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Review

Engineering chitosan-functionalized liposomes for targeted drug delivery and biomedical applications

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ABSTRACT

Chitosan (CS) is a naturally derived cationic polysaccharide that has attracted sustained interest in drug delivery due to its favorable biocompatibility, biodegradability, and chemical versatility. Liposomes are well-established lipid-based nanocarriers capable of encapsulating both hydrophilic and hydrophobic therapeutics; however, their clinical performance is often compromised by limited physicochemical stability, premature drug leakage, rapid clearance, and insufficient interaction with biological barriers. Surface functionalization of liposomes with CS has emerged as an effective hybridization strategy that integrates the structural advantages of lipid bilayers with the mucoadhesive, stabilizing, and tunable surface properties of CS. This review systematically summarizes the design rationale, fabrication methods, and physicochemical characteristics of CS-functionalized liposomes, with particular emphasis on how CS coating influences colloidal stability, drug loading efficiency, release kinetics, and interactions with cells and tissues. The preparation strategies for both CS nanoparticles and liposomes are discussed to provide a foundation for understanding the formation and optimization of CS–liposome hybrid systems. In addition, the impact of CS functionalization on different administration routes, including intravenous, ocular, nasal, transdermal, and oral delivery, is critically examined. The biomedical applications of CS-functionalized liposomes are comprehensively reviewed, covering cancer therapy, antimicrobial treatment, antioxidant and anti-inflammatory interventions, phototherapy, wound healing, and the management of fibrotic and inflammatory lesions. Across these applications, CS coating is shown to enhance liposomal stability, bioadhesion,

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cellular uptake, and controlled or stimuli-responsive drug release, while also providing a versatile platform for further functionalization with targeting ligands or responsive moieties. Overall, CS-functionalized liposomes represent a flexible and multifunctional drug delivery platform that addresses key limitations of conventional liposomes and CS nanoparticles when used independently. By combining lipid-based encapsulation with polymer-mediated stabilization and targeting, these hybrid systems hold considerable promise for the development of next-generation nanomedicines and translational biomedical applications.

1. Introduction

1.1. An overview of chitosan

Chitin is distinguished as an excellent nitrogen source for various classes of living things, both on land and in the water [1–3]. The exoskeletons and interior components of several invertebrates, including arthropods such as spiders, crabs, and insects, have been found to contain high levels of chitin [4]. Structurally, chitin is made up of *N*-acetyl-2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-D-glucose residues linked together in a β chain [1]. The high crystalline characteristics of chitin result from the presence of hydrogen bonds between the acetamido groups, causing low water solubility [5,6]. Additionally, fully deacetylated chitin dissolves in water [7,8]. The deacetylation of chitin may be a mechanism for improving water solubility. Chitin possesses a molecular weight of up to 1–2.5 × 10^1 Da and a degree of deacetylation of less than 10%, which is in line with a degree of polymerization of about 5000–10,000 monomeric residues [9]. The primary byproduct of *N*-deacetylation of chitin with a hot alkali is CS (Fig. 1) [10]. Another point to consider is that the molecular weight of CS can range from 5 × 10^1 Da to 2 × 10^4 Da, and the degree of deacetylation can be in the range of 40% to 98% [11]. CS gains free amino functional groups through deacetylation, which can be used to protonate it, making it more polymer-solubilizing, or chemically reacted and grafted to create novel CS derivatives with targeted biological and physical characteristics.

CS is a polysaccharide, and it is highly adaptable for targeted medicinal or pharmacological modification due to its multiple functional groups, including N—H and OH- [12]. To create polyelectrolyte complexes, the cationic amino groups at the C2 position of CS repeating units easily engage electrostatically with anionic groups of other polyions [13]. To impart specific drug delivery features, CS has been complexed with a wide variety of natural and synthetic polyanions, including pectin, alginate, xanthan gum, carrageenan, chondroitin sulfate, carboxymethyl cellulose, hyaluronic acid, and dextran sulfate [14–16]. Nanocarriers with the desired sizes and zeta potentials can be created from CS by adjusting their molecular weight and degree of deacetylation [17]. Additionally, CS, being a plastic substance, can be molded into amorphous shapes [18]. The molecular chains can be compacted to the nanoscale through hydrogen bonding, electrostatic interactions, and van der Waals forces, depending on the processing and formulation circumstances [19]. The mucoadhesive and viscous properties of CS, a polysaccharide, are crucial for the encapsulation, release, and regulation of drug absorption kinetics [16]. As a cationic polyelectrolyte, CS can bind strongly to the sialic acid and O-sulfosaccharide-rich, negatively charged mucosal interface [19]. By releasing calcium from calcium channels within the epithelial cells, CS diminishes the electrical resistance across the epithelial membrane [20]. The Protein Kinase C pathway can facilitate paracellular and transcellular drug transport by

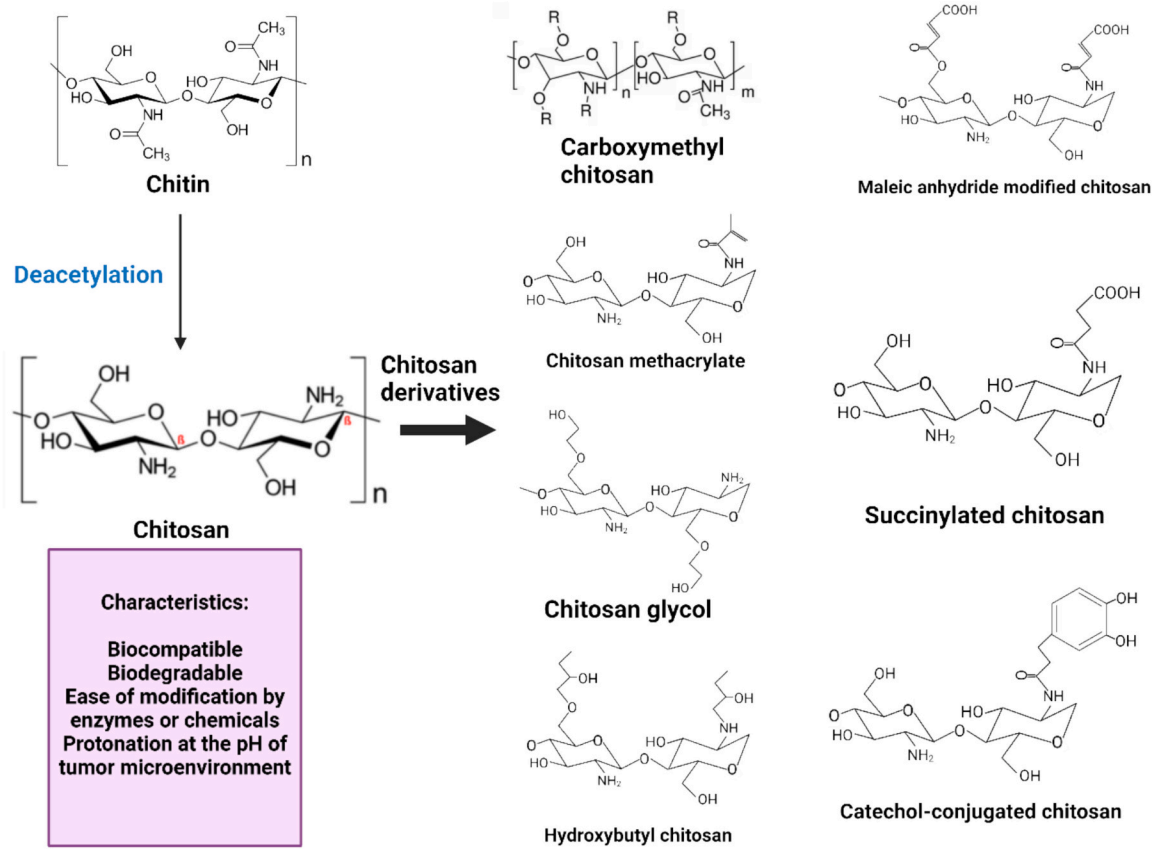

Fig. 1. Schematic illustration of chitin deacetylation to form chitosan and its key properties relevant to nanoscale drug delivery and surface functionalization.

loosening the mucosal tight junction and transferring tight junction proteins to the cytoskeleton [21–23].

1.2. Biomedical applications of chitosan

Additionally, CS is listed as not only biodegradable but also biocompatible [24,25]. It has a significant number of applications as a medicinal agent, including the suppression of carcinogenesis [26,27], antibacterial properties [28–30], antifungal properties [31–33], the amelioration of oxidative stress [34], the alleviation of inflammation [26], and antidiabetic effects [26]. In cancer nanomedicine, the size, shape, surface charge, surface morphology, nature, and availability of targeting ligands are some of the physicochemical attributes of CS-based drug carriers that are determined to have a significant impact on the efficacy of cancer therapeutics in terms of cell targeting, internalization, and antitumor action [27,28]. The uptake by cancer cells is facilitated by positively charged nanocarriers with a reduced surface area and an increased attraction for the negatively charged surfaces of cancer cells. Poor bioavailability of therapeutics, resulting from insufficient ligand or steric obstruction from overcrowding ligands in receptor binding, occurs when a suboptimal or excessive fraction of the targeted ligand is used, leading to inadequate contact between the nanocarrier and the cancer cell surface receptor. When it comes to infectious nanomedicine, the results are rather similar. Since tubercle bacilli attracts alveolar macrophages, it is crucial to target these cells when treating infectious disorders, such as pulmonary tuberculosis [29]. More opsonization by macrophages is performed on the hydrophobic carrier. The transport of drugs into macrophages across transmembrane channels can be impeded by nanocarriers composed of CS with high molecular weight or viscosity [30]. When attached to the extracellular membranes of macrophages, this nanocarrier can form a thick film that prevents drugs from diffusing or entering the cell through endocytosis.

One of the most notable features of CS is its lack of inflammation and immune responses [31]. CS nanoparticles and CS generated from succinyl both have minimal levels of toxicity [32–34]. This is true regardless of the molecular weight or degree of deacetylation of the CS. The bactericidal and bacteriostatic characteristics of CS solutions are typically attributed to the polymer's cationic nature. A polymer chain with a positive charge can cling to the surface of bacteria, altering their membrane permeability and, hence, inhibiting their capacity to multiply [35]. Furthermore, CS with a low pH and little deacetylation is more effective against microbes. As the molecular weight decreases, the antibacterial effects on Gram-negative bacteria are amplified, while those on Gram-positive bacteria are reduced. Due to its broad-spectrum antibacterial effect against both types of bacteria, as well as its contact with the bacterial cell wall, CS and its derivatives have a high killing rate [36]. CS may interact with bacterial cells via their hydrophilic cell walls, which may explain why it is less hazardous to mammalian cells [37].

Antioxidants play a critical role in maintaining cellular redox homeostasis. They prevent the decomposition of cell membrane lipids, proteins, and DNA by reactive oxygen radicals [38]. CS and its byproducts can neutralize oxygen-free radicals. Low-weight CS molecules are preferred instead of high-weight CS molecules for free radical elimination [39]. CS may possess antioxidant properties due to its amino and carboxyl groups, which help stabilize free radicals [40]. In living organisms, bioenzymes can depolymerize CS. The breakdown products, which include glucosamine and *N*-acetylglucosamine, pose no health risks to humans. Neither immunogenicity nor the buildup of degradation intermediates is observed in the human body. New studies employing in vitro and in vivo models have demonstrated that CS and its derivatives have anticancer properties. CS derivatives' anticancer effects are due to cytolytic T-lymphocyte maturation and infiltration, stimulated by upregulation of interleukin (IL)-1 and 2 secretion [41]. Research on blood clotting has extensively utilized CS, as CS can accelerate wound healing by interacting with platelets and the amino groups of CS [42]. The hemostatic features of CS make it promising for application in wound healing. These features include chemotaxis, macrophage and neutrophil activation, re-epithelialization, and acceleration of granulation tissue, as well as contraction and limited scar formation, analgesic effects, hemostasis, and intrinsic antibacterial properties [43]. Additionally, CS exhibits several notable properties, one of which is its adhesiveness. Adsorbing compounds without an affinity for mucus is another benefit of this property, which also facilitates the development of new methods for delivering beneficial chemicals through mucosal routes [44]. CS aids in opening the tight epithelial junction by increasing the adhesivity of polymers via penetration [45]. Collectively, these properties highlight the broad relevance of CS in biomedical applications. Fig. 2 shows an overview of the biomedical application of CS-based structures.

Several reviews have previously discussed CS-based nanocarriers or liposomal drug delivery systems separately. However, a comprehensive and up-to-date analysis focusing specifically on CS-functionalized liposomes as hybrid nanoplatforms remains limited. In contrast to earlier reports, the present review systematically integrates recent advances, with particular emphasis on the design principles, functional advantages, and biomedical applications of CS–liposome hybrids. Importantly, this review provides a comparative perspective, highlighting how CS-coated liposomes outperform CS nanoparticles or conventional liposomes alone in terms of stability, targeting capability, controlled release, and therapeutic versatility. By covering emerging applications beyond oncology, such as bone regeneration, cardiovascular therapy, phototherapy, wound healing, and inflammation, this work aims to update and expand upon prior reviews and to offer a unified framework for the rational design of next-generation chitosan-functionalized liposomal systems.

2. Chitosan administration routes

2.1. Ocular

Due to its biocompatibility, CS is suitable for ocular medication delivery [46]. With mucoadhesive properties, CS can prolong the time medications remain on the eye surface [47]. It has advantages in situ gelling capabilities; thus, it can also solidify when applied to the eye

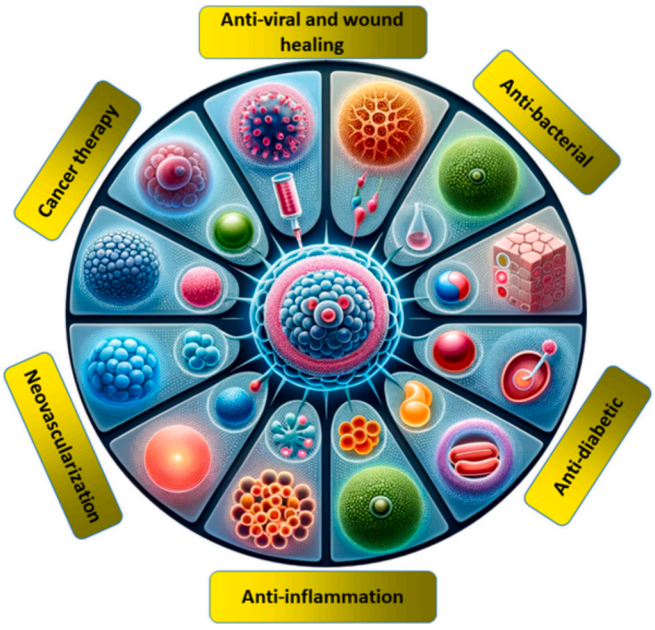

Fig. 2. Overview of the main biomedical applications of chitosan-based structures, including cancer therapy, angiogenesis, inflammation control, diabetes management, wound healing, and antimicrobial treatment.

surface in a liquid state. As a result, ocular medications have become more effective in their therapeutic roles. Notably, CS-based nanoparticles can enhance the bioavailability of drugs like naringenin in the aqueous humor, making them a possible substitute for ocular pharmaceuticals that are not very soluble. The experiment on rabbit eyes demonstrated the biocompatibility of CS, with no signs of irritation [48].

2.2. Pulmonary

Pulmonary delivery offers advantages such as both local and systemic effects, high efficacy, and the option for short- and long-term drug administration. Lungs with a large surface area, plenty of blood vessels, and a porous absorption barrier are ideal for transporting medications [49]. The anti-tubercular drug rifampicin was developed as a CS-based dry nanoparticle powder for inhalation. Without harming cells or organs, this creation showed continuous drug release for 24 h [50]. The anti-tubercular drug prothionamide was administered by loading on CS nanostructures via the pulmonary system. The half-life of the medication inhaled into the lungs was increased by this modification [51].

2.3. Nasal

Nasal delivery is a non-invasive option for systemic and local pharmaceutical administration that circumvents the typical gastrointestinal issues and hepatic metabolic consequences associated with oral administration [52]. The blood-brain barrier (BBB) is an effective conduit for drug transfer from the nose to the brain (N2B). The nasal epithelium presents a significant barrier to hydrophilic drugs, nucleic acids, proteins, and peptides due to its low permeability; however, CS makes them more permeable. The efficiency with which a medicine is absorbed through the nasal passages depends heavily on its molecular weight, lipophilicity, and charge. The mucociliary system clears medications that cannot pass through the nasal membrane. The mucoadhesion characteristics, low toxicity, biodegradability, and biocompatibility of CS (as a result of its nasal delivery) may mitigate this concern [52].

Additionally, the blood-cerebrospinal fluid barrier and the BBB prevent molecules with a significant molecular weight from entering the brain. Despite these obstacles, N2B delivery has emerged as a critical approach for drug delivery to specific brain regions in recent years. The CS-functionalized human serum albumin nanostructures was designed to transport the anti-Alzheimer drugs tacrine and R-flurbiprofen from the nasal passages to the brain. Compared to unmodified structures, CS-functionalized nanocarriers demonstrated better mucoadhesion and greater penetrating capacity on ex vivo rabbit nasal mucosa [53].

2.4. Transdermal

The drawbacks of conventional administration techniques inspire the development of a transdermal drug delivery system. When developing transdermal dose forms, the primary challenge is to conquer the skin's restricted permeability. To enhance the transport of therapeutics over the skin, several strategies have been deployed to circumvent its barrier characteristics [54–56]. The application of CS in transdermal patches has been rising [56]. The application of nanostructures can significantly increase the permeability of drugs through the skin. The characteristics of the CS structures that enhance penetration into the mucosa include being mucoadhesive, biocompatible, and biodegradable. They facilitate transdermal medication diffusion by fluidizing the lipid and protein domains of the epidermis and relating to the skin mucosa. Furthermore, they may have therapeutic value for both systemic diseases like diabetes and hyperlipidemia, and local ones, such as skin infections and malignant melanoma [57].

2.5. Dermal

Traditional oral and injection delivery strategies have systemic, undesirable impacts, and topical therapy has been proposed as a solution. The skin and mucous membranes around the affected area might be penetrated quickly and directly by this [58]. Nanostructures can enhance the skin bioavailability of therapeutics through controlled release, making them suitable for treating acne. Potential cosmeceuticals or nutraceuticals recently utilized to treat acne include niacinamide. This drug is purported to reduce sebum production and possess anti-inflammatory properties. Clinical trials were conducted to improve, characterize, and test the nanostructures in patients with acne vulgaris. CS nanostructures were beneficial topically, an ex vivo study was evaluated that showed skin adherence and increased nicotinamide deposition across all skin layers [59]. In addition, clinical evaluations of patients revealed a 73% reduction in inflammatory acne lesions compared to untreated areas, suggesting that the delivery system could be a valuable alternative for treating skin problems [59].

2.6. Mucosal

Mucosal transport is facilitated by CS and its derivatives since hydrophilic molecules, such as peptides and protein medications, are more effectively absorbed. Mucus is viscoelastic as it is composed of glycoproteins that are exceptionally hydrated, such as lysozymes, salts, and mucins [60]. By opening the compact intercellular connections, CS improves the paracellular trafficking of therapeutics. Living cell monolayers exhibit reduced transepithelial electrical resistance and paracellular permeability, which are elevated by positively charged CS nanostructures bound to their cells. The amount of deacetylation and molecular weight of the CS determines how paracellular and transcellular permeability the CS solution promotes [61]. One way CS interacts with proteins in the compact junction is through its interaction with ZO-1 and occludin. It also redistributes F-actin and somewhat destabilizes the plasma membrane.

2.7. Chitosan administration for wound healing

When germs enter and colonize the damaged epidermis, they can easily reach the deeper tissues underneath [62]. Infection is a crucial factor that is believed to impede wound healing. It is significant for wound dressings to avoid mechanical injury in addition to decreasing surface necrosis, being oxygen permeable without dehydrating the wound, being congenial, and providing a moist environment to minimize wound dryness [63]. In addition to being biocompatible and biodegradable, a wound dressing material should have low toxicity [64]. The monomer unit of CS, *N*-acetylglucosamine, was shown to enhance cell proliferation, increase hemostasis, and accelerate wound healing. The contact of CS with human cells does not have any negative consequences in terms of biocompatibility [65]. Furthermore, CS's ability to attach to red blood cells (RBCs) expedites blood coagulation. Finally, drug aggregation is increased by the consistent medicine delivery provided by CS nanostructures [65]. Fig. 3 provides an overview of several strategies used to administer CS nanoparticles.

3. Preparation of chitosan nanoparticles

Both the “bottom-up” and “top-down” approaches, or a hybrid of the two, are used to synthesize CS nanostructures [66]. Ionotropic gelation, microemulsion, solvent evaporation, and polyelectrolyte techniques are examples of “bottom-up” approaches, whereas milling, high-pressure homogenization, and ultrasonication are examples of “top-down” approaches [67].

3.1. Ionotropic gelation

In this process, a polyanionic crosslinker is deployed to crosslink the cationic amino groups of CS. A solution of tripolyphosphate (TPP) is produced, and aqueous acidic CS is added dropwise while stirring

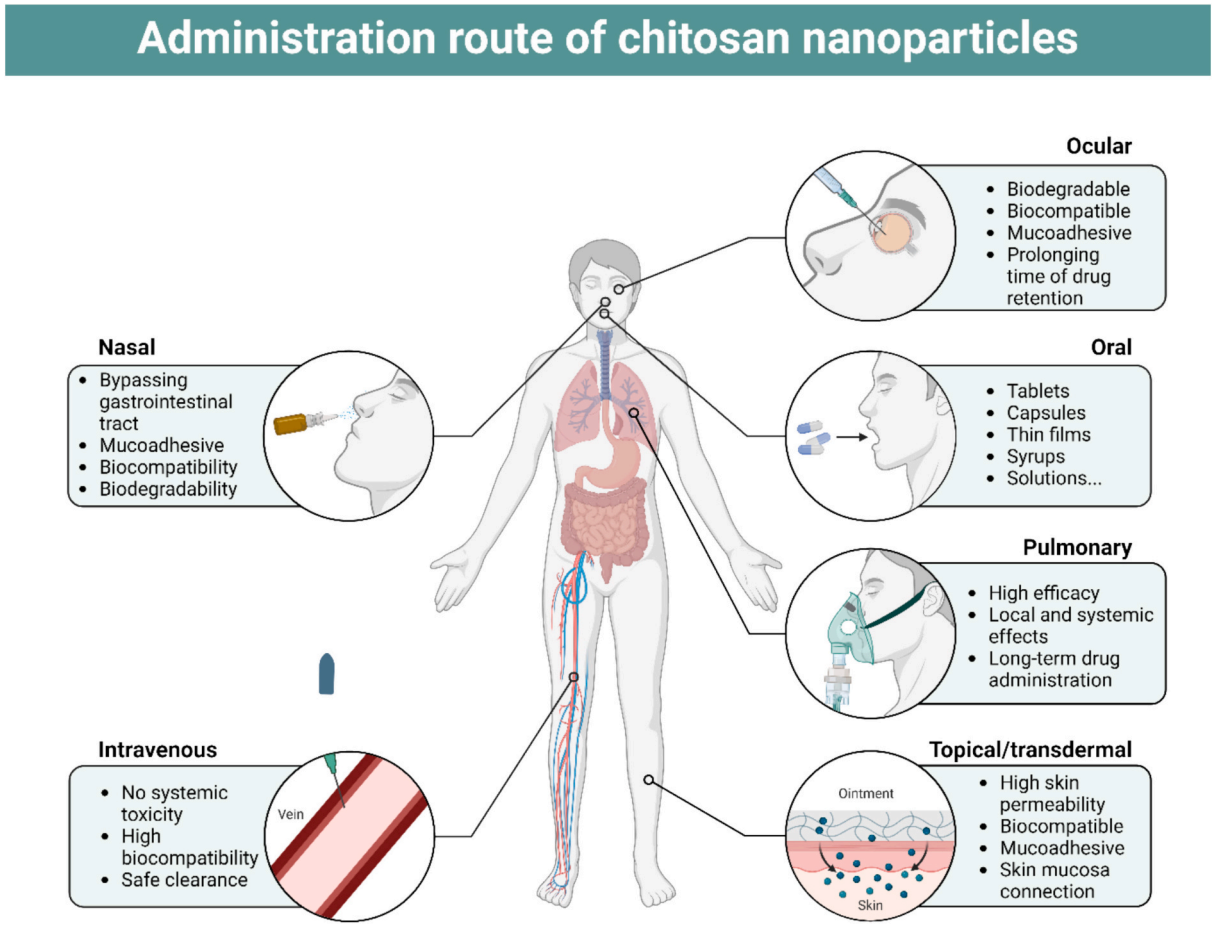

Fig. 3. Schematic representation of the main administration routes for chitosan-based nanoparticles and liposomal systems.

continuously at a steady pace. CS-TPP nanostructures are made during the crosslinking of anionic TPP with CS. Therapeutics are encapsulated and transported by this complex, and these nanocarriers have the potential to be refined into effective delivery systems. Notably, using an aqueous medium renders this technique harmless and straightforward to implement, eliminating the risks and toxicity associated with organic solvents. However, this method has a drawback: the low mechanical strength of nanostructures [68].

3.2. Co-precipitation

This strategy develops nanostructures with a uniform distribution by first preparing a CS solution in an acidic medium with a low pH and then adding a high-pH solution, including ammonium hydroxide. Reportedly, this approach can be utilized to generate CS-functionalized iron oxide nanoparticles [69].

3.3. Solvent evaporation

The process starts with the preparation of two polymer solutions in volatile solvents. Then, the medicine is added to the mixture. The solvent is subsequently evaporated to produce precipitated nanostructures. The diabetic patients are reportedly being treated with repaglinide-loaded CS nanoparticles produced using this approach [70].

3.4. Spray drying

This strategy is famous for constituting granules, agglomerates, and powders from suspensions or solutions of drugs and excipients. It involves dissolving CS in an acetic acid solution, adding a crosslinking agent to the drug solution, and then atomizing the mixture with a hot air stream. Small droplets form, and when the solvent evaporates, nanoparticles are produced. This approach was utilized to generate spray-dried inhalable powders with nanoaggregates for the pulmonary administration of anti-tubercular therapeutics [71].

3.5. Reverse micellar method/microemulsion

This process requires four ingredients: a polymer, a surfactant, a crosslinker, and an organic solvent. The process starts with dissolving the surfactant in an appropriate organic solvent. In the following stage, a blend of polymer and crosslinker is prepared and added to the surfactant mixture. The required polymer-crosslinker nanoparticles are produced by combining the two solutions in the solvents according to the crosslinking principle, which is based on the Schiff reaction [72]. Following this, any excess surfactant is removed using calcium chloride.

3.6. Polyelectrolyte complexation

This technique achieves charge neutralization through electronic interactions between the positively charged amine groups of CS and the negatively charged anions, including the carboxyl group of alginates or the dextran group of sulfates. Charging the anionic solution with CS in acetic acid and stirring it continuously at room temperature causes the polyelectrolyte complexes to self-assemble [70,73]. Patients undergoing bone regeneration therapy reportedly benefited from CS-guar gum nanostructures generated using this approach [74].

3.7. Emulsion-droplet coalescence

The process involves both precipitation and cross-linking. Therefore, two emulsions are generated: (a) A solution of CS and the therapeutic compound is created into an emulsion by adding it to liquid paraffin oil and stirring constantly. (b) By combining paraffin oil with a sodium hydroxide-CS aqueous solution, a second water/oil emulsion is generated. Once the two emulsions are combined, they are stirred at high speed until their droplets collide, creating coacervates. The coacervates are then separated by centrifugation and filtered to obtain CS-drug nanostructures [75]. In a study involving rheumatoid arthritis, this approach was found to be effective in producing dexibuprofen nanoparticles [76].

3.8. Covalent crosslinking

CS, or its derivatives, and the functional cross-linking agents generate covalent bonds in this approach. Glutaraldehyde, polyethylene glycol (PEG), and monofunctional agents are among the most commonly utilized agents [77]. More information regarding the synthesis of CS nanoparticles can be found in these reviews [52,67,78,79]. Fig. 4 illustrates the various strategies employed for the synthesis of CS nanostructures.

4. Liposomes: preparation and biomedical application

4.1. An overview of liposomes

Liposomes are lipid bilayer–based nanocarriers widely used for therapeutic delivery, demonstrating several benefits compared to other nanostructures, including the encapsulation of both hydrophilic and hydrophobic drugs. Liposomes are chemically versatile, and they possess high biocompatibility and low immunogenicity [80].

The safety, stability, and efficiency of liposomes are determined by several features, including the ratio of liposome components, the selection of phospholipids, the head group, and chain length [81]. A wide range of factors can influence the efficacy of liposomes as a delivery system, including the quantity and stiffness of lipid bilayers, size, surface charge, lipid organization, and surface modification [82,83].

Liposomes are mostly made up of glycerophospholipids, which are amphiphilic lipids that include a glycerol molecule linked to a phosphate group and two chains of fatty acids, one of which can be saturated and the other unsaturated [84,85]. There are different organic bonding possibilities for the phosphate group [86]. Natural phospholipids are categorized as follows by this organic group: phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylglycerol (PG), and phosphatidylserine (PS) [87]. Two main categories of glycerophospholipids are responsible for liposome creation, including natural and synthetic ones. Plant and animal phosphatides, PC and PE, are the most frequent phospholipids utilized to develop liposomes [88]. Moreover, natural phospholipids are primarily found in egg yolks or soybeans, and molecules derived from natural lipids are used to make synthetic phospholipids. Stable synthetic phospholipids have been synthesized by modifying natural phospholipids, including head groups, aliphatic chains, and alcohols. There are some instances of phospholipids in the synthetic form, such as 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dioleoyl-snglycero-3-phosphocholine (DOPC), 1,2-Distearoyl-sn-glycero-3-phosphoglycerol (DSPG), 1,2-Dipalmitoyl-sn-glycero-3-phosphoglycerol (DPPG), 1,2-Dioleoyl-snglycero-3-phosphoethanolamine (DOPE), and 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) [89].

Liposomes can have a single lipid bilayer or several phospholipids. They can take up positive, negative, or neutral charges, which is determined by the phospholipid head groups [90]. Their stability can be enhanced by employing phospholipids that have longer tails, little tail unsaturation, and ether linkages. Phospholipids can connect and create bilayer structures with considerable rigidity and discipline when their saturated hydrocarbon chains are extended. Liposomes, which are composed of phospholipids with shorter unsaturated hydrocarbon chains, are characterized by fluid and disordered bilayers [81,91].

Incorporating glycols is a different approach to modifying the liposomal structure. To acquire delivery systems for improved skin drug

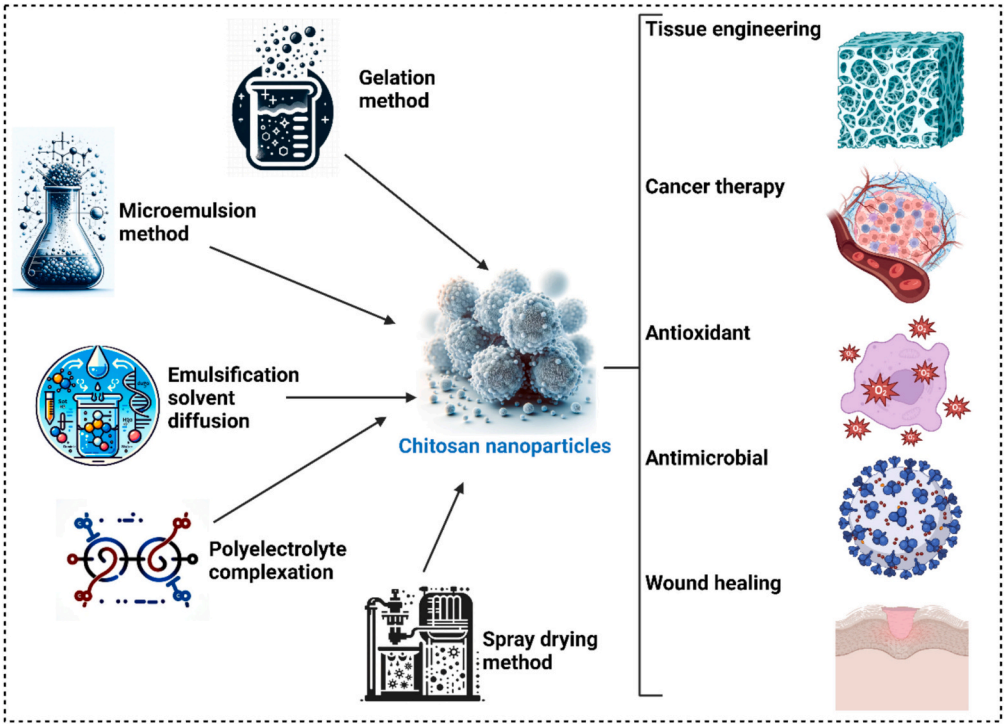

Fig. 4. Overview of representative preparation methods for chitosan nanoparticles, including ionotropic gelation, microemulsion, spray drying, and related approaches.

administration, phospholipid vesicles containing propylene glycol have been proposed [92,93]. An efficient method for elevating the half-life of liposomes in circulation from a few minutes for regular liposomes to many hours for stealth liposomes, also known as PEGylated liposomes, is conducted by affixing various PEGs to their surface [86]. A major limitation of conventional liposomes is their rapid clearance from systemic circulation [94]. The amount of grafted PEG, along with the molecular weight or length of the polymer, determines the increase in the circulation lifetime of the liposomes [95]. Blood circulation time is typically improved most noticeably by longer-chain PEGs [96].

Additionally, the bilayer lipid fluidity can be influenced by several critical parameters, one of which is the transition temperature of phospholipids (Tc). This is the temperature at which phospholipids go from a gel phase to a liquid crystalline phase [97]. Several factors contribute to the determination of Tc, including the type of polar head group, the ionic strength of the suspension medium, the saturation level of the hydrocarbon chains, and the length of the fatty acid chains [98,99]. Phospholipid bilayers with long, saturated hydrocarbon chains should be less porous and stiffer, as the interactions between the chains are much stronger, leading to a higher Tc. This means that longer saturated hydrocarbon tails have greater hydrophobic interactions [100]. Phospholipids are in a gel phase at temperatures below Tc, when they are not only very inhomogeneous but also very slightly permeable, allowing molecules inside the bilayer to relocate very slowly. They enter a liquid crystalline phase at temperatures greater than Tc; the lipid bilayer molecules travel at fast speeds due to their high fluidity and often low permeability. Since the gel and liquid crystalline phase domains of the liposome bilayer contain highly permeable interfacial regions, their permeability expands dramatically at temperatures near Tc [86].

In addition, size and the number of lipid bilayers (lamellae) are the two primary structural features allowing for the categorization of liposomes. Liposomes are often categorized as either unilamellar (ULV, any size range), multilamellar (MLV, >500 nm), or multivesicular (MVV, >1000 nm) vesicles regarding their lamellarity [100,101]. More investigations have resulted in the identification of three sizes of ULVs, including small (SUVs, 20–100 nm), large (LUVs, >100 nm), and very large (GUVs, >1000 nm). Since ULVs only have one bilayer, they can better encapsulate hydrophilic substances. The onion-like structure of MLVs, which consists of two or more concentric lipid bilayers, is ideal for encasing lipophilic substances. MVVs are perfect for enclosing large volumes of hydrophilic material, as they consist of several tiny, non-concentric vesicles trapped inside a single lipid bilayer [101,102]. Both the vesicle size and the number of lamellae influence the amount of a particular substance that can be contained in liposomes [100,103]. The multicompartment liposome (MCL) represents a novel alternative in vesicle technology. These MCLs were established as single-vehicle delivery systems for combinatory chemicals; they consist of two sorts of vesicles linked by a tight bilayer interface [104,105]. Fig. 5 provides an overview of various kinds of modifications in liposomes.

4.2. Biomedical applications of liposomes

Liposomal delivery techniques are highly beneficial in cancer therapy. By incorporating chemotherapeutic elements into liposomes, these small vesicles can be more precisely targeted to cancer cells and tumor tissues through either passive or ligand-mediated active targeting. This action reduces drug toxicity and extends the anticancer effectiveness of the drug by enhancing the accumulation of liposomes within tumors [107,108]. PEGylated liposomal doxorubicin (Doxil®) was the first FDA-approved liposomal nanomedicine for cancer therapy. It should be mentioned that the European Medicines Agency (EMA), along with the U.S. Food and Drug Administration (FDA), has confirmed numerous liposomal chemotherapeutic formulations for the treatment of various cancers in the past few years after the approval of Doxil® in 1995 and several other cytotoxic agent-containing liposomes for clinical use [109–111].

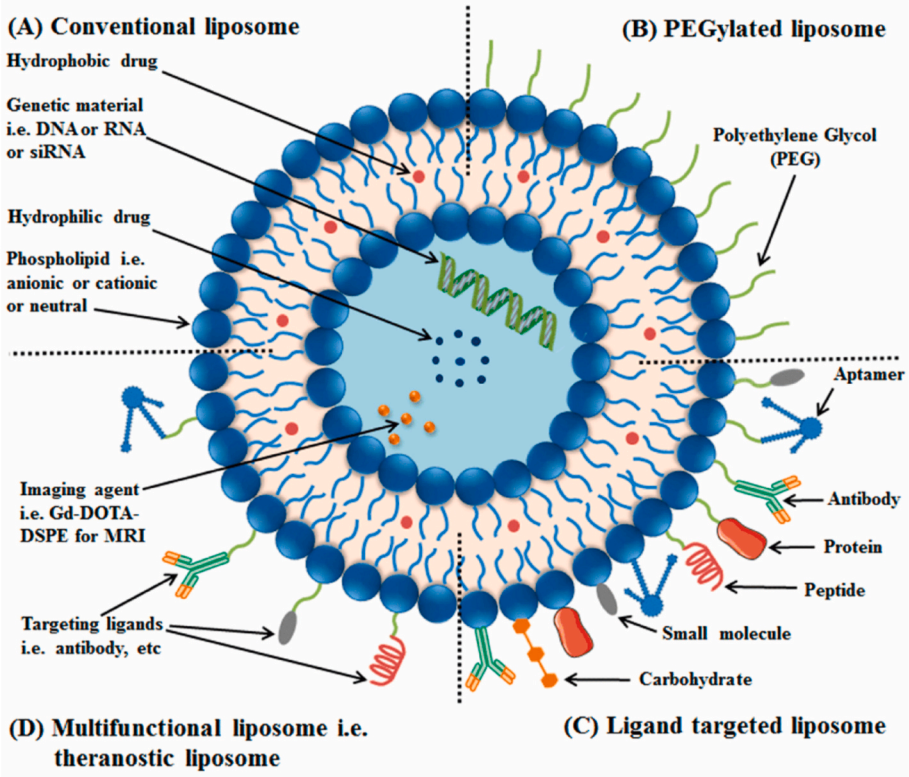

Fig. 5. Schematic illustration of different liposome modification strategies. (A) Conventional liposomes. (B) PEGylated liposomes. (C) Ligand-functionalized liposomes. (D) Multifunctional and theranostic liposomal systems.
(Reprinted with permission from MDPI [106].)

There have been numerous cases of traditional liposome failure due to their lack of selectivity, despite liposomal anticancer medications being successful through the enhanced permeability and retention (EPR) effect. To express it more precisely, in some instances, the medication builds up in healthy tissue and mucosa, leading to treatment failure, even while a minimum therapeutic concentration of liposomes is supplied within tumor tissues [112,113]. On the other hand, the active "ligand-mediated" targeting method has been noticeably studied for its potential to enhance the intracellular delivery of a medication capsule to tumor tissue. For the purpose of improving anticancer treatments, liposomes have been investigated in association with a wide variety of molecules, such as charged molecules, peptides, antibodies, proteins, ligands with low molecular weight, and aptamers [110,114].

A remarkable issue in modern medicine is the increase in bacterial diseases that are resistant to many drugs, making it difficult to treat these infections using traditional methods [115]. The constitution of a biofilm enables bacteria to be a thousand times more resistant to antibiotics than plankton [116]. A potential strategy for treating harsh infections, such as biofilms and intracellular infections like Salmonellosis, is the localized delivery of antimicrobials [117,118]. These days, the treatment of *Mycobacterium avium* complex lung illness is possible with the use of liposome-encapsulated amikacin, which is sold under the brand name Arikace [119]. Arikace is an innovative inhaled liposomal amikacin formulation that has recently been developed to treat patients with chronic *Pseudomonas aeruginosa* biofilms.

In addition, vaccination is regarded as not only the best but also the most economical way to prevent numerous diseases, including rheumatoid arthritis, malignant lesions, infectious disorders (viral, bacterial, fungal, or parasitic), and pathogenic infections [120]. The liposome-based vaccines Epaxal, Inflexal, and Mosquirix have since received clinical acknowledgment [120,121]. Additionally, all three are virosomes, a type of liposome that contains a protein produced by a virus within a phosphatidylcholine membrane vesicle. It was proven that there is no risk of adverse reactions from using any of these three vaccines, and they all work by stimulating the immune system. The encapsulation of particle vaccines provides better protection of antigens from enzymatic degradation [122]. These vaccines can transmit molecular adjuvants containing antigens to antigen-presenting cells (APC), which in turn expand both cellular and humoral immune responses [123].

In recent years, numerous preclinical and clinical trials have focused on antibodies and antibody fragments as targeted therapeutic agents. Antibody-conjugated liposomes, also known as immunoliposomes, will substantially aid in the precision diagnosis and treatment of cancer. Phase I clinical studies are underway for a doxorubicin (DOX)-loaded immunoliposome that targets the human epidermal growth factor receptor-2 (HER2).

5. Why chitosan-functionalized liposomes outperform chitosan nanoparticles or liposomes alone?

CS-functionalized liposomes represent a hybrid nanoplatform that integrates the advantages of both CS nanoparticles and lipid-based vesicles while overcoming key limitations associated with each system. CS nanoparticles are widely recognized for their biocompatibility, mucoadhesion, and ability to enhance epithelial permeability; however, their application is limited by several drawbacks, including a limited capacity for hydrophobic drug loading, susceptibility to aggregation, and relatively poor control over payload release profiles under physiological conditions. These limitations restrict their utility in complex therapeutic scenarios that require high drug-loading efficiencies, protection of hydrophobic therapeutics, or prolonged systemic circulation [124].

Conversely, conventional liposomes efficiently encapsulate both hydrophilic and hydrophobic agents, providing a biomimetic lipid environment for sensitive therapeutics. Nevertheless, unmodified liposomes often suffer from rapid clearance by the reticuloendothelial system, insufficient stability, premature drug leakage, and weak mucoadhesive or cell-interactive properties, all of which reduce their bioavailability and therapeutic impact [125].

Surface modification of liposomes with CS creates a synergistic hybrid system that addresses many of these shortcomings. The CS coating establishes a cationic, mucoadhesive, and often pH-responsive shell that can improve vesicle stability, reduce premature leakage, and promote cellular internalization through electrostatic interaction with negatively charged biological membranes. Multiple recent studies show that CS-coated liposomes exhibit more sustained and controllable release profiles and improved bioactivity compared with uncoated liposomes, for example, in lysozyme-responsive, CS-coated levofloxacin liposomes and other CS-functionalized liposomal systems for antimicrobial or mucosal delivery [126,127].

CS-functionalized liposomes preserve the intrinsic advantage of liposomes in accommodating both hydrophilic drugs in the aqueous core and hydrophobic drugs within the lipid bilayer, while the CS layer provides additional functional groups for subsequent ligand conjugation. This combination enables multi-modal strategies, including stimuli-responsive release, targeted delivery, and co-delivery of multiple agents, which cannot be readily achieved with CS nanoparticles or unmodified liposomes alone [126,128].

Overall, by combining the structural flexibility of lipid bilayers with the mucoadhesive, protective, and functional characteristics of CS, preclinical studies indicate that CS-functionalized liposomes can provide enhanced stability, improved tissue targeting, prolonged residence at the site of action, and more controlled release profiles, resulting in a nanoplatform with superior therapeutic potential compared to CS nanoparticles or conventional liposomes used alone.

6. Chitosan-functionalized liposomes: biomedical applications

6.1. Anticancer activity

The CS oligosaccharide (CSO) results from the chemical or enzymatic degradation of CS [129]. There are several limitations associated with CS, including its low molecular weight and poor water solubility. The application of CSO can solve that, and it has been proven to be an effective carrier for drug delivery [130,131]. Liposomes were functionalized with CSO for the treatment of lung cancer. For this purpose, liposomes were modified with CSO-Pluronic P123 conjugates, demonstrating high cellular uptake in lung cancer cells and high accumulation in the tumor region. Such modified liposomes provide massive absorption of collagen, which undergoes upregulation in lung cancer. These nanoparticles delivered paclitaxel, which suppressed tumorigenesis up to 86.4% [132]. In addition to lung cancer, CSO-functionalized liposomes have shown high potential in the treatment of breast cancer through the delivery of evofosfamide. The CSO-functionalized liposomes delivered evofosfamide as an anticancer agent and photochlor as a photosensitizer, providing both imaging and therapy for breast cancer. They demonstrated high safety and targeting ability, capable of suppressing tumorigenesis in vitro and in vivo [133].

Coating liposomes with CS enables them to facilitate the absorption of drugs with considerable retention time, and makes them valuable and effective in drug delivery [134,135]. CS-coated liposomes were utilized to treat colorectal cancer. 5-FU was loaded in liposomes functionalized with CS, and in vitro drug release was investigated, illustrating that the nanostructures release 5-FU slowly. 5-FU-loaded CS-functionalized liposomes were more efficient in eliminating cancer cells in a consistent manner than liposomes and the 5-FU solution [136]. In addition to colorectal cancer, CS-coated liposomes have inhibitory influences on MCF-7 breast cancer cell growth through the encapsulation of curcumin. Although curcumin has been significantly applied in cancer treatment, the poor pharmacokinetic profile of this compound restricts its therapeutic index, and therefore, delivery approaches are suggested [137].

Encapsulation of curcumin in CS-coated liposomes resulted in greater release efficiency and represented a more substantial inhibitory impact on the growth of MCF-7 breast cancer cells [138]. The targeting ability of liposomes can be improved through functionalization with aptamers. In lung cancer therapy, CS-functionalized liposomes were modified with anti-EGFR aptamers to co-deliver erlotinib and PFOB. The resulting liposomes demonstrated favorable physicochemical features, desirable biostability, and prolonged drug release. The presence of PFOB increased the uptake of nanoparticles in tumor cells. Moreover, such nanostructures elevated apoptosis and suppressed proliferation. Hypoxia increases drug resistance, while aptamer/CS-functionalized liposomes downregulate HIF-1α to alleviate hypoxia and enhance erlotinib sensitivity (Fig. 6) [139].

Essential features, such as biodegradability and biocompatibility, of CS polysaccharide and omega-3 fatty acid nanoparticles have introduced them as effective drug carriers [140,141]. Consequently, glycol CS-docosahexaenoic acid liposomes were functionalized to treat breast cancer. DOX and rapamycin (RAPA) were loaded in a liposomal glycol CS that revealed considerable loading efficiencies for RAPA and DOX at 6.2% and 4.1%, respectively. They not only exhibited anticancer effects on DOX-resistant MDA-MB-231 cells but also demonstrated noticeable colloidal stability under physiological conditions [142]. When the liposomes are functionalized with CS, they can be conjugated with folic acid, which increases their selectivity and specificity toward tumor cells [143]. Therefore, CS not only improves the biocompatibility and other features of liposomes, such as blood circulation time, but also provides an anchor for functionalization with other ligands.

Nanoparticles embellished with CS can target CD44+ cancer stem cells (CSCs) and increase drug accumulation in these cells. Nanoparticles establish a powerful interaction with CD44+ CSCs due to the partial structural similarity of CS to the CD44 ligand hyaluronic acid (HA) and its positive charge [144]. Therefore, 89Zr-labeled CS-conjugated multifunctional liposomes were deployed to treat triple-negative breast CSCs. CS-functionalized liposomes were labeled with zirconium-89 (89Zr), demonstrating that CS could be stably connected to the CD44 active site. In addition, 89Zr@CS-GA-MLPs revealed remarkable radiochemical stability as they aggregated in tumors of xenograft-bearing mice and bound selectively to CD44+ triple-negative breast cancer (TNBC) stem-like cells. In vivo, 89Zr@CS-GA-MLPs loaded with gambogic acid (GA) demonstrated impressive antitumor effectiveness [145]. A new and promising cancer treatment strategy combines genes and drugs in cancer therapy. However, the enzymes can degrade genes during their circulation in the bloodstream, and the mildly acidic pH of the tumor microenvironment may affect their function. Therefore, nanostructures have been developed for the co-delivery of genes and drugs. Because CS has a positive charge, it can produce stable complexes with genetic materials such as siRNA. In this line, the liposomes were loaded with siRNA-VEGF and etoposide, and they were functionalized with the polymer PEGylated histidine-grafted CS-lipoic acid (PHLC). The tailor-made surface charge reversal characteristic of nanostructures enhances tumor microenvironment mimicking, ultimately improving tumor penetration and cellular uptake. The pH of the tumor microenvironment and redox status facilitate the release of cargo from nanostructures, thereby accelerating drug accumulation in tumor cells. Moreover, nanoparticles significantly reduced VEGF expression, suppressing angiogenesis. The function of the PHLC layer was to improve the stability of liposomal nanocarriers for enhancing lung cancer suppression [146].

An amphoteric polysaccharide known as carboxymethyl CS (CMCS), which has pH-sensitive properties, is involved in various applications such as gene delivery, sustained-release drug delivery, and pH-responsive drug delivery [147]. As a result, carboxymethyl CS-

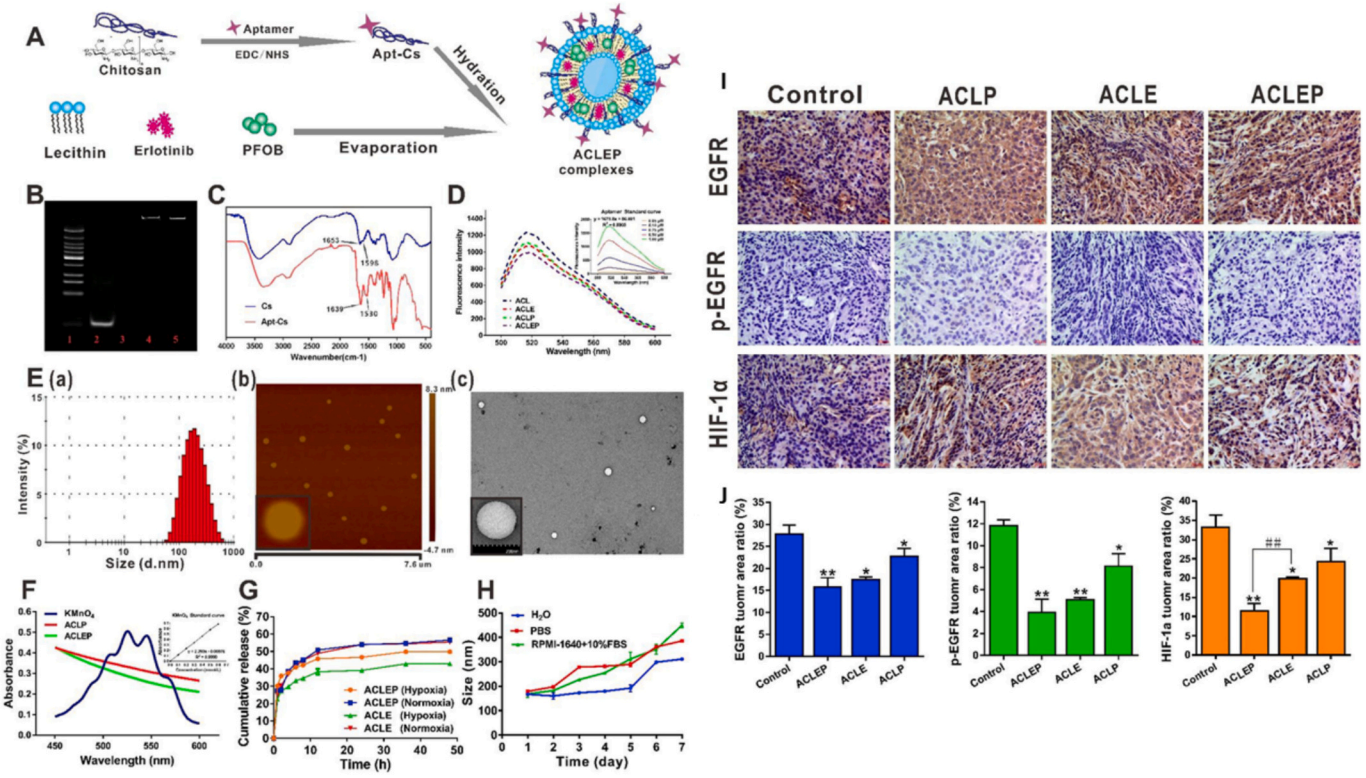

Fig. 6. Preparation and characterization of multifunctional chitosan-functionalized liposomal complexes. (A) Schematic illustration of the preparation process. (B) Gel electrophoresis analysis of aptamer–chitosan conjugation. (C) FTIR spectra of chitosan and aptamer–chitosan conjugates. (D) Fluorescence analysis of aptamer conjugation. (E) Particle size and morphology analysis. (F) Oxygen content analysis. (G) In vitro drug release profiles under different conditions. (H) Colloidal stability in different media. (I, J) Immunohistochemical analysis of EGFR and HIF-1α expression in tumor tissues.
(Reprinted with permission from Elsevier [139].)

functionalized cationic liposomes were utilized to suppress tumor progression. For this aim, pH-sensitive CMCS-modified cationic liposomes were applied for the co-delivery of sorafenib and siRNA, exhibiting CMCS-SiSf-CL, which effectively protected siRNA from serum and RNase degradation while condensing it. As compared to the free Sf solution, CMCS-SiSf-CL had a noticeable inhibitory impact on tumor growth [148].

CS-functionalized liposomes represent a highly adaptable drug-delivery platform that preclinical studies demonstrated their ability to encapsulate and deliver clinically relevant therapeutics with widely different physicochemical properties, including hydrophilicity, lipophilicity, molecular weight, charge, and biological stability. This versatility arises from the intrinsic compartmentalized structure of liposomes combined with the multifunctional polymeric shell provided by CS (Table 1). Hydrophilic drugs and biomacromolecules, such as nucleic acids (siRNA, plasmid DNA) and small polar drugs (e.g., sorafenib), can be efficiently loaded into the aqueous core of liposomes, where the CS coating provides electrostatic stabilization and protection against enzymatic degradation. The cationic nature of CS further enables strong complexation with negatively charged genetic cargos, improving condensation efficiency, cellular uptake, and transfection performance, as demonstrated in siRNA- and gene-loaded systems.

Hydrophobic and poorly water-soluble drugs are commonly used in clinical oncology (e.g., paclitaxel, docetaxel, curcumin, exemestane) and can be incorporated into the lipid bilayer of liposomes. CS coating enhances the colloidal stability of these formulations, reduces premature drug leakage, and enables sustained release profiles, thereby improving the pharmacokinetics and therapeutic efficacy of lipophilic agents. This dual-compartment loading capability allows CS-functionalized liposomes to accommodate single or multiple drugs with distinct solubility profiles within the same nanocarrier.

Importantly, CS offers chemical flexibility for further functionalization, including thiolation, quaternization, carboxymethylation, or conjugation with targeting ligands (e.g., aptamers or hyaluronic acid). These modifications enable stimulus-responsive behavior (pH- or redox-triggered release), enhanced mucoadhesion, and receptor-mediated targeting, thereby facilitating the delivery of drugs with different stability requirements and site-specific therapeutic needs. Such structural tunability allows CS-based liposomes to serve as a unified platform for the delivery of small-molecule drugs, combination therapies, and nucleic-acid-based medicines currently used or under investigation in clinical settings.

In these systems, CS primarily contributes to improved colloidal stability, enhanced interaction with tumor cell membranes, and controlled drug release, collectively supporting efficient liposome-mediated anticancer delivery.

6.2. Antibacterial activity

One of the factors that can improve the stability of liposomes in laboratory and in vivo conditions is to modify their surface with CMC [162,163], because it has better biocompatibility, biodegradability, bacteriostatic, fungistatic, and solubility than CS [164]. CMC-modified photo-responsive Camellia sapogenin derivative cationic liposomes with intricate structures demonstrated greater storage stability and gastrointestinal stability, as well as no apparent hemolytic toxicity to rabbit RBCs, and no cytotoxicity after incubation with HeLa cells. Moreover, liposomes can bind to bacteria, impair their morphology and structure, and have a considerable bactericidal impact on amoxicillin-resistant *E. coli* and *S. aureus* [165].

CS has also been explored as a functional additive in antimicrobial formulations [166]. Therefore, cinnamaldehyde-loaded liposomes were

Table 1
A summary of chitosan-functionalized liposomes in cancer therapy.

Nanoparticle	Payload	Cancer type	Size (nm)/zeta potential (mV)/ encapsulating or drug loading efficiency(%)	Remark	Refs
CS-lipoic acid-coated liposomes	VEGF siRNA + Etoposide	Lung cancer	176.5 nm/−12.06 mV/89.88%	Co-delivery of nucleic acid and small-molecule drug; pH/redox-triggered release; improved tumor penetration and efficacy	[146]
Thiolated CS–coated liposomal hydrogel	Curcumin	Breast cancer	414 nm/+37.3 mV	Injectable in situ system; sustained local delivery	[149]
Liposomal gel formulation	Erlotinib	Oral cancer	<200 nm/−50 mV and + 25 mV	Local gel delivery; tumor volume reduction; improved local exposure	[150]
Aptamer–CS anchored liposomes	Erlotinib	Lung cancer	179 nm/+36 mV/40%	Active targeting; increased uptake and efficacy in EGFR-driven cells	[151]
Layer-by-layer CS stabilized multilayer liposomes	Paclitaxel	Cervical cancer	215 nm/+27.9 mV/70.93%	High stability in the gastrointestinal tract; prolonged release; anticancer effect	[152]
Thiolated CS-functionalized liposomes	Curcumin	Breast cancer	406 nm/+36.6 mV/93.95%	High encapsulation efficiency; improved antitumor performance	[153]
HA/CS-coated liposomes	Doxorubicin + Berberine	Lung cancer	362 nm/up to 64%	Co-delivery of doxorubicin and berberine; enhanced cytotoxic activity; high cellular uptake	[154]
Quaternized CS/lipid cationic polymeric liposomes	Gene cargo	Glioma	184.4 nm/+27.5 mV	High transfection efficiency; high gene delivery; high biocompatibility	[155]
Carboxymethyl CS-coated pH-sensitive cationic liposomes	Sorafenib + siRNA	Liver cancer	200.1 nm/−10 mV/90.36%	Co-delivery; CMCS shell enables pH-responsive behavior	[156]
CS-coated nanoliposomes	Exemestane + Genistein	Breast cancer	120.3 nm/+22.4 mV/77%	Dual lipophilic drug loading; sustained release; enhanced cytotoxicity	[157]
Injectable thiolated CS-coated liposomal hydrogel	Curcumin	Breast cancer	414 nm/+37.30 mV/88.75%	Thermosensitive, sustained release; inhibited breast cancer recurrence in vivo after tumor resection; enhanced cytotoxic activity	[158]
CS-coated liposomes	Indocyanine green	Melanoma	1983 nm/+43.2 mV	Increased cellular uptake and photocytotoxicity cancer cells; significantly improved skin permeation; topical PDT	[159]
CS oligosaccharide modified liposomes	Paclitaxel	Lung cancer	75 nm/+3 mV/10%	Delivery of hydrophobic chemotherapeutic agent; improved nanoparticle stability, cellular uptake, and anticancer efficacy	[160]
Nanoliposomes coated with mucoadhesive CS	Docetaxel	Laryngeal/head and neck cancer	120 nm/+24.8 mV/82.6%	Improved cellular internalization and enhanced cytotoxicity; loco-regional anticancer drug delivery	[161]

amended for antibacterial activities. CS decoration was employed to enhance the antibacterial properties of cinnamaldehyde-loaded liposomes, where the encapsulation proficiency and storage stability of liposomes improved. Liposomes decorated with CS achieved apparent antibacterial activity against *S. aureus*. CS and cinnamaldehyde exerted a cumulative and synergistic bacteriostatic impact on the liposomes (Fig. 7) [167].

Gentamicin-loaded liposomes were developed to modify their biodistribution, enhance accumulation at the desired location, and reduce nephrotoxicity induced by frequent daily injections [168,169]. Therefore, CS nanofiber meshes immobilized with gentamicin-releasing liposomes were used for bactericidal activity against *E. coli*, *P. aeruginosa*, and *S. aureus*. This approach is also promising for utilization in wound dressing and suppresses infections caused by these pathogens [170].

The amalgamation of CS and membrane-active antimicrobials in drug delivery systems can enhance antibacterial capabilities [171]. A CS-based delivery system was developed to increase the antimicrobial activity of chlorhexidine. Chlorhexidine was incorporated into three different vesicles: simple liposomes (without CS), comprising CS, and coated CS. The CS-containing vesicles improved the chlorhexidine release rate and cell compatibility, and a 60% decrease in inflammatory responses was observed in murine macrophages treated with these vesicles compared to untreated cells. Liposomes combining CS and chlorhexidine were the most effective against *S. aureus* [172].

CS is considered an excellent choice for incorporation into dosage forms and delivery systems targeting the vaginal area due to its superb mucoadhesive properties. By adding CS to the medicine dosage form or drug delivery mechanism, its vaginal shelf life could be prolonged [173–175]. CS-based nanomedicines were applied to combat genital candida infections. CS was incorporated into liposomes and used as a coating layer, with metronidazole serving as a model drug for antimicrobial activity, which prevented the growth of *C. albicans*. The antifungal effect of chitosomes mixed with the antibacterial potential of entrapped metronidazole provided improved effectiveness in the treatment of mixed or complicated vaginal infections [176].

Within antibacterial formulations, CS enhances liposome stability and surface interaction with microbial membranes while promoting sustained release of antimicrobial agents.

6.3. Antioxidant and anti-inflammatory activity

The unique antioxidant activity of CS, coupled with its significant biocompatibility, has led to its use in tissue engineering. In addition, CS is a material that can be applied for tissue repair and regeneration [177–181]. Even though CS has inherent antioxidant features, it is unable to tolerate the oxidative stress microenvironment in MI [177]. Consequently, α-tocopherol (AT) liposomes are functionalized for suppressing oxidative stress injury in cardiomyocytes. AT was encapsulated in a liposomal vector, and then the liposomes were formed into a CS-based hydrogel. Liposomes were able to resist the oxidative stress environment and enhance the survival of cardiomyocytes [182].

CS is insoluble in neutral or basic pH ranges and soluble in acidic media such as the stomach. Chemists have formed N-succinyl-CS (NSC) by adding succinyl groups to CS for the purpose of improving its solubility and pH sensitivity [183]. Astaxanthin-loaded PEG-liposomes were proposed for antioxidant activities. NSC-coated AST PEG-liposomes induced much harder antibacterial and antioxidant activities against *Escherichia coli* and *Staphylococcus aureus* than AST PEG-liposomes [183]. CS and its derivatives are considered very suitable options for target delivery for anionic liposomes due to their positive charge properties. Quercetin-loaded liposomes were functionalized to hinder acute liver injury. Liposomes were amended with galactosylated CS, which illustrated that these liposomes were able to alleviate lipid oxidation while keeping AST, ALT, and ALP rates low and GSH rates high, which protected the liver from damage (Fig. 8) [184].

Inflammatory diseases can be alleviated by CS-functionalized liposomes. CS-coated liposomes were arranged for the treatment of inflammatory bowel disorders. Thus, glycyrrhizic acid (GA) was encapsulated in CS-coated liposomes, which revealed that these liposomes do not exhibit cytotoxicity toward the fibroblast cell line, thereby verifying their cytocompatibility. CS was responsible for reducing the release level of GA [185]. The CS coating is responsible for making liposomes stable against digestion in the gastrointestinal tract, as well as expanding the in vitro release of the encapsulated chemicals [186,187]. Thereby, spray-dried CS-coated liposomes were utilized as delivery carriers of apigenin. These liposomes led to enhanced antioxidant capacity and greater stability against simulated gastrointestinal digestion [188]. Therefore, CS-functionalized liposomes can be considered promising structures for alleviating oxidative stress and inflammation.

In antioxidant and anti-inflammatory applications, CS improves the physicochemical stability of liposomes and modulates drug release kinetics, thereby prolonging the local bioactivity of encapsulated agents.

6.4. Phototherapy activity

Phototherapy has emerged as a promising modality for the treatment

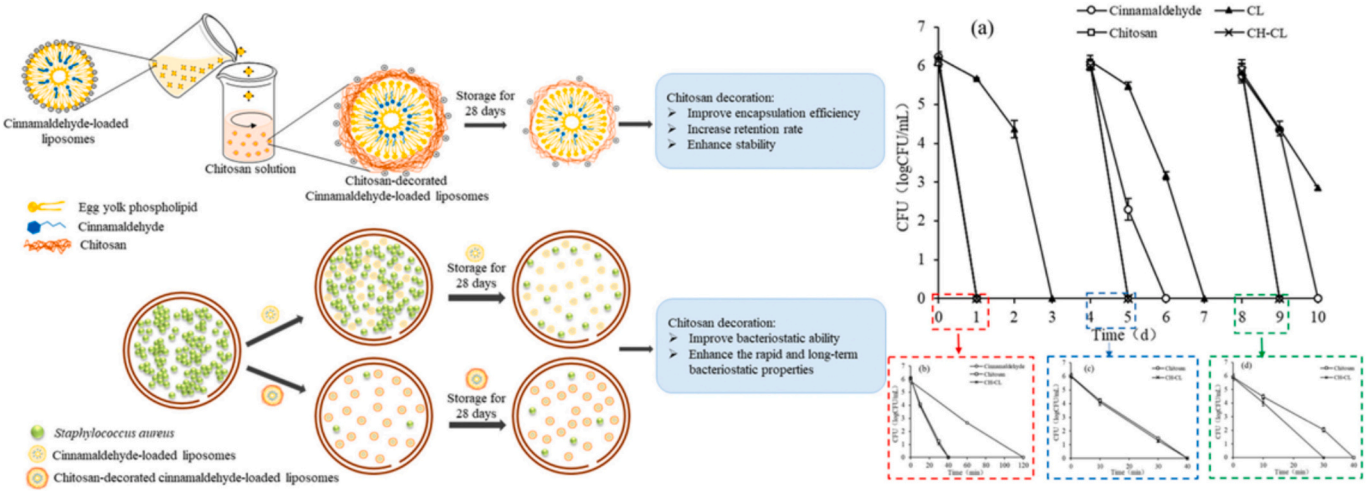

Fig. 7. Antibacterial performance of chitosan-decorated liposomal formulations against *Staphylococcus aureus*. (A–D) Growth behavior and colony formation under different treatments.
(Reprinted with permission from Elsevier [167].)

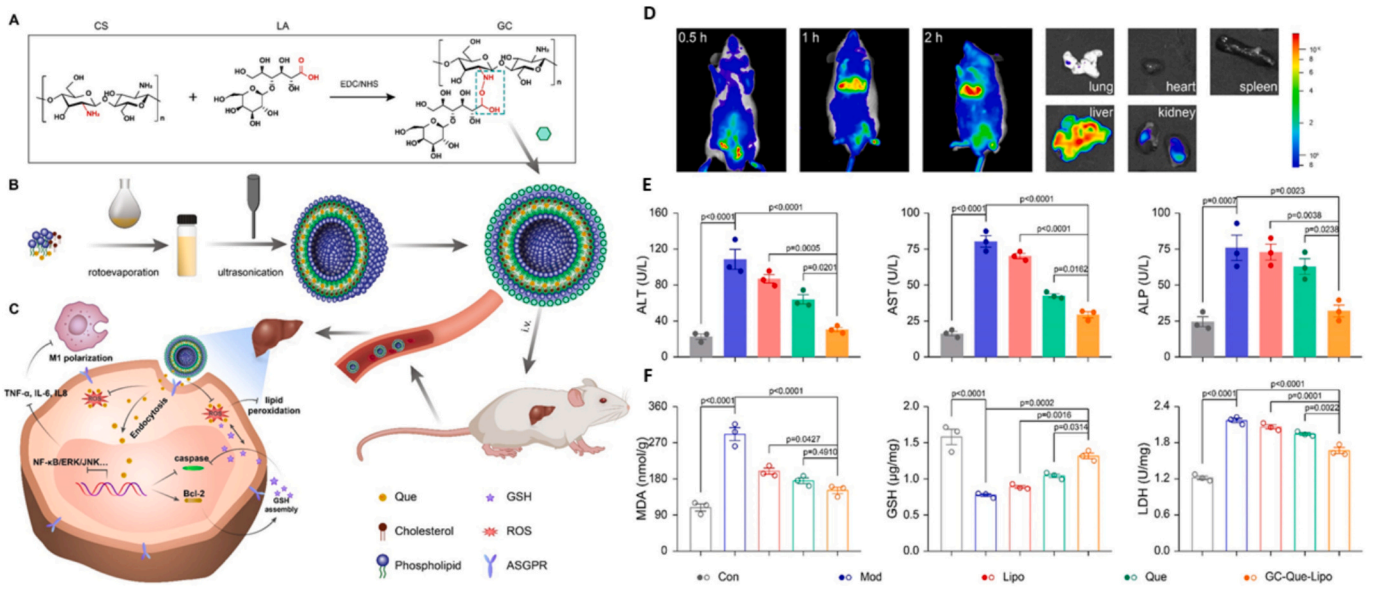

Fig. 8. Design and in vivo evaluation of galactosylated chitosan-modified quercetin-loaded liposomes. (A) Schematic representation of galactosylated chitosan synthesis. (B) Preparation process of surface-modified liposomes. (C) Proposed protective mechanism against acute liver injury. (D) In vivo fluorescence imaging of liposome biodistribution. (E, F) Biochemical analysis of liver injury markers and oxidative stress indicators.
(Reprinted with permission from Elsevier [184].)

of various diseases. It can be categorized into two main categories: photothermal (PTT) and photodynamic therapy (PDT). Photosensitizers are used to convert light into energy for stimulation in phototherapy. In PTT, the light is converted into heat; in PDT, the light is transformed into singlet oxygen. However, a problem with phototherapy is the poor pharmacokinetic profile of photosensitizers; therefore, nanoparticles were introduced for the targeted delivery of photosensitizers. The nanostructures can deliver photosensitizers to cause both PTT and PDT [189–191]. Several nanostructures, such as gold nanoparticles and carbon dots, can absorb light to induce phototherapy [192–194]. This section evaluates the function of CS-coated liposomes or their combination in phototherapy.

Injectable hydrogels can be utilized for accurate drug delivery in tumor tissues and local antitumor treatment due to their unique privileges [195]. Olaparib-liposomes (OLA-lips) and CS-capped gold nanoparticles (CS-AuNPs) were enclosed in a new composite hydrogel known as OLA-Au-Gel, which was composed of CS and β-glycerophosphate (β-GP). The hydrogel responded well to light and was biocompatible and

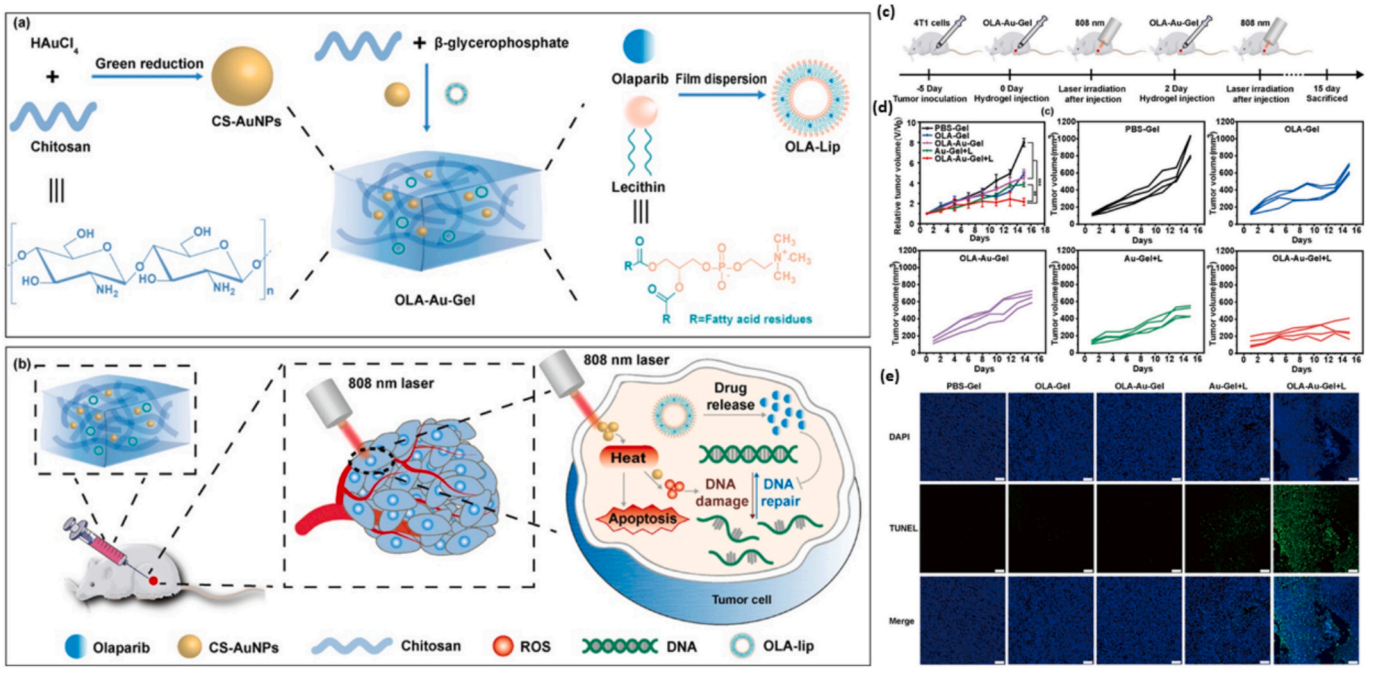

Fig. 9. Photothermal and photodynamic therapy using chitosan-based injectable liposomal hydrogel. (A) Schematic illustration of hydrogel preparation. (B, C) Proposed therapeutic mechanism and treatment protocol. (D) Tumor growth curves following different treatments. (E) Histological analysis of tumor tissues. Scale bars: 50 μm.
(Reprinted with permission from ACS [196].)

injectable. OLA-Au-Gel suppressed the growth of breast cancers in vivo. In vitro, it inhibited tumor cell proliferation and induced the formation of reactive oxygen species (ROS) when exposed to NIR light. Exposure to 808 nm laser irradiation increased heat and induced apoptosis. Moreover, hyperthermia caused DNA damage to impair tumorigenesis (Fig. 9) [196].

Drug delivery systems made of ionically crosslinked CS hydrogels have demonstrated much greater potential than those composed of covalently crosslinked hydrogels [197]. A novel platform for drug delivery systems is a hybrid matrix combining hydrogels with liposomes [198–200]. Hydrogel films were applied as a potential drug delivery system for zinc (II) phthalocyanine (ZnPc) to improve PDT. ZnPc liposomes and CS were combined on a hybrid matrix, which demonstrated that incorporating Zn-Pc liposomes into the films reduces cell viability by 95% [201]. CS oligosaccharide (CO) can target breast cancer cells. Some scientists have recently focused on CO-decorated nanoparticles that target cancers overexpressing CD44, such as TNBC [144,145]. CO-decorated liposomes were functionalized for PDT in triple-negative breast cancer. Thus, a CO-HPPH-TH302/Lipo-modified nanoparticle was established by incorporating the photosensitizer HPPH and the hypoxia-activated prodrug TH302 into hydrophobic bilayers. Both in vitro and in vivo, liposomes loaded with HPPH and TH302 had better antitumor impacts than the other monotherapy groups. The targeted liposomes demonstrated superior biocompatibility and targeting in vitro. In vivo, they exhibited enhanced fluorescence imaging capability compared to the nontargeted liposomes. Exposure to 660 nm irradiation can increase ROS and reduce oxygen (O_2) levels, thereby inducing apoptosis. Moreover, 660 nm irradiation generated a hypoxic region for activating drugs in cancer therapy (Fig. 10) [133].

There have been reports that CS is involved in functions that increase skin permeability, such as opening tight connections, altering the stratum corneum's keratin secondary structure, and improving cell membrane fluidity [202,203]. CS-coated liposomes were organized to elevate transdermal delivery of green indocyanine for PDT of melanoma. Amphiphilic ICG was encapsulated in liposomes, which revealed that these liposomes not only protect ICG from degradation but also facilitate expanded skin penetration of ICG. Their use resulted in extended phototoxicity and cellular uptake of ICG in a CS-dependent manner [204].

For phototherapeutic applications, CS facilitates improved liposomal retention, cellular association, and payload protection, contributing to more effective delivery of photoactive compounds.

6.5. Wound healing

The presence of electrostatic interaction between the negative charge of phospholipids of liposomes and the positive amino acid group of CS leads to the surface modification of liposomes [205]. CS plays a prominent role in wound healing due to its antibacterial activity [37,206]. Tailored citicoline-loaded CS-functionalized liposomes were applied for wound healing in diabetic rats. They enhanced the wound healing process by reducing inflammation, angiogenesis, connective tissue regeneration, fibroblast proliferation, and accelerated re-epithelialization, which led to rapid wound closure [207].

The biocompatibility and adhesion of CS, along with its inherent bacteriostatic impact, not only promote wound healing but also effectively prevent biofilm formation [208,209]. A liposome-in-hydrogel system was designed to deliver curcumin and improve the treatment of chronic wounds. Deformable liposomes containing curcumin with neutral (NDL), cationic (CDLs), and anionic (ADLs) surface properties were incorporated into the CS hydrogel. Incorporating CDLs into the hydrogel maintained the adhesion of the hydrogel to a greater extent than NDLs and ADLs. Furthermore, the CDLs in the hydrogel created the most stable penetration of curcumin into the skin [210].

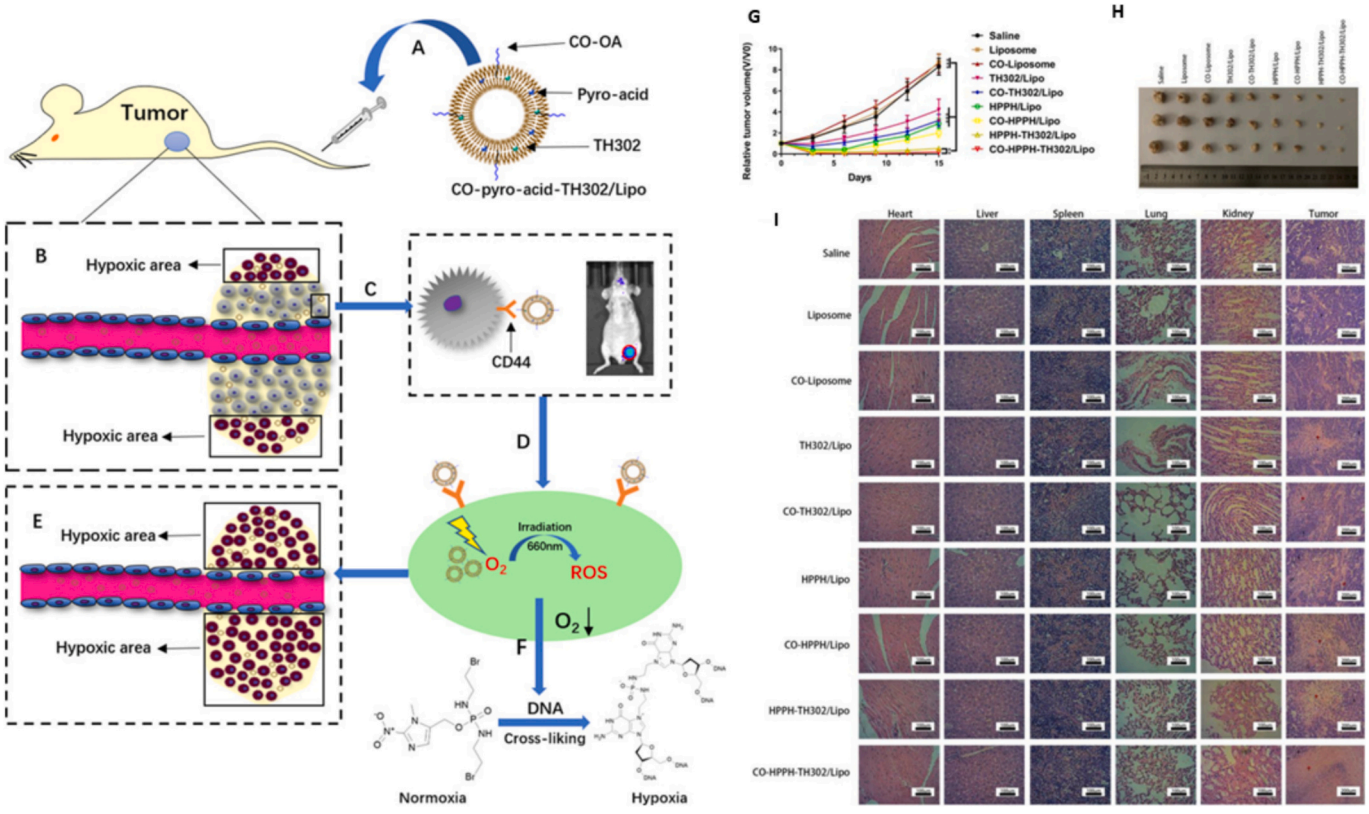

Fig. 10. Chitosan oligosaccharide-decorated liposomes for synergistic chemotherapy and photodynamic therapy. (A–F) Schematic illustration of the delivery, targeting, and therapeutic mechanism. (G) Tumor growth curves following treatment. (H) Representative tumor images. (I) Histological analysis of tumor tissues. (Reprinted with permission from BMC [133].)

Based on the mucoadhesive characteristics of CS, CS-coated liposomes may prolong residence periods at the site absorption due to the increased interaction of the vector with the absorbing mucosa. Additionally, CS's antibacterial action against both Gram-positive and Gram-negative bacteria is essential for wound healing [37,206,211]. A CS-based liposome formulation was used to raise the efficacy of substance P (SP) neuropeptide in in vitro wound healing. CS-functionalized liposomes were loaded with SP (SP-CH-LP), which revealed increased motility and cell proliferation after treatment with free and encapsulated neuropeptides. The influence of SP on wound healing was elevated by entrapment on CH-LP [212].

CS increases the function of inflammatory cells such as fibroblasts, macrophages, and polymorphonuclear leukocytes [213]. The compatibility of CS with human skin is due to the absence of irritating or allergic effects [214], and it can be effective in treating burn wounds. The effect of CS gel, containing liposome-loaded epidermal growth factor (EGF), on burn wound healing was investigated. Multilayer liposomes comprising EGF were prepared, as well as EGF gel and liposome formulations containing EGF, all of which were carried in a CS gel. The rate of cell proliferation in liposomes containing EGF in the CS gel (ELJ) formulation noticeably increased. Both histochemical and histological results indicated a greater degree of epithelialization in the ELJ group than in the other groups [215].

When CS is diluted with acids, unpleasant aromas can irritate the wound's mucous tissue [216]. Hydrogel preparations can induce cross-infection, result in non-uniform dosage, and lead to uneven drug distribution [217]. A film-forming spray of water-soluble CS, containing liposome-coated human EGF, was designed for wound healing. The hydration film method was used to prepare hEGF liposomes, and the ion gel method was applied to prepare FFSWSC. The use of hEGF-liposomes in FFSWSC significantly accelerated the healing process, and the wound was closed entirely by day 6 [218].

In wound-healing systems, CS provides bioadhesive properties and antibacterial support while enabling sustained release from liposomal carriers, which favors prolonged therapeutic exposure at the wound site.

6.6. Fibrosis and lesions

With the help of CS, polar medications can be transported across epithelial surfaces [219]. Liposomes were functionalized as nanocarriers of amphotericin B (AmB) for a non-invasive treatment model of cutaneous *leishmaniasis*. The classic anti-leishmanial drug AmB was encapsulated in liposomes, illustrating that CS gels had non-Newtonian behavior and plastic flow. Compared to the drug contained in CS gel and the CS gel alone, the liposomal AmB represented superior activity at all concentrations, even in the absence of parasites [220].

The naturally occurring anionic polysaccharide alginate and the cationic polysaccharide CS are incompatible due to their opposite charges. Thus, alginate can use electrostatic contact to self-assemble with CS, creating PEC, which forms a protective film on the surface of the liposomes (Lip). This film results in extending the retention duration of medicines on the skin surface and the drug action time [221]. Thus, tetramethylpyrazine(TMP)-loaded liposomes, surrounded by hydrogels based on sodium alginate and CS, were used as a multifunctional drug delivery system for treating atopic dermatitis. The hydrogel not only possessed the antibacterial property but also enhanced the anti-inflammatory and antioxidant effects of TMP. Additionally, it improved skin permeability, constituted a moist healing environment for dry atopic dermatitis skin, and accomplished prolonged drug release [222].

One effective way to enhance the bacterial membrane's antimicrobial capacity is the combination of membrane-targeted antimicrobials with chitosomes [223]. Thus, chitosomes-in-CS hydrogels were formulated to evaluate their impacts on acute skin injuries. Lipid nanocarriers and CS-comprising nanocarriers with membrane-active antimicrobial chlorhexidine were optimized and incorporated into a CS hydrogel. The chitosomes and CS hydrogel containing CS demonstrated a more potent antibacterial action against *Staphylococcus aureus* and *Staphylococcus epidermidis* in comparison with formulations without CS [171].

In the treatment of fibrosis and lesions, CS enhances mucosal adhesion and stabilizes liposomal formulations, supporting localized drug retention and controlled delivery.

6.7. Bone regeneration and cardiovascular applications

In recent years, CS-functionalized liposomes have emerged as promising delivery systems for bone-related therapeutics due to their ability to combine the high drug-loading capacity of liposomes with the osteoconductive, biodegradable, and cationic properties of CS. The CS coating improves vesicle stability, reduces premature drug leakage, and enhances interaction with negatively charged bone tissue components, thereby supporting localized and sustained drug release. CS-coated liposomes have been explored for the delivery of osteogenic drugs and anti-resorptive agents. For example, alendronate-loaded CS-coated liposomes were developed to improve drug stability and bioavailability while reducing gastrointestinal and systemic side effects. This CS-liposomal system demonstrated prolonged drug release and enhanced therapeutic performance compared with free alendronate, highlighting its potential for osteoporosis treatment and bone remodeling applications [224]. In addition to classical anti-osteoporotic drugs, CS-coated liposomes have also been explored for preventing therapy-associated bone loss, particularly in cancer-related settings. A representative example is the co-delivery of exemestane and genistein using CS-coated liposomes, which was designed to simultaneously enhance antitumor efficacy and mitigate bone loss in breast cancer therapy. The CS coating improved liposomal stability and enabled sustained release of both agents, while genistein contributed osteoprotective effects that counteracted exemestane-induced bone deterioration. In vivo evaluation demonstrated that the CS-coated liposomal formulation effectively suppressed tumor growth while significantly preserving bone microarchitecture and reducing bone loss compared with free drug administration. This study highlights the potential of CS-functionalized liposomes as dual-action platforms capable of integrating anticancer therapy with bone protection, further expanding their relevance in bone-related applications beyond conventional osteoporosis treatment [225].

CS–coated liposomes have also been explored in cardiovascular therapy, particularly in thrombolytic drug delivery, where site-specific retention and controlled release are essential to reduce systemic bleeding risks. Tissue plasminogen activator (tPA)–loaded liposomes coated with CS-polysulfate were reported, demonstrating that the CS coating enhanced liposome interaction with fibrin-rich thrombi and enabled more sustained release of tPA compared with uncoated liposomes or free drug. The CS layer improved thrombus localization and reduced premature drug diffusion, contributing to more effective and localized clot dissolution. In addition, the CS-coated liposomes showed synergistic performance under laser-assisted thrombolysis, highlighting their potential as responsive cardiovascular drug carriers [226]. In addition to thrombolytic therapy, CS-decorated liposomes have been investigated for the prevention of vascular restenosis, a major complication following angioplasty and stent implantation. Sirolimus-loaded liposomes functionalized with CS were developed for local vascular delivery, where the CS coating enhanced vessel wall adhesion and prolonged drug retention at the injury site. This CS-decorated liposomal system enabled sustained release of sirolimus, effectively suppressing smooth muscle cell proliferation and neointimal hyperplasia, thereby significantly attenuating restenosis compared with non-modified formulations. These findings further highlight the utility of CS-functionalized liposomes as localized cardiovascular drug carriers, particularly for applications requiring controlled release and enhanced interaction with vascular tissues [227].

7. Various routes for administration of chitosan-functionalized liposomes

7.1. Intravenous

The most effective method of administering substances into the bloodstream for diagnostic or therapeutic purposes is intravenous injection, the most common form of parenteral administration. The drug can take effect quickly and achieve complete bioavailability when administered intravenously, as it may bypass all absorption barriers. To achieve the greatest possible therapeutic efficacy, it is preferable to develop medication formulations that can be administered by injection. Liposomes are among the most extensively studied injectable nanocarriers for drug delivery [228–230]. Liposomal carriers can alter the pharmacokinetics of drugs to decrease their systemic clearance and the occurrence of unwanted side effects [229]. A limitation is that conventional liposomes can easily dissolve, clump, and fuse, which means that the medications inside can be secreted when the liposomes are stored [231]. Conversely, once injected, they are quickly recognized and removed by the mononuclear phagocyte system [232,233]. With respect to these limitations, research has indicated that surface modification of liposomes using polymers such as PEG, polyvinyl pyrrolidone, and CS and its derivatives is a promising strategy to improve liposome stability following intravenous injection [234–236]. More recently, CS-coated liposomal formulations have been proposed for the intravenous delivery of a wide range of medications, particularly those with a limited therapeutic index, which can represent a significant threat to healthy tissues.

In an effort, the mitoxantrone-loaded liposomes were modified with CS. The drug release validated the elevated stability of liposomes. The drug's plasma concentration and mean retention time were considerably improved due to liposomal encapsulation [234]. A pH-sensitive liposomal formulation was developed to co-deliver sorafenib and siRNA to tumor tissues. To enhance the antitumor effectiveness of the drug delivery system, cationic liposomes containing both chemicals were coated with CMCS, a CS derivative that is pH-sensitive. The results indicated a pH-sensitive release behavior of the suggested formulation, which demonstrated a substantially increased fluorescence intensity at acidic pH compared to physiological pH. In addition, the CMCS-functionalized liposome exhibited a remarkable reduction in tumor growth, attributed to the enhanced accumulation of sorafenib and siRNA in tumor cells. This was explained by the delivery system's protective impact against degradation and passive targeting through EPR [237]. Therefore, liposomes coated with polymers offer a promising strategy for facilitating the effective intravenous administration of harsh medications.

7.2. Oral

Among the various administration routes, the oral route remains attractive for delivering therapeutic agents because of its convenience and relatively low cost [238]. Oral bioavailability depends on pharmacological properties, gastrointestinal physiology, and the physicochemical characteristics of the drug [239]. However, the intestinal mucosal barrier can reduce the bioavailability of hydrophilic macromolecules by limiting permeation across the epithelium, whereas lipophilic small molecules cross more readily [240]. Surface functionalization of liposomes with CS and its derivatives has been investigated to improve oral delivery performance [241]. However, peptides and proteins are generally poorly absorbed via the oral route because of their considerable molecular weight, hydrophilic nature, enzymatic degradation, and short residence time at the absorption site [242,243]. A CS-coated liposomal carrier was introduced as a practical approach to surmounting these obstacles. CS-decorated insulin-loaded liposomes increased the residence time of insulin in the mucosa, promoting enteral absorption and prolonging hypoglycemic responses. Hence, this study confirmed the value of CS-liposome in achieving effective oral insulin delivery [244]. Furthermore, mucoadhesive CS-liposome was developed to increase the oral absorption of alendronate, a member of the bisphosphonate family. Evaluation of cellular uptake of various formulations using Caco-2 cells indicated that intracellular accumulation of CS-liposome was higher than that of uncoated liposomes and nonliposomal formulations. In vivo investigations of the multiple formulations revealed that mucoadhesiveness and, therefore, the prolonged retention time significantly enhanced the absorption of alendronate [245].

7.3. Transdermal

Human skin can prevent water loss and foreign substances from entering by functioning as a selective barrier to penetration. Skin protective behavior is reflected in its multilayered structure, which comprises the epidermis, which contains the stratum corneum, the dermis, and the subcutaneous tissues [246,247]. For these reasons, intact liposomes cannot be stably incorporated into topical creams; thus, it is essential to develop an approach to improve their potential for efficient transdermal delivery. Surface modification of plain liposomes via polymer coating can enhance the rigidity and surface properties of liposomes, thereby strengthening vesicle stability and facilitating drug penetration. Among the vast number of polymers currently available, CS is extensively used in transdermal delivery owing to its bioadhesivity, biocompatibility, biodegradability, and inherent antimicrobial properties. Another benefit of CS as a penetration enhancer is its ability to loosen tight junctions, which allows more product to penetrate the skin [248]. Accordingly, coating the liposomes with CS has recently been introduced to develop an effective transdermal delivery system. CS-coated liposomal formulations displayed faster and higher quantities of drug detection in the receptor phase than uncoated liposomal formulations. Conversely, CS-coating might improve liposomal formulation accumulation in the skin. Antioxidant delivery via CS-caged liposomes has thus been suggested as a perfect transdermal delivery technique for anti-aging skin care products [249].

7.4. Ocular

Several physiological and anatomical obstacles make ocular medication administration highly difficult [250]. Impaired corneal permeability, fast drainage via the nasolacrimal duct, and the quick and extensive precorneal elimination of medicines are significant challenges to effective ocular medication delivery [251]. Nevertheless, positively charged liposomes, commonly composed of cationic lipids such as dioleoyl trimethylammonium propane (DOTAP) and stearylamine (SA), may result in irritation and potential toxic effects [252]. A promising strategy for developing new cationic liposomes involves modifying their surfaces with biocompatible, positively charged components [252]. CS has attracted much interest as a cationic polysaccharide in topical ocular drug delivery [253]. CS can form electrostatic interactions with the negatively charged residues in extraocular structures, making it an ideal bioadhesive biopolymer. Additionally, by interacting with the negatively charged surface of the cornea, CS can increase the permeability of the corneal epithelial cells, thereby extending the transcorneal penetration level [254]. One important consideration is that CS is insoluble at physiological pH, which is often viewed as a significant challenge. However, this can be overcome by utilizing its derivatives. Researchers have recently concentrated on low-molecular-weight CS (LMWCS) and water-soluble CS derivatives like N-trimethyl chitosan chloride (TMC) to coat liposomes for ocular administration.

LMWCS-coated liposomes were designed for ocular delivery of cyclosporin A. The proposed formulation indicated privileges, including prolonged retention and enhanced permeation of the drug, leading to an improvement in ocular bioavailability while concurrently decreasing the toxic effects [255]. To evaluate their ability to protect human lens epithelial cells from H_2O_2-induced oxidative damage, TMC-

functionalized liposomes loaded with coenzyme Q10 were proposed. To improve transcorneal permeability, vesicles can be coated with TMCs using rhodamine-B-tagged liposomal carriers. Additionally, the interaction of diverse formulations with the corneal specimens was visualized, and the results displayed that in the case of TMC-coated liposomes, the distribution of fluorescence signals was deeper into the corneal epithelium. Coenzyme Q10-loaded TMC-functionalized liposomes revealed improved cell viability, less oxidative damage, and a lower percentage of apoptotic cells, suggesting they could be an effective ocular delivery strategy for treating cataracts [256].

7.5. Other routes of administration

The use of CS-liposome for cargo delivery via the nasal, pulmonary, or vaginal routes has been considered. To efficiently deliver drugs and antigens, the nasal route has recently attracted much attention. This is because the nasal cavity has a large surface area, a substantially vascularized epithelium, and a porous endothelial basement membrane, which allows drugs to be systemically available while avoiding the hepatic presystemic [257–259]. Moreover, the nasal-associated lymphoid tissue, a principal structure of the nasal immune system, plays a remarkable role in mucosal host defense energy metabolism [260]. Enzymatic degradation and intranasal mucociliary clearance, which occur when administered formulations penetrate the nasal epithelial barrier, can significantly reduce their bioavailability following intranasal delivery [261,262]. CS-liposomes have attracted considerable interest in nasal drug delivery due to their ability to prolong nasal residence time, protect encapsulated drugs from degradation, and enhance permeability across the nasal epithelial barrier, thereby improving bioavailability [263,264]. A CS-liposome system was developed as an efficient intranasal delivery system to expand the bioavailability of fexofenadine. These modified liposomes were found to be stable over 6 months at 4 °C, with no detectable leakage of the entrapped drug or change in the particle size of the liposomes. CS-liposomes demonstrated a mucoadhesive capability that was three times stronger than that of unmodified vesicles in mucin adsorption assays, resulting in a longer retention duration and improved drug transport across the nasal membrane. These findings were supported by the results of pharmacokinetic investigations in rats, indicating that the intranasal route of administration significantly enhanced the systemic exposure of fexofenadine compared to the oral route, even with a non-liposomal formulation. Compared to unmodified liposomes, CS-liposomes had far better bioavailability and a more prolonged release duration after intranasal delivery [263]. For both local and systemic delivery of therapeutic elements, the pulmonary pathway of drug administration has garnered considerable attention in recent decades due to its efficiency and minimally invasive nature [263]. Lungs offer a large absorption surface area, an easily permeable alveolar epithelium, a robust blood supply, minimal enzymatic activity, and the ability to bypass hepatic first-pass metabolism, resulting in excellent drug bioavailability and a rapid onset of action. Thus, relatively low doses of drugs are required for pulmonary delivery, which reduces systemic exposure to drugs and minimizes their adverse side effects [265,266]. On the other hand, it is essential to remember that the respiratory system's unique features, including airway shape, humidity, mucociliary clearance mechanism, and alveolar macrophages, can pose significant challenges to achieving optimal treatment outcomes [267]. Several approaches have been proposed to overcome these obstacles; one approach that has garnered interest in pulmonary medication administration is the use of colloidal drug carriers, particularly liposomes [268]. More recently, the coating of liposomes with CS has been used to improve liposomal stability and maximize their effectiveness in pulmonary drug delivery. CS-liposomes were prepared to deliver rifampicin to the lungs through nebulization. Their outcomes represented that for drug delivery to alveolar sites after nebulization, several benefits achieved by CS-liposomes include: 1) Stability of liposomes during the nebulization process can be enhanced, mainly when negatively charged liposomes are used as core vesicles; 2) CS-liposomes possess greatly enhanced mucoadhesive properties; and 3) all the types of rifampicin liposomal formulations, especially the CS-coated ones, demonstrated much-reduced toxicity toward human lung epithelial cells compared to free drugs. For this reason, CS-liposomes have been proposed as a viable option for nebulization-based treatment of the lungs [269].

8. Conclusion and perspectives

CS-functionalized liposomes have emerged as a versatile class of hybrid nanocarriers that integrate the structural advantages of lipid bilayers with the functional properties of polysaccharide-based coatings. As summarized in this review, surface modification of liposomes with CS provides a rational strategy to address several inherent limitations of conventional liposomes, including limited stability, premature drug leakage, and insufficient interaction with biological interfaces. By tailoring the physicochemical characteristics of the CS layer, these hybrid systems can be adapted for diverse therapeutic applications and administration routes.

Across a broad range of biomedical contexts, including cancer therapy, antimicrobial treatment, phototherapy, wound healing, and inflammatory disorders, CS coating has been shown to enhance liposomal stability, bioadhesion, cellular uptake, and controlled drug release. In addition, the chemical versatility of CS enables further functionalization with targeting ligands or stimulus-responsive moieties, expanding the design space for multifunctional and combination delivery systems. These features position CS-functionalized liposomes as a flexible platform capable of accommodating drugs with diverse physicochemical properties, including small molecules, biomacromolecules, and nucleic acids.

Despite these advantages, several challenges remain that must be addressed to facilitate the broader translational potential of CS-functionalized liposomes. Variability in CS molecular weight, degree of deacetylation, and substitution patterns can lead to inconsistent formulation performance and complicate reproducibility. Moreover, scalable manufacturing, long-term storage stability, and systematic evaluation of in vivo behavior across different administration routes require further investigation. Standardized characterization protocols and more direct comparisons with clinically approved liposomal formulations are also needed to better define structure–function relationships and therapeutic relevance.

From a future perspective, rational material design will be central to advancing CS-functionalized liposomes toward clinical translation. Fine control over CS chemistry, combined with advances in lipid composition, surface engineering, and stimulus-responsive design, may enable improved targeting precision and spatiotemporal control of drug release. Integration with emerging therapeutic modalities, such as gene editing, immunotherapy, and combination regimens, represents another promising direction. Overall, continued interdisciplinary efforts in materials science, pharmaceutical engineering, and translational biology are expected to further refine CS–liposome hybrid systems and expand their applicability in advanced biomedical applications.

CRediT authorship contribution statement

Zihan Ren: Writing – original draft. **Wei Gao:** Writing – original draft. **Xin Li:** Writing – original draft. **Yuchen Jing:** Writing – original draft. **Ming Gu:** Writing – original draft. **Peng Xing:** Writing – original draft. **Zuoqian Jing:** Writing – original draft. **Milad Ashrafizadeh:** Writing – original draft. **Jun Ren:** Supervision. **Gorka Orive:** Writing – review & editing, Supervision. **Martin F. Desimone:** Writing – review & editing, Supervision. **Xinwang Zhu:** Writing – review & editing, Conceptualization. **Qun Liu:** Writing – review & editing, Conceptualization. **Yavuz Nuri Ertas:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

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

Data availability

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

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