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Review

Recent advances in functionalized nanomaterials for the diagnosis and treatment of bacterial infections

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ABSTRACT

The growing problem of resistant infections due to antibiotic misuse is a worldwide concern that poses a grave threat to healthcare systems. Thus, it is necessary to discover new strategies to combat infectious diseases. In this review, we provide a selective overview of recent advances in the use of nanocomposites as alternatives to antibiotics in antimicrobial treatments. Metals and metal oxide nanoparticles (NPs) have been associated with inorganic and organic supports to improve their antibacterial activity and stability as well as other properties. For successful antibiotic treatment, it is critical to achieve a high drug concentration at the infection site. In recent years, the development of stimuli-responsive systems has allowed the vectorization of antibiotics to the site of infection. These nanomaterials can be triggered by various mechanisms (such as changes in pH, light, magnetic fields, and the presence of bacterial enzymes); additionally, they can improve antibacterial efficacy and reduce side effects and microbial resistance. To this end, various types of modified polymers, lipids, and inorganic components (such as metals, silica, and graphene) have been developed. Applications of these nanocomposites in diverse fields ranging from food packaging, environment, and biomedical antimicrobial treatments to diagnosis and theranosis are discussed.

1. Introduction

The growing problem of resistant infections is becoming a global threat to healthcare systems, as recognized by the World Health Organization [1]. Bacterial mutations are accelerated by the abuse and misuse of antibiotics, which lead to multidrug-resistant strains that cause common healthcare-associated and community-acquired infections [2]. Consequently, there is an urgent need to improve existing treatments and search for new strategies to combat infections and overcome antimicrobial resistance. However, there is a lack of new prospective molecules with antibacterial activity. In this context, nanotechnology offers alternatives for developing novel compounds with different antibiotic actions. These antimicrobials have unique physical and chemical properties, such as a large surface area to volume ratio, that facilitate their interaction with microbial membranes [3]. Notably, great progress has been made in the development of engineered inorganic nanomaterials. These materials include several metallic and metal oxide nanoparticles NPs, which are highly toxic to pathogens owing to their multifaceted mechanisms of action against microbial cells [4,5]. Although they constitute a promising weapon for fighting bacteria, there are currently several drawbacks, such as their instability in solution and toxicity. To address these problems, nanocomposites have been developed in recent years to improve antibacterial activity and create new types of functionality. These nanomaterials exhibit different physical and chemical properties that are superior to those of the individual components [6]. In addition, these materials can be modified to suit specific applications in areas such as biomedicine and the environment as well as in various industrial uses [6–9].

Alloys obtained from combinations of various metals show different and controllable optical and electronic properties with superior antimicrobial activity and mechanical properties [10,11]. Another strategy involves the incorporation of metallic NPs into inert supports, which allow for their uniform dispersion. In addition, the overall cytotoxicity of metal-based nanomaterials can be reduced by their incorporation into suitable biodegradable matrices [12]. Some applications, such as wound dressings, bone scaffolds, food packaging, and waste-water treatment, benefit from some of the features of biomaterials produced by mixing various components, such as different types of polymers [6,13,14].

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In addition, in antibiotic treatments, it is important to achieve a high drug concentration at the infection site [15]. In recent years, the development of stimuli-responsive systems has allowed antibiotic vectorization to the site of infection. These functionalized nanomaterials can be triggered by various mechanisms, such as changes in pH, light, temperature, magnetic fields, and the presence of enzymes. The ability to selectively release antibiotics in response to a stimulus can increase the drug concentrations achieved at the target site. In turn, this can considerably improve antibacterial efficacy, reduce drug accumulation in healthy tissues and related side effects, and overcome antimicrobial resistance [16].

Although antimicrobial nanomaterials are promising alternatives, their clinical use requires careful assessment of issues such as the proper dose to achieve effective treatment. Furthermore, the biocompatibility of these products is an important factor that is often excluded from the characterization of new materials as well as any potential toxic effects in humans. In addition, any toxic effects on the environment must be considered.

This review highlights nanocomposite-based antimicrobial strategies that rely on associations of metallic NPs or their combinations with inorganic and organic materials to achieve improved properties, such as enhanced stability and synergistic antimicrobial activity. In addition, we summarize the most recently developed stimuli-responsive systems that are sensitive to pH, bacterial enzymes, magnetic fields, and light. The main strategies used for these triggering mechanisms are provided, and pertinent examples of their use in antimicrobial applications are presented. Finally, a more sophisticated strategy of NP functionalization is reported by combining NPs with cellular membranes derived mainly from erythrocytes, platelets and bacteria.

The categorization of nanocomposites in this review is mainly based on the principal component, but most of them can be assembled into multiple nanomaterials; thus, they are presented in more than one of the sections of this review. Hence, overlaps cannot be avoided in some cases in our classification. In addition, owing to the large number of reports published within this research area, this review primarily focuses on the more recent and relevant examples. Therefore, this review aims to provide an overview of current nanocomposite strategies for antimicrobial treatments and their promising perspectives and applications.

2. Metal-based nanomaterials

Metallic and metal oxide NPs are considered to be good alternatives to conventional antibiotic treatments. They can be fabricated by physical synthesis or chemical reduction of metal salts. Recently, research has focused on developing environmentally friendly alternatives [17–24].

Ag and Cu NPs are the most studied inorganic NPs for application as antimicrobial agents owing to their potent and broad spectrum of activity [25,26]. Currently, several products containing Ag NPs are being manufactured by various companies [6]. However, the underlying mechanism of the antibacterial activity of Ag NPs is not yet completely understood. Ag NPs can impair the bacterial membrane, causing permeability changes that lead to the leakage of intracellular components. Moreover, they release Ag^{+} ions that induce the generation of reactive oxygen species (ROS) that can damage DNA, proteins, and enzymes, and can also bind to subcellular organelles, leading to their malfunction (Fig. 1) [3,25].

Cu NPs constitute a cheaper and safer alternative to Ag because Cu is an essential micronutrient required by living organisms and acts as an enzyme cofactor.

Cu atoms oxidize into Cu^{2+} ions that generate ROS. This leads to lipid peroxidation, protein oxidation, and DNA degradation in the bacterial cell. They also cause cell wall disruption by electrostatic attraction between the positively charged Cu ions and the negatively charged cell membrane of the microorganism [27]. However, their rapid oxidation limits their use [28]. Other metallic and metal oxide antimicrobial NPs, such as Fe_3O_4, ZnO, AgO, CuO, and Al_2O_3 NPs, have been extensively applied in various fields [4,29]. The antimicrobial action described for these NPs also involves several mechanisms, even though it has been mainly attributed to the disruption of cell membranes and the production of ROS [3,28]. CuO and ZnO NPs induce ROS production, metabolism changes from the released Zn^{2+} and Cu^{2+} ions, and cell wall destruction followed by NP internalization [30–32]. Iron oxide (Fe_3O_4)

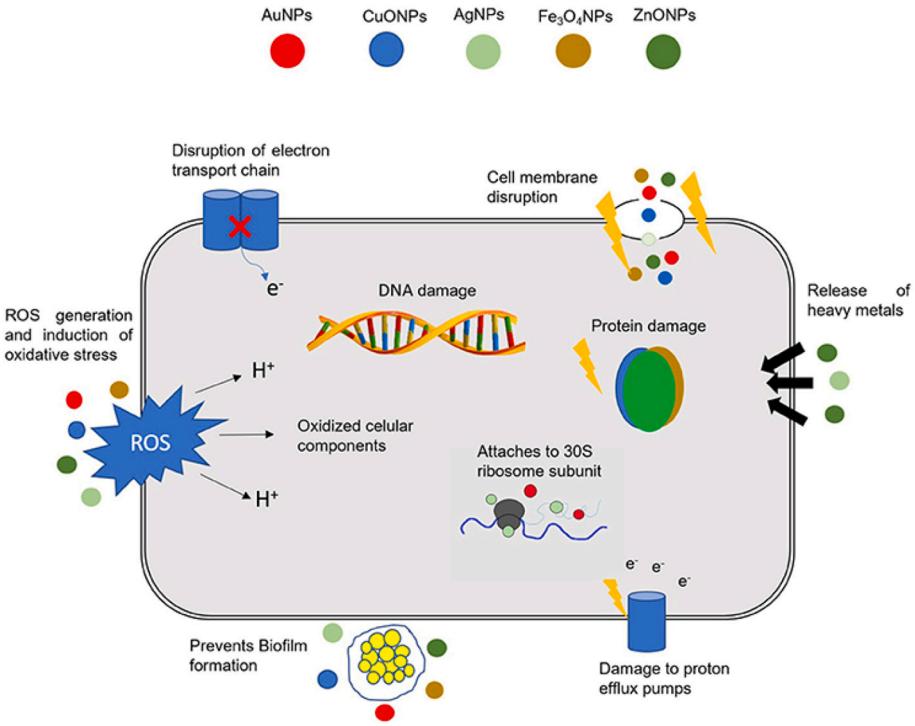

Fig. 1. Antimicrobial mechanisms of metallic nanomaterials. Reproduced with permission from [5].

NPs may interact with membranes and penetrate bacterial cells [29]. Their radical scavenging capacity and ability to interact with bacterial cell walls are the mechanisms proposed for CeO_2 and Al_2O_3 NPs [4]. Fig. 1 shows several mechanisms of action for different metallic nanomaterials.

Despite their numerous beneficial properties, metal-based nanosystems have some drawbacks that must be overcome. The most significant ones are their physical and chemical instability due to aggregation and oxidation, which may influence their antibacterial activity and their toxicity [3,23,25,33,34].

The properties of metallic NPs, such as surface characteristics, size, morphology, and type of capping agent, influence their interaction with bacteria. Size is one of the most important features, with increased antimicrobial activity for smaller NPs due to the higher surface area to volume ratio [3,23,25,33–35]. Gram-negative bacteria are more susceptible to the toxic action of metallic or metal oxide NPs than gram-positive bacteria. This has been explained by differences in the cell wall [26,36]. However, the bacterial behavior of metallic NPs does not always match that classification because there is a species-dependent bacterial sensibility that depends on the capacity of the bacteria to handle metal ions. This would explain the lower EC50 of ZnO NPs for gram-positive *Bacillus subtilis* than that for gram-negative *Escherichia coli* [37,38].

2.1. Metal and metal oxide combinations

Metals have been associated to create bi- or tri-metallic NPs, which provide additional benefits, such as a higher chemical stability, a lower cytotoxicity, and particularly, an enhanced antimicrobial effect. The properties of the metals and the preparation methods lead to the formation of phase-separated and homogeneous alloys or core-shell structures. Au has been proposed to increase the antibacterial properties and reduce the cytotoxicity of Ag in bimetallic AuAg NPs [39]. Other mixtures of metals and metal oxides that have shown an enhanced antimicrobial effect over single-metal NPs are AgCu, ZnOAg, FeZnO, CuNi, CuO/ZnO, AgZnO, and PdZnO NPs [40–46]. In the same way, ternary nanocomposites, such as Cu_2O–Ag/ZnO, may also show an increased antibacterial effect in comparison with that of the bimetallic ones (Cu_2O/ZnO and Ag/ZnO) [47].

Recently, better antibacterial activity was reported for homogeneous AgZn alloys than for heterogeneous alloys, which was attributed to a higher Ag^+ release [44]. However, the results obtained with various combinations are difficult to compare owing to methodology heterogeneity.

Core-shell nanosystems include spherical ones, such as AuAg and CuPt NPs with Au and Cu cores, respectively [42,48], but also other structures, such as mesoporous monoliths [49], Janus-like NPs [50] and fibers [51]. The shape of these systems influences antibacterial behavior. As an example, CuZn nanofibers show better activity than CuZn NPs [51]. In addition, high porosity and high surface area are desirable properties for these systems [49].

The synergistic activity of bi- or tri-metallic NPs has been explained by diverse mechanisms, such as the combined action of the different released ions [46,50], increases in ROS production, and/or enhanced antibacterial ion release [39,44].

The antimicrobial activity of the system also depends on the microorganism. For example, AgZnO showed better antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* than ZnO, but the minimum inhibitory concentration (MIC) did not change for the other assayed microorganisms [43].

Although biocompatibility is claimed as an important advantage of these combined nanosystems, it has been scarcely addressed. An increase in biocompatibility has been reported for bimetallic AuAg NPs relative to that of Ag NPs [39]. Changes in morphology, size, and zeta potential could be the basis for the lower ROS production of FeZnO NPs, leading to a lower toxicity to human cells than that of ZnO [46]. However, most of these nanosystems are toxic unless they are used at low concentrations [39]. Strategies such as the addition of subtilisin to bimetallic NPs may reduce their cytotoxicity [42].

The main proposed applications for these nanocomposites are the nanocoating of medical implants and devices, such as cardiovascular stents, and wound dressings [42,52,53].

Metallic associations may focus on other objectives, such as Fe–Mn–Cu, Cu–Zr–Al, and Zn–Ag–Zr combinations that produce biocompatible materials with mechanical, chemical, and antimicrobial properties suitable for use in internal fracture fixation devices [54–56]. Ternary Zn–Cu–Fe alloys also exhibit excellent mechanical properties and an increase in antibacterial properties due to higher Zn^{2+} and Cu^{2+} release during the degradation process, which is promoted by Fe. They are intended for use as stents [57].

2.2. Metals and support materials

Metallic NPs aggregate easily in solution, which reduces their antibacterial activity. Their association with inorganic carriers, such as silica and graphene, or various types of organic polymers, which provide a large surface area for the dispersion and stabilization of NPs, may reduce their toxicity [58,59] and increase and prolong their antibacterial activity through sustained ion release [59]. To achieve maximum antimicrobial activity, there is an optimal percentage of NPs that can be incorporated into the carrier because above this proportion, aggregation occurs [60,61].

These nanomaterials have been proposed for use in various biomedical devices, such as prostheses, catheters, and wound healing products. The aim is to reduce the prevalence of infection and to prevent bacterial growth, which can readily occur under moist conditions, particularly in the case of plastic materials [62].

2.2.1. Inorganic supports

2.2.1.1. Silica. Silica is composed of silicon dioxide (SiO_2). Its characteristics are easily controlled by the experimental parameters of the synthesis method. Mesoporous silica materials, with ordered structures of pores between 2 and 50 nm, show an ultra-high surface area and a high pore volume, which facilitate the incorporation of metallic NPs [63]. Silica NPs are a very suitable inert carrier for metals because of their easy preparation, tunable properties, and the high reactivity of the superficial silanol groups. The antibacterial activity of metal–silica composites is dependent on the size, morphology, and porosity of the silica NPs because a higher surface to volume ratio results in a better NP dispersion and higher activity. This enhanced antimicrobial effect was found for spherical core-shell SiO_2@Cu in comparison with that of rods [64]. In addition, Ag–silica wrinkle (DPSNs) and rough spiky surface (RHMSNs) nanospheres showed higher toxicity to bacteria than that of nanospheres with smooth surfaces. However, in addition to the surface of the support material, the size of the metallic NPs may also influence the antibacterial activity [65].

Mesoporous silica-based bioactive glasses are new materials made of silicate and other oxides, such as CaO, K_2O, Na_2O, or MgO. They show excellent bone-bonding capacity and a bactericidal effect in aqueous medium through the increase in pH and osmotic pressure due to the liberation of ions. Moreover, they can be functionalized with metals, such as Ag, Cu, Zn, or ceria, to improve their activity against bacteria. Most of these composites are prepared by sol-gel methods, and the use of micelle-forming agents facilitates the production of highly ordered mesoporous structures, as illustrated in Table 1 [66].

Metals provide antimicrobial activity to the silica but also induce changes in their structural properties [8], such as a reduction in porosity and surface area [67–69].

The antibacterial activity of the nanocomposites is governed by the release of the added metallic ions, which depends on porosity. A smaller

Table 1
Preparation method, antibacterial activity, and intended use of recent examples of antibacterial metal–silica-based nanocomposites.

Nanocomposite	Preparation method	Bacteria	Antibacterial activity	Intended use	Ref.
AgNPs-mesoporous silica	Sol-gel/Thermal	*S. aureus* (MRSA)	ZOI/mm 15.1 ± 0.2	–	[69]
Se-mesoporous silica	*In situ*-one pot	*S. aureus*	MIC/μg/mL 66 ± 13	Nanomedicine	[78]
Zn-mesoporous silica	*In situ*-one pot	*S. aureus*	MIC/μg/mL 0.15	Bone fillers, bioactive coatings and bone cements.	[72]
Ag-mesoporous silica-based power	Evaporation-induced self-assembly (EISA)	*Streptococcus faecalis*	ZOI/mm 9.6–10.6	Root canal infections	[79]

pore size limits the cargo capacity of the silica but achieves a slower ion release, while large pores promote a rapid release. The silica features must be adapted to particular application requirements [70]. Mesoporous cellular foams with pore sizes ranging from 30 to 40 nm exhibit a high water absorption capacity, and when associated with Ag NPs, show hemostatic and antibacterial properties [71].

Metal–silica composites are very useful for preventing infections in prosthetic hip replacement, in which they are used as bone fillers, bioactive coatings, and bone cements, because they show prolong antibacterial activity and biocompatibility [68,69,72]. In fact, the incorporation of metallic NPs, such as Ag, ZnO, or MgO NPs, in dental cements is a good alternative to provide bacterial anti-adherence and antimicrobial activity without compromising their physical properties [73,74]. The presence of metallic NPs may reinforce the mechanical properties of the resin [75–77].

2.2.1.2. Graphene. Graphene is a single-layer sheet of C atoms packed in a two-dimensional honeycomb lattice [7]. It has excellent properties, such as biocompatibility, high specific surface area, mechanical strength, flexibility, excellent conductivity, and easy functionalization [80]. Materials related to graphene, such as graphene oxide (GO) and reduced graphene oxide (rGO), are also widely used to support metallic NPs because of their outstanding properties. Moreover, they are toxic to bacteria [80,81]. The proposed mechanisms for their antimicrobial activity include physical damage to bacterial membranes, production of ROS, electron transfer from the bacterial membrane, coverage of bacteria, and interference with protein–protein interactions [80]. The lateral size of graphene oxide sheets influences their antibacterial effect. Larger sheets usually show higher toxicity against bacteria due to a better wrapping capacity, but there are controversial results relating to ROS production [82]. However, graphene tends to aggregate in aqueous solutions [83]. The incorporation of other materials, facilitated by the intermolecular forces between the sheets, increases its stability [84]. Association with metals results in nanocomposites with better stability of both components and increased antimicrobial activity [84,85], as shown in Table 2.

Graphene nanomaterials are produced by physical and chemical methods, such as exfoliation of graphite or reduction processes, and metallic NPs are incorporated through covalent or non-covalent bonds to obtain nanomaterials with increased antibacterial activity. Recent examples are shown in Table 2. Currently, efforts are focused on optimizing simple and environmentally friendly methods for preparing these systems [86]. The use of mussel-inspired polydopamine (PDA) allows non-covalent adhesion of NPs with a non-toxic, environmentally friendly method that maintains the properties of graphene [86]. Hybrids of reduced graphene oxide and Ag NPs, synthesized by green processes, exhibit enhanced stability of Ag NPs due to the uniform dispersion of NPs on the graphene [61]. The two materials show a synergistic effect against gram-positive and gram-negative bacteria [35,84,87,88]. The graphene prevents the agglomeration of Ag NPs, which favors their contact with bacterial cells, and the sharp edges of the graphene sheets damage the bacterial membranes, inducing changes that lead to necrosis [84,89]. Furthermore, the antibacterial activity depends on the shape of the Ag NPs incorporated into the graphene, and it was found to be

Table 2
Recent examples of the antibacterial activity of metal–graphene nanocomposites.

Nanocomposite	Concentration	Bacteria	Antibacterial activity		Ref.
			Parameter	Value	
rGO-AgNPs	4 mg/mL	*E. coli*	ZOI/mm	30.6 ± 0.89	[87]
		P. aeruginosa		37 ± 1.22	
		Salmonella typhimurium		26 ± 1	
		Proteus mirabilis		18.8 ± 1.09	
		S. aureus		29.8 ± 0.44	
		Staphylococcus saprophyticus		35.6 ± 0.89	
		Streptococcus pyogenes		34 ± 1	
		Bacillus subtilis		33.8 ± 1.09	
GO-AgNPs	5 mg/mL	*E. coli*	ZOI/mm	11.3 ± 0.9	[94]
GO-CuNPs				12.5 ± 2.1	
rGO-Fe_2O_3 nanorods	5 mg/mL	*Methicillin-resistant S. aureus* (MRSA)	ZOI/mm	18 ± 0.25	[95]
		Vancomycin-resistant S. aureus (VRSA)		16 ± 0.65	
		Ciprofloxacin-resistant S. aureus (CRSA)		18 ± 0.16	
GO-AgNPs	5 mg/mL	*E. coli*	ZOI/mm	20 ± 0.29	[96]
		S. aureus		16 ± 0.32	
		Bacillus subtilis		15 ± 0.22	
	0.05 M	*Listeria monocytogenes*	MIC/μg/mL	4.43 ± 0.05	[97]
		S. aureus		4.96 ± 1.00	
		Bacillus subtilis		4.01 ± 0.95	
		E. coli		3.93 ± 0.28	
		Salmonella typhimurium		6.17 ± 1.13	
		Klebsiella. pneumoniae		9.62 ± 2.95	
CuO-GO-Ag	–	*E coli*	MIC/mg/mL	2.6 ± 0.5	[98]
		S. aureus		2.6 ± 0.5	

greater for triangular NPs than for spherical ones [35] (Fig. 2).

Apart from Ag, reduced graphene oxide may also promote the dispersion of other nanomaterials, such as Cu_2O and CuO. These combinations may achieve long-term antibacterial activity [90] through the sustained release of Cu ions [59]. However, the mechanism of action is controversial. It has been attributed to the ability of CuO to transfer electrons from bacterial cells and to the wrapping of bacterial cells by the nanocomposite [90,91]. The size and shape of NPs considerably influence the nanocomposite activity [90,92].

Nanocomposites of metals with graphene have numerous applications. They are used as coatings for medical instruments owing to their anti-biofilm properties [88,90]. The excellent mechanical properties of graphene promote their use in caries treatments or bone regeneration [93]. It has been reported that the incorporation of reduced graphene oxide–Ag NP nanocomposites into dental cements improves their antibacterial properties while maintaining the desired mechanical properties [88].

Hence, the combination of graphene derivatives with metallic and metal oxide NPs leads to the improvement of their antibacterial and other properties. Although it has been claimed that metal–graphene nanocomposites have higher biocompatibility than that of metallic NPs alone [99], composite toxicity remains a problem that needs further study [100]. All of these issues have been addressed in recent reviews [7,80,101].

2.2.2. Organic supports

2.2.2.1. Carbohydrates. Carbohydrates are natural polymers composed of saccharide units. They are abundant in nature, biocompatible, and capable of forming hydrogels and bio-adhesives. Their structure and functional groups modulate their properties, such as solubility and mechanical behavior. Drug delivery, tissue engineering, and wound dressing are some of their uses [102]. However, because they lack antimicrobial toxicity, metallic NPs are incorporated into these compounds to generate nanocomposites with antibacterial activity.

Cellulose is the most abundant natural polysaccharide. It is insoluble, and diverse soluble derivatives have been developed. Among cellulose-based compounds, sodium carboxymethylcellulose (CMC) is a water-soluble cellulose derivative capable of hydrogel formation and is widely used for preparing wound dressings. CMC hydrogels bind to numerous cations, and Ag, CuO, or ZnO NPs may be prepared *in situ* within the hydrogel matrix, providing it with antimicrobial activity against gram-positive and gram-negative pathogens [103–105].

Related cellulose-soluble compounds are used for fabricating antibacterial membranes. For example, hydroxyethyl cellulose (HEC) was crosslinked with citric acid and supplemented with tungsten oxide for use as a wound dressing [106].

The presence of metallic NPs reduces the water absorption capacity of the hydrogels, which is dependent on the NP concentration [103]. Moreover, ZnO and CuO also show anti-inflammatory and increased re-epithelialization properties. They may induce proliferation of fibroblasts and angiogenesis because Cu and Zn are used by the body for collagen, elastin, and elastic fiber production, contributing to wound reparation [107,108].

Nanocellulose, a nanometer-sized material with a high specific surface area, low density, and good mechanical strength, is an ideal material for obtaining more uniform and higher ratios of metal NPs in the composites used in biomedical applications [109].

Nanocellulose hydrogel is also capable of retaining a large amount of water and provides the necessary moisture for healing wounds. Its combination with Ag or Cu NPs generates hybrid composites with antibacterial activity and greater biocompatibility than that of metallic NPs [109,110]. Various polymers are frequently incorporated to combine their properties, such as in the bacterial cellulose/alginate/chitosan/copper sulfate (BC/AG/CS–Cu) composites intended for use as wound dressings, which show suitable compatibility and high antibacterial activity against methicillin-resistant *S. aureus* (MRSA) and *E. coli* [60].

Another frequently used supporting material matrix for metallic NPs is alginate, a linear, ionic, and water-soluble polysaccharide that forms a gel with divalent cations, such as Ca^{2+}, Zn^{2+}, or Ba^{2+}, under extremely mild conditions. It is widely used in wound dressings owing to its excellent properties, and there are some commercialized products, such as Nu-derm®, Algisite M®, and Melgisorb® [111]. Alginate is commonly combined with other polymers, such as in antibacterial and biocompatible wound dressings composed of carboxymethyl chitosan

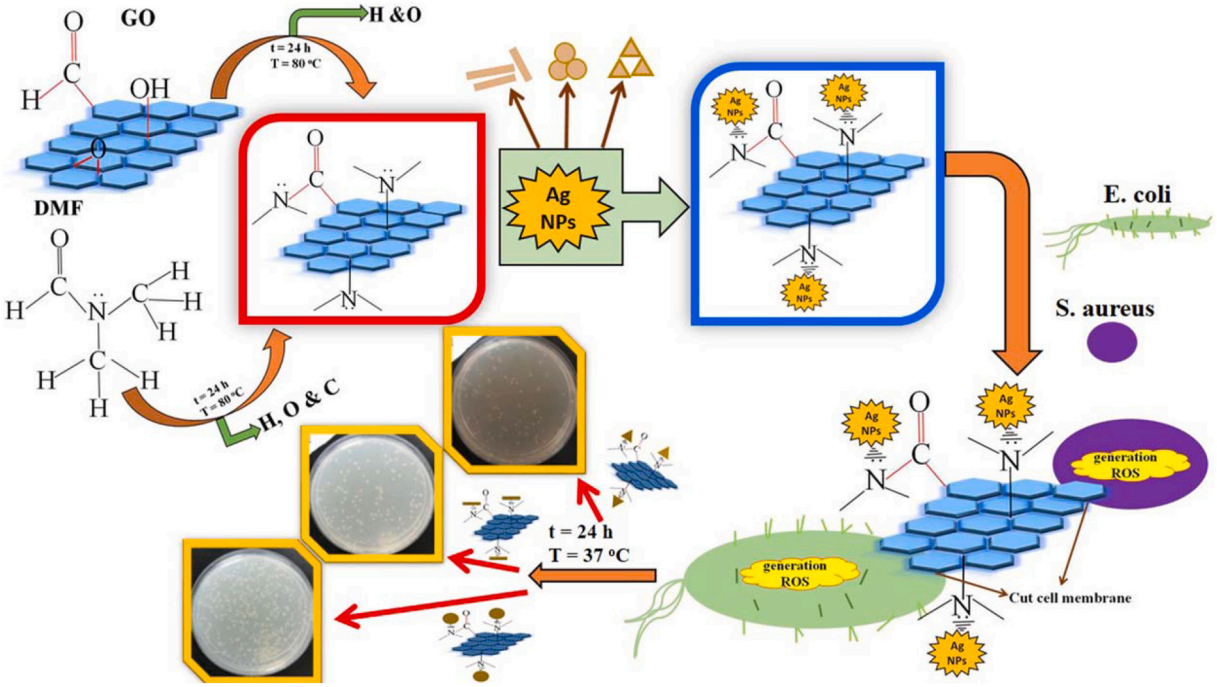

Fig. 2. Amine-functionalized graphene decorated with silver nanostructures as an antibacterial platform. Reproduced with permission from [35].

(CMCS), sodium alginate (SA), and polyvinyl alcohol (PVA) with Ag NPs formed *in situ* [112]. In another recent example, an alginate/silica network used as the carrier of zinc oxide NPs showed a slow release of Zn ions and antibacterial activity against *S. aureus* and *E. coli* [113].

These nanocomposites have also been applied to prepare packaging films [114,115] and in water treatments. The last one is the proposed aim for a reusable nanocomposite containing ZnO NPs encapsulated in an alginate biopolymer [14].

Other compounds, such as agar, carrageenan, hyaluronic acid, starch, and pectin, are also combined with metallic NPs to confer antimicrobial properties and take advantage of their good wound repair properties, as shown in Table 3 [102].

Currently, there are several wound dressings on the market that contain Ag NPs, such as Aquacel Ag®, DynaGinate™, ALGICELL®, Biatain Alginate Ag, ACTICOAT™, ALGISITE, and SilvaSorb®.

However, chitosan, a natural cationic polysaccharide obtained from chitin deacetylation, is currently the most investigated polymer for metallic NP incorporation. It has excellent properties owing to its antimicrobial activity against gram-positive and gram-negative bacteria, in addition to other features common to carbohydrates, such as low toxicity, high biodegradability, biocompatibility, and bioadhesivity [61,122]. Various mechanisms of action have been proposed for chitosan, including damage to the bacterial membrane structure, which causes leakage of intracellular components; enclosure of the bacterial cell in a polymer envelope, which impedes the exchange of nutrients; and chelating activity with trace metals and oligo-elements, which are essential for bacterial growth [123,124].

Table 3
Preparation methods and intended uses of recent nanocomposites composed of metals and polysaccharides.

Nanocomposite	Method	Advantages	Intended use	Ref.
Starch/AgNPs	*In situ* reduction	Antibacterial activity Enhanced tensile strength Lower vapor permeability	Wound dressing	[116]
Chitosan/pectin/ZnONPs	Freeze-drying	Antibacterial and antifungal activity Increase in tensile and compressive strength Increased porosity and surface area Lesser rate of degradation	Wound healing	[117]
Glucomannan/chitosan/AgNPs	Ultrasonication	Antibacterial activity Slower release of Ag+ Increase in hydrogel strength	Wound healing	[118]
Carrageenan/AgNPs	One-pot green reduction	Antibacterial activity Increase of thickness and tensile strength Increased swelling ratio	Wound dressing	[119]
Pectin/AgNPs	One pot reduction	AgNPs stabilization Antibacterial activity	–	[120]
Hyaluronic acid-ZnO NPs (HA-ZnO)	One pot reduction	Antibacterial activity Higher swelling capacity Better blood clotting ability	Wound dressing	[121]

When combined with metallic NPs, chitosan allows the formation of composites with increased antimicrobial strength and better compatibility. In addition, its gelling properties make chitosan a useful material for the preparation of films for wound dressing as well as in other types of applications.

The preparation of Ag NPs using chitosan as a capping agent enhances the biocompatibility of the NPs [12,125]. Moreover, it reduces their size, and the zeta potential switches from negative to highly positive, which leads to greater colloidal stability of the NPs and stronger interaction with the negatively charged bacterial membrane [12].

Chitosan also exhibits synergistic activity in combination with other metals or metal oxides, such as zinc oxide (Cs–ZnO) [126], copper (Cs–Cu) [127], copper oxide (CHCuO) [127], and molybdenum disulfide (MoS_2) [128]. The nanocomposites show better antibacterial activity against gram-negative and gram-positive bacteria than that of the individual components [128] as well as some reference antibiotics, such as streptomycin [126], ampicillin, and gentamicin [129].

Other functionalities can be achieved by using different types of materials. In an Er-doped hydroxyapatite (HAp)–chitosan film, chitosan provides antimicrobial activity against *E. coli* and *S. aureus*. HAp works as a biomaterial for engineering tissues, and the Er contributes to the fluorescent properties that make it suitable for bioimaging techniques. Biocompatibility studies on human lung fibroblasts showed ~80% viability [123].

Chitosan films have been applied to cover medical devices, such as chitosan/PVA/ZnO films with antibacterial and antifungal activities [130]. Chitosan composites are also widely used in wound dressings, and some recent examples are shown in Table 4. In addition to antimicrobial activity, their biocompatibility is also a key property for these types of applications [26,131–133].

In fact, there is a relationship between the concentration of metallic NPs, activity, and cellular toxicity that should be clearly defined to approach clinical applications [60]. The biological medium may also influence the antibacterial ion release, thus affecting the antimicrobial activity of wound healing devices [134].

Moreover, some nanocomposites, such as gelatin/chitosan/Ag porous sponges, can promote wound healing through water absorption and moisture retention [135].

The lack of mechanical properties is an important drawback for the use of chitosan as a wound dressing and in other applications. Therefore, attempting to improve the mechanical performance of chitosan is essential, and it is another aspect of future investigations. Crosslinking or the incorporation of other polymers may improve this property [138].

This was applied to chitosan films that were proposed for food packaging as an interesting alternative for dealing with the serious environmental pollution caused by plastic. To achieve the properties required for food preservation, diverse nanocomposite films have been developed to improve chitosan behavior. Bio-based films composed of three components (chitosan, metallic or metal oxide NPs, and another polymer, such as sodium alginate, cellulose, or starch) allow to overcome the weaknesses of chitosan, providing adequate tensile strength, water vapor resistance, and good antibacterial activity [13,139–142].

2.2.2.2. Synthetic polymers. Metallic NPs have also been associated with synthetic polymers, such as PVA, polyesters, methacrylates, and polyurethane.

PVA is a biocompatible, neutral, soluble, linear, synthetic polymer that has numerous applications in biomedicine and food packaging. Its tensioactive properties facilitate the electrospinning process, which also enables metallic NP incorporation. Polymer crosslinking allows control of the release of metallic ions, as reported for Ag NPs dispersed on PVA nanofibers crosslinked with glutaraldehyde [143,144]. PVA has excellent film-forming capacity and good mechanical and chemical strength and is frequently used to provide these properties to chitosan. The

Table 4
Recent examples of metallic chitosan-containing nanocomposites that can potentially be used as wound dressings. ZOI: zone of inhibition (mm); MIC: minimum inhibitory concentration (μg/mL); IR: inhibition rate (%).

Nanocomposite	Bacteria	Antibacterial activity		Advantages	Ref.
		Parameter	Value		
Chitosan-$AgNO_3$ films	*S. aureus*	ZOI (mm)	27.60 ± 0.26	Stabilization of AgNPs	[22]
	P. aeruginosa		36.83 ± 0.29	Better Ag ions release	
	MRSA 10		20.50 ± 0.50	Synergistic effect	
	MRSA 11		24.73 ± 0.46		
Chitosan graphene oxide and silver	*S. aureus*	MIC (μg/mL)	10 ± 0.32	Synergistic effect	[83]
	Streptococcus mutans		10 ± 0.35		
	E. coli		8 ± 0.41		
	Klebsiella pneumoniae		8 ± 0.42		
	P. aeruginosa		7 ± 0.32		
	Salmonella typhi		8 ± 0.38		
Chitosan-AgNP PEG hydrogel	*E. coli*	ZOI (mm)	20.2 ± 1.0	AgNPs slow release	[136]
	P. aeruginosa		21.8 ± 1.5	Synergistic effect	
	Bacillus subtilis		15.5 ± 0.8		
	S. aureus		21.5 ± 0.5		
Chitosan- AgNPs hydrogels	*E. coli*	IR (%)	I99.86 ± 0.12	Synergistic effect	[137]
	S. aureus		99.94 ± 0.10	Better mechanical properties	

combination of both polymers aims to obtain films with adequate properties for food packaging and wound dressing applications. The incorporation of metals into these nanomaterials increases their antibacterial properties [145]. Nanocomposites of metals, PVA, and polysaccharides (such as starch or alginates) have also been proposed as wound dressings to improve their electrospinability [108,143,146]. Moreover, the incorporation of inorganic fillers, such as graphitic carbon nitride (g-C_3N_4), improves the physical properties of the membranes for wound dressing applications [147].

Polylactic acid (PLA) is a polyester type of polymer. It is biocompatible, biodegradable, and easy to manufacture, but has poor mechanical properties. PLA is combined with metals, such as Mg, to obtain bioresorbable reinforced membranes for use in bone regeneration. The mechanical properties of this membrane are superior to those of PLA alone, and the degradation rate and ion release may be tuned depending on the intended application [148]. The PLA matrix improves the stability of Ag NPs, while they simultaneously provide antimicrobial activity and an improved tensile strength to the biocomposite for use as a wound dressing [149]. PLA improves the lack of adhesiveness of HAp. Ag–HAp–PLA films show good coating properties and antimicrobial activity [150].

PLA has good properties but also some drawbacks for application in food packaging films, such as brittleness, slow crystallization, inferior barrier properties, and thermal stability [151]. Nanocomposites composed of PLA with metallic oxides, such as ZnO and MnO, show antimicrobial activity and may improve certain properties, such as thickness, tensile strength, water vapor impermeability, and ultraviolet (UV) light penetration, maintaining film transparency [151–153].

Other polymer options include acrylate derivatives, such as polymethyl methacrylate (PMMA), whose nanocomposites benefit from the high transparency and good mechanical strength of PMMA, while the metallic component provides antibacterial and antifungal activity [62] for various applications, including their use as dental cements [157,158].

The incorporation of TiO_2 or HAp into all these polymers produces nanocomposites with appropriate mechanical properties and antibacterial activity for their application as tissue scaffolds and wound dressings. They are frequently associated with Ag NPs [159–161].

Metals and polymers have been conjugated to obtain hospital devices. Ag NP-based technologies for covering medical instruments have been commercialized, such as Agento I.C., Logicath™, AgTive, and Silverline®. As an innovative application in hospital beds, CuO NPs incorporated in open-cell flexible polyurethane foams (PUFs) have been proposed [162]. However, polyurethanes are very versatile polymers with multiple uses, and recently, associations with MgZnO or ZnAg NPs have been proposed for food packaging or wound dressing applications, respectively [155,156].

Table 5 shows the preparation methods, advantages, and intended uses of recently proposed metallic–synthetic polymer nanocomposites.

3. Responsive systems

Intelligent systems prepared from various nanomaterials can be used for the selective vectorization of antibiotics to the site of infection. These systems respond to different types of stimuli, such as pH, enzymes, and magnetic fields.

3.1. pH-responsive nanosystems

For infection by bacteria or viruses, inflammation occurs as an immune response in the organism. These inflammatory processes involve changes in the pH of the tissues. For infections such as sepsis, lactic acidosis is produced.

The functionalized pH-responsive nanomaterials used for the diagnosis and treatment of infectious diseases can be composed of various materials [163]. Recently, various pH-responsive nanosystems with antibacterial activity based on polymeric, metallic, silica, and solid-lipid NPs; microparticles; micelles; or nanotubes have been developed and are described below.

3.1.1. Polymeric nanoparticles

Various pH-sensitive polymeric NPs with antibacterial activity have been developed for different types of applications [164,165].

Polymeric NPs composed of L-lactic-*co*-glycolic acid-b-poly (L-histidine)-b-poly (ethylene glycol) are sensitive to pH and have shown high affinity for bacteria in acidic media. This type of NP was tested *in vitro* against various bacteria, such as *E. coli* and *S. aureus*. A greater binding to bacteria was demonstrated at pH 6.0 compared to that at pH 7.4 [164].

Cationic polymeric NPs containing pH-sensitive diblock copolymers that contain farnesol have also been effectively developed to fight *Streptococcus mutans* biofilms, and extended zero-order kinetics have been obtained with this kind of formulation. In addition, it is possible to correlate the pH-responsive antibacterial activity with the molecular weight of the polymers used in the different tested formulations [165].

In addition, pH-responsive polylactic-*co*-glycolic acid (PLGA) and chitosan NPs containing natural antimicrobials have been developed to improve food safety. These NPs incorporate trans-cinnamaldehyde (TCIN) and are manufactured by an emulsion/evaporation method. Drug release is produced by a pH-trigger mechanism with a rapid release

Table 5
Recent examples of synthetic polymer–metallic nanocomposites preparation methods and applications. HAp: hydroxyapatite; PVA: polyvinyl alcohol; PU: polyurethane.

Nanocomposite	Preparation method	Advantages	Intended use	Ref.
PLA/ZnO	Ultrasonication-electrospinning	Antibacterial activity Increased tensile strength Increased solubility and swelling capacity Higher UV –visible barrier	Food packaging	[152]
PLA/PEG/MgO	Solvent casting	Antibacterial activity Increased elongation at break Increased visible-UV barrier	Food packaging	[151]
PLA/ZnO	Solvent-casting	Antibacterial activity Increased UV barrier Increased thickness Decreased water vapor permeability	Food packaging Wound dressing	[153]
PLA/Ag nanofibers	Electrospinning	Antibacterial activity Better NPs stability Higher tensile strength Lower water vapor transmission rate	Wound dressing	[149]
HAp/PLA/Ag	Spin coating	Antibacterial activity	Metal coatings	[150]
PVA/Chitosan/CeO_2NPs	Freeze-thaw	Antibacterial activity Increase in average pore size and pore density. Increased swelling properties	Wound healing	[154]
PVA/starch/AgNPs	Electrospinning	Antibacterial activity Controlled silver ions release	Wound dressing	[143]
Zinc oxide/sodium alginate/PVA	Electrospinning	Antibacterial activity	Wound dressing	[108]
ZnAg NPs/PU	Electrospinning	Antibacterial activity	Wound dressing	[155]
MgZnONPs/PU	Solvent-casting	Antibacterial activiy	Food packaging Biomedical applications	[156]

of the drug at low pH. This system was successfully tested *in vitro* against *Salmonella typhimurium* and *Staphylococcus aureus* [166].

3.1.2. Silica nanoparticles

pH-responsive composites with folic acid (FA) and calcium phosphate (CaP) covering the surface of MSN and containing antibiotics, such as ampicillin, were developed to inhibit antibiotic-resistant bacteria. The presence of FA in the nanocomposites facilitates their uptake by bacteria because it is an essential vitamin for bacterial growth. In addition, this type of nanocomposite alters membrane proteins, overcoming the bacterial efflux pump system, causing the death of the bacteria. CaP can be controlled by a pH-responsive mechanism that modulates ampicillin release. In acidic media, greater antibiotic release is produced, inhibiting *in vitro* and *in vivo* bacterial growth, as can be seen in Fig. 3 [171].

In another study, MSNs that combine chlorhexidine (CHX) and Ag ions were developed. They act synergistically in acidic media against gram-negative bacteria, such as *E. coli*, and gram-positive bacteria, such as *S. aureus*, through a pH/glutathione (GSH)-responsive release mechanism. This mechanism is based on the introduction of a carboxylate functional group on the surface of the NP to positively charge chlorhexidine by electrostatic interactions. The release of the antibiotic is produced through the protonation and dissociation of carboxyl functional groups in acidic media. These mesoporous NPs show controlled drug release by matrix degradation through GSH-induced disulfide bond cleavage. In addition, Ag ions are released from the degraded matrix. This system can release chlorhexidine and Ag ions simultaneously *via* a redox/pH dual-controlled release and shows anti-biofilm properties [172].

3.1.3. Microparticles

pH-responsive carmellose microspheres (CMC) crosslinked with Cu ions have been developed using an external ionic gelation method that shows activity against vaginal microorganisms, such as *Escherichia coli* or *Candida albicans* [173]. Carmellose is a hydrogel with pH-dependent swelling. Consequently, changes in the pH of the medium can determine the diffusion characteristics and therefore the release of drugs [174]. In the range of pH values found in the vagina, corresponding to physiological values (pH = 4.5) and inflammatory conditions (pH = 6.0), this system presents pH-responsive behavior and antibacterial activity against different vaginal microorganisms [173].

Alternatively, systems prepared using silica microspheres containing tea polyphenol have been developed and subsequently included in sodium alginate gel microspheres. The outer layer of the microspheres contained pH-sensitive $CaCO_3$. As a result, the mineral cover of the microspheres neutralizes the acidic environment caused by the bacteria, and the encapsulated tea polyphenol is released in a pH-responsive way, decreasing oxidative stress, as illustrated in Fig. 4. This system has antibacterial efficacy against *S. aureus,* promotes the proliferation and differentiation of osteoblasts, and appears to be beneficial in the treatment of osteomyelitis [175].

3.1.4. Solid-lipid nanoparticles

Solid-lipid pH-responsive NPs can incorporate antibiotics and have proven to be effective against gram-positive bacteria, such as methicillin-susceptible and resistant *S. aureus*. The NPs are based on the use of a new lipid with a cleavable acetal linkage, which allows lipids that are solid at body temperature to be obtained. This system allows vancomycin to be released by a pH-sensitive mechanism based on the acidic environment of the infection site [176].

Hybrid nanocarriers for topical administration that allow the sustained release of antibiotics at the site of infection have been developed. The system consists of pH-sensitive hybrid NPs that are generated by combining NPs with metals to form complex hybrids. In this study, humic acid NPs were functionalized with ZnO and loaded with ciprofloxacin. This hybrid nanosystem exhibited bacteriostatic and bactericidal activity against *Pseudomonas aeruginosa* and *Bacillus cereus*. The antibiotic can be delivered in a sustained manner for 24 h at pH values ranging from 2.5 to 6.8 [177].

pH-responsive lipid-dendrimer hybrid (LDH) NPs containing vancomycin for the treatment of intracellular pathogens have been developed. NPs containing the polyamidoamine dendrimer and oleylamine (OLA) as the lipid phase were prepared by an emulsification solvent

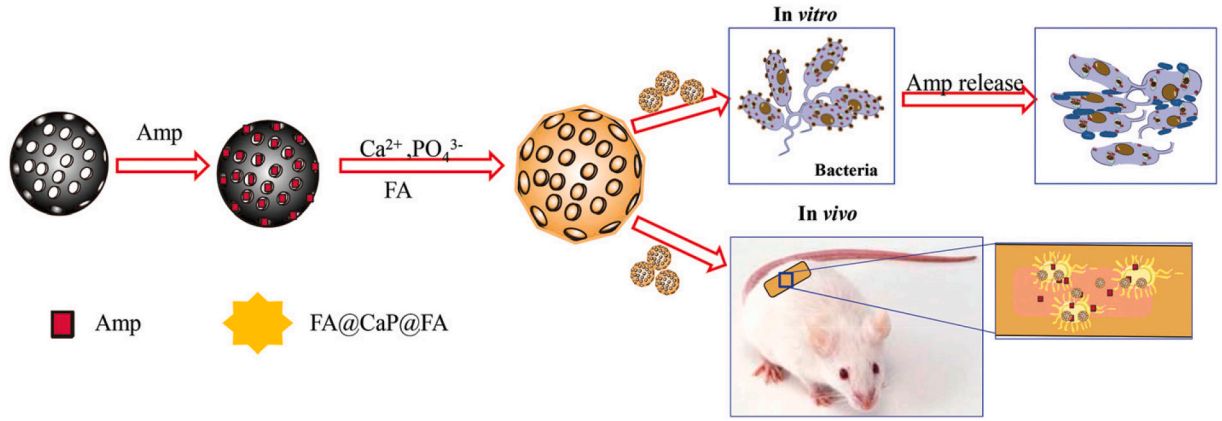

Fig. 3. *In vitro* and *in vivo* release of ampicillin in an acidic environment from MSN@FA@CaP@FA nanocomposites against antibiotic-resistant bacteria. Reproduced with permission from [171].

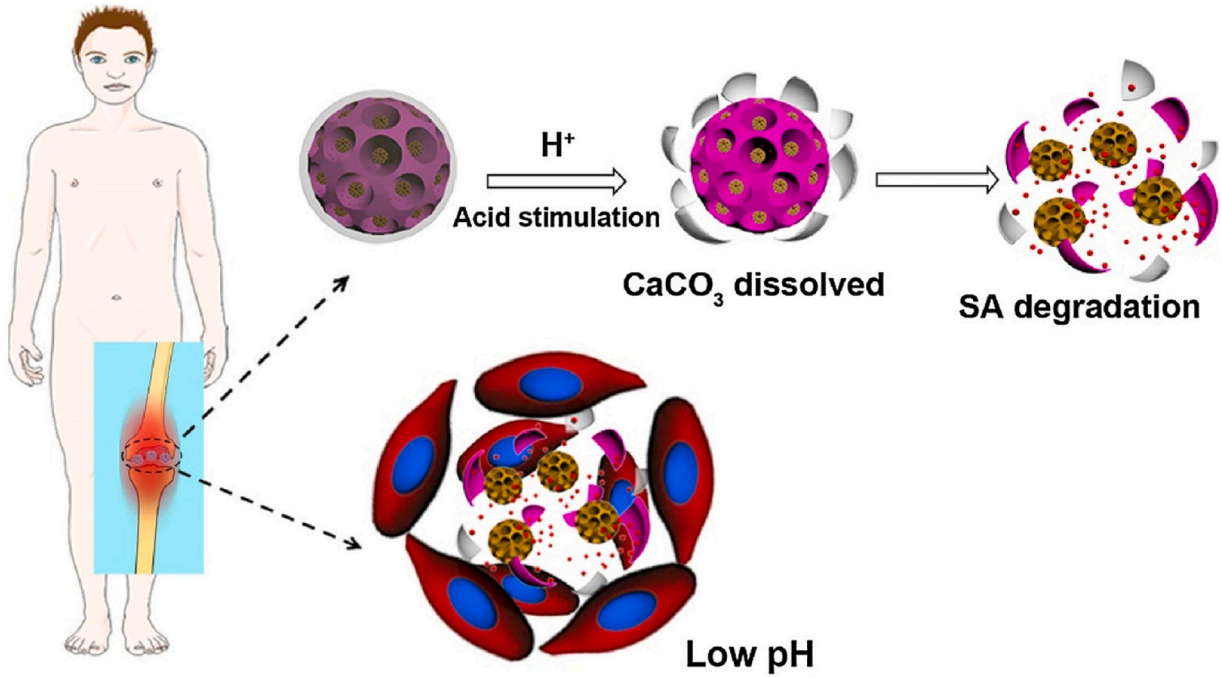

Fig. 4. Release mechanism of tea polyphenol from silica microspheres for the treatment of osteomyelitis. Reproduced with permission from [175].

evaporation procedure. The interaction between the dendrimer and the lipid phase was produced by van der Waals forces. The positively charged system can be attached to the bacterial wall, which is negatively charged by a pH-responsive mechanism. This system has shown intracellular accumulation *in vitro* in HEK 293 cells and pH-dependent antibacterial activity against MRSA [178].

3.1.5. Micelles and liposomes

Micelles are composed of molecular aggregates that have a polar and an apolar component, which can be used as drug delivery systems. The therapeutic use of micellar suspensions is particularly interesting in areas such as cancer and antibiotic therapy, among others [179,180].

pH-responsive nanostructured multi-layer micelles containing tobramycin, prepared by a layer-by-layer (LBL) method, have also been developed. Heparin micelles (negatively charged) were loaded with tobramycin (positively charged) using electrostatic interactions. Tobramycin micelles and chitosan were included in the LBL building block. At pH >7, the micelles are dismantled, and a rapid release of the antibiotic occurs; however, in an acidic environment, drug release occurs more slowly. This system demonstrated a high loading efficiency and *in vitro* antibacterial activity against gram-positive bacteria, such as *S. aureus*, and gram-negative bacteria, such as *E. coli* [181].

In addition, pH-responsive oleic acid-based dendritic lipid amphiphile (OLA-SPDA) has been assembled in micelles for the delivery of vancomycin. Micelles encapsulating vancomycin showed a faster release of the antibiotic at a pH of 6.0, *in vitro* activity against MRSA, and *in vivo* antibacterial activity in a mouse (BALB/c) skin infection model [182].

In the field of liposomes, pH-responsive systems for intracellular delivery of antibiotics have been developed.

Liposomes functionalized with a multifunctional diblock copolymer have been proposed for intracellular delivery of antibiotics. When liposomes functionalized with this type of pH-sensitive polymer are taken up by cells *via* endocytosis, they can release the antibiotic into the cytosol, destabilizing the *endo*-lysosomal membrane in acidic environments. This type of functionalized liposome containing streptomycin showed higher bactericidal activity *in vitro* than that of non-functionalized liposomes against *Francisella novicida*-infected RAW 264.7 murine macrophage cells [183].

Another system is based on "on" and "off" pH-responsive switches within the bilayer membrane of the liposome. The liposome includes an oleic acid-derived quaternary lipid and the parent oleic acid as pH-responsive components that can form a supramolecular complex in the lipid bilayer of the liposome. This complex works as an "on and off" switch to release the antibiotic contained in the liposome depending on the pH of the environment. This system has shown the ability to eliminate intracellular microorganisms *in vitro* in either HEK 293 or THP-1 microphage cells and has also shown efficacy *in vivo* using a MRSA-infected mouse experimental model [184]. In addition, vancomycin pH-responsive liposomes based on two-chain fatty acid-based lipids (FAL) containing amino acid head groups have been developed. The pH-responsive mechanism of these lipids is based on the protonation and deprotonation of secondary amine and free carboxylic groups depending on the pH of the environment. Vancomycin sustained release and antibacterial activity were successfully tested *in vitro* against *S. aureus* and MRSA bacterial cultures and *in vivo* against *S. aureus*-infected mice [185].

3.1.6. Metallic nanoparticles

Surface-adaptive Au-charged NPs sensitive to pH showed high adhesion to the surface of negatively charged bacteria in MRSA biofilms at a pH of approximately 5.5. The aggregation ability responds to pH stimuli, and bacteria can be killed by photothermal ablation from irradiation of the metal NPs with near-infrared (NIR) light. This anti-biofilm activity has been shown in both *in vitro* and *in vivo* studies using rabbits with local MRSA infections [167].

Other researchers are also working on pH-responsive NPs that allow the codelivery of beta-lactam antibiotics and beta-lactamase. These NPs comprise mesoporous silica NPs (MSNs) coated with metal–carbenicillin. The antibiotic coordinates with Fe^{3+} to form a metal–nanolid antibiotic that blocks the pores of the NP. The pH-responsive mechanism of this system is based on the breakage of the carbenicillin/Fe coordination complex in the acidic environment at the infection site, which leads to antibiotic release. This system has been shown to be effective *in vitro* and *in vivo* against antibiotic-resistant bacterial strains, such MRSA [168].

For the treatment of cariogenic biofilms, pH-responsive polymeric micelles composed of citraconic amide in a polyethylene glycol (PEG)-b-PAECOEMA/CA copolymer have been developed for the release of chlorhexidine. At low values, positively charged molecules interact with the negatively charged bacterial cell membrane. At an acidic pH, the micelles disassemble and quickly release the drug [169].

Antimicrobial systems have also been developed by combining metallic NPs with hydrogels. PVA-based hydrogels crosslinked with citric acid and containing Ag NPs incorporated *in situ* within the polymeric matrix were developed. These hydrogels showed pH-dependent swelling that controlled the release of antibiotics, such as ciprofloxacin, with antibacterial activity against *E. coli* and *S. aureus*. This system may potentially be used for the treatment of bacterial intestinal infections [170].

3.1.7. Nanotubes

Nanotubes have traditionally shown antibacterial activity and have been used as carriers for various types of antibiotics, particularly against multi-resistant bacteria. The mechanism of their antibacterial activity is related to the physical damage to the bacterial membrane and to the induction of ROS that can affect the viability of the cell [186]. The morphology and size of nanotubes can affect their antibacterial activity. Single-walled carbon nanotubes (SWNTs) have shown higher antibacterial activity against *E. coli* K12 cells than that of multi-walled carbon nanotubes (MWNTs). This is because as the size of the carbon nanotubes decreases, the specific surface area increases, facilitating interaction with the bacteria [187].

Titanium (as well as other biomaterials) is used in orthopedic implants owing to its mechanical properties and biocompatibility. However, it presents the problems of bacterial adhesion, the formation of biofilms, and the risk of developing orthopedic infections [188].

Ti nanotubes loaded with bone morphogenetic protein 2 (BMP2) and a multilayer film composed of alginate dialdehyde–gentamicin (ADA–-Gen) and chitosan were prepared by a LBL method. They exhibited osteogenic activity and long-term pH-responsive antibacterial activity against *E. coli* and *S. aureus* [189].

In addition, TiO_2 nanotubes loaded with Ag NPs and sealed with chitosan/dialdehyde alginate multilayer films were developed. This system promotes osteoblast response, inhibits bacterial growth against *S. aureus* and *E. coli*, and shows cytocompatibility with osteoblasts [190].

pH-responsive nanocomposites have also been used, which are based on combinations of acrylamide-co-acrylic acid hydrogels with chitosan-decorated MWNTs. These nanocomposites showed antibacterial activity against *S. aureus in vitro*. These nanocomposites also showed good mechanical properties, bacterial adhesion, and biocompatibility by MTT assay in MDCK and 3 T3 cell lines [191].

3.2. Enzyme-responsive nanosystems

Enzyme-responsive systems are characterized by changes in their chemical structure or in their physical properties due to the action of enzymatic systems, which can be used to control the release of drugs. These responsive nanosystems can be, among others, polymeric assemblies or nanocomposites [192].

3.2.1. Polymeric vesicles

Surgical site infections caused by MRSA occur frequently and are usually treated using a wide range of antibiotics [193].

Enzyme-responsive polymeric vesicles have been developed for the specific release of antibiotics, such as vancomycin or gentamicin, for the treatment of wound infections. This system is based on the use of copolymer-block vesicles that are self-assembled from amphiphilic diblock copolymers based on PEG derivatives. During the formation of the vesicles, the antibiotics are loaded in the hydrophobic bilayers or in the aqueous interior of the vesicles. Side-chain cleavage of the vesicles is produced by drug-resistant enzymes, such as penicillin G amidase (PGA) and beta-lactamase (Bla), which produce the sustained release of the antibiotic incorporated into the polymeric vesicle. These vesicles can function as carriers of antibiotics, facilitating their stability, reducing side effects, and achieving selective delivery against resistant bacteria, such as MRSA, *in vitro*. In addition, enhanced wound healing was observed using vesicles loaded with vancomycin in a wound infection *in vivo* murine model [194].

3.2.2. Nanocomposites

Enzyme-responsive nanocomposites for the prophylaxis of surgical wounds in burn patients have been developed. The nanocomposites used were fluorescent hyaluronan nanocapsules containing polyhexamethylene biguanide (HYA-PHMB-NC) as well as poly (L-lactic acid) NPs loaded with octenidine (PLLA-OCT-NP) [195]. The nanocomposites can have theranostic use; they can be degraded by bacterial enzymes and release the antibiotic or a fluorescent substance at the site of the infection. These systems are biocompatible with primary human endothelial cells and have therapeutic potential for the prophylaxis and treatment of burn injuries [192].

Enzyme-responsive chitosan–Ag nanocomposites coated with hyaluronic acid for the manufacture of antibacterial surfaces on synthetic materials have been developed. This system allows the controlled release of Ag ions mediated by the enzyme hyaluronidase secreted by bacteria and showed antibacterial activity *in vitro* using glass, polyethylene, and Ti surfaces as substrates [196]. In addition, protease-functionalized nanogel carriers for various types of antibiotics have been developed using carbopol as a hydrogel-forming polymer. This nanosystem was coated with the protease Alcalase 2.4 L FG, which

digests the polymeric matrix of biofilms and shows antibacterial activity against various biofilm-forming bacteria, such as *S. aureus, P. aeruginosa*, and *E. coli* [197].

For the elimination of biofilms, both enzyme- and pH-responsive nanocomposites with antibacterial activity as well as those using a magnetic guidance strategy have also been proposed. These nanocomposites are composed of multilayer films that contain the antibiotic gentamicin, tannic acid, and Ag NPs that are coated with magnetic NPs; hyaluronic acid is also placed on the surface. The release of the antibiotic and Ag ions to exert antibacterial activity occurs through a dual enzyme and pH-responsive mechanism in the microenvironment of bacterial infection, which is characterized by an acidic pH and high hyaluronidase content. High concentrations of Ag ions are released in acidic environments through a pH-responsive mechanism. In contrast, the release of gentamicin occurs through an enzyme-responsive mechanism through the action of the enzyme hyaluronidase. The incorporation of magnetic NPs into the nanosystem facilitates their deep penetration into the biofilm when subjected to an external magnetic field. The system showed *in vitro* efficacy against colonies of *S. aureus* and *E. coli* bacteria in biofilms [198].

3.2.3. PLGA ultrafine fibers

Antibacterial drug delivery systems based on ultrafine PLGA fibers that incorporate fusidic acid as an antibacterial agent have been formulated [199,200]. PLGA is a biodegradable polymer that is sensitive to hydrolytic degradation by bacterial enzymes. PLGA nanofibers were prepared using an electrospinning method [201]. Bacterial growth as well as the biochemical changes that occur in the culture of wound bacteria disrupt the integrity of the ultrafine fibers, affecting the structure of the polymer and the release of the drug. This system has been tested against various bacterial strains, such as *P. aeruginosa, S. aureus*, and MRSA. Fusidic acid has been shown to re-emerge, killing bacteria over a prolonged period of time [200].

Kefiran is a polysaccharide extracted from grains of kefir that shows antimicrobial properties and cicatrizing activity and can be degraded by bacterial enzymes, showing potential for use in wound healing and skin lesions. Kefiran nanofibers can be obtained through an electrospinning method, and artificial neural networks can be used to optimize the process parameters, such as polymer concentration, voltage use, and polymer feeding rate [202].

3.2.4. Titanium nanotubes

NPs composed of TiO_2 nanotubes show antibacterial activity due to their photocatalytic properties and have been extensively studied in the literature. Their photocatalytic activity is related to their geometry and size. By varying the anodization potential, the diameter of the nanotubes can increase to 100 nm. TiO_2 nanotubes prepared by anionic oxidation and decorated with Ag NPs showed that the photoinactivation kinetics against *E. coli* were faster when the anodizing potential of the nanotubes was increased [203].

In addition, the bactericidal capacity of TiO_2 nanotubes decorated with Ag NPs is related to their size. In this study, TiO_2 nanotubes 30–100 nm in diameter and *E. coli* as model bacteria were used. It was observed that the bactericidal activity was correlated with the size and percentage of Ag as well as with the surface density of the nanotubes [204].

To treat infections associated with orthopedic implants, multilayers of chitosan/sodium hyaluronate–lauric acid (SL) sensitive to hyaluronidase were deposited on the surface of Ti nanotubes loaded with BMP2. This system is known to inhibit *in vitro* bacterial growth of *S. aureus* and *E. coli*. Moreover, hyaluronidase can control the release of lauric acid from the multilayer system and facilitate the release of BMP2. This system has shown potential for use in antibacterial implants in orthopedics [205].

Enzyme-responsive systems based on hyaluronic acid–gentamicin conjugates (HA–Gen) and chitosan multilayers built on deferoxamine-loaded Ti nanotubes with antibacterial activity and osteo/angiogenic potential were developed [206]. This hyaluronidase-sensitive system can adhere and kill bacteria by releasing gentamicin through the action of hyaluronidase. This system showed osteo/angiogenic activity and antibacterial action *in vitro* against *S. aureus* and *E. coli* [206].

3.2.5. Nanokeepers

Nanokeepers are enzyme-sensitive nanocapsules with potential applications in the field of drug delivery. Nanokeepers consist of silica nanocapsules functionalized with a sulfo-linker to facilitate coupling with oligonucleotides. Nanokeepers incorporate an oligonucleotide that retains the drug inside the system and makes it specific for micrococcus nucleases. When the system interacts with nucleases caused by bacteria, such as *S. aureus*, the oligonucleotide is dissociated by the action of the nuclease and the antibiotic is released, killing the bacteria [207].

A modification of this system is based on the use of magnetic NPs or MSNs containing oligonucleotides. This modification is achieved through a similar mechanism based on the release of fluorophore molecules mediated by nucleases. It allows the detection of *S. aureus* in blood samples with high specificity and sensitivity [208].

3.2.6. Enzyme-responsive implants

Enzyme-responsive implants with simultaneous functions of antimicrobial therapy and tissue regeneration have been developed. MSN–Ag NPs were assembled with poly (L-glutamic acid) (PG) and polyallylamine hydrochloride (PAH) to form LBL@MSN–Ag NPs. Enzyme glutamyl endonuclease produced by *S. aureus* generates an enzyme-responsive release of Ag ions from the LBL@MSN–Ag NPs. The antibacterial mechanism of Ag NPs and Ag ions is based on the interaction of positively charged Ag NPs with the negatively charged bacterial membrane and the transport across cell membranes and combination with proteins of Ag ions released from NPs. In addition, Ag NPs produce an increase in ROS levels with bactericidal effect [209].

3.2.7. Photothermal mesoporous ruthenium nanoparticles

Enzyme-responsive photothermal mesoporous Ru NPs loaded with the prodrug ascorbic acid and encapsulated by hyaluronic acid have been developed. Molybdenum disulfide (MoS_2) precoated with ciprofloxacin was used as a catalyst for turning the prodrug ascorbic acid into $^{\cdot}OH$ to the outer surface. Hyaluronic acid may be decomposed by the hyaluronidase secreted by bacteria. This system combines bacterial microenvironment-responsive chemotherapy with photothermal therapy based on the photothermal properties of Ru. The system showed efficacy *in vitro* against drug-resistant gram-positive and gram-negative bacteria. This system also appears to be effective in inhibiting biofilms produced by gram-negative bacteria [210].

Table 6 shows a summary of some enzyme-responsive nanosystems and the enzymes involved in the drug release mechanism.

3.3. Magnetically responsive nanosystems

NPs possessing magnetic properties have been widely applied to improve existing diagnostic techniques that can be used even in remote regions as point-of-care assays. The versatility and potential multifunctionalization of NPs, or even their association with other types of NPs, offer numerous advantages in this field, leading to the development

Table 6
Characteristics of some enzyme-response nanosystems with antibacterial activity.

Nanosystem	Enzymes	Drug	Reference
Polymeric vesicles	Penicillin G-amidase Beta-lactamase	Vancomycin Gentamicin	[194]
Nanocapsules	Bacterial enzymes	Biguanide	[195]
PLGA fibers	Bacterial enzymes	Fusidic acid	[200]
Nanotubes	Hyaluronidase	Morphogenic protein 2	[205]
Nanokeepers	Nucleases	Vancomycin	[207]

of various types of nanosystems that can be used for the detection of pathogenic agents [211–214]. In fact, NPs with magnetic properties are one of the types of NPs that have originated numerous marketed products for various applications, such as Dynabeds® and the MRI contrast agent Endorem®.

These NPs have sizes that are similar to macromolecules, together with high surface-to-volume ratios and superparamagnetic behavior [212]. Although they have their own therapeutic effects, they have been functionalized to improve their intrinsic properties and/or add new ones.

Magnetic NPs have been applied in diagnostics and theranostics. They can be used as reporter labels in biosensors for magnetic detection-based techniques of different natures, and there is a wide range of analytical techniques that harness NP magnetic properties, such as magnetic permeability, remanence, and magnetoresistance. It is beyond the scope of this paper to discuss them here, and comprehensive and detailed reviews summarizing the variety of analytical techniques based on magnetic detection of NPs have been published recently [215].

Nevertheless, in many cases, they have been implemented to improve bioassays based on other detection mechanisms because they provide an interesting manipulation opportunity simply by applying magnetic fields.

The inclusion of magnetic properties in bacterial detection systems has been used for separation or in additional steps applied to existing procedures, such as enrichment [216–219].

For isolation purposes, they have been applied to a wide variety of analytical techniques, from the most traditional dye-based ones to the most complicated immunoassays or PCR techniques [220,221], allowing bacterial material extraction (in some cases even without pre-enrichment steps) from complex matrix samples, such as biological fluids, food, and soils, while avoiding background interference [222–224]; simultaneous detection of different pathogens; and even to distinguish different strains of the same microorganism [224–226].

Regarding the treatment of bacterial infections, in addition to the intrinsic antimicrobial activity that some magnetic NPs possess, functionalization with magnetic materials has been performed as a method of controlling drug delivery under magnetic stimuli, to develop magnetic targeted delivery systems that can guide drugs to specific organs and tissues or to improve penetration into biofilms [227–229].

Various antiseptic substances and antibiotic molecules have been studied in association with magnetic NPs, although here we will focus mainly on published studies from recent years. Systems with antibiotics, such as ciprofloxacin, together with magnetic NPs and exposure to different magnetic fields have shown potential against *P. aeruginosa* films [230].

Studies with polyethylene glycol dimethacrylate (PEGDMA) cross-linked chitosan microbeads loaded with superparamagnetic NPs and vancomycin confirmed that magnetic stimulation can modulate the antibiotic release from this system to increase or maintain drug levels [229].

Nanosystems based on Fe_3O_4 NPs were loaded with isoniazid. Studies on these systems have demonstrated their loading capacity, biocompatibility, and sustained release profile, which indicate that they are good candidates for drug targeting by magnetic guidance [172].

Geilich et al. developed a methicillin nanocarrier with iron oxide-encapsulating polymersomes (IOPs). IOPs consist of multiple co-encapsulated superparamagnetic iron oxide NPs (SPIONs) and appear to have beneficial properties against *Staphylococcus epidermidis* biofilms. They can be better positioned (*i.e.*, have access to the whole biofilm thickness) more quickly and with weaker magnetic stimuli than free SPIONs [231].

Another multifunctional platform consisting of graphene oxide and iron oxide magnetite particles was developed and loaded with ethambutol. Its sustained release profile for 50 h and high biocompatibility confirmed their beneficial characteristics as an anti-tuberculosis strategy [232].

In addition to classical antibiotics, other molecules with antibacterial activity have been included in NPs, acting as drug delivery systems. The potential of magnetic NPs associated with membrane-active compounds, such as cathelicidin LL-37 or ceragenins mimicking the structure of natural cationic antibacterial peptides, against anaerobic and antibiotic-resistant bacteria has been explored [233,234]. In addition, the combination of magnetic NPs and other nano-antimicrobials may enhance antibacterial activity or access to the desired location [235,236].

Some authors have even implemented magnetic NPs in macroscopic forms to control drug release, as shown in the use of amoxicillin patches containing magnetic NPs in a polymeric matrix. The oscillation of NPs due to the application of an external magnetic field causes mechanical vibrations in the matrix that induce the release of antibiotics. Thus, it has been shown that amoxicillin release can be controlled by a non-invasive and low-cost stimulus (an external magnetic field), revealing a quasi-Fickian profile [237].

3.4. Cellular membrane-functionalized nanosystems

There is also a highly sophisticated NP functionalization strategy, which is more complex than those previously mentioned. Beyond the possibility of multifunctionalizing NP systems with a wide variety of ligands with specific and different objectives, some authors have explored the possibility of combining NPs with cellular membranes. Thus, a new field arises, full of opportunities, which involves attaching or surrounding the NPs with cell membranes that give the NPs the complexity and structure of membrane surfaces [238–242].

The inclusion of NPs in natural membranes provides the so-called biomimetic NPs with innately valuable properties, such as targeting, drug delivery modulation, longer clearance times, and reduction in toxicity due to the protection offered by this NP cloaking [238,242,243].

The use of platforms based on cell derivatives presents numerous advantages, such as great biocompatibility and biodegradability, and in some cases significant selectivity due to their own original tropisms [244,245]. Membranes can also be suitably customized with specific ligands that can be used for a wide variety of purposes, such as targeting, controlled release, or even greater access through physiological barriers [214,246]. Moreover, some types of cells can be engineered using proteins or genes to modulate their innate properties. It has been found that many cellular sources, from circulating blood cells to cells involved in immune processes or even cancer cells, can act as NP carriers [247,248].

In the field of drug delivery systems, erythrocytes are the most studied cell type [249–251]. Various types of drugs, macromolecules, and genetic material have been included in erythrocytes, and even NPs. The membrane coating technology of red blood cells (RBCs) with NPs was initially developed by Zhang and his group using a simple procedure based on hypotonic treatment and extrusion, as shown in Fig. 5 [252].

Hybrid systems based on erythrocytes and NPs have also been studied for detoxification against certain bacterial toxins. A nanosponge that combines polymeric NPs and erythrocyte membranes has shown effective virulence neutralization *via* absorption of staphylococcal alpha-hemolysin, generating a strong immune response [253].

Considering the functional similarity of other pore-forming toxins, this immunization process could be extrapolated to infections caused by other bacteria [254]. Nanosponges consisting of NPs and cell-membrane-derived vesicles are capable of capturing bacterial toxins, such as MRSA and streptolysin-O toxins [254–256]. Although these systems could be applied for infection treatment without antimicrobials, and they have been proposed for antibiotic-resistant pathogens [257], some authors have loaded them with antibiotics, such as vancomycin. Macrophage uptake studies corroborated the efficacy of this kind of system, even for intracellular infections [258].

A platform based on Fe_3O_4–polyethylenimine NPs coated with macrophage membranes was designed for endotoxemia treatment. This system possesses advantageous properties for lipopolysaccharide (LPS) detoxification, such as an enhanced LPS affinity due to the positive

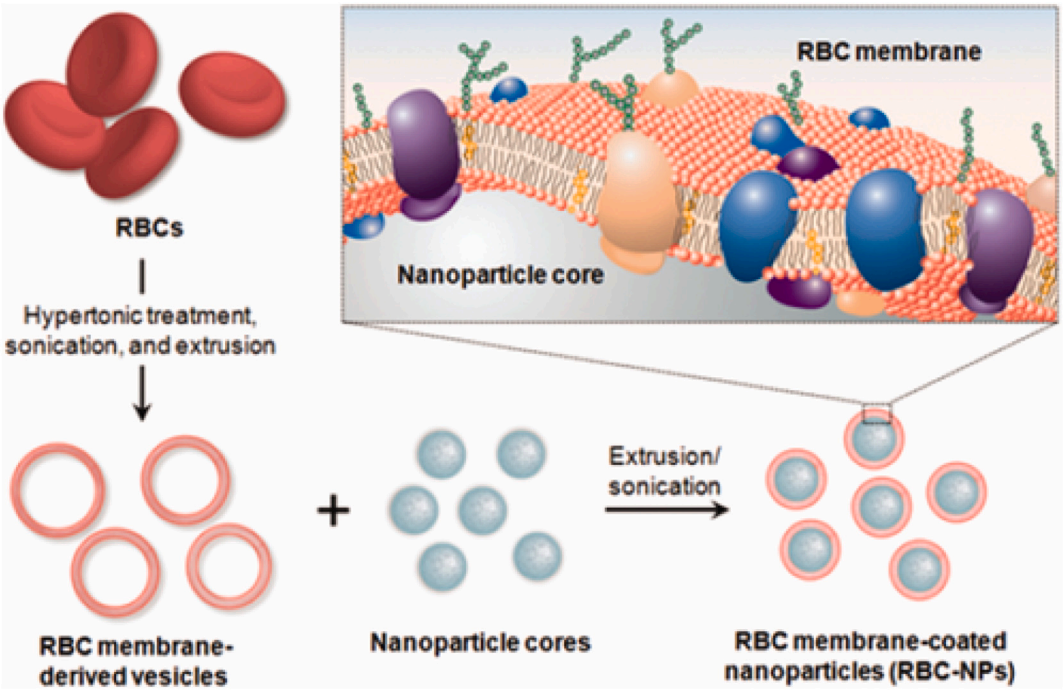

Fig. 5. Schematic representation of the process proposed by Zhang et al. for preparing erythrocyte-membrane-coated nanoparticles. Reproduced with permission from [252].

charge of the particles and the ability to be magnetically separated, which reveals its outstanding potential in endotoxemia and other LPS-related conditions [259].

Platelets have also been proposed as NP carriers and studies in a mouse model of systemic infection with vancomycin-loaded polymeric NPs cloaked in human-platelet membranes have demonstrated enhanced antimicrobial efficacy compared with free drug administration [260].

Concerning other types of blood cells, the use of leukocytes as vehicles of NPs is an obvious and logical field to explore owing to their implication in pathological processes. Although they have been mainly studied in tumor treatments or as carriers of antiviral drugs, systems based on macrophages and NPs have also been studied for bacterial infection, based on their ability to recognize bacteria. Wang et al. developed a system based on Au–Ag nanocages coated by macrophage membranes with enhanced expression of toll-like receptors, which could also be loaded with antimicrobial drugs. The so-called Sa-M-GSNCs have exhibited a photothermal effect that triggers release under NIR irradiation, together with promoted adherence to specific bacteria [261].

Bacteria are also one of the most studied resources in the field of cell-based drug delivery systems, as carrier systems or as a source of polymers for the development of NPs. A wide range of pathogenic or non-pathogenic species have been used, either genetically modified or from the patient's microbiota [261,262]. Regarding their use in the treatment of bacterial infections, and without forgetting their obvious application in vaccination, their association with NPs has led to fascinating hybrid systems that combine the benefits of both sources [263].

3.5. Light-responsive nanosystems

3.5.1. Photoactive therapy

The antibacterial activity of some nanomaterials increases in the presence of UV, visible, or NIR light [264,265].

Certain nanomaterials, such as ZnO and TiO_2 NPs, can absorb UV light, which activates their antimicrobial activity by generating ROS. Under irradiation, redox reactions occur at the surface of these semiconductors, generating ROS, such as hydroxyl radicals ($^{\cdot}OH$), superoxide anions ($^{\cdot}O_2^-$), and hydrogen peroxide (H_2O_2). Free radicals penetrate the membrane and inactivate microorganisms [266–268] in the so-called photodynamic therapy.

TiO_2 NPs have been associated with polymers such as poly (L-lactic acid) matrices, yielding nanocomposites that exert antibacterial activity with UV-light irradiation or prior photoactivation [269]. Other combinations, such as reusable $TiO_2/ZnCr_2O_4$ core-shell structures, exhibit greater antibacterial activity against *E. coli* compared to single-phase TiO_2 under UV-light irradiation [270].

However, TiO_2 NPs have little antimicrobial activity under visible-light irradiation, which limits their potential applications. In recent years, they have been combined with noble metals or metal oxide semiconductors to extend the light absorption spectrum of TiO_2 toward the visible-light region [271]. Composites of Ag NPs on a TiO_2 substrate show enhanced antibacterial effect under visible-light irradiation, increasing the formation of active $^{\cdot}O_2^-$ radicals that cause conformational changes in the bacterial membrane [272,273]. A similar effect was achieved by incorporating Cu NPs into TiO_2 NPs on a solid support of reduced graphene oxide [271]. The amount of loaded NPs modifies the hydrodynamic composite size and its light absorption behavior [274].

ZnO NPs are more biocompatible than TiO_2 NPs [4] and their enhanced activity in the presence of a light source has been explained by the sum of two mechanisms. One is the generation of ROS *via* photocatalytic water splitting. The second is the release of Zn^{2+} ions that interact with the thiol group of respiratory enzymes, which is the main mechanism for antibacterial activity in dark conditions [275]. The addition of Ag enhances the toxicity against bacteria under UV-light irradiation in comparison to that of bare ZnO NPs [267,275]. This effect has been explained by the release of Zn^{2+} and Ag^+ ions from the surfaces and the enhanced generation of ROS, which could induce serious damage to the bacteria that results in cell death [267,275,276].

Other metals may also increase ZnO light absorption in the visible range, such as in the proposed multifunctional Cd:Ag:ZnO:PVP nanocomposite [264] and thiolated chitosan-coated Co–ZnO NPs [277].

The main applications of these composites are their potential use in waste-water treatment [264,278].

3.5.2. Photothermal therapy

Photothermal antimicrobial therapy (PTT) is a non-invasive treatment based on the conversion of photons into heat energy that denatures proteins and enzymes and causes irreversible cell damage, leading to the destruction of pathogens [80,279]. This technique requires the use of a photothermal transducer capable of absorbing NIR light and effectively converting it into heat. The denaturation of proteins and the death of microbial cells require temperatures of 50 °C or higher, which may be used for devices or water sterilization. These high temperatures may cause inflammation and thermal damage to nearby tissues; therefore, combined synergetic strategies that use lower temperatures are more suitable for the *in vivo* implementation of these methods [280].

Au NPs and nanorods (NRs) are the most studied nanomaterials for PTT because they are capable of absorbing and scattering a wide range of visible and NIR light, depending on their particle size and shape. NIR laser-induced electronic oscillations on the surface of Au NPs are transformed into heat, elevating the temperature of the Au NPs and the surrounding environment [281].

In many cases, Au nanomaterials are associated with other components, such as Ag, to achieve better antibacterial activity. The antibacterial activity of Au–Ag NPs [167], core–shell–shell Au–Ag–Au NRs, and Au–Ag nanoshells [282,283] is the result of enhanced NIR absorption due to NP aggregation on the bacterial surface and the combination of physical photothermal ablation caused by the Au and the antibacterial effect of the Ag shell. When used to cover Ti surfaces, these nanocomposites prevented implant-associated infections. Moreover, they were compatible with osteoblast precursor cells, and the antibacterial activity exhibited under 808 nm laser irradiation was stable after multiple laser exposures.

Photothermal therapy has also been proposed for treating skin wounds using a PDA coating on a mixture of HAp with Au NPs (Au–HAp). The antibacterial efficacy of the PDA@Au–HAp NPs against *E. coli* and *S. aureus* was 96.8% and 95.2%, respectively, at a controlled photo-induced temperature of 45 °C, which causes no damage to normal tissues [280].

As a cost-effective alternative to Au, nanocomposites based on other photoactive metals, such as Ag–molybdenum oxide [265] and CuS–MoS_2 [284], C-based nanomaterials [267,275] and polymers such as polydopamine [285], have been developed. Association with Ag is very common because the photothermal effect triggers the release of Ag^+ and the generation of ROS. Moreover, these composites show better biocompatibility than Ag nanosystems [265].

This combined approach allows an optimal antibacterial activity at low temperatures due to the synergistic actions of a high yield of ROS and hyperthermia achieved by the combination of ion release with photodynamic and photothermal effects. An excellent review has recently been published covering this issue [286].

4. Diagnostic and theranostic applications

The nature, functionalization, and characteristics of NPs make them ideal candidates for implementation in diagnostics. Methodologies based on various characteristics of NPs have allowed the detection of specific infectious agents or to distinguish between gram-positive and gram-negative bacteria [211,287].

In fact, some automated systems for infectious pathogen detection based on NPs, such as Verigene®, can be found on the market.

They have led to the development of devices that allow the miniaturization and simplification of preexisting pathogen detection methods, from ELISA to genomic and metagenomic sequencing [288,289].

Thus, by applying the advantages of NPs, different research groups have developed diagnostic techniques that are easier, faster, and cheaper than conventional methods employed in infection detection, which have been proposed as portable point-of-care assays that can be used *in situ* [290–292].

In addition to the intrinsic properties of some NPs that allow the development of diagnostic techniques, NP-based systems can include a wide variety of molecules that allow for the identification and/or quantification of specific substances, even for multiplex detection. They have been implemented in biosensors, devices that detect biological, biomimetic, and biologically derived materials with a transducer system, which allow detection of the signal produced by a specific analyte. This concept, initially developed for cancer biomarkers, has been applied to specific molecules that can be observed when infection occurs [217,223,293] as illustrated in the example shown in Fig. 6.

Furthermore, multifunctionalization provides the possibility of incorporating diagnostic agents. Thus, by harnessing their own antibacterial properties (in some cases) or by including other active compounds, functionalized NPs offer a versatile platform for theranostics [295].

Metallic NPs are one of the most studied types of NPs for theranostics of bacterial infections. Applying their optical, mechanical, magnetic, or electrical and chemical properties as well as intrinsic characteristics, such as plasmon resonance and the photothermal properties of certain types of metallic NPs, they have been exploited alone or with additional functionalization for the simultaneous implementation of treatment and diagnostics [296–299].

5. Conclusions and future perspectives

In recent years, numerous systems based on functionalized nanomaterials have been developed for the diagnosis and treatment of infectious diseases caused by various pathogens responsible for serious infections, such as *S. aureus, E. coli,* and *P. aeruginosa*. Some of these nanosystems allow the selective release of different classes of antimicrobials in response to stimuli, increasing their concentrations at specific target sites. They present different compositions and functions, ranging from nanomaterials functionalized with metals or cell membranes to polymer-based responsive systems that are triggered by changes in pH, enzymes, magnetic fields, or light. These nanocomposites inhibit bacterial growth *in vitro* and *in vivo* and have numerous biomedical applications in the diagnosis and treatment of infectious diseases as antibiofilm agents, bone scaffolds, and wound dressings. They also behave as antimicrobial agents in environmental and industrial applications, such as water treatment and food packaging.

Nevertheless, despite the potential of these systems in bacterial diagnosis and therapy, there are still issues that must be solved to exploit all their possibilities. In some cases, the mechanism of action is not completely understood, and the toxicity is not fully characterized. Other hurdles include material stability or variability among batches and observed efficacy. Future work in the field should improve these drawbacks before these systems are translated into routine clinical practice [298].

Another critical issue is industrial production because most NP achievements are in basic research. Although a number of NP-based products are already on the market for heterogeneous applications, the use of complex functionalization in clinics still presents certain challenges that are difficult to cope with.

In addition, the translation of positive results in basic research to their industrial production presents additional hurdles compared with common small molecules.

The production of these systems is complex and typically requires the optimization of multiple stages, which intrinsically involves higher costs and variability in the obtained product. Thus, the commercialization of functionalized NPs poses important technical and legal challenges in scaling and translating these systems into marketable products [300].

Despite these difficulties, NPs are an important and promising sector in the pharmaceutical market, and a 16% compound annual growth rate is estimated for the global NP market during 2015–2020 [301], which undoubtedly supports the potential of NP systems. This growth may also increase when solutions to the previously mentioned unresolved issues are found in the future.

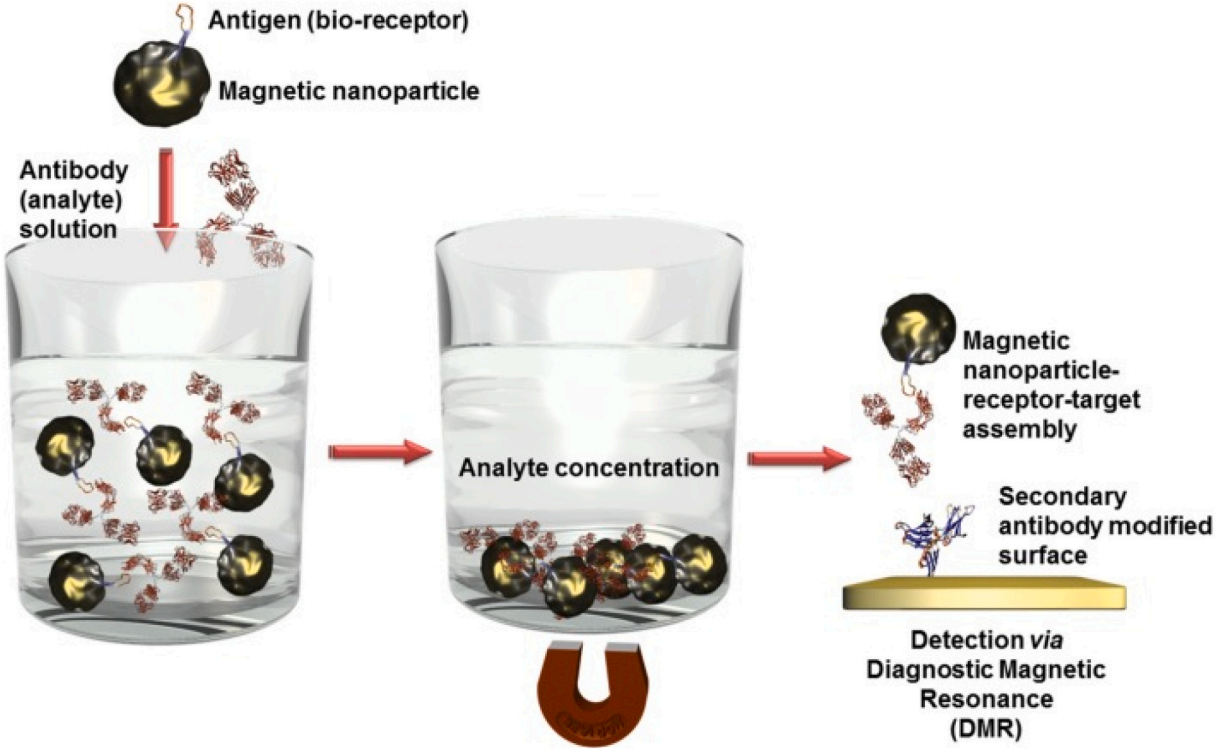

Fig. 6. Application of functionalized magnetic nanoparticles for the separation and detection of analytes. Reproduced with permission from [294].

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Declaration of competing interest

The authors declare that they don't have any conflict of interest regarding this manuscript.

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