistance function [4]. In recent years, a growing number of researchers have focused on the positive effects of polyphenolic compounds *in vitro* and *in vivo* studies. The biological properties include antibacterial, anticancer, anti-inflammation, antioxidant, cardioprotection, and anti-major depression activity [5–9]. Due to the potential versatile therapeutic effects and wide range of natural sources, polyphenols are expected to be a potential biomedical material

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for multi-purpose therapeutic applications. Particularly for bacterial infections, as a class of natural products, polyphenols hold great promise as a therapeutic alternative to antibiotics. A series of polyphenolic compounds with antibacterial effects have been reported, such as tannic acid (TA), curcumin, epigallocatechin gallate (EGCG), and resveratrol. The antibacterial properties of these compounds include direct antibacterial activity, suppression of bacterial virulence, and synergism with antibiotics [10]. Recently, dietary polyphenols have been made into healthcare products for healthcare functions and have been identified as therapeutic drugs for prophylaxis and regulation of antibiotic activity [11]. Several formulations containing polyphenols (either alone or in combination with other compounds) are undergoing preclinical and clinical evaluation [12].

However, the inherent properties of polyphenols limit their therapeutic activity. Low water solubility and poor stability to environmental conditions are important reasons for the low absorption rate of polyphenolic compounds [13]. The water solubility of polyphenols depends on their affinity with water molecules and molecular weight (MW). Higher MW had been reported to result in poorer aqueous solubility [14]. The instability in the gastrointestinal tract is affected by several factors such as enzymes, pH, microbiota, and the occurrence of other nutrients [15]. For example, resveratrol is mostly soluble in alcohol while poorly soluble in water (21 µg/mL at pH 7.4), which affects its bioavailability. At the same time, after oral administration, resveratrol is quickly absorbed in the gastrointestinal tract, but its bioavailability is less than 1% due to a general first-pass effect [16]. On the other hand, polyphenolic compounds are also susceptible to environmental factors such as heat, moisture, oxygen, and light irradiation [17,18]. Consequently, the low bioavailability of polyphenols limits their uptake of potential health benefits. Therefore, polyphenols are often loaded into carriers to increase biocompatibility and prevent environmental degradation.

As an emerging nanotechnology, nanoformulations can overcome the existing shortcomings of polyphenols and have the following advantages: (1) Enhance the aqueous solution of low-water soluble polyphenols. Due to the mutual repulsion and hydration of polar groups on the surface, NPs can maintain good stability in dispersed systems [13]. Curcumin, for example, is a polyphenolic compound present mainly in the spice turmeric (*Curcuma longa*). Many types of polymer-based NPs are designed to encapsulate and deliver curcumin due to their insolubility in the water. Compared with free curcumin, curcumin-loaded chitosan NPs showed better concentration and dispersity in aqueous solutions [19]. (2) Reduce the risk of oxidation and degradation of polyphenols. For example, EGCG has been proven to be unstable under alkaline and neural pH condition while relatively stable in acidic solutions, resulting in low bioavailability in the gut and blood [20]. However, in simulated gastric and intestinal fluids studies, the stability of hordein NPs encapsulated-EGCG was significantly improved compared to free EGCG [21]. (3) Provide controlled and stable release with therapeutic drug loading. By way of example, curcumin-loaded nanofibers prepared by electrospinning amphiphilic-block segmented polyurethanes showed a steady curcumin release during 432 h after a burst release in 24 h and played continued antibacterial ability to *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) [22]. Based on the positive therapeutic effects of polyphenols in various fields and the advantages of nanotechnology, a series of related reviews have been conducted. The previous reviews mainly focus on 1) the encapsulation technology of polyphenols to improve the bioavailability; 2) other biomedical applications such as anti-cancer, anti-diabetes, anti-inflammation, and cardiovascular protection of polyphenol-based nanomaterials; 3) nanomaterials to improve the antibacterial function of a certain type of polyphenols (such as tea polyphenols, curcumin, and resveratrol, etc.). However, a comprehensive review of the nanoformulations for enhanced antibacterial effects is still lacking. This review highlighted the design and antibacterial applications of polyphenol-based nanoformulations in the biomedical field. The

delivery nanoformulations were systematically reviewed, including NPs (SLNs, metallic NPs, and mesoporous silica NPs) and nanoscaffolds (nanogels, nanofibers, and nanoemulsions) which performed the enhanced antibacterial functions of polyphenols (Fig. 1). We hoped to provide a new strategy for treating infectious diseases and promoting the clinical application of polyphenols.

2. Classification and antibacterial activity of polyphenols

Many secondary metabolites of plant origin, such as polyphenols, alkaloids, and terpenes, have antimicrobial effects. Various antibacterial mechanisms have been proved in plant-derived compounds, including disruption of bacterial membranes, inhibition of biofilm formation and efflux pump, and suppression of DNA and protein synthesis [23]. Among them, alkaloids are organic nitrogenous bases generally synthesized from amino acids. These compounds are water-soluble at acidic pH, which is beneficial to play a role in bacterial infection environment [24, 25]. Terpenes are a diverse group of organic compounds produced by a variety of animals and plants, which are hydrocarbons with the 5-carbon isoprene unit as the main structural component of their biosynthesis [26]. By contrast, polyphenols have a prominent antibacterial activity. For example, a comparative study of terpenoids, alkaloids, and polyphenols against MDR showed that the antibacterial activity of terpenoids was not as active as that of polyphenols. In addition, terpenoids also have some difficulties in crossing through the bacterial membrane barrier [24,27]. Furthermore, the toxicity of carvacrol (a monoterpenoid compound) should be further considered due to the toxicity of its antibacterial therapeutic concentration on animal cells [25]. The high antimicrobial effect of polyphenols can be mainly attributed to the presence of phenolic hydroxyl groups and through multiple antibacterial mechanisms. In this section, we classified polyphenols according to their chemical structures and presented their properties and main biological activities.

2.1. Classification of polyphenols

Polyphenolic compounds consist of one or more aromatic rings connected to at least two phenolic hydroxyl groups and can be classified as flavonoids and non-flavonoids [28]. Polyphenolic compounds are a variety of molecules, including catechin, EGCG, TA, resveratrol, curcumin, etc. Fig. 2 showed the formula for the structure of common polyphenols.

2.1.1. Flavonoids

Flavonoids are comprising 15 carbons with two benzene rings

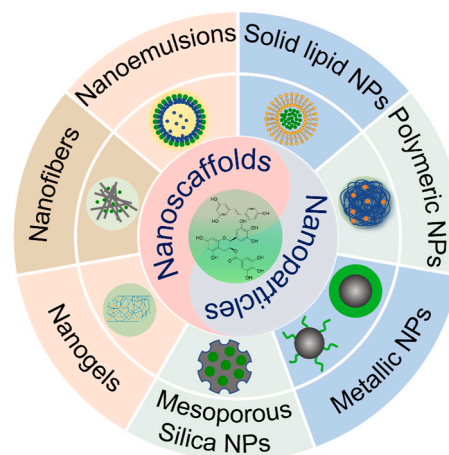


Fig. 1. Different types of nanoformulations for delivery of polyphenols with antibacterial activity.

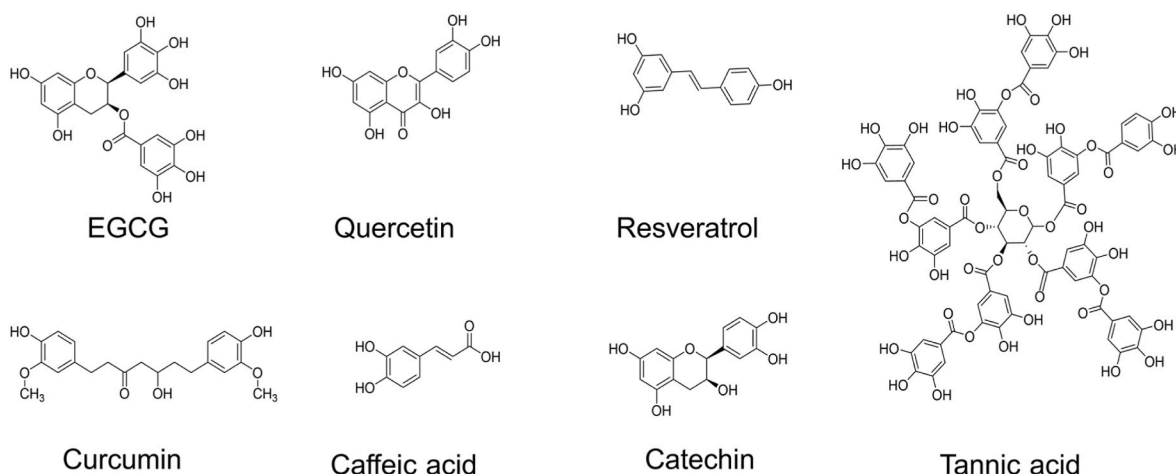


Fig. 2. The structural formula for common polyphenolic compounds.

connected through a three-carbon chain (C6–C3–C6). The two benzene rings are linked by a heterocyclic pyran ring. Depending on the degree of oxidation, hydroxylation, saturation, and the hydroxylation pattern of the heterocyclic pyran rings, as well as their junction position with the benzene rings, flavonoids can be subclassified as flavones, flavanols, flavanones, isoflavones, and anthocyanins. The bioavailability and chemical properties are related to the substitution of chemical groups of the flavonoid compound structures [29]. Tea polyphenols, including flavonoids, flavanols, phenolic acids, and anthocyanins, are the main polyphenolic substances that exist in green tea with many positive biological effects [30]. Flavanol compounds, the most studied are catechins including epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) [31].

2.1.2. Non-flavonoids

Non-flavonoids include phenolic acids (hydroxycinnamic and hydroxybenzoic acids based on C6–C3 and C6–C1), stilbenes (C6–C2–C6), and lignans (C6–C3–C3–C6). In addition, tannins (C6–C1) and xanthenes (C6–C6–C6) are also involved in this category. These compounds have two or more benzene rings in their structure, whereas tannins consist of multiple benzene rings.

Phenolic acids have a carboxyl group attached to a benzene ring and include cinnamic acid and benzoic acid. Examples of hydroxycinnamic derivatives are ferulic, caffeic, sinapic, and *p*-coumaric acids, whereas gallic, vanillic, syringic, and *p*-hydroxybenzoic acids belong to hydroxybenzoic acid [32]. Hydroxycinnamic is mainly present in fruits (especially those red ones), vegetables, coffee, tea, and whole grains [33]. Hydroxycinnamates exist as monomers, dimers, and as the bound form ester or amides. For example, chlorogenic acid is an ester formed by condensation of one or more *trans*-cinnamic acids (caffeic acid, ferulic acid, erucic acid) and quinine or their derivatives. Chlorogenic acid mainly exists in green coffee beans, which is widely concerned due to their potential health benefits, including anti-inflammatory, anti-bacterial, anti-diabetic, and anti-carcinogenic effects [34]. Besides chlorogenic acid, rosmarinic acid is another ester of 3,4-dihydroxy phenyl lactic acid and caffeic acid, which is widely found in the plant kingdom [35]. It has potent antibacterial activity against *S. aureus* strains, methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacteriaceae* spp., and *Pseudomonas* spp [36]. Gallic acid (3,4,5 trihydroxy benzoic acid) is a representative of the hydroxybenzoic acid group, which can be extracted from natural plants or synthesized chemically. Gallic acid widely exists in, as an organic material, widely used in medicine, food, and dyes [37]. It also shows broad antibacterial effects. For example, gallic acid inhibits the growth and formation of biofilm of *Escherichia coli* and *Staphylococcus mutans*. Furthermore, it possesses an inhibitory effect on the growth and the capsular polysaccharide biosynthesis of *Klebsiella*

pneumoniae [38].

Stilbenes exist widely in grapes, grapevines, wines, blueberries, cranberries, mulberries, almonds, and beans. The absorption and metabolism rates of stilbenes are determined by their various phenolic structures (polymerization and chemical substituents) [39]. Stilbenes have been reported to have medicinal properties, such as anti-inflammation and antioxidant activity [39,40]. The main component of stilbene is resveratrol (3,5,4'-trihydroxystilbene), which has been widely studied for its potent antibacterial activity against a broad range of bacteria. Resveratrol can reduce toxin expression and inhibit the biofilm formation of bacteria. Furthermore, in combination with antibiotics, it can enhance the effect of aminoglycosides against *Staphylococcus aureus* [41].

Tannins are water-soluble polyphenols rich in benzene rings and hydroxyl groups. Tannins are generally classified into hydrolyzable (ellagitannins and gallotannins) and non-hydrolyzable (condensed) according to their chemical structures and constitutive monomers [42]. Condensed tannins are derivatives of flavanols where the 2 position is bound to catechol or phloroglucinol. Gallotannins, also called tannic acid, contains multiple hydroxyl groups forming hydrogen bonds with other molecules, and is popular in biomedical research and used in the development of new drugs for many infectious diseases [43].

2.2. Mechanisms of antibacterial activity of polyphenols

The broad range of antibacterial activity of polyphenols is attributed to the following mechanism: inhibiting bacterial DNA replication and bacterial energy metabolism, altering the function of the bacterial membrane, reducing the cell attachment and formation of biofilm, suppressing the porin protein on the membrane of cells and changing the permeability, and synergizing with other agents [44–48].

At the genetic level, polyphenols act as antibacterial agents by inhibiting the DNA replication of bacteria. The inhibition of DNA gyrase is the dominant mechanism in this category. Green tea polyphenols and chebulinic acid showed an inhibitory ability against gyrase and can modify the DNA topology [49]. EGCG from green tea exerts antibacterial effects by inhibiting the B-subunit of gyrase at the ATP binding site. In addition, EGCG has attracted wide interest and is considered a promising antibacterial agent through multiple antimicrobial mechanisms (inhibition of efflux pump and chromosomal penicillinase) [50]. Curcumin has been reported to inhibit bacterial DNA expression, in combination with interactions with DNA molecules. The oxidation products of curcumin form many free radicals, some of which are necessary for bacterial synthesis, thus interfering with the replication of bacterial DNA [51]. When bacterial DNA is damaged, it activates the SOS response, which is an antibacterial self-protection response and also a

factor in bacterial drug resistance [52]. An early study reported that curcumin exerted antibacterial effects against *Salmonella typhimurium* and *Escherichia coli* by inhibiting the SOS induction and genetic mutation by UV light. At the same time, curcumin also effectively inhibited phage regeneration [53].

The structural integrity of cell walls and membranes and the stability of membrane potentials play key roles in the spatial structure of mitotic and cytoskeletal proteins in bacteria. The hydroxyl group of polyphenols affects the instability of cell membrane potentials and pH gradients, both of which contribute to antibacterial activity. α -Mangosteen (a polyphenolic compound) has an antibacterial effect on resistant strains of MRSA. Under scanning electron microscopy, it can destroy the integrity of the cell membrane, and destroy bacterial cell components [54]. The present study showed the antibacterial activity of curcumin against Gram-positive bacteria (*Enterococcus faecalis* and *Staphylococcus aureus*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) [55]. Scanning electron microscopy, fluorescence microscopy, and membrane permeabilization assays confirmed the membrane damage of bacteria on exposure to curcumin [56]. Besides, polyphenols can play antibacterial activity by destroying the biosynthesis of the cell wall and inhibiting the key enzymes including dihydrofolate reductase, urease, and sortase [57]. D-alanine: D-alanine ligase is a key enzyme in the assembly of the peptidoglycan precursors to bacterial cell walls. Quercetin is a flavonoid compound that could destroy the activity of *E. coli* and *H. pylori* by inhibiting the D-alanine: D-alanine ligase [58]. Some other polyphenols can interact directly with peptidoglycan to inhibit the biosynthesis of the cell wall [59].

In addition, biofilms are collections of microbial tissues that surround bacterial cells. It has been shown that the bacteria in biofilms grow more slowly than planktonic bacteria, resulting in resistance to the biotic antiproliferative activity. Curcumin has been proven to inhibit the formation, reduce the thickness, and loosen the structure of biofilm by various pathogens in host organisms [7,57,60]. A study was conducted to directly observe the urinary tract pathogenic biofilm and the amount of microorganisms in the biofilm by laser confocal scanning microscopy. The curcumin-treated urinary tract pathogens were identified to have reduced biofilm thickness. Biofilms of *E. coli* and *Proteus mirabilis* were reduced to varying degrees. In terms of other antibacterial mechanisms, polyphenols (extract of *glycyrrhiza inflata*) could inhibit oxygen consumption and electron transfer in the respiratory chain of sensitive bacteria and interfere with the energy metabolism of bacteria [61].

3. Different types of nanoformulations for the delivery of polyphenols

3.1. Nanoparticles

The advantages of NPs include the size and surface can be easily modified, the release under certain environments can be maintained and controlled, and distribution and clearance from the body of the drug can be altered [62,63]. Thanks to their versatile properties, NPs are increasingly being used in drug delivery systems for both active and passive drug targeting. According to the literature, a variety of materials have been used to produce NPs for the delivery of polyphenols, ranging from lipid and polymeric molecules to inorganic compounds [64]. In this section, the properties and antibacterial applications of the most commonly studied NPs for polyphenol delivery were summarized in the field of biomedicine.

3.1.1. Solid lipid NPs (SLNs)

Considerations for encapsulation include the size and solubility of the loaded compound, the characteristics of the carrier, and the route of delivery. Lipid carriers are a suitable choice for the delivery of polyphenolic compounds due to their affinity for hydrophobic compounds and their similar constitution to biological membranes. In 1991, Muller

developed an encapsulation method, SLNs, which remain solid at the temperature of the human body and room [65]. The particle size of SLNs typically ranges in size from 40 to 1000 nm and meets a variety need of nanoparticle possibilities [66]. Compared with other colloidal carriers, the advantages of SLNs include higher stability with both lipophilic and hydrophilic compounds, non-toxicity, and ease of large-scale production [67]. Particularly, the properties of the reduced particle size, controlled and targeted drug release, and cheaply manufactured, make SLNs one of the most popular systems in drug delivery [66]. SLNs are made of lipids, which are usually physiological lipids, including glycerides, fatty acids, sterols, partial glycerides, and waxes. These lipids are dispersed in water and stabilized by surfactants, including neutral, ionic, and non-ionic can help prevent the agglomeration of particles [67]. Herein, we reviewed the primary preparation methods, enhanced antibacterial ability, and the major biomedical applications of polyphenol-loaded SLNs.

High-pressure homogenization (HPH) is the most used method in SLNs preparation for the encapsulation of polyphenolic compounds. Shtay et al. prepared EGCG-loaded SLNs by a hot HPH method. *In vitro* release studies were conducted using simulated gastric juice (pH 1.2) and intestinal juice (pH 6.8), and longer release times were observed under both conditions, which might improve the bioavailability of EGCG [68]. At the same time, solvent emulsification/evaporation is also a satisfactory method due to its good solubility in the organic solvent for lipids without any thermal stress [69]. On account of the lipid matrix of SLNs being hydrophobic, the double-emulsion technique seems to be a promising approach to encapsulate the hydrophilic compounds [66]. Parisa et al. prepared stable curcumin-loaded SLNs by the HPH method with mannitol as cryoprotectant. The size of the particle was 112 nm and the loading efficiency was $70.4 \pm 1.2\%$. The curcumin particles showed increased antibacterial activity against *E. coli* and *S. aureus* compared to free curcumin at the same concentration. More than 85% and 92% of the curcumin was released after 36 and 48 h. They demonstrated that 5% mannitol was the preferred cryoprotectant compared to 15% mannitol due to their particle size being 163 nm and 306 nm [70]. To improve the loaded capacity and stability, He et al. used propylene glycol monoesters (PGMEs) instead of glyceryl tripalmitate to fabricate carvacrol-loaded SLNs (Car-SLNs) against *S. aureus* and *E. coli* O157: H7. The size of the Car-SLNs remained stable and remained smaller than 200 nm after 30 days of storage. Since purified PGMEs and glyceryl monostearate could form stable α -form crystals, they could provide stably controlled release scaffolds for drug delivery [71].

In addition, Lin et al. prepared curcumin-loaded SLNs with Chinese white wax (Cur-cwSLNs) using high-shear homogenization and ultrasound technique. *In vitro* antibacterial study, the (minimum inhibitory concentration, MIC) of Cur-cwSLNs and free curcumin was $62.5 \mu\text{g/mL}$ and $500 \mu\text{g/mL}$ respectively against *S. aureus*. At the same time, colorimetric assays of biofilms showed that Cur-cwSLNs significantly inhibited biofilm formation in *S. aureus* compared to free curcumin. Furthermore, the Cur-cwSLNs had a slow release of curcumin without burst release over 96 h under both pH 4.5 and pH 7.4 conditions [72]. The higher release rate in acid conditions suggested that these SLNs might be more suitable for acid-infected environments, such as skin, dental caries, and the vagina. For topical infection, SLNs are best suited for transdermal delivery due to their property of combining lipid and polymeric NPs. Fakhara et al. designed a curcumin-loaded SLNs patch for transdermal delivery to enhance the anti-microbial effect [73]. For oral mucosal infection, Heba et al. designed a curcumin-loaded SLNs with five lipids as surfactants to evaluate the antibacterial properties against *S. aureus*, *Streptococcus mutans*, *E. coli*, *Viridansstrept*, and *Lactobacillus acidophilus*. Compared with the free curcumin, CurSLNs showed an increased antibacterial effect by eightfold, fourfold, twofold, fourfold, and twofold, respectively [74].

3.1.2. Polymeric NPs

Among organic macromolecular-based drug carriers, polymeric NPs have been widely chosen as drug delivery vectors due to their offered

advantages: firstly, chemical and physical stability under physiological environments and storage conditions; secondly, excellent biocompatibility and biodegradability, low toxicity, and immunogenicity; thirdly, surface modification with ligands; and finally ease of production [75]. Depending on the nature of the polymer, various substances such as macromolecules and hydrophobic drugs can be delivered to cells and specialized organs. Polymer-based NPs include two main categories, natural and synthetic origin. Natural polymers mainly include chitosan (CS), dextran, hyaluronic acid, starch, cellulose, and gelatin. Synthetic polymers mainly include polylactic acid (PLA), polyethylene glycol (PEG), polylactic-glycolic acid (PLGA), and polycaprolactone (PCL). In this section, we reviewed the most widely used natural and synthetic polymeric NPs as polyphenol delivery carriers for antibacterial applications.

3.1.2.1. Chitosan-based NPs. CS, a natural origin polymer, is derived from chitin (extraction with the exoskeleton of crustaceans) and has advantages including non-toxic and low-cost. CS is generally recognized as safe and approved by FDA for dietary and medical use [76]. In addition, due to the inherent character of positive charge, mucoadhesion, in situ gelling, permeation enhancing, controlled release, and efflux pump inhibition, CS has become a preferred candidate for antimicrobial delivery [77].

Nanoencapsulation and chemical modification are two main techniques to produce drug-loaded chitosan NPs (CSNPs) [78]. The encapsulation process may occur based on the interaction of hydrophobic, electrostatic, and/or hydrogen bonding between CS and drug molecules [79]. Ionic gelation is the most studied preparation method for CSNPs synthesis [80]. This method is based on the electrostatic interaction between CS positively charged amino sugar monomer unit and negatively charged polyanion such as triphosphosphate (TPP) [81]. Tan et al. used the ionic gelation method to encapsulate curcumin in CSNPs for polymicrobial biofilm-related infection (Fig. 3). The NPs played a role in enhancing antibacterial activity against *S. aureus* and a sustained release of curcumin under different pH conditions (7.4 and 5.4) and inhibited biofilm formation due to the binding of the positively charged CS and anionic biofilm components [82].

As an example of chemical modification, curcumin, a natural pigment, has also been used in photodynamic therapy for antibacterial applications. Zhao et al. prepared a novel nanomaterial by the esterification reaction of curcumin and carboxylated chitosan [83], which had an effective ROS scavenging ability as well as photodynamic antibacterial activity against *S. aureus* and *E. coli*. Numerous studies have shown that CS had desirable properties of mucoadhesion, through the electrostatic interaction between the positively charged amino groups of CS and the N-acetyl neuraminic acid in the gastric mucus [84,85]. In addition, CSNPs with sizes less than 500 nm may contribute to crossing the intestinal mucous barrier and interact with the underlying epithelial cells. In particular, when the zeta potential of NPs was positive, the adhesion ability of intestinal tissue would be facilitated [86]. Therefore, for oral administration, drug delivery systems with CS shells have often been used to increase the residence time in the gastrointestinal tract and for the purpose of controlled release of drugs. For example, Lin et al. developed NPs composed of fucose-conjugated CS with gelatin of EGCG and proved that the EGCG-loaded NPs had a significantly higher infectious targeting and greater clearance effect of *Helicobacter pylori* (*H. pylori*) *in vitro* and *in vivo* studies than that of EGCG solution (Fig. 4A–C). At the same time, the NPs showed a relatively stable morphology under the acidic environment (pH 2.5 and 6.0) but collapsed and led to the release of EGCG at pH 7.0 (Fig. 4D) [87].

Smaller size and suitable surface discharges of NPs are critical for antibacterial effects, as they can provide desirable stability and penetration into bacterial cells. According to the literature, CS with low MW has a stronger antibacterial ability for resistant strains [88,89]. To obtain a smaller size and a higher encapsulation efficiency (EE) of CSNPs, Zhang et al. used β -CS with a MW of ~ 160 kDa and a ratio to TPP of 5:1. Compared with catechin solution, catechin-loaded β -CSNPs played a better antibacterial effect against *L. innocua* and *E. coli* [90]. In addition to the MW of CS, the number of polyphenol hydroxyl groups loaded onto it also affects the properties of NPs and their antibacterial effects. Madureira et al. capsulated protocatechuic acid (PA), rosmarinic acid (RA), and 2,5-dihydroxybenzoic acid (DHBA) into CSNPs with low and high MW of CS to investigate their antibacterial effect against *B. cereus*, *E. coli*, *L. innocua*, *Y. enterocolitica*, *S. aureus*, and

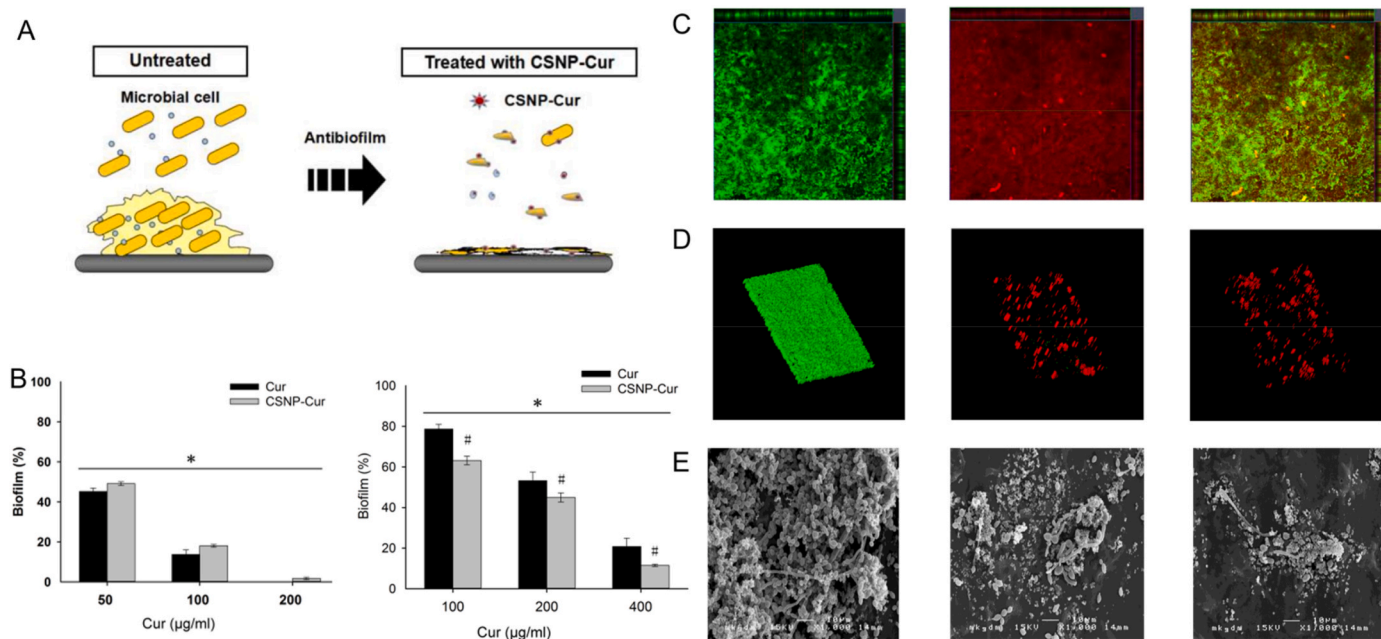


Fig. 3. Antibacterial activity of curcumin-loaded CSNP (CSNP-Cur). (A) Antibiofilm graphical abstract of CSNP-Cur. (B) Inhibition and disruption activity of CSNP-Cur on biofilm of *S. aureus*. (C) Penetration of biofilm by CSNPs labeled by Syto 9 (green) and Rhodamine B isothiocyanate (red). (D) Confocal laser scanning microscopy (CLSM) images of polymicrobial biofilm with and without treatment of CSNP-Cur. (E) SEM images of polymicrobial biofilm with and without the treatment of CSNP-Cur (Reprinted from Ref. [81] with permission from ELSEVIER).

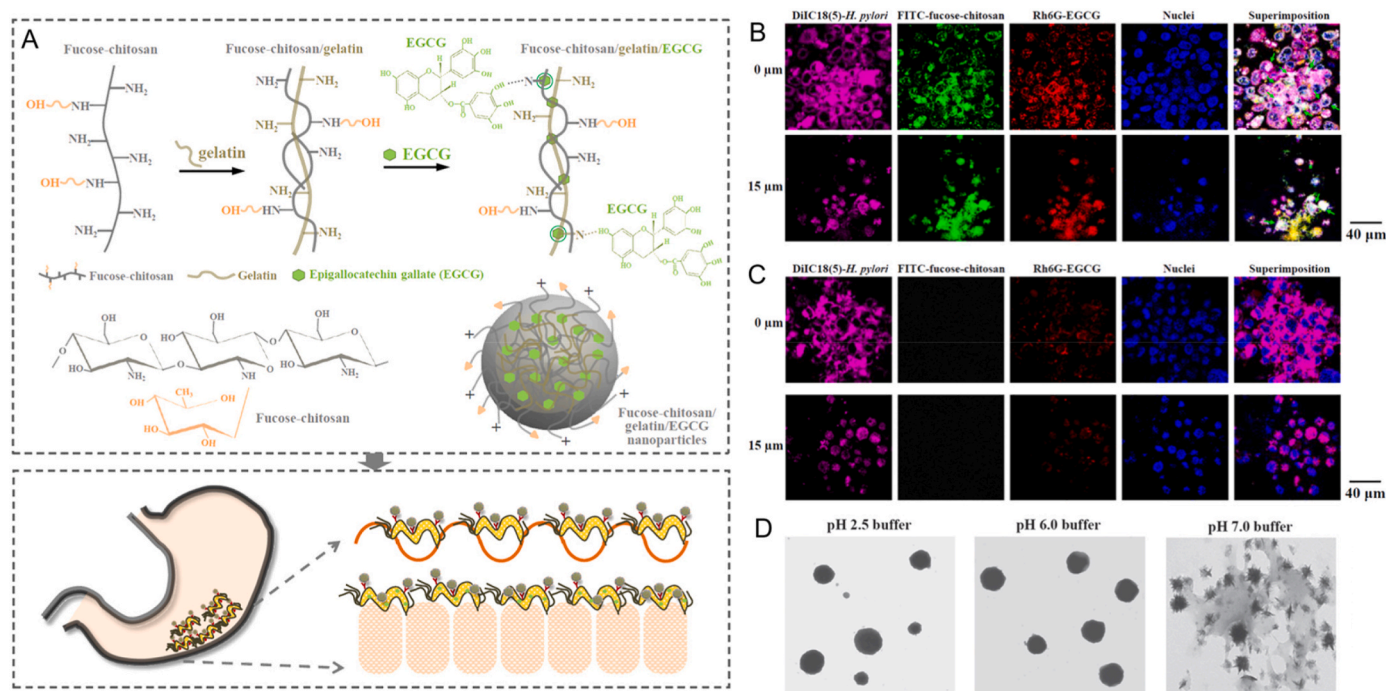


Fig. 4. Preparation of fucose-CS/gelatin/EGCG NPs and their antibacterial ability. (A) Scheme of preparation and gastric epithelium targeting of fucose-CS/gelatin/EGCG NPs. (B) Fluorescence images of *H. pylori*-infected AGS cell (human gastric adenocarcinoma cell line) monolayers treated with fucose-CS/gelatin/EGCG NPs at different depths. (C) Fluorescence images of *H. pylori*-infected AGS cell monolayers treated with EGCG solution at different depths. (D) TEM micrograph of fucose-CS/gelatin/EGCG NPs under different pH environments (Reprinted from Ref. [86] with permission from National Institute for Materials Science).

S. typhimurium. Their outcomes showed that low MW chitosan with RA obtained the higher EE and the best inhibitory effects [91]. Some other recent examples of polyphenol-containing CSNPs are summarized in Table 1.

3.1.2.2. Poly (lactic-co-glycolic acid) (PLGA) based NPs. PLGA-based NPs are another widely studied and applied polymeric nanoformulations in nanomedicine due to their biodegradability and low toxicity, which was approved by FDA for human therapy [97]. In line with the development of encapsulation techniques, PLGA polymers have been successfully used to load natural products including polyphenols. Several *in vitro* and *in vivo* studies have proved that nanoencapsulation of polyphenols with PLGA polymer was a potential method to protect and enhance their bioactivity.

PLGA polymers can be hydrolyzed in the body into lactic acid and glycolic acid monomers, both of which are endogenous and easily metabolized via the Krebs cycle. Emulsification-solvent evaporation is

Table 1
Antibacterial effect of chitosan NPs loaded with active polyphenols.

Polyphenols-loaded Nanoformulations	Antibacterial against	Ref.
Tannin-lysozyme@ CSNPs	<i>S. aureus</i> ; <i>Salmonella enteritidis</i> ; <i>Listeria monocytogenes</i>	[92]
Green tea oil-loaded CSNPs	<i>E. coli</i>	[93]
Ferulic acid encapsulated CSNPs	<i>Pseudomonas aeruginosa</i>	[94]
Curcumin-loaded CSNPs	<i>S. aureus</i> ; <i>C. albicans</i>	[76]
Catechin and quercetin-loaded CSNPs	<i>E. coli</i> ; <i>S. aureus</i> ;	[95]
Carvacrol-loaded CSNPs	<i>Bacillus subtilis</i>	[78]
<i>P. dactylifera</i> extract-loaded CSNPs	<i>E. coli</i> ; <i>S. aureus</i> ; <i>Bacillus cereus</i>	[96]
	<i>Bacillus subtilis</i> ; <i>Bacillus cereus</i>	

applicable to liposoluble drugs and is the most employed method for the preparation of PLGA-based NPs. This technique includes oil in water (O/W) and water in the oil-water (W/O/W) method [97]. For example, Duranoglu et al. used a single emulsion-solvent evaporation technique to encapsulate hesperetin (a flavonoid compound) into PLGA-based NPs for the antibacterial therapeutic application. Compared with free hesperidin, the optimized hesperetin-loaded NPs showed significant inhibition against *S. aureus* and *E. coli* [98]. In addition, Arasoglu et al. used the same method to produce quercetin-loaded PLGA-based NPs with different initial quercetin amounts. The results showed that cell walls got wrinkled and damaged under TEM observation after 24 h exposure to quercetin-loaded PLGA-based NPs, which indicated the antibacterial mechanism might be attributed to the abruption of cell walls and surface charges of microorganisms [99].

PLGA polymer is a polyester of PLA and polyglycolic acid (PGA) and comprises different formations according to the ratio of the two components. The higher the content of glycolide, the more hydrophilic and easier to degrade, while the higher the content of lactic acid, the more hydrophobic and more gradual to degrade [100]. This feature can be used to increase the EE of a hydrophilic or hydrophobic substance in a drug delivery system [101,102]. Pereira et al. prepared PLGA-based NPs from natural plant extracts rich in hydrophobic polyphenols, including epicatechin, gallic acid and ellagic acid, and assessed their inhibitory effects against *Listeria innocua*. Their result showed the lactide: glycolide ratio of 65: 35 exhibited a significantly higher EE and more gradual initial burst compared with ratio of 50: 50 [103].

Despite the favorable biodegradability and biocompatibility, PLGA-based NPs are susceptible to being cleared from circulation by macrophages in the mononuclear phagocyte system after being administrated through an intravenous route [104]. To overcome this dilemma, PLGA-based NPs are imparted with surface modifications, that may prevent them from being cleared by the natural defense systems. PEG, a hydrophilic polymer, is the most commonly used technique due to its advantages of high molecular weight, long chain length, and high surface density. With the help of PEG polymer, PLGA-based NPs could

increase the solubility and retention time *in vivo* [105]. For example, Deepika et al. loaded rutin (a flavonoid) in the PEG-modified PLGA-based NPs, which exhibited the synergetic antibacterial ability against MDR last for several days [106]. Antibacterial analysis showed that the MIC of PLGA-based NPs was 2 times lower than that of the free drugs, and their disruption of biofilms was observed.

3.1.2.3. Other synthesized polymer-based NPs. A recent study used three synthetic polymers (polyethyleneimine (PEI), polyvinyl alcohol (PVA), and polyacrylic acid (PAA)) loaded with curcumin to enhance their antibacterial activity against MRSA. The antibacterial ability of the three curcumin-loaded NPs was significantly improved when used alone or in combination with methicillin, and PEI-based NPs exhibited the strongest inhibitory effect [107]. Gutierrez et al. synthesized curcumin-loaded anionic and cationic NPs using PLA and dextran sulfate, combined with photodynamic therapy (PDT), to improve the solubility of curcumin and its antibacterial ability against *Streptococcus mutans* and MRSA [108]. Synthesized nanoformulations showed high antibacterial photodynamic activity against planktonic bacteria, and even in the absence of light, cationic NPs revealed an enhanced antibacterial effect.

3.1.3. Inorganic NPs

Inorganic NPs are widely preferred due to their advantages of adjustable size and shape. In addition, the high specific surface allows the NPs to attach high concentrations of functional ligands, and act as carriers to deliver other active compounds, improving their interaction with target bacteria [109]. Inorganic NPs consist of both metallic and non-metallic NPs. Silver and gold NPs are increasingly being used among metallic NPs, and some typical examples of polyphenol-containing metallic NPs were summarized in Table 2. Metal oxides and mesoporous silica NPs (MSNs) have also been attracted to use as delivery of natural products attributed to their various surface modifications [110].

3.1.3.1. Metallic NPs. Potential antibacterial properties have been demonstrated in metallic NPs such as Ag, Au, Cu, and Zn particles. The antibacterial mechanisms of metallic NPs include (1) Disruption of bacterial metabolism by binding with sulfhydryl or disulfide groups of essential enzymes. (2) Interruption of bacterial membranes by releasing ions from metallic NPs. (3) Inhibition of DNA replication, induction of protein denaturation, and destruction of the cell wall by generating reactive oxygen species (ROS) [121].

Silver NPs (AgNPs) and gold NPs (AuNPs) are the most widely used NPs for antibacterial purposes due to their large specific surface area and good contact with microorganisms. For example, in the research of Song et al. the curcumin-AgNPs (cAgNPs) had an increased inhibition activity against *E. coli* and *B. subtilis* than that of free curcumin. More ROS was generated by cAgNPs, resulting in membrane damage and leakage of intracellular contents. The bacteria treated with cAgNPs showed dramatically changed shape and shrunken cell walls observed under

SEM [108]. Fei et al. produced a core-shell structure in which the core was AgNPs and the shell was the polymerized tea polyphenol (TP) [114]. The Ag@TP NPs were produced by the one-pot microwave self-assembly method within 1 min and the core-shell structure was proved by SEM (Fig. 5A–B). The NPs strongly inhibited *E. coli* without significant toxicity to normal cells (Fig. 5C).

Reducing agents and stabilizers are associated with the size and dispersion of metallic NPs [122]. Polyphenols, known as powerful antioxidants, have opened the way for “green synthesis” by providing efficient reduction and capping potential instead of traditional chemical agents during the procedure of metallic NPs [123]. In Onitsuka’s study, catechin-rich tea leaves were used as reducing and capping agents to prepare AgNPs and AuNPs. The outcome showed that the synthetic nanoformulations enhanced antibacterial activity against *S. aureus* and *K. pneumoniae* compared with commercially available silver nanopowder [117].

The size and dispersion of NPs play an important role in their antibacterial effectiveness. Generally, AgNPs and AuNPs follow the pattern that the smaller the size, the stronger the antibacterial ability [109]. However, the antimicrobial performance of smaller particles can be limited, because the smaller particles tend to aggregate and reduce the contact area with bacteria [124]. Polyphenols can act as stabilizers during the process of metallic NPs by enhancing their stability. For instance, Podstawczyk et al. produced stable catechin-capped CuNPs with a size of less than 5 nm at a pH value of 11 (Fig. 6A) [125]. In addition, Park and his colleagues synthesized the antibacterial resveratrol-delivered AuNPs and AgNPs with a size range from ~8.3 nm to ~21.8 nm, and the as-prepared NPs maintained a good dispersion state after ultracentrifugation and re-dispersion (Fig. 6B). Besides, Fourier-transform infrared spectra (FTIR) indicated the C=C and hydroxyl groups in the phenyl ring of resveratrol were participated in the reduction reaction [116].

Metal-Phenolic Networks (MPNs), inorganic-organic networks based on coordination between electron-dense phenolic hydroxyl groups and positively charged metal ions, have been widely considered as new powerful antibacterial agents [126]. The formation of MPNs chelated with metals enhances the antibacterial efficacy of polyphenols compared to polyphenols alone. The efficacy of polyphenols in MPNs is attributed to the following advantages of polyphenols (1) Playing a synergetic antibacterial role with metal ions. (2) Providing a slow release of metal ions and achieving the sustained antibacterial effect. (3) Easy to dissociate with metal ions and plays an antibacterial effect under the environment of acidic conditions (bacterial infection) [127]. For instance, Zhang et al. developed a biocompatible composite incorporating TA and magnesium chloride (MgCl₂) into bacterial cellulose for antibacterial and antibiofilm purposes (Fig. 7A) [128]. With the help of coordination with Mg²⁺, TA revealed a sustained release from the nanoformulation. Qin and his colleagues developed MPNs coated NPs based on the coordination between TA and iron ions, which showed significant antibacterial effects. TA revealed a highly efficient release under acidic conditions (Fig. 7B). [129]. Additionally, MPN can be fabricated into ROS-response nanoformulations, which can be used to act as antibacterial agents in infected environments. In the study of Li et al., copper-poly (TA) scaffold could degrade under high ROS levels, followed by sustained release of Cu²⁺ and the peroxidase/peroxidase-mimic effect, with a powerful antibacterial material for the infectious wound [130]. Moreover, the addition of carboxylic acid to a phenol-Fe nano-network could effectively control the peroxidase-like activity through the acidic microenvironment and the proximity effect of the carboxyl group. For example, Wang et al. tested the peroxidase-like activity of a nano-network constructed by five kinds of polyphenols and Fe. They found that gallic acid with a carboxylic acid structure was more likely to catalyze hydrogen peroxide to generate hydroxyl radicals under acidic conditions and play an antibacterial role [131].

In addition, the photothermal effect of metallic NPs also plays an

Table 2
Antibacterial effects of polyphenols in the synthesis of metallic NPs.

Polyphenols	Composition	Bacteria	Ref.
Curcumin	Cur-AgNPs	<i>P. aeruginosa</i> ; <i>E. coli</i> ; <i>S. aureus</i>	[111]
Curcumin	Cur-AgNPs	<i>E. coli</i> ; <i>B. subtilis</i>	[112]
Tannic acid	TA-AgNPs	Gram-negative bacteria	[113]
Tea polyphenol	Ag@TP NPs	<i>E. coli</i>	[114]
Gallic acid	AuNPs	<i>E. coli</i> ; <i>S. aureus</i>	[115]
Resveratrol	Res-AuNPs; Res-AgNPs	<i>Streptococcus pneumoniae</i>	[116]
EGCG	AuNPs; AgNPs	<i>S. aureus</i> ; <i>K. pneumoniae</i>	[117]
Curcumin	Cur@TA-Cu ^{II} Cur@TA-Fe ^{III}	<i>E. coli</i> ; <i>S. aureus</i>	[118]
Tea polyphenol	Cu@TPNPs	<i>S. aureus</i>	[119]
Tannic acid	TA-CuNPs	<i>E. coli</i> ; <i>S. aureus</i>	[120]

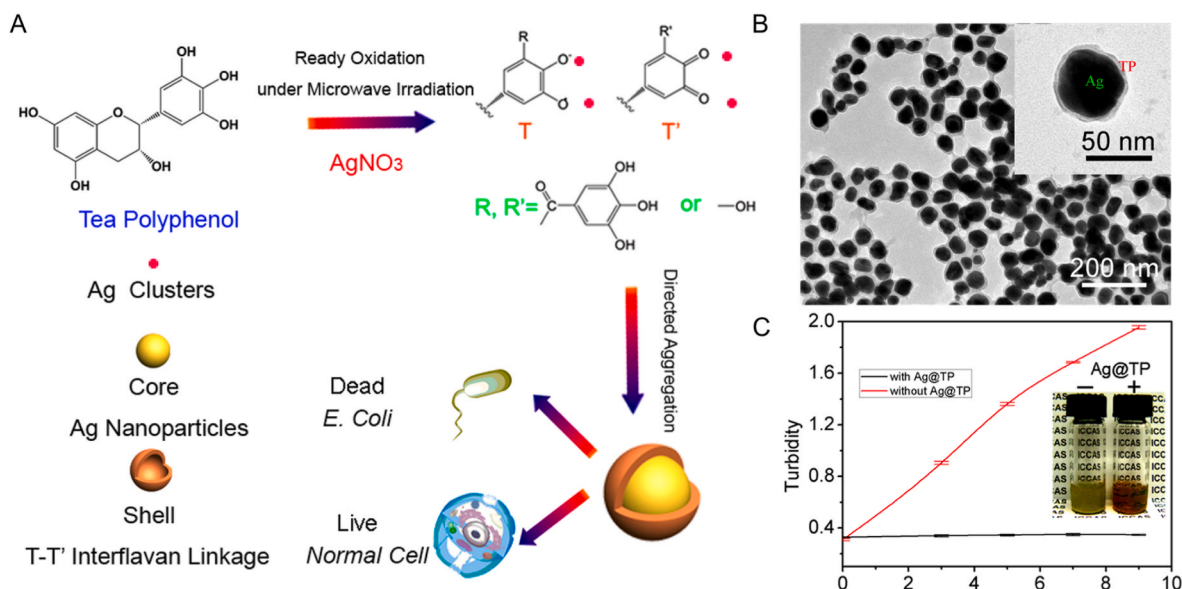


Fig. 5. Antibacterial ability of TP-loaded AgNPs. (A) Self-assembly scheme of Ag@TP NPs. (B) SEM image of the core-shell nanostructure. (C) Turbidity at 600 nm in *E. coli* cocultured with and without Ag@TP NPs (Reprinted from Ref. [113] with permission from American Chemical Society).

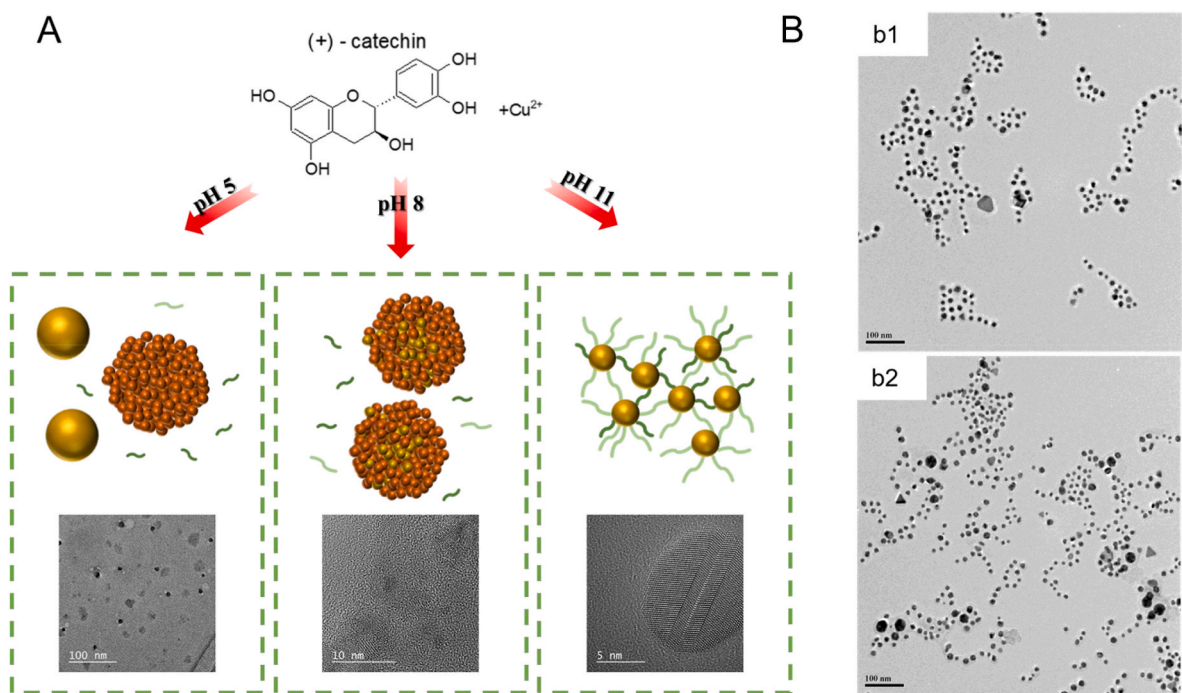


Fig. 6. (A) Preparation of stable and small CuNPs (Reprinted with permission from Yang Qin et al. [122]). (B) High-resolution transmission electron microscopy (HR-TEM) images of resveratrol-AuNPs before (b1) and after (b2) the ultracentrifugation and re-dispersion process (Reprinted from Ref. [124] with permission from American Chemical Society).

important role in enhancing their antibacterial capabilities. For example, gold nanorods (AuNRs) as photothermal agents (PTAs) have been widely researched due to their remarkable photon harvesting properties, which can transform NIR into heat and kill the bacteria by increasing the temporal temperature of the focus infection [132]. Sun et al. encapsulated AuNRs in the MPNs which coordinated iron with polyphenols (EGCG, TA, and procyanidins) [133,134]. The results showed a remarkably potent role in destroying cell membranes and biomolecules of *E. coli* and *S. aureus* and accelerated the healing of the wound infected by MRSA (Fig. 7C). Yu et al. demonstrated a hybrid nanoformulation by the composite of TA, Fe³⁺, CS, and silk fibroin for

wound dressing applications. The nanoformulation exhibited an excellent antibacterial ability for both Gram-positive and Gram-negative bacteria, benefiting from the synergistic and high photothermal transition effect of the TA/Fe³⁺ (Fig. 7D) [135].

3.1.3.2. Non-metallic NPs. Metal oxide NPs. Metal oxide NPs, such as ZnO, TiO₂, Fe₂O₃, Fe₃O₄, and CuO, exert antibacterial effects against Gram-positive and Gram-negative bacteria [136,137]. Among metal oxide NPs, zinc oxide NPs (ZnO NPs) have presented excellent antibacterial properties and thus have been of great interest because of their good biocompatibility at the same time. ZnO NPs have been approved by

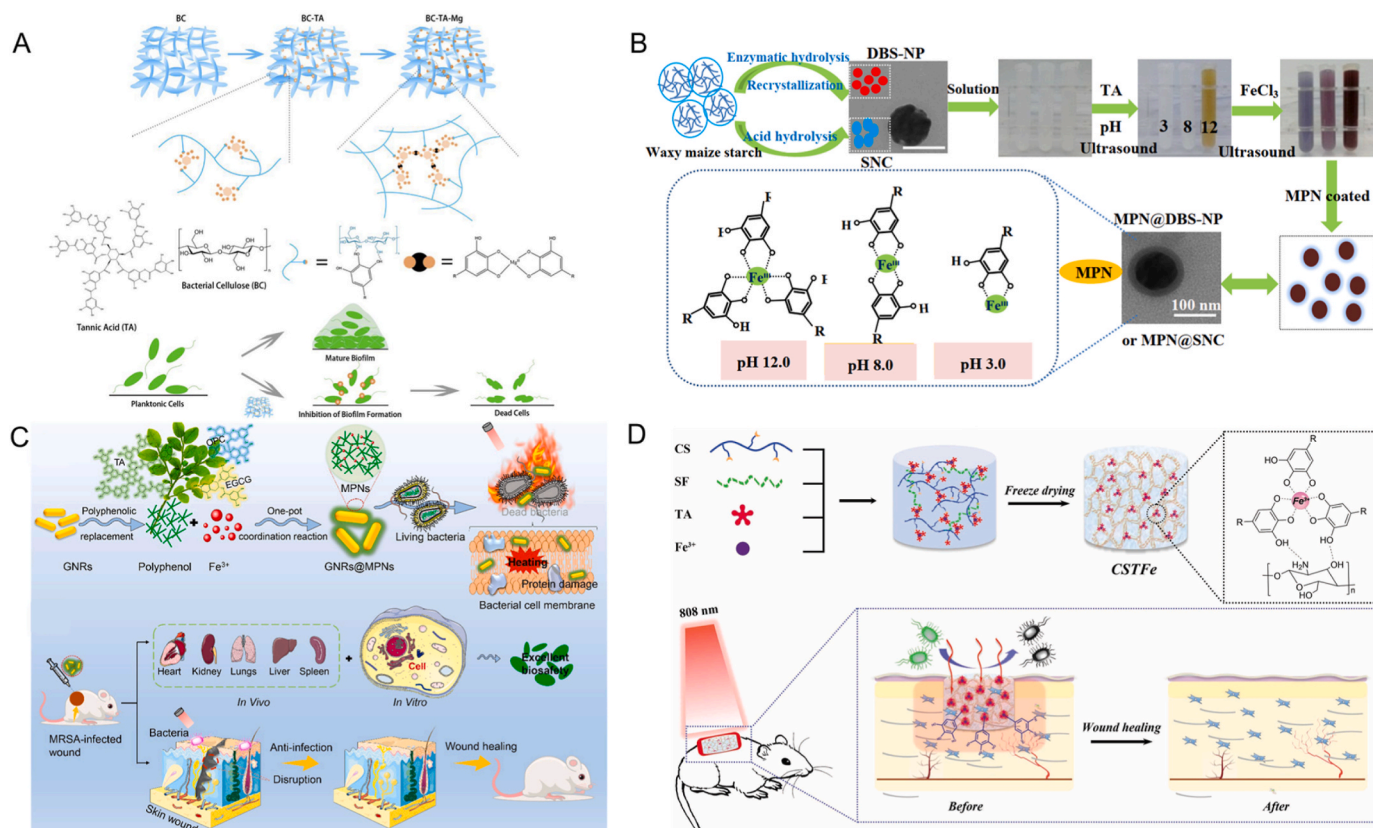


Fig. 7. Fabrication and the antibacterial effect of MPNs. (A) The coordination interaction between TA and Mg²⁺ in bacterial cellulose and its inhibitory effect on biofilm formation (Reprinted from Ref. [127] with permission from ELSEVIER). (B) MPNs based on coordination between TA and ferric ion (Fe³⁺) and the release of TA under different pH values (Reprinted from Ref. [128] with permission from American Chemical Society). (C) Preparation of GNRs@MPNs and their antibacterial effect against *S. aureus* and *E. coli* under near-infrared light (NIR) (Reprinted from Ref. [132] with permission from ELSEVIER). (D) Hybrid nanoformulation based on the coordination between TA and Fe³⁺ and its antibacterial effect under NIR (Reprinted from Ref. [134] with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim).

FDA for drug delivery applications due to their easy synthesis, tailoring of shape, and non-toxic nature [110]. Lee et al. fabricated ZnO@GA NPs by coordinated covalent bonding of GA to ZnO NPs surfaces. The functionalized ZnO NPs showed good antibacterial activity against MRSA and *E. coli* [138]. To target the site of infection, Ghaffari et al. prepared the pH-dependent ZnO NPs to enhance the antibacterial activity of curcumin which was released faster under mildly acidic conditions compared with the neutral pH condition [139,140]. In recent years, titanium dioxide NPs (TiO₂ NPs) have also attracted great attention due to their significant antibacterial ability. For instance, Dessai et al. used rutin (derivatives of flavonoids) to fabricate TiO₂ NPs, which was an eco-friendly and cost-effective material with antibacterial properties [141]. Additionally, iron oxide NPs (IONPs) were also an attractive candidate for antimicrobial preparation due to the balance of antibacterial effect and biocompatibility [142]. Synthetic methods with the application of natural extracts used as reducing agents have attracted considerable interest. By way of example, Aliya et al. used polyphenols of *Nigella sativa* seeds as reducing agents to produce IONPs with sizes 5–6 nm, which had a prominent effect on *E. coli* and *Salmonella typhi* [143]. In a recent study by Ke et al. TA was used as forming coordination bonds with Fe₃O₄ NPs [144]. The nanoformulation contributed synergistically to local wound infection, benefiting from the adhesion ability and photothermal properties.

Silica NPs. Studies in the past decade have shown that silica materials, especially ordered MSNs, are attractive due to their unique tunable particle size, polar volume, and high loading capacity [140]. The structure of silica nanomaterials (such as particle size and shape, pore characteristics, and morphology) and surface traits (surface

functionalities and surface roughness) affect drug loading and release rates [145]. In an earlier study, the researchers formed silica NPs by condensation of the carboxyl or hydroxyl groups of GA to improve the stability and antibacterial effect of the polyphenolic compounds. Compared with free GA, the antibacterial activity of silica NPs against *Paenibacillus larvae* was significantly improved [146]. Moreover, Petrisor et al. loaded GA in MSNs with different ratios and observed their inhibitory ability of gram-negative bacteria [147]. The release of GA from the MSNs was rapid in both simulated gastric fluid and simulated intestinal fluid. To overcome the shortcomings of rapid release, the optimization approach was the functionalized surface of the mesoporous materials [148]. For example, Shabana et al. synthesized PEG-coated MSNs to deliver quercetin [149]. The PEG-coated MSNs showed strong antibacterial effects against *S. agalactiae* and *K. pneumoniae* by oral route and a sustained release for more than 48 h.

3.2. Scaffolds (or matrix)-based formulations

3.2.1. Nanogels

Hydrogels are a kind of material synthesized by water-soluble natural or synthetic polymers, which form gels under the change of temperature, ion strength, pH value, ultraviolet radiation, and other different signals [150]. The properties such as good mucoadhesion, biocompatibility, controlled release, and enhance bioavailability of drugs by encapsulating or surface-adsorbing make nanogels promising biological materials for polyphenol delivery in local infection [151, 152].

Nanogels can also entrap other nanostructures, known as

“nanohybrid hydrogel” or “functionalized nanogels”. Metallic and metal oxide NPs are frequently embedded into the hydrogels to improve their mechanical, physicochemical, and biological properties by increasing the specific surface area and stability. For example, to increase the loading capacity, Dhanya et al. inserted ZnO NPs into the quercetin-loaded nanogels and significantly increased the quercetin loading by 39% [153]. These hybrid nanogels showed significant inhibitory effects against the strain of *S. aureus* and *Trychophyton rubrum*. Additionally, the introduction of metallic ions with a photothermal effect can play a cooperative role in antibacterial activity. As an example, Cao et al. prepared thermo-response functionalized nanogels against drug-resistant bacteria infection in local wounds [154]. The high temperature induced by AgNPs accelerated the release of TA and Ag⁺ under NIR, exerting a strong antibacterial function (~97% of MRSA and ~96% of *E. coli* were killed) (Fig. 8A). The preparation of stimulus-responsive nanogels involved hydrogen bonds, ionic bonds, van der Waals interactions, etc. For instance, in another study on localized infections, Tao et al. prepared thermal-response and on-demand release of polydopamine (PDA)@curcumin nanogels for antibacterial activity of wound healing [155]. Under NIR laser irradiation, curcumin released sharply increased attributed to π - π stacking, and hydrogen bonding interactions changed with increasing temperature of NIR (Fig. 8B).

In recent years, stimuli-responsive (such as pH, glucose, and ROS) nanogels have gained much attention due to their potential applications in infectious wounds. Controlled and triggered drug release is a desired property of responsive nanogels. In general, nanogels with ionizable groups tend to exhibit pH-sensitive swelling and release properties. Ninan et al. produced the TA/carboxylated agarose nanogels cross-linked with zinc ions for pH-responsive and controlled release of TA. At low pH conditions, phenolic hydroxyl groups of TA were protonated, and relatively few polyphenols bonded to metal ions to facilitate the release of TA and exert antibacterial activity against *E. coli*, *S. aureus*, and *P. aeruginosa* [156]. In addition to the weak acidic pH of the locally infected wound microenvironment, the pH-responsive nature of the nanogels is required for drug delivery from the gastrointestinal tract. For example, Hu et al. bonded EGCG with amyloid fibrils to form reversible nanogels [157]. Under human small intestine pH (pH = 6), EGCG could be released well and exerted antibacterial effects on gram-positive bacteria (*Listeria monocytogenes*, MRSA, and *Streptococcus oralis*) and

gram-negative bacteria (*Pseudomonas aeruginosa*, *E. coli*, and *Klebsiella pneumoniae*) coating the mucosal surface of the small intestine, without obvious cytotoxic effect on the colon epithelium. The ROS-responsive nanogels are based on the forming of ROS-responsive chemical bonds such as borate ester [158]. For example, Ni et al. prepared a multistage ROS-responsive nanogel based on the phenylborate ester between TA, PVA, and phenylboronic acid-modified polyphosphazene [159]. The nanogel could inhibit the growth of *E. coli* within 4 h and effectively scavenge ROS *in vitro* study. For another example, Wu et al. fabricated a pH/ROS dual-responsive injectable nanogel based on a boronic ester bond formed between the catechol of caffeic acid and phenylboronic acids [160]. The nanogel had a spatiotemporal release of the natural polyphenol mangiferin and showed the effective against infection during the early stages of wound repair.

3.2.2. Nanofibers

Nanofibers are polymeric materials with diameters on the nanometer scale and lengths in meters. In recent years, taking advantage of the high mesh porosity and specific surface area of nanofibers, some scholars have reported using nanofibers as drug delivery carriers to improve the therapeutic activity of polyphenols [161]. Nanofibers with therapeutic activity are usually manufactured by combining selected polymers with polyphenolic compounds through different methods, such as (1) Blending polyphenolic compounds with the polymers before spinning. (2) Coaxial spinning fabrication of core/shell structures. (3) Pre-treatment of encapsulated polyphenols mixed with polymers. (4) Post-treatment of the nanofibers. (5) Attachment of polyphenolic compounds to the surface of nanofibers [162]. To improve production efficiency and reduce production time and cost, several techniques for preparing nanofibers have been developed, such as electrospinning, solution blow spinning, centrifugal spinning, and carbon dioxide laser supersonic drawing [163–167]. Wang et al. used an electrospinning technique to load curcumin in zein fibers successfully with a high EE of nearly 100%, and the nanofibers manifested a remained antioxidant capability and an enhanced antibacterial effect against *S. aureus* and *E. coli* [168].

The polymers fabricating nanofibers include natural polymers (such as CS, collagen, zein, gelatin, silk fibroin, and cellulose) and synthetic polymers. Among the synthetic polymers, PLGA, PLA, PGA, PCL, and

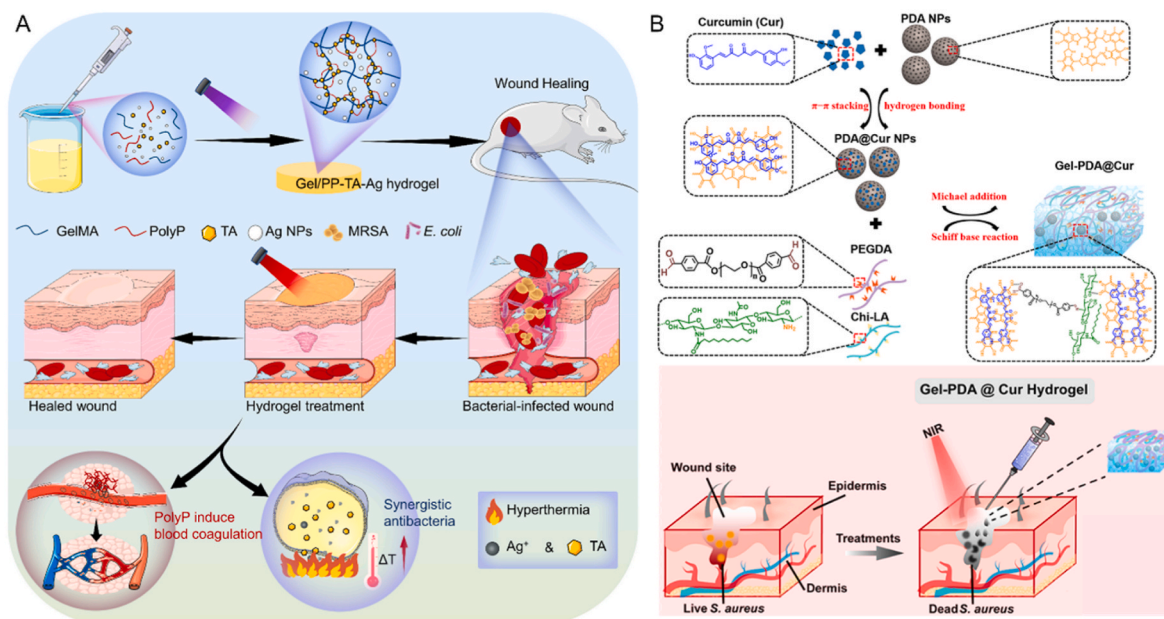


Fig. 8. (A) The preparation of TA-loaded hybrid nanogel and the enhanced antibacterial activity under NIR (Reprinted from Ref. [153] with permission from ELSEVIER). (B) The synthesis route of curcumin-loaded nanogel and the bacterial inactivation effect under NIR (Reprinted from Ref. [154] with permission from ELSEVIER).

PVA are commonly used to improve the mechanical properties and degradation kinetics due to their biocompatible and biodegradable characteristics [169–171]. For example, Zhang et al. prepared nanofibers with antibacterial and ultraviolet protection application potential based PVA and tea polyphenol [172]. This composite was blended through H-binding interaction and had good biodegradability and mechanical property.

The parameters affecting polyphenols release from nanofibers are related to the physical properties of fibers, polymers, and polyphenolic compounds. Firstly, the diameter of nanofibers affects the drug release, following the pattern that the thinner the nanofibers, the faster the release. Fallha et al. used the electrospinning technique to prepare PCL/gelatin/curcumin nanofibers to exert antibacterial activity against Gram-positive and Gram-negative bacteria [173]. As the voltage increased, the diameter of nanofibers drastically increased, thereby providing a longer-term antimicrobial environment. Secondly, the composition of polymers and the porosity also affect the kinetics of drug release. According to the study of Wang et al. curcumin cumulative release from nanofibers increased with the decrease in the weight ratio of PEG: PLA [174]. At the same time, due to the porous structure, curcumin was released from the nanofibers in a controlled manner, which resulted in sustained antibacterial effects. Drug-loaded nanofibers prepared by single electrospinning usually exhibited an initial burst release due to the high density of drug distribution on the nanofiber surface. To prevent the burst release of the drug, Wang et al. produced core-shell structure nanofibers with tea polyphenol as the core and PLA as the shell material [175]. This nanofiber showed a better release of tea polyphenol for 141 h. Finally, the loading parameters of polyphenols such as loading amount, solubility, and polymer-compound interaction, can also affect the release behavior of nanofibers [162,176]. For local wound dressings, besides long-term antibacterial activity, satisfactory biocompatibility, and skin adaptability should also be considered. Wu et al. established a kind of nanofibrous mats with CS and polydopamine on the surface [177], which resulted in a durable tensile stress of 6.7 MPa and a powerful inhibition against *S. aureus* and *E. coli* for 14 days. A recent study used different contents of GA to fabricate cellulose acetate nanofibers and investigated their potential antibacterial effects and release characteristics as wound dressing applications [178]. The researchers found that the cumulative release of 20% GA was greater than that of 40% GA because the average diameter of 20% GA was smaller and easier to release from nanofibers.

3.2.3. Nanoemulsions

Emulsions are widely used as one of the most desirable encapsulation and delivery systems for hydrophilic, lipophilic, and amphiphilic bioactive compounds due to their high encapsulation efficiency, viscoelastic, and visual properties, as well as the maintenance of the bioactive stability of encapsulated molecules. The droplet sizes of nanoemulsions range from ten to several hundred nanometers. Emulsions for encapsulation and delivery of polyphenols can be classified according to the literature into nanoemulsions (droplets size 200–500 nm) and microemulsions (droplets size <100 nm) [179,180]. The oil phase usually contains 5–20% oil/lipid droplets, sometimes significantly up to 70%. Re-esterified sections derived from soybean oil, cottonseed oil, safflower oil, and rice-bran oil (labeled as long-chain triglycerides, medium-chain triglycerides, and short-chain triglycerides according to the chain length) are used alone or in combination to fabricate nanoemulsions [181–183]. McClements et al. explored the influence of formative oil/lipid and droplet size on the bioavailability of curcumin [184]. Their biorelevant tests showed that nanoemulsions made with long-chain triglycerides and medium-chain triglycerides achieved maximum systemic availability.

Different ratios of the aqueous phase and organic phase, as well as the concentration of surfactant, can affect the stability of nanoemulsions [179,185]. In the study of Kaur et al., curcumin-loaded nanoemulsions were prepared to use against drug-resistant strains of uropathogenic

bacteria [186]. The nanoemulsions with the composition of soybean oil (13.09%) and water (71.22%) showed higher inhibitory ability on bacteria and biofilm formation than the natural compounds. Lou et al. used low-energy methods to produce *trans*-cinnamic acid nanoemulsion to enhance the antibacterial and antibiofilm effect of *Pseudomonas aeruginosa* [187]. They found that as the concentration of tween 80 (surfactant) increased from 1% to 5%, the particle size decreased from more than 100 nm to ~47 nm, while the polydispersity index (PDI) decreased from 0.58 to 0.29 as the concentration of tween 80 increased from 3% to 5%.

Several factors, such as pH, temperature, enzyme activity, and ionic concentration of the surrounding media, may trigger drug release from the nanoemulsion system. Very lipophilic drugs are released when the oily or lipid components have been digested. The small droplet size of nanoemulsions suggests that the diffusion rate of the drug across the oil phase may be quite rapid. Therefore, nanoemulsions are always fixed in structured carriers such as organogel or coated by thick layers of polymer to provide controlled release methods [188]. In a recent study, curcumin-loaded nanoemulsions were encapsulated in a hybrid hydrogel of CS, alginate, gelatin, and polyethylene oxide to enhance the antibacterial activity of curcumin [189]. At the same time, curcumin was released faster in simulated gastric fluid (pH 2.1) than in simulated intestinal fluid (pH 7.4) because alginate was protonated and curcumin was beneficial to the release under the low pH. That was, the hydrogel covering of nanoemulsion had a significant effect on drug release kinetics under an infectious environment.

4. Conclusion and outlook

With the increasing incidence of drug-resistant bacteria around the world, considerations regarding the application of antibiotic-free strategies will be a focus of future research. Polyphenolic compounds have been shown to have a positive effect on antibacterial therapy, however, their poor stability, low water solubility, and low bioavailability characteristics have created several limitations for their therapeutic application. By overcoming these limitations and controlling their release under specific conditions, nanoformulations have made important contributions. In this review, we have summarized the nanoformulations which enhanced the antibacterial effect of polyphenolic compounds and the advantages of different nano-systems and their potential application fields. For instance, polyphenol-loaded antibacterial nanogels can be applied to wound dressings, catheter-associated infections, urinary tract coating, etc. due to their local administration, controlled and prolonged release, and stimulated switch-on and off release. SLNs and CS-based nanoformulations are useful for systemic administration due to their low toxicity and good biocompatibility. Nanoemulsions provide greater opportunities to increase the bioavailability of lipophilic polyphenols.

However, some crucial challenges are still faced in the clinical translation of polyphenolic antibacterial nanoformulations: (1) Based on the excellent performance of polyphenolic compounds, considerations regarding antibiotic-free strategies should be a focus and be expanded from biomedicine to other fields such as environmental protection, animal welfare, and food safety. Simple, general, and cost-effective methods are needed to prepare polyphenolic nanoformulations. (2) Numerous studies have shown that polyphenolic nanoformulations have good antibacterial effects, but there is a lack of cross-sectional comparisons of the antibacterial capabilities of different formulations, and the mechanism of their antibacterial effect needs to be further explored and confirmed. At the same time, similar to the shortcomings of traditional drug delivery systems, polyphenolic compounds suffer from a relatively low effective utility. Smart nanoformulations designed to target infectious sites and to release favorably under infectious micro-environments would further enhance their effectiveness [190]. (3) The biological safety of nanoformulations is an important consideration for further application, especially for the use of inorganic

nanoformulations. Although CS and other food-grade biopolymers are considered safe, the process of preparation often involves organic chemicals, which may create a potential risk upon ingestion [39]. Strategies that use hybrid nanoformulations or combined therapy such as photothermal therapy should be considered to reduce the amount of metal ions use. Moreover, the processes of degradation, digestion, and elimination of nanoformulations are still not well understood, and their accumulation in different organs is also an important concern for human health. Nevertheless, a systematic and careful investigation of the biosafety of the nanoformulations is required.

On all accounts, nanotechnology has paved the promising path for drug delivery, and polyphenolic nanoformulations have potential prospects in antibacterial biomedical applications. The diversity of procedures from manufacture to the analysis of polyphenolic nanoformulations affects their physical properties, chemical behavior, and biological interactions, and therefore their applications. With a further understanding of the intrinsic properties of polyphenols, smart nanoformulations with low cost, ease of assembly, and facilitated site-specific targeting will play a critical role in the antibacterial applications. We expect this review to provide researchers with a framework for the advanced development of polyphenol-based nanomaterials and to guide more exploration in the field of antibiotic-free strategies to fight against bacterial infections.

4.1. Study highlight

- (1) Polyphenols are rich in nature and possess excellent antibacterial potential. Most polyphenols have poor water solubility and are liable disrupted by environmental acidity, temperature, enzymes, etc, which limit their therapeutic activity.
- (2) Nanoformulations (nanoparticles and nanoscaffolds) have played an important role in improving the bioavailability and antibacterial effect of polyphenols. Polyphenol-loaded nanoformulations have a promising prospect in non-biotic antibacterial applications in the biomedical field.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

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