

## REVIEW PAPER

## Chitosan-based nanocomposites and nanomaterials for drug delivery of antimicrobial agents: a review

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### ABSTRACT

With the indiscriminate use of antibiotics and increasing environmental issues, microbial resistance has emerged as a serious and growing global challenge. Moreover, the discovery and development of new antimicrobial agents remain difficult, expensive, and time-consuming. Therefore, the use of advanced drug delivery systems that enhance drug efficacy while reducing side effects has been proposed as a promising alternative strategy. To collect relevant literature, databases such as PubMed and Scopus, as well as search engines such as Google Scholar, were used. Nanomaterials—including nanocomposites, nanoparticles, nanoclays, and nanofibers—play a critical role in these delivery systems. Among them, chitosan, a non-toxic natural polymer with inherent antimicrobial properties, is fundamental because it can overcome many of the limitations of conventional delivery systems. Combining antimicrobial compounds with chitosan not only facilitates effective drug delivery but can also produce synergistic effects, thereby enhancing antimicrobial activity, improving bioavailability, prolonging release, and reducing microbial resistance. The structural characteristics of chitosan, such as its mucoadhesive properties, enable strong binding to biological tissues, which can be further modified for targeted delivery of antimicrobial agents. Chitosan-based nanocomposites also exhibit a high loading capacity for antibacterial agents, owing to their porous architecture, large surface area, and abundant functional groups that facilitate efficient drug binding. Recent advances emphasize the potential of these materials in treating bacterial infections, particularly in wound dressings, biomedical implants, and mucosal drug delivery systems. This review highlights various antimicrobial agents that can be incorporated into chitosan-based nanomaterials, including antibiotics, antifungals, metallic nanoparticles, antivirals, and other bioactive compounds such as toxins and natural products.

**Keywords:** Antimicrobial; Chitosan; Drug delivery; Nanocomposites; Nanomaterials

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### INTRODUCTION

Nanotechnology is a scientific field that focuses on materials at the nanoscale (1–100 nanometers) and encompasses a wide range of applications in medicine, drug delivery, and pharmacotherapy [1, 2]. Nanocomposites (NCs) are solid materials composed of multiple phases, with at least one phase containing nano-sized constituents such as nanoparticles (NPs), nanofibers, or nanoclays. These nanoscale components offer several advantages, including an increased surface-to-

volume ratio, improved physical properties, and enhanced resistance to mechanical stress. Based on the material used as the matrix, NCs are categorized into various types, such as ceramic matrix nanocomposites (CMNCs), metal matrix nanocomposites (MMNCs), and polymer matrix nanocomposites (PMNCs) [3, 4]. Among polymer matrix NCs, chitosan represents one of the most prominent and widely utilized biopolymers for forming the matrix phase. In such systems, the reinforcing phase may consist of NPs, nanofibers, or

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nanoplates embedded within the chitosan matrix [5]. Chitosan is a non-toxic, cost-effective, and recyclable material characterized by a robust, stable structure that resists degradation under harsh environmental conditions, such as high temperatures. These desirable properties have contributed to its widespread application in the synthesis and structural design of nanomaterials [6].

Among their diverse applications, one of the most significant is targeted drug delivery. Owing to their unique physical and chemical characteristics, the structure of nanomaterials can be precisely engineered to enable penetration into target tissues while minimizing adverse effects on other organs. This selective delivery helps to prevent the undesirable side effects commonly associated with conventional drug delivery methods [7].

In recent years, the indiscriminate use of antimicrobial agents such as antibiotics has resulted in widespread drug resistance, which represents one of the most serious biological and medical challenges worldwide. This phenomenon has led to reduced treatment efficacy and a consequent increase in the prevalence, severity, morbidity, and mortality of infectious diseases. Collectively, these complications impose significant economic, social, and psychological burdens on individuals, families, and healthcare systems [8]. It is estimated that approximately 700,000 people die each year due to antibiotic resistance, while the economic burden of treatment in the United States alone has increased by 55–70 billion USD annually. Moreover, many conventional antibiotics suffer from limitations, including poor bioavailability, low solubility, limited stability, and low patient compliance. At the same time, the discovery and

development of new antibiotics have faced considerable challenges in recent decades. Therefore, increasing attention has been directed toward alternative strategies, particularly nanotechnology-based drug delivery systems that can be combined with antibiotics to achieve synergistic antimicrobial effects [9, 10].

In this context, chitosan stands out as a suitable candidate from two perspectives. First, it possesses inherent antimicrobial, anticancer, and antioxidant properties [11-13]. Second, polymer-based nanocomposites (NCs) such as chitosan not only exhibit high bioavailability and biodegradability but also possess a large drug-loading capacity, providing an excellent platform for the incorporation of antimicrobial agents [14]. The process of drug loading within chitosan matrices is illustrated in Figure 1.

In addition to being used in the formulation of nanocomposites (NCs) containing antibacterial agents, chitosan itself exhibits broad-spectrum antibacterial activity against various species, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus cereus*, *Bacillus megaterium*, *Listeria monocytogenes*, *Lactobacillus brevis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, and *Salmonella typhimurium*. Moreover, the use of low molecular weight chitosan has been shown to reduce the proliferation and colonization of drug-resistant *P. aeruginosa* and *S. aureus* strains [15]. In a study conducted by Jamil et al., the synergistic effects of cefotaxime-loaded chitosan nanoparticles (NPs) were investigated, demonstrating the potential for developing novel strategies to combat multidrug-resistant pathogens [16].

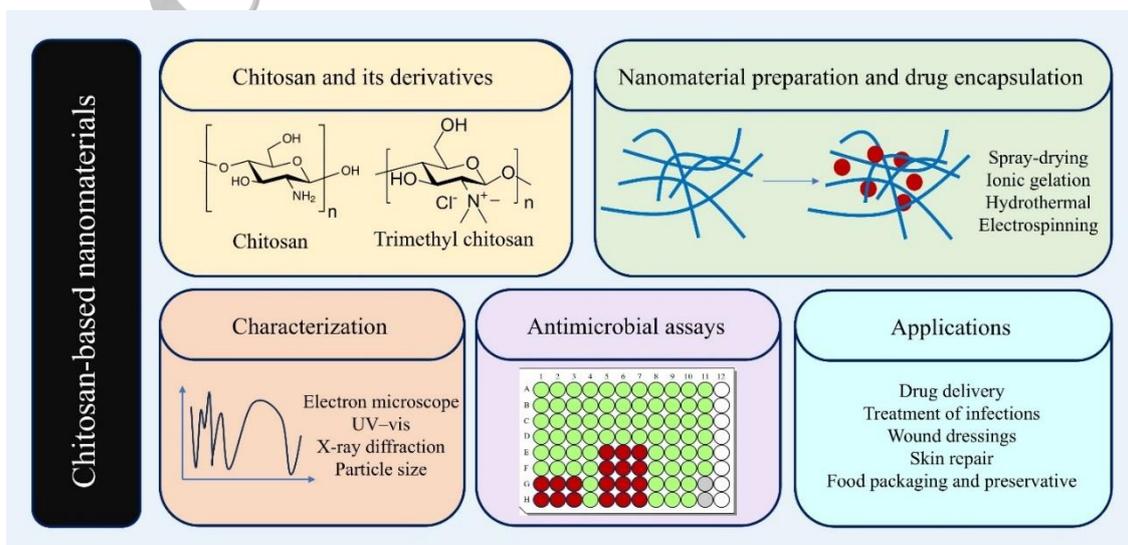


Fig. 1. Summary of drug loading procedures in chitosan-based nanomaterials

The prevalence of fungal infections has been increasing due to the emergence of new pathogens, rising drug resistance, and changes in epidemiological patterns [17]. However, the number of available antifungal drugs remains limited, and their effectiveness is further compromised by drug resistance and toxic side effects [18]. To address these challenges, antifungal agents can be incorporated into chitosan nanoparticles (NPs). For instance, it has been demonstrated that econazole and tioconazole can be successfully encapsulated within chitosan nanocapsules for use in vaginal drug delivery systems [19].

Viral pathogens cause most infectious disease epidemics. The spread of such epidemics can affect multiple countries or even entire continents, resulting in substantial public health and economic burdens [20]. Chitosan and its derivatives have also been reported to exhibit antiviral activity, particularly against SARS-CoV-2. In addition, studies have demonstrated that trimethyl chitosan (TMC) nanofibers exert significant antiviral effects against HIV [21, 22].

The present study aims to review chitosan-based nanocomposites (NCs) and nanomaterials, focusing on their potential as substrates for loading antimicrobial agents in drug delivery applications. Furthermore, the structural characteristics, reported synergistic effects, and future perspectives of these NCs as promising candidates for targeted drug delivery systems, the reduction of side effects, and the overcoming of antibiotic resistance are discussed. To identify relevant literature, systematic searches were conducted across databases and search engines, including Scopus, PubMed, Google Scholar, and other scientific sources, using keywords such as nanocomposite, nanomaterial, chitosan, antimicrobial, antibiotic, antifungal, antiviral, metallic nanoparticle, and related terms. In a complementary search phase, each antimicrobial agent was examined individually, yielding 493 articles after screening titles, abstracts, keywords, and, when necessary, complete texts. The most relevant studies were selected. Ultimately, 151 articles published between 2014 and 2025 (along with one key article from 2007 due to its exceptional relevance) were included, emphasizing recent publications and eliminating redundant studies.

#### ***Chitosan, a suitable candidate for drug delivery***

Chitosan is a biopolymer composed of glucosamine units, whose hydroxyl ( $-OH$ ) and

amine ( $-NH_2$ ) functional groups influence its solubility at different pH levels. It is suitable for a variety of drug delivery systems, including microspheres, nanoparticles (NPs), nanofibers, tablets, and films [5].

The amine groups in the chitosan structure confer a positive charge, a characteristic that is among the most important of this polymer. This cationic nature enhances drug permeability across biological membranes, improves adhesion to mucosal tissues, and enables controlled drug release [23, 24]. Furthermore, increasing chitosan's molecular weight has been shown to improve its permeation through epithelial cells. Therefore, chitosan facilitates sustained drug release, making it an excellent candidate for targeted drug delivery [24].

Methylation of chitosan's amine groups increases its cationic charge density. For example, one of its key derivatives, trimethyl chitosan (TMC), exhibits superior tissue adhesion compared to native chitosan because it can interact with mucosal components such as sialic acid and sulfate esters, thereby demonstrating a high capacity for drug delivery to mucosal tissues [25]. These advantages play a significant role in gastrointestinal drug delivery, improving both drug stability and therapeutic efficacy [26]. TMC is soluble over a broad pH range (1–9) and retains its positive charge throughout the gastrointestinal tract, allowing prolonged binding to mucosal surfaces and making it a promising candidate for colon-specific drug delivery [27]. Most of the compounds encapsulated within TMC-based nanocarriers are hydrophilic drugs, including insulin, methotrexate, and 5-fluorouracil [25]. In one study, amphotericin B-loaded TMC nanoparticles (TMC-NPs) demonstrated enhanced antifungal activity and reduced systemic toxicity, highlighting their potential for use in oral drug delivery systems [28]. As the positive charge of TMC increases, electrostatic interactions with negatively charged phospholipids in cell membranes are strengthened, resulting in improved antimicrobial efficacy against both Gram-positive and Gram-negative bacteria. Therefore, TMC generally exhibits greater antimicrobial activity than unmodified chitosan [29]. Furthermore, another study reported that TMC-NPs effectively inhibit biofilm formation by *Enterococcus faecalis* and show excellent biocompatibility with human periodontal ligament fibroblasts, suggesting their potential as a novel therapeutic approach for dental infections [30].

Targeted drug delivery approaches utilizing chitosan nanoparticles (NPs) include ocular, oral,

pulmonary, nasal, buccal, and vaginal delivery routes. [31]. Chitosan represents a promising platform for the delivery of anticancer agents owing to its strong mucoadhesive properties, which enable efficient binding to mucosal tissues. Moreover, the surface of chitosan NPs can be chemically modified to incorporate specific ligands, thereby enhancing their binding affinity to target antigens. This feature markedly improves the selectivity and therapeutic efficacy of drug delivery systems in cancer treatment [32]. In addition to anticancer therapy, other therapeutic compounds can also be delivered using chitosan as a biocompatible carrier. For instance, in a recent study, polyadine—an effective agent for the treatment of type 2 diabetes—was successfully encapsulated within chitosan NPs. The results demonstrated that these nanoparticles act as non-toxic and efficient carriers, providing a potentially safe and effective platform for targeted drug delivery [33].

One antimicrobial agent that can be incorporated into chitosan nanoparticles (NPs) is probiotics. Probiotics are beneficial bacteria that compete with pathogenic microorganisms for nutrients, thereby exerting antimicrobial effects. The combination of chitosan NPs with probiotics offers several advantages: the nanoparticles protect probiotics from environmental stressors, enhance their stability and transport to target sites, and increase their bioavailability. Moreover, chitosan NPs enable controlled release of probiotics. When co-administered, the antifungal

properties of chitosan NPs and the biological activity of probiotics exhibit synergistic enhancement [34]. Another antimicrobial compound encapsulated within chitosan NPs is hexaconazole. Hexaconazole-loaded NPs demonstrate potent antifungal activity against *Ganoderma boninense* and enable efficient drug delivery to fungal cells in plants. *G. boninense* is the causative agent of Ganoderma disease, which significantly reduces oil yield in oil palm plantations. Therefore, chitosan NPs can serve as an effective nanocarrier system for the prevention and treatment of fungal plant infections [35].

Thus, chitosan represents a promising candidate for the drug delivery of antimicrobial agents. The types of antimicrobial compounds incorporated into chitosan-based systems are summarized in Figure 2.

### Chitosan-based NCs for drug delivery of antimicrobial agents

#### Antibiotics and antibacterial agents

Antibiotics are essential therapeutic agents that combat infectious diseases by inhibiting bacterial growth and replication. Their crucial role in modern medicine underscores their importance in effectively managing bacterial infections [36]. Based on their chemical and molecular structures, the major classes of antibiotics include  $\beta$ -lactams, macrolides, tetracyclines, quinolones, aminoglycosides, sulfonamides, glycopeptides, and oxazolidinones [37]. Unfortunately, the efficacy of these antibiotics has declined over time, posing serious health and economic challenges to society.



Fig. 2. Antimicrobial agents which can be delivered by chitosan-based nanocomposites and nanomaterials

Moreover, the discovery and development of novel antibiotics are both costly and time-consuming [38]. Therefore, the design of innovative drug delivery systems has become an important strategy to overcome these limitations. For instance, conventional antibiotics can be encapsulated in micro- or nanocarriers to enhance cellular uptake and targeted transport [39]. Chitosan, as an efficient biopolymeric carrier for antibacterial agents, plays a vital role in this context. A study demonstrated that chitosan-based nanocarriers can effectively deliver hydrogen peroxide and antimicrobial peptides, exhibiting synergistic antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [40]. In

another study, vancomycin-loaded chitosan–hydroxyapatite–gelatin composites demonstrated strong antibacterial activity against *S. aureus*, suggesting their potential for localized treatment of osteomyelitis [41]. Similarly, levofloxacin, a key antibiotic used in the treatment of respiratory infections, was successfully formulated within inhalable chitosan nanoparticles (NPs) capable of delivering the drug to deep lung regions and providing sustained release characteristics [42]. A summary of the most relevant antibiotics incorporated into chitosan-based nanocomposites (NCs), along with their key physicochemical and therapeutic features, is presented in Table 1.

Table 1. Chitosan-based nanocomposites and nanomaterials for drug delivery of antibiotics

No.	Antibiotic	Other ingredients	Chitosan derivative	Preparation method	Bacterial species	Application	Particle size	Note	Ref.
1	Amoxicillin	Polyethylene glycol	Chitosan nanoparticles	N/A	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	N/A	696.20 ± 24.8 6 - 359.53 ± 7.4 1 nm	N/A	[43]
2	Amoxicillin	N/A	N-2-Hydroxypropyl trimethyl ammonium chloride chitosan, N,O-carboxymethyl chitosan nanoparticles	N/A	<i>E. coli</i> , <i>Acinetobacter baumannii</i> , <i>Streptococcus pneumoniae</i> , <i>S. aureus</i>	N/A	N/A	Sustained release, better drug transport efficiency and bioavailability	[44]
3	Ampicillin	Starch	Chitosan nanocomposites	Spray-drying	<i>E. coli</i>	N/A	300-400 nm	Loading efficiency: 75.3-77.3%, cost-effective	[45]
4	Ceftriaxone	N/A	Chitosan nanoparticles	Ionic gelation	Gram positive and Gram negative bacteria <i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Enterococcus faecalis</i> , <i>P. aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i>	N/A	250 nm	Ceftriaxone encapsulated, sustained release	[46]
5	Cephalexin	N/A	Chitosan nanoparticles	Ionic gelation	<i>S. aureus</i> , <i>P. aeruginosa</i>	N/A	30±15 nm, PDI: 0.2	Synergistic outcome was observed against all of the mentioned bacteria, reduced cytotoxicity, antibiofilm activity	[47]
6	Clarithromycin	N/A	Chitosan nanoparticles	Ionotropic gelation	<i>S. aureus</i> , <i>P. aeruginosa</i>	Ocular drug delivery	152±5 nm	N/A	[48]
7	Ciprofloxacin	N/A	Methacrylated chitosan	Ionic gelation	N/A	Transmucosal drug delivery	206 ± 9 nm	N/A	[49]
8	Erythromycin	Hydroxyapatite	Chitosan nanoparticles	N/A	<i>Bacillus cereus</i> , <i>Salmonella enterica</i>	Osteomyelitis treatment	100-200 nm	Non-toxic in blood erythrocyte and chorioallantoic membrane	[50]
9	Gemifloxacin	N/A	Chitosan nanoparticles	Ionic gelation	<i>S. aureus</i> , <i>P. aeruginosa</i>	Ocular drug delivery	158.4 nm	Prolonged residence time	[51]
10	Gentamicin	Collagen, Cerium hydroxyapatite	Fluorescence chitosan nanocomposites	Hydrothermal	<i>E. coli</i>	N/A	N/A	<i>In-vitro</i>	[52]
11	Gentamicin	N/A	Chitosan nanobiocomposites	Ionic gelation	N/A	Wound healing, skin repair	151–212.9 nm	The entrapment efficiency range: 36.6–42.7% w/w, <i>in-vitro</i> and <i>in-vivo</i> study	[53]

No.	Antibiotic	Other ingredients	Chitosan derivative	Preparation method	Bacterial species	Application	Particle size	Note	Ref.
12	Levofloxacin	N/A	Chitosan nanoparticles	Ionic gelation	<i>S. aureus</i> , <i>P. aeruginosa</i>	Ocular drug delivery	79.64 ± 2.18 nm– 456.24 ± 6.26 nm, PDI: 0.228 ± 0.01– 0.484 ± 0.04	N/A	[54]
13	Levofloxacin	Sulfobutyl-ether-β-cyclodextrin	Chitosan nanoparticles	Ionic gelation	<i>P. aeruginosa</i> , <i>E. coli</i>	Ocular drug delivery	80-170 nm, PDI: 0.2	High positive zeta potential which ensures the interaction of nanoparticles with the negatively charged ocular surface	[55]
14	Linezolid	N/A	Chitosan nanoparticles	Ionic gelation	<i>Bacillus subtilis</i> , <i>S. aureus</i> , <i>Streptococcus pneumoniae</i> , Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Ocular drug delivery	213.7 nm, PDI: 0.387	1.4-1.6 times improved antibacterial activity	[56]
15	Metronidazole	N/A	Chitosan nanoparticles	Ionic gelation	<i>Entamoeba histolytica</i>	Colon target delivery (treatment of amoebiasis)	558.06 ± 2.52 nm	Sustained release	[57]
16	Metronidazole	N/A	Chitosan nanoparticles	N/A	<i>Clostridium perfringens</i>	Wound infections	73-163 nm PDI: 0.3-0.6	Non-hemolytic and non-cytotoxic	[58]
17	Moxifloxacin	Pectin cationic polyelectrolyte	Chitosan nanocapsules	N/A	<i>S. aureus</i>	Ocular drug delivery (bacterial keratitis)	242.0 ± 0.30 nm	Sustained release, improved the corneal adhesion	[59]
18	Mupirocin	Polyallylamine hydrochloride, pectin	Quaternized chitosan nanoparticles	N/A	N/A	Wound healing, skin repair Skin and wound healing, treatment of infections in orthopedic surgery	66.05 nm	Biocompatible, sustained release	[60]
19	Teicoplanin	Polyethylene oxide	Chitosan nanofibers	N/A	<i>S. aureus</i>	Wound healing, skin repair Skin and wound healing, treatment of infections in orthopedic surgery	Diameter: 601.80 ± 135.99 nm	Cytotoxicity was not observed for human fibroblasts, <i>In vivo</i> studies showed safety	[61]
20	Tetracycline	N/A	Chitosan nanoparticles	N/A	<i>Porphyromonas gingivalis</i>	Periodontitis	30-50 nm	Reducing bacterial resistance	[62]
21	Tobramycin	N/A	Thiolated chitosan nanoparticles	Ionic gelation	<i>P. aeruginosa</i>	Ocular drug delivery	73 nm	The thiol group increases the permeability	[63]

### Antifungal agents

Unfortunately, fungal infections have emerged as an increasing threat to global public health. These infections encompass various clinical forms, including superficial, cutaneous, subcutaneous, mucosal, and systemic manifestations. With increasing resistance to antifungal agents, fungal infections are becoming increasingly challenging to manage and treat. The primary mechanisms underlying fungal drug resistance involve physiological adaptations and genetic mutations [64].

*Aspergillus*, *Cryptococcus*, and *Pneumocystis* species are among the most common opportunistic fungal pathogens. Such infections predominantly occur in immunocompromised patients, including those with diabetes, AIDS, extensive skin burns, or those undergoing chemotherapy [65]. Each year, approximately 6 per 100,000 individuals develop an invasive fungal infection, and nearly half of these cases remain undiagnosed during the patient's lifetime [66]. During the COVID-19 pandemic, hospitalized patients frequently developed opportunistic fungal co-infections caused by *Aspergillus*, *Mucorales*, and *Candida* species,

among which *Candida auris* emerged as the most significant pathogen [67].

The treatment of fungal infections remains one of the most challenging issues in modern medicine. Only a limited number of antifungal agents are currently available, leading to prolonged treatment durations and increased drug resistance [68]. The high toxicity, narrow spectrum of activity, and difficulties associated with discovering new antifungal drugs have further restricted the development of effective therapeutics. Because fungi and humans are both eukaryotic organisms, identifying antifungal agents that selectively target fungi without inducing adverse effects on human cells remains particularly challenging [69].

Amphotericin B is one of the most potent antifungal drugs used in the treatment of systemic fungal infections and leishmaniasis; however, its clinical application is limited by severe toxicity and adverse side effects [70]. One of its most significant side effects, nephrotoxicity, was shown in a study to be significantly reduced when amphotericin B was encapsulated within chitosan–dextran nanoparticles (NPs) [71]. Similarly, another study demonstrated that chitosan–chondroitin NPs effectively delivered amphotericin B with markedly reduced toxicity [72]. A summary of the antifungal agents encapsulated in chitosan-based nanocomposites (NCs), along with their key formulation features and therapeutic highlights, is presented in Table 2.

Table 2. Chitosan-based nanocomposites and nanomaterials for drug delivery of antifungal agents

No.	Antifungal agent	Other ingredients	Chitosan derivative	Preparation method	Fungal species	Application	Particle size	Note	Ref.
1	Amphotericin B	N/A	Trimethyl chitosan nanoparticles	Ionic gelation	<i>Candida albicans</i>	Oral drug delivery	365±10 nm, PDI: 0.4	Release profile based on the Higuchi model, reducing cytotoxicity and the adverse effect	[73]
2	Amphotericin B	N/A	Sulfated chitosan nanoparticles	N/A	<i>Candida glabrata</i>	N/A	310 ± 14 nm	Safe and nontoxic, specific delivery of drug to macrophages for treatment of fungemia	[74]
3	Amphotericin B	N/A	Trimethyl chitosan nanoparticles	Ionic gelation	N/A	Wound care applications	202.1 nm	Mucoadhesive delivery system, controlled drug release	[75]
4	Amphotericin B	Silk fibroin	Chitosan nanoparticles	N/A	<i>Fusarium solani</i>	Fungal keratitis, Ocular drug delivery	220 nm	Prolonged ocular residence time	[76]
5	Clotrimazole	N/A	N-(2-hydroxy)propyl-3-trimethylammonium, O-palmitoyl chitosan nanoparticles	N/A	<i>Candida</i> spp.	Vaginal drug delivery (topical treatment of vulvovaginal candidiasis)	280 nm	Enhanced epithelial drug permeability, pH-independent sustained drug release	[77]
6	Clotrimazole	Lecithin	Chitosan nanoparticles	Direct injection method	<i>C. albicans</i>	Treatment of fungi-infected wounds	189 nm	The use of lecithin in chitosan nanoparticles as a lipophilic core improves the low solubility and permeability of clotrimazole	[78]
7	Clotrimazole	N/A	Chitosan nanoparticles	Ionic gelation	N/A	Vaginal drug delivery	101.7 nm, PDI: 0.108	Encapsulation efficiency: 98.36%	[79]
8	Fluconazole	Albumin	Chitosan nanocomposites	N/A	<i>C. albicans</i>	Vaginal drug delivery	60 -100 nm	Stable and sustained drug release, 7-14% toxicity on human HGF normal cells	[80]
9	Fluconazole	N/A	Chitosan nanoparticles	Spontaneous emulsification and cross-linking	N/A	Ocular drug delivery	152.85±13.7 nm	Sustained drug release	[81]
10	Fluconazole	Poly(lactico-glycolic acid) (PLGA)	Chitosan nanoparticles	Coacervation	<i>C. albicans, Candida auris</i>	N/A	110 ± 7 nm	Nephrotoxicity and hepatotoxicity was negligible, pH-tuned slow sustained drug release	[82]

No.	Antifungal agent	Other ingredients	Chitosan derivative	Preparation method	Fungal species	Application	Particle size	Note	Ref.
11	Ketoconazole	Polyvinyl alcohol (PVA) film	Quaternized chitosan nanoparticles	Ionic gelation	N/A	N/A	N/A	Entrapment efficiency: 80-90%	[83]
12	Miconazole	N/A	Chitosan nanoparticle gels	Ionotropic gelation	<i>C. albicans</i>	Oral drug delivery (treatment of oral candidiasis in diabetic patients)	54 nm	The effects of this formulation have been investigated in a clinical study with 80 patients and the formulation had a significant effect in improving clinical symptoms	[84]
13	Miconazole	N/A	Chitosan nanoparticles	Ionotropic gelation	<i>C. albicans</i>	Vaginal drug delivery Topical drug delivery	200-300 nm	Similar therapeutic effects to traditional formulations Entrapment efficiency: 98.44%	[85]
14	Terbinafine	Xanthan gum	Chitosan nanoparticles	Polyelectrolyte complexation	N/A	Topical drug delivery (treatment of onychomycosis)	194.28–406.67 nm	this formulation has a better antifungal activity for cutaneous infection as compared to control and marketed formulation	[86]
15	Terbinafine	Poloxamer 407 gel	Chitosan nanoparticles	Nanoprecipitation	N/A	Topical drug delivery (treatment of onychomycosis)	229 ± 5 nm	Sustained drug delivery properties and enhancing drug penetration into the nail plate	[87]
16	Voriconazole	Tween 20, Tween 80, sodium lauryl sulfate, propylene glycol, polyethylene glycol-4000	Chitosan nanoparticles	Spray drying	<i>C. albicans</i>	Topical drug delivery	167- 475 nm	Surfactants and polymers utilized in chitosan nanoparticles enhance permeability, facilitating drug delivery to the skin	[88]
17	Voriconazole	N/A	Chitosan nanoparticles	Ionic gelation	N/A	Ocular drug delivery	N/A	High thermal stability, slow sustained drug release	[89]

### Metallic nanoparticles (MNPs)

Nanoparticles (NPs) are materials with sizes ranging from 1 to 100 nanometers, encompassing various structural forms such as fullerenes, metallic nanoparticles (MNPs), ceramic NPs, and polymeric NPs [90]. Among these, MNPs represent a particularly prominent category, widely recognized for their broad-spectrum antimicrobial properties. Common types of MNPs include silver (Ag), silver oxide (Ag<sub>2</sub>O), titanium dioxide (TiO<sub>2</sub>), copper oxide (CuO), zinc oxide (ZnO), gold (Au), and magnesium oxide (MgO) [91]. Due to their unique physicochemical characteristics—including biodegradability, low toxicity, and high catalytic activity—MNPs have found extensive applications in diverse fields such as drug delivery, tissue engineering, medical diagnostics, and bioimaging [92].

Three key factors determine the antibacterial activity of metallic nanoparticles (MNPs). The first factor is particle size. Reducing the size of MNPs increases their surface area-to-volume ratio, thereby enhancing the generation of reactive

oxygen species (ROS) and improving antibacterial efficacy. The formation of ROS induces oxidative damage to bacterial cell membranes, ultimately leading to cell lysis and death. The second factor is the nanoparticles' surface charge. A higher positive surface charge strengthens the electrostatic interactions between the MNPs and the negatively charged bacterial cell wall, thereby increasing their antibacterial potential. These interactions disrupt the cell membrane integrity, allowing MNPs to penetrate the bacterial cell [93]. The third factor is the particle shape. Although its effect is not yet fully understood, MNPs with sharper edges or corners are generally observed to exhibit greater surface instability, leading to increased generation of reactive oxygen species and, consequently, enhanced antibacterial activity [93, 94].

Metallic nanoparticles (MNPs) can themselves be incorporated into nanocomposite (NC) structures, a strategy that has recently attracted considerable attention due to their extensive use in drug delivery applications [95]. In an animal study using immunosuppressed rats, silver and copper

NPs loaded into chitosan-based NCs exhibited synergistic antifungal activity against *Candida albicans* [96]. In another study, selenium and silver NPs embedded within a chitosan matrix demonstrated reduced toxicity, while silver–chitosan NCs showed strong antibacterial effects against Gram-positive pathogens [97]. Furthermore, comparative analysis of silver NPs and silver–chitosan NCs revealed that both

exhibited antiviral activity against coronaviruses, but the combination with chitosan significantly enhanced the antiviral efficacy [98]. Overall, incorporating MNPs into chitosan-based NCs offers distinct advantages, including reduced toxicity and synergistic antimicrobial effects. A summary of MNPs with antimicrobial activity encapsulated within chitosan nanocomposites, along with their key formulation highlights, is presented in Table 3.

Table 3. Chitosan-based nanocomposites and nanomaterials for drug delivery of metallic nanoparticles with antimicrobial activities

No.	Nanoparticle	Other ingredients	Chitosan derivative	Preparation method	Microbial species	Application	Particle size	Note	Ref.
1	Gold	N/A	Chitosan nanocomposite	Chemical reduction process	<i>Candida albicans</i> , <i>Aspergillus niger</i> , <i>Aspergillus terreus</i> , <i>Aspergillus umigatus</i> , <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i>	Wound healing	20 to 120 nm	Non-toxic to normal skin cells, its antifungal effects against unicellular fungi outweigh multicellular fungi, ability to heal wounds quickly	[99]
2	Gold	N/A	Chitosan nanocomposite	Solvent evaporation	<i>S. aureus</i> , <i>P. aeruginosa</i>	Wound healing	16 ± 4 nm	Non-toxic to human cells, bacterial cell wall degradation (not effective on eukaryotic cells)	[100]
3	Gold	N/A	Chitosan nanocomposite	Solvent evaporation	<i>S. aureus</i> , <i>Escherichia coli</i>	Reducing bacterial infections and respecting the integrity of mammalian cells	14 ± 5 nm	Non-toxic to human cells, displaying high selectivity	[101]
4	Iron	N/A	Chitosan nanoparticles	A surfactant-assisted chitosan chelating Fe <sup>2+</sup> , Fe <sup>3+</sup> and ionic gelation	<i>E. coli</i> , <i>S. aureus</i> , <i>C. albicans</i>	Food preservative	206.4 and 195.2 nm	N/A	[102]
5	Magnesium	N/A	Chitosan nanocomposites	N/A	<i>Acidovorax oryzae</i> , <i>Rhizoctonia solani</i>	Plant disease management	29 -60 nm	Antibacterial activity through damaging the structure of cell wall and cellular organelles	[103]
6	Nickel	N/A	Chitosan nanocomposites	Ionotropic gelation	<i>Fusarium solani</i>	Management of rot disease in plants	21 - 124 nm	N/A	[104]
7	Silver	Polycaprolactone	Chitosan nanofibrous	Layer-by-layer electrospinning	<i>S. aureus</i> , <i>E. coli</i>	Wound healing	27 ± 4.3 nm	Super-hydrophilic membrane	[105]
8	Silver	Polyethylene oxide	Chitosan nanofibers	Electrospinning	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	Wound healing, mixed aerobic-	N/A	Rapid released formulation	[106]

No.	Nanoparticle	Other ingredients	Chitosan derivative	Preparation method	Microbial species	Application	Particle size	Note	Ref.
						anaerobic infections			
9	Silver	N/A	Chitosan nanocomposites	N/A	Alfalfa mosaic virus (AMV)	Agriculture (Antiviral activity against plant's pathogen)	11.33 nm	Silver chitosan nanocomposite increases phenolic compounds in the pepper plant, which have antioxidant properties and ultimately cause antiviral effects	[107]
					<i>Fusarium oxysporum</i>			Chitosan silver nanocomposites causes cell death by damaging the membrane and increasing its permeability but have no effect on cell growth or cell growth inhibition	
10	Silver	N/A	Chitosan nanocomposites	Ionotropic gelation, chemical reduction		Agriculture, human opportunistic infections	373 ± 28 nm	The efficacy of the formulation has been tested on albino Wistar rats	[108]
11	Silver	Fibrin	Chitosan nanocomposites	Freeze drying	<i>P. aeruginosa, E. coli, S. aureus, Lactobacillus bulgaricus</i>	Wound healing	N/A	Increased antimicrobial effect due to the addition of aminophosphate chain	[109]
12	Silver	N/A	Three α-aminophosphate-chitosan nanocomposites	Eco-friendly solid-state	<i>Streptococcus mutans, P. aeruginosa, C. albicans, Rhizopus oryzae</i>	N/A	30.4 nm		[110]
13	Silver, Copper	N/A	Chitosan nanocomposites	N/A	<i>P. aeruginosa, Acinetobacter baumannii, S. aureus, Staphylococcus epidermidis, C. albicans</i>	N/A	70-120 nm	N/A	[111]
14	Silver, Copper	N/A	Chitosan nanocomposites	N/A	<i>C. albicans</i>	N/A	44-55 nm	The combination of silver, copper, and chitosan nanocomposite creates a synergistic effect, resulting in increased antifungal effect	[112]
15	Silver, Fe <sub>3</sub> O <sub>4</sub>	Polyvinyl alcohol	Chitosan nanocomposites	One-pot	<i>E. coli, S. aureus</i>	Wound healing	N/A	Destruction of bacterial cell walls, non toxic	[113]
16	Titanium dioxide	N/A	Chitosan nanocomposite films	N/A	<i>S. aureus, E. coli, Salmonella typhimurium, Pseudomonas spp, Aspergillus spp, Penicillium spp</i>	Food packaging and preservative	N/A	N/A	[114]
17	Titanium dioxide	N/A	Chitosan nanocomposite	Ionic gelation	<i>E. coli, Proteus mirabilis,</i>	N/A	85 ± 2 nm	High cytotoxicity	[115]

No.	Nanoparticle	Other ingredients	Chitosan derivative	Preparation method	Microbial species	Application	Particle size	Note	Ref.
				(Chitosan nanoparticle)	<i>S. aureus</i> , <i>S. epidermidis</i>			against HepG2 human liver cancer cell, DNA binding through groove binding mode	
18	Zinc	N/A	Chitosan nanocomposites	Bio-inspired (using <i>Solanum lycopersicum</i> leaf extract)	<i>S. aureus</i>	Skin infection	21–47 nm	The nanocomposite incorporated cotton fabrics	[116]
19	Zinc	N/A	Chitosan nanocomposites	Green route (using pure bioflavonoid rutin)	<i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>S. aureus</i> , <i>B. subtilis</i>	N/A	20 to 150 nm	Photocatalyst for dye degradation, better antibacterial effects against Gram-negative bacteria compared to Gram-positive bacterial pathogens	[117]

### Combination of antimicrobial agents

Chitosan demonstrates remarkable versatility as a drug carrier, with the proven ability to efficiently encapsulate multiple therapeutic agents simultaneously [118, 119]. The effectiveness of antimicrobial therapy is often enhanced when two or more agents are used in combination, compared with a single agent, primarily due to synergistic interactions. In one study, colistin and meropenem were co-loaded into chitosan–polyvinyl alcohol (PVA) nanofibers, resulting in synergistic antibacterial effects and enhanced overall activity. In addition to their efficacy in wound healing, these nanofibers demonstrated excellent cytocompatibility with fibroblasts. Notably, the synergistic antibacterial activity was explicitly observed against extensively drug-resistant (XDR) *Acinetobacter baumannii*. This enhanced effect was attributed to the combined action of the two antibiotics along with the intrinsic properties of the chitosan nanofiber matrix [120].

Combining an antimicrobial agent with a metallic nanoparticle (MNP) can offer significant advantages. Selenium nanoparticles (SeNPs), for instance, possess inherent antibacterial activity, but when used in conjunction with another antimicrobial agent, their efficacy can be further enhanced. Selenium disrupts the bacterial cell wall and induces the generation of reactive oxygen species (ROS), both of which facilitate nisin penetration by compromising the bacterial membrane's integrity. In one study, selenium and nisin were co-loaded into chitosan nanocomposites

(NCs), resulting in synergistic antimicrobial effects against both Gram-positive and Gram-negative intestinal bacteria [121]. A summary of antimicrobial agent combinations with potential for delivery through chitosan-based NCs, along with their key formulation characteristics, is presented in Table 4.

Various antiviral agents can also be incorporated into chitosan-based nanocomposites (NCs). For instance, acyclovir faces challenges in topical formulations due to its polarity, limited solubility, and poor bioavailability. In a study, Donalisio et al. developed chitosan nanospheres conjugated with acyclovir, achieving a loading capacity of 8.5%. The resulting nanosystem exhibited controlled drug release and permeation, along with superior efficacy against herpes simplex virus (HSV) strains compared to the free drug. Importantly, no antiproliferative or cytotoxic effects were observed [130]. In another study by the same authors, a sulfobutyl ether- $\beta$ -cyclodextrin (SBE- $\beta$ -CD)-decorated chitosan nanodroplet system was formulated for vaginal topical therapy of HSV type 2. This nanocarrier demonstrated high encapsulation efficiency (~97%) and sustained drug release. The enhanced intracellular accumulation of acyclovir in the nanoformulation, compared to the conventional sample, was likely responsible for its improved antiviral efficacy [131]. Similar beneficial effects have been reported for valacyclovir. In these nanocarriers, SBE- $\beta$ -CD enhances both stability and mucoadhesiveness [132].

Table 4. Chitosan-based nanocomposites and nanomaterials for drug delivery of multiple antimicrobial agents simultaneously

No.	Combination	Other ingredients	Chitosan derivative	Preparation method	Microbial species	Application	Particle size	Note	Ref.
1	Silver, Eugenol	N/A	Alginate-chitosan nanocomposite	N/A	<i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Klebsiella</i> , <i>Staphylococcus aureus</i>	Wound healing	30 nm	Increased anti-inflammatory, antioxidant, and antibacterial properties due to the presence of silver nanoparticles coated with eugenol	[122]
2	Selenium, nisin	N/A	Thiolated chitosan nanoparticles	N/A	<i>Vibrio cholera</i> , <i>Campylobacter jejuni</i> , <i>Salmonella enterica</i> subsp, <i>Shigella dysenteriae</i> , <i>E. coli</i> , <i>Listeria monocytogenes</i> , <i>S. aureus</i>	Enteric pathogens	136.26 ± 4 3.178 nm	Immunomodulatory effects, cytotoxic effects on Caco-2 cells	[121]
3	Silver, Bromelain	Polycaprolactone	Chitosan nanofibrous gel-based	Electrospray	<i>E. coli</i> , <i>S. aureus</i>	Wound healing	176 ± 63 nm	Accelerates wound healing based on animal studies (Male Wistar rats) The antifungal effects of green propolis and the adhesion properties of chitosan to mucosal tissues have increased the antifungal effect.	[123]
4	Fluconazole, green propolis	N/A	Chitosan nanoparticles	Ionic gelation	<i>Candida albicans</i>	Vulvovaginal candidiasis	316.5 nm	pH-sensitive controlled release formulation, antibacterial effect under the combined application of photothermal (PTT) and photodynamic therapy (PDT), Light irradiation generates active oxygen radicals within the formulation, which exhibit antibacterial properties	[124]
5	Gold, curcumin	N/A	Chitosan nanoparticles	Electrostatic adsorption	<i>E. coli</i> , <i>S. aureus</i>	N/A	N/A	and photodynamic therapy (PDT), Light irradiation generates active oxygen radicals within the formulation, which exhibit antibacterial properties	[125]
6	Gold, <i>Punicagranatum</i> L. extract	N/A	Chitosan nanoparticles	N/A	Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	N/A	N/A	Physicochemical properties were enhanced	[126]
7	Clotrimazole, Egyptian <i>Vitis vinifera</i> juice	N/A	Chitosan nanoparticles	Ionic gelation, Incorporation	<i>C. albicans</i> , <i>Aspergillus niger</i>	Wound healing, anti-dermatophytic agent	35.4 nm, PDI: 0.24	Synergistic effect, accelerates wound healing based on animal studies ( <i>Rattus norvegicus albinus</i> )	[127]
8	Clotrimazole, natamycin	Poly (lactico-glycolic acid) (PLGA)	Chitosan nanoparticles	Co-Electrospinning, electrospray	<i>C. albicans</i>	Ocular delivery	309-406 nm	Sustained drug release	[128]
9	Gentamicin, ascorbic acid	N/A	Chitosan nanoparticles	Ionotropic gelation	<i>S. aureus</i> , <i>Pseudomonas aeruginosa</i>	N/A	278 nm	Ascorbic acid increases cell permeability to antibiotics by generating hydrogen peroxide and can reduce the effect of bacterial resistance genes by interfering with protein synthesis	[129]

Furthermore, chitosan has proven to be effective as a carrier for antiviral agents such as saquinavir, used in the treatment of COVID-19 and AIDS. In addition to its carrier function, chitosan and its derivatives possess intrinsic antiviral properties, likely through neutralization of the positive charge on pathogen surface receptors, thereby preventing their attachment to host cell surfaces [133].

Toxins with antibacterial properties can also be incorporated into chitosan-based formulations for the treatment of infectious diseases such as acne vulgaris. For instance, melittin, a major component of bee venom, can be integrated into the structure of chitosan nanofibers. This composite demonstrates favorable physicochemical characteristics and exhibits significant antimicrobial activity, along with anti-inflammatory effects that reduce redness and inflammation in both in vitro and animal models [134]. Another example involves chitosan nanoparticles (NPs) loaded with amphotericin B via ionic gelation, achieving an encapsulation efficiency of 88%. This nanocarrier has shown promising efficacy against the *Leishmania tropica* parasite [135].

#### **Future perspective**

The positive charge of chitosan is crucial to its antimicrobial activity. Chitosan is a potent antimicrobial agent that inhibits the growth and proliferation of bacteria, fungi, and yeasts. Its mechanisms of action are primarily attributed to the electrostatic interactions between the positively charged amino groups of chitosan and the negatively charged components of microbial cell membranes, leading to disruption of membrane integrity and altered permeability. In addition, by interacting with metal ions in the cell wall, chitosan can stimulate the generation of toxic reactive species, ultimately leading to cell death. Chitosan also chelates essential metal ions that are required for cellular metabolism and growth regulation. Furthermore, it binds to the cell's genetic material, thereby inhibiting transcription and protein synthesis. Another mechanism involves the induction of oxidative stress through the formation of reactive oxygen species. Its antifungal efficacy is also demonstrated by its ability to inhibit spore germination and prevent fungal reproduction. Collectively, these actions disrupt critical cellular processes, ultimately leading to the suppression of microbial growth or cell death [136, 137].

In recent years, chitosan has also been utilized in vaccine formulations as a stabilizing agent and

preservative. In one study, tetanus toxoid was encapsulated within chitosan nanospheres to evaluate its immunogenicity. Animal experiments demonstrated significantly higher immunoglobulin G (IgG) titers in the group vaccinated with the chitosan-based nanoformulation compared to the control. Moreover, chitosan exhibited greater growth-inhibitory activity against *Escherichia coli* than thimerosal [138]. Similarly, polio vaccines have been successfully formulated using chitosan and trimethyl chitosan nanoparticles (TMC-NPs), which provide excellent stability and biocompatibility [139].

The importance of chitosan in wound dressing applications has increased significantly in recent years. For instance, chitosan-based nanoscaffolds have shown great potential for the development of antileishmanial wound dressings, contributing to effective ulcer healing [140]. Among these nanostructures, nanofibers are particularly promising due to their broad applicability. Compared with native chitosan, chitosan nanofibers exhibit distinct features, including smaller size, higher porosity, and enhanced drug-loading capacity, making them ideal candidates for drug delivery and wound-healing applications [141, 142]. Various fabrication techniques have been employed to produce these nanostructures, including electrospinning, thermally induced phase separation, ultrasonication, self-assembly, and chemical synthesis [143-145]. Nanofibers composed solely of chitosan generally exhibit limited wound-healing efficacy. However, electrospinning enables modification of their physicochemical properties through blending with other polymers, thereby producing membranes with improved mechanical strength and cell-binding ability. Commonly used polymers combined with chitosan include polycaprolactone (PCL), polyethylene oxide (PEO), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) [146]. The porous architecture of nanofibers facilitates gas exchange and water-vapor permeability, both of which promote more effective wound healing [147]. The mechanisms underlying this effect may include hemostatic activity via red blood cell binding and blood-loss prevention [141], enhanced neutrophil migration to injured tissues, and stimulation of fibroblast collagen synthesis [145]. In one study, chitosan/PEO nanofibers electrospun and loaded with moxifloxacin demonstrated significant wound-healing and antibacterial effects [148]. Another formulation incorporating norfloxacin, 2-formylphenylboronic acid, and imino-quaternized chitosan nanofibers exhibited

superior antimicrobial activity against *Staphylococcus aureus* and *Candida glabrata*, thereby accelerating wound healing [149]. Beyond biomedical applications, chitosan-based nanostructured films—owing to their antioxidant, antibacterial, and biodegradable properties—have also been introduced as promising candidates for the food packaging industry. Nevertheless, chitosan alone presents challenges such as a strong cationic nature and high crystallinity, which often necessitate combination with other materials to optimize performance [150]. Notably, these nanofibers have demonstrated antimicrobial activity against *Escherichia coli*, *Salmonella enterica* serovar Typhimurium, *S. aureus*, and *Listeria innocua* in food products, thereby extending the shelf life of meat [151].

## CONCLUSIONS

This review highlights the significant advantages of employing chitosan-based nanomaterials for the drug delivery of antimicrobial agents. Structural modifications of chitosan—such as adjustments in molecular weight, surface charge, and degree of deacetylation—can tailor its physicochemical properties, making it highly suitable for diverse pharmaceutical formulations, including vaginal, ophthalmic, intestinal, and wound-healing systems. These formulations are generally non-toxic, exhibit excellent biocompatibility, and provide sustained drug release. The incorporation of chitosan into antibiotic delivery systems not only facilitates targeted transport of the active compound to specific tissues but also enhances antimicrobial activity against both Gram-positive and Gram-negative bacteria, particularly multidrug-resistant strains such as Methicillin-resistant *Staphylococcus aureus* (MRSA). Similarly, the use of chitosan in antifungal drug delivery offers substantial benefits by minimizing side effects and improving antifungal efficacy. Chitosan-based nanocomposites (NCs) also enable the effective delivery of metallic nanoparticles (MNPs), which enhance drug solubility, provide synergistic antimicrobial effects, and enable controlled release, making them highly valuable for wound-dressing applications. Moreover, these nanosystems are versatile platforms capable of co-delivering multiple therapeutic agents, allowing synergistic outcomes in combination therapy. In addition to antibiotics and antifungals, toxins and antiviral compounds are emerging as potential candidates for encapsulation within chitosan nanomaterials to improve their safety and therapeutic performance. In conclusion, chitosan is a highly promising biopolymer with

exceptional drug delivery capabilities. Its unique combination of biocompatibility, biodegradability, mucoadhesive properties, and inherent antimicrobial activity positions it as an ideal candidate for the development of advanced therapeutic systems to overcome biological barriers and combat antibiotic resistance.

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## AUTHOR CONTRIBUTION

**YH:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **JM:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **VS:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **RM:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **BSFB:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

## CONFLICTS OF INTEREST

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

## DATA AVAILABILITY

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

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During the preparation of this work, we did not use any artificial intelligence tools except for grammar and spelling corrections (ChatGPT). After using this, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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