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Supramolecular Assembly of Triterpenoids: Current State and Biomedical Perspectives

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ABSTRACT

Triterpenoids exhibit remarkable pharmacological characteristics and have garnered significant research attention, owing to their unique backbone structures and numerous modification sites. Recent advancements in supramolecular chemistry have highlighted the potential of triterpenoids to form organized assemblies through noncovalent interactions, affording versatile functional properties. By leveraging their unique structural characteristics and biological activities, innovative strategies can be developed to enhance the efficacy and safety of biomedical therapies. This review describes the recent advances in triterpenoids serving as (i) functional groups for aggregation-induced emission, (ii) building blocks for self-transportation and drug delivery, (iii) potential gelators for rational hydrogel design, and (iv) cholesterol alternatives for optimizing lipid-based nanoparticles. The biomedical perspectives of triterpenoid-based supramolecular assemblies and potential bottlenecks in clinical translation are also discussed, with the hope of offering insights into future research and biomedical applications.

1 | Introduction

Triterpenoids are a diverse group of natural products derived from squalene precursors [1, 2] with a wide range of structural and functional characteristics. They are renowned for impressive biological activities and remarkable ability to undergo supramolecular assembly [3–6]. Bag's identification of the first nano-sized supramolecular oleanane-type triterpenoid, arjunolic acid, presented a significant opportunity for the development of supramolecular architectures at the nanoscale and the fabrication of triterpenoid nanomaterials [7]. Arjunolic acid and its derivatives exhibited excellent assembly performance and efficient gelation in various solvents at low concentrations [7]. Subsequent studies further emphasized the importance of chirality in the assembly behavior of triterpenoids [8]. These findings were the foundation for a new research area for triterpenoid compounds in supramolecular chemistry.

During the assembly process, the hydrophobic effects and van der Waals interactions between the rigid triterpenoid skeletons and intermolecular hydrogen bonds are the primary driving forces for the formation of supramolecular entities. The optimal conformations of the different molecules result in varying directions and steric hindrances of the intermolecular forces, leading to the formation of diverse assemblies. By artificially modifying the triterpenoid skeleton with new functional groups, such as oxime [9], oligopeptides [10], and benzoyl [11] groups, additional interactions can be introduced, further enhancing the diversity

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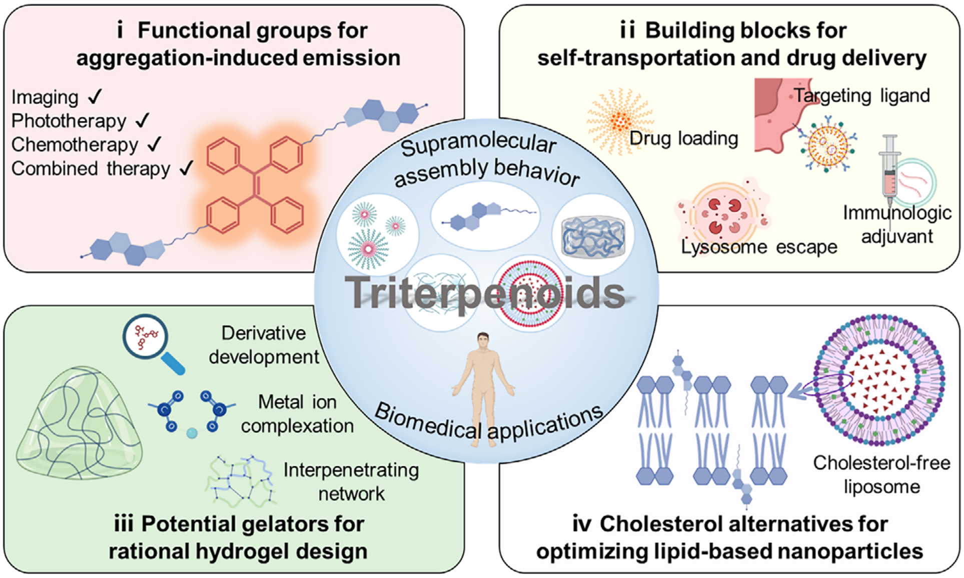

SCHEME 1 | Schematic of triterpenoid-based supramolecular assembly behavior and biomedical applications.

of the assembly properties. Currently, this approach represents a simple and effective strategy for constructing triterpenoid assemblies.

Despite the rich three-dimensional (3D) structures and chiral centers revealed in various naturally occurring triterpenoids, there remains a significant gap in understanding their self-assembly mechanisms in supramolecular chemistry and how these self-assembly processes influence specific biological properties. In this review, we systematically summarize the self-assembly properties of triterpenoids, highlighting their potential as structural frameworks for diverse biomedical applications (Scheme 1). By discussing the current knowledge on triterpenoid supramolecular assemblies, we seek to provide valuable insights into their self-assembly behavior and pave the way for future research on supramolecular design, with the aim of developing new triterpenoid-based therapeutics.

2 | Structural and Functional Characteristics of Natural Triterpenoids

Naturally occurring triterpenoids include a diverse group of organic compounds that are widely found in plants, fungi, and marine organisms (Figure 1A) and are characterized by their complex structures and various biological functions [12].

These compounds typically feature a thirty-carbon skeleton (C-30), which varies from acyclic to hexacyclic, exhibiting over 20,000 known structural variations. Despite their considerable structural diversity, triterpenoids share a common biosynthetic pathway and adhere to analogous synthetic routes [1, 2, 13]. Indeed, all terpenoids are enzymatically cyclized products derived from substrate alkene chains that contain a specific number of linear, head-to-tail condensed C-5 isoprene units [13]. The number of repeated isoprene units dictates the type of terpenoid produced. For triterpenoids, six C-5 isoprene units combine to form C-30 squalene, which is then cyclized into one of the signature carbon skeletons [14]. Based on scaffold variations, natural triterpenoids are mainly classified into several major types (Figure 1B), including tetracyclic triterpenoids (lanostane, dammarane, tirucallane, cucurbitane, cycloartane, and meliacane), pentacyclic triterpenoids (oleanane, ursane, lupane, and friedelane), and their glycoconjugates—triterpenoid saponins [12, 15]. As cyclization increases, the rigidity of triterpenoids also

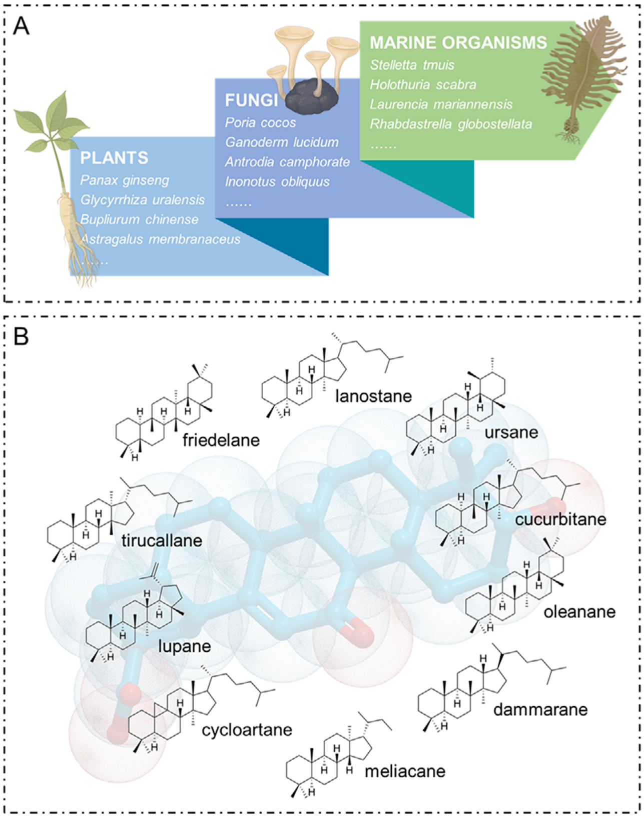

FIGURE 1 | (A) Sources of triterpenoids and some representative species. (B) Different skeletons of triterpenoid sapogenins.

increases, which is accompanied by the formation of multiple chiral centers. Combined with the conformational rigidity of the side chains, this results in more complex triterpenoid molecules. Additional artificial modifications, such as the addition of hydroxyl, carbonyl, glycosyl, and acyl chains, endow triterpenoids with greater structural diversity, together with a wide range of biological properties. Triterpenoids are known to have numerous important pharmacological characteristics (e.g., hepatoprotective, antioxidant, anti-inflammatory, antitumor, antimicrobial, and antiparasitic properties), making them protagonists in traditional Chinese medicine (TCM) and modern drug development since the 1930s [12, 15].

3 | Supramolecular Assembly Behavior and Gelation Properties of Natural Triterpenoids

Triterpenoids exhibit remarkable self-assembly properties influenced by their unique structural characteristics [4]. The supramolecular assembly of triterpenoids mainly involves noncovalent interactions, including hydrophobic effects, hydrogen bonding, electrostatic interactions, and van der Waals forces [4]. Self-assembly can lead to the formation of micelles, vesicles, or fibrous hydrogel networks, depending on the specific triterpenoid and its environment [16–18]. For example, ursolic acid, a natural pentacyclic triterpenoid carboxylic acid extracted from various medicinal plants, exhibits antitumor activity against various cancer types [19]. However, its poor aqueous solubility greatly limits its clinical applications. After self-assembling into nano-micelles using a solvent exchange method, it showed increased water solubility and improved therapeutic efficiency [20]. More recently, studies revealed that tuning the solvent system can result in a change in the microstructure of triterpenoids. For example, Li et al. [21] demonstrated that the elastic modulus of self-assembled oleanolic acid could be regulated by adjusting the ethanol content in an antiparallel zigzag manner. Compared with flexible oleanolic acid nanogels, rigid oleanolic acid nanoparticles showed enhanced antitumor efficacy accompanied by decreased collagen production.

Interestingly, many triterpenoids exhibit remarkable gelation properties that allow them to form hydrogels [22, 23] or organogels [7, 24–28] in different solvent systems. The gelation process is often driven by the molecular interactions within the triterpenoid aggregates, which can trap solvents and create a 3D network with a highly porous structure and large surface area [29]. This property is particularly valuable in pharmaceutical applications, where gels can serve as sustained-release matrices for therapeutic agents. Furthermore, owing to their intrinsic biological activity, triterpenoids can exhibit dual functionality, serving as both gel matrices and therapeutical agents. The ability of natural triterpenoids to self-assemble into micro-/nanostructures and form gels makes them promising candidates for various biological applications, especially in imaging, drug formulations, tissue scaffolds, and wound dressings [5, 30–32].

Currently, the supramolecular assembly and gelation properties of triterpenoids present exciting opportunities for innovation in materials science and biomedicine, warranting further investigation into their underlying mechanisms and practical applications. In the following sections, we briefly outline the four main biomedical applications of triterpenoid-based assemblies to provide a general understanding of the development of versatile therapeutic platforms that will propel the biomedical field forward.

4 | Design and Biological Applications of Functional Triterpenoid-Based Assemblies

4.1 | Triterpenoids as Functional Groups for Aggregation-Induced Emission

Aggregation-induced emission (AIE) refers to the phenomenon in which certain molecules exhibit enhanced fluorescence upon aggregation, in contrast to traditional fluorophores, which typically quench in concentrated solutions [33]. Triterpenoids possess complex multi-ring frameworks, largely chiral structures, multiple modification sites, and various functional groups, such as hydroxyl and carbonyl groups. These structural features not only contribute to their biological activity but also play a crucial role in the construction of modified AIE micro-/nanomaterials. Leveraging the super self-assembly abilities of natural triterpenoids, triterpenoid functionalization can significantly regulate strong intra-/inter- molecular interactions that are essential for the optimization of AIE micro-/nanomaterials [34–37]. First, self-assembling triterpenoid compounds are often used as template materials for the preparation of supramolecular chiral materials (Figure 2A) [38–41]. For example, Gao et al. [39] reported the use of an oleanolic acid-derived ideal amphiphilic molecule, C4-MOP, as a template to create novel chiral silica materials via a sol-gel silica mineralization process. Building on this research and to address the thermal stability issues of AIE-based circularly polarized luminescence materials, C4-MOP was utilized as a template to fabricate two helical organic-inorganic hybrid silica ribbons with single-handed helicity [40]. The template-removed helical silicas exhibited circularly polarized luminescence activities with enhanced luminescence efficiency (Figure 2B). This supramolecular templating polymerization approach offers a straightforward and effective method for preparing imprinting supramolecular chiral silica and enhances the application of chiral natural triterpenoids in materials science.

Secondly, the unique structures of compounds (such as tetraphenylethylene and triphenylamine) which are typical building blocks for AIE, enable them to dissipate energy through molecular rotation and vibrational processes when in a high-energy excited state in solution. This results in a significantly low fluorescence quantum yield in the solution phase [42]. Conversely, in the aggregated state, intramolecular interactions restrict the motion of the rotatable groups within the molecules (Figure 2A). Additionally, the twisted, nonplanar molecular structure effectively mitigates the strong π–π interactions commonly observed in conventional fluorescent dyes, which stem from their rigid planar configurations. This helps prevent fluorescence quenching caused by planar stacking. After conjugated with triterpenoids, which inherently possess self-assembly capabilities, the motion of the rotatable groups within the molecules is further constrained (Figure 2A). Collectively, these factors contribute to the maintenance of high-efficiency fluorescence emission in AIE molecules when in the triterpenoid aggregated state. For example, after

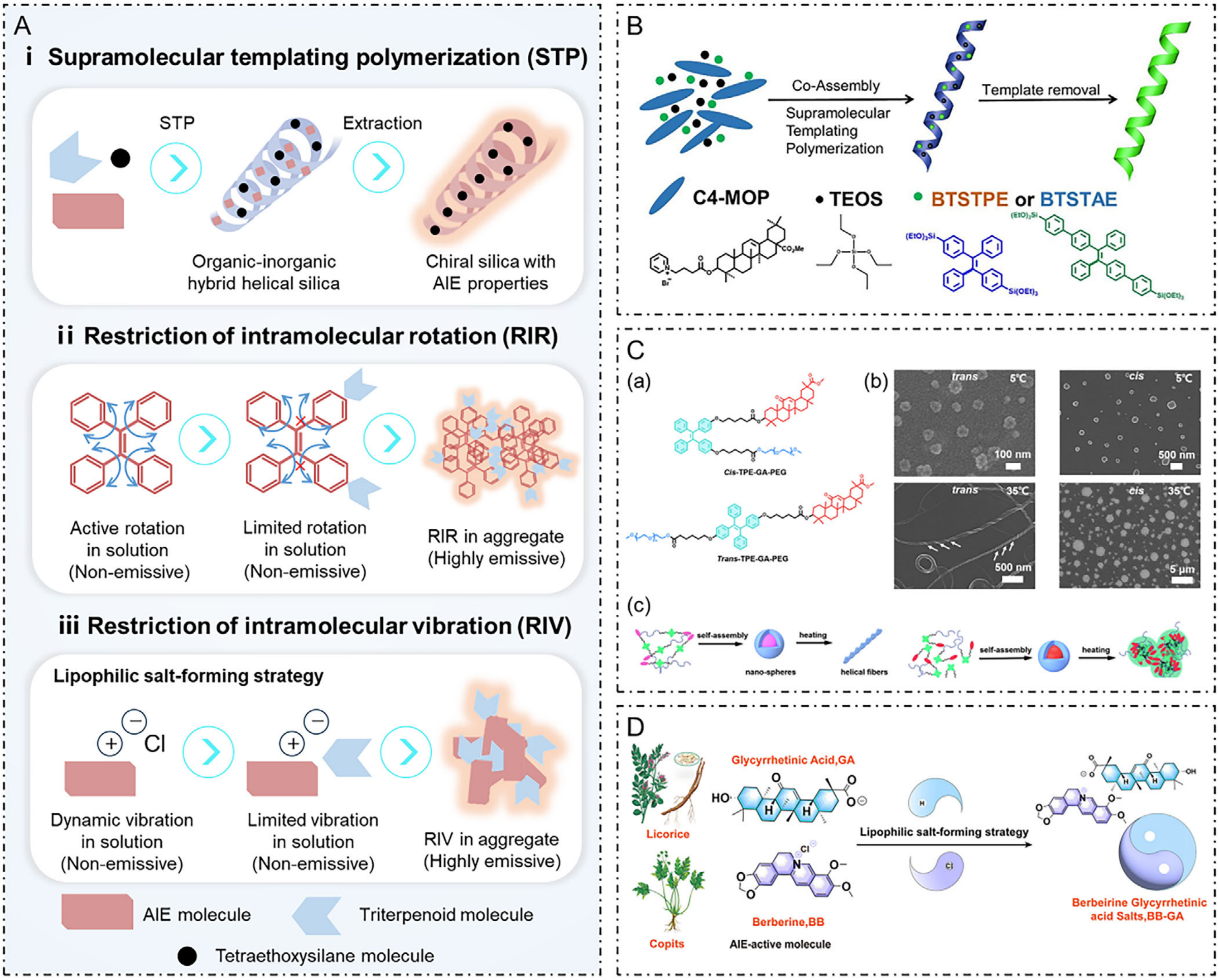

FIGURE 2 | (A) Schematic of strategies for boosting the performance of AIE molecules with triterpenoids. (B) Schematic of the formation of chiral hybrid silicas with AIE properties using a triterpenoid template and chemical structures of assembly motifs. Reproduced with permission [40]. Copyright 2022, Elsevier. (C$_a$) Chemical structures, (C$_b$) TEM images, and (C$_c$) proposed schematic of the self-assembly process. Reproduced with permission [35]. Copyright 2023, American Chemical Society. (D) Schematic of the fabrication of berberine–glycyrrhetinic acid salts via the lipophilic salt-forming strategy. Reproduced with permission [44]. Copyright 2024, American Chemical Society.

conjugation with glycyrrhetinic acid, the thermo-responsive amphiphilic cis-/trans-tetraphenylene-glycyrrhetinic acid-polyethylene glycol (TPE-GA-PEG) isomers displayed different self-assembly behavior in different solvent systems under light irradiation (Figure 2C) [35]. As the water content increased in the tetrahydrofuran/water solution, trans-molecules exhibited characteristic AIE properties, leading to the formation of nanospheres. In contrast, isomers demonstrated enhanced fluorescence, accompanied by a red shift in wavelength and the generation of nanovesicles (Figure 2C). This strategy can also be observed in some other studies [37, 43]. In addition, when conjugated with AIE luminogens (AIEgens), the resulting triterpenoid–AIEgen complexes have been reported to enhance cancer treatment through chemotherapy combined with photodynamic therapy. A recent example is mitochondria-targeted triterpenoid–AIEgens comprising betulinic acid/oleanolic acid/ursolic acid and triphenylamine with pyridinium groups [36]. These triterpenoid–AIEgen fluorescent derivatives possessed near-infrared-activated and AIE properties, which endowed them with imaging and potent chemo-photodynamic combined therapy activities both in vivo and in vitro.

Finally, in addition to molecular conjugation, the lipophilic salts self-assembled with acidic triterpenoids and alkaline AIE molecules often exhibit a limited dynamic vibration in solution, thus enhancing the performance of AIE (Figure 2A) [44, 45]. For instance, berberine–glycyrrhetinic acid salt nanodrugs have been successfully fabricated following a proprietary lipophilic salt formation strategy (Figure 2D) [44]. An almost 10-fold increase in fluorescence intensity was observed compared with berberine alone, which is beneficial for in vivo imaging [44].

Triterpenoid–AIE conjugated materials, with their unique structural features and enhanced AIE properties, represent a compelling field of research that bridges natural products with advanced materials science. The unique molecular architecture of triterpenoids contributes to their biological activity and facilitates their application in innovative material technologies. Their ability to enhance fluorescence upon aggregation holds great potential for innovative applications, particularly in enhanced imaging techniques and photodynamic therapy, making them valuable research subjects in the ongoing exploration of AIE-based functional materials. To sum up, their dual function of being both therapeutic agents and advanced materials renders them highly promising for applications in the field of AIE-based technologies.

4.2 | Triterpenoids as Building Blocks for Self-Transportation and Drug Delivery

4.2.1 | Co-Assembled Triterpenoid Nanoparticles for Self-Transportation and Drug Delivery

Inspired by the self-assembly of natural triterpenoids, studies have focused on the capacity of self-transportation and drug loading of natural triterpenoids and their derivatives in different solvent systems (Figure 3A) [46–53]. The ability to control these assemblies opens new avenues for designing novel drug delivery systems with unique properties. For example, maslinic acid is a naturally occurring bioactive triterpenoid containing dihydroxyl and mono-carboxyl groups. Sodium and potassium salts of the nanosized maslinic acid can efficiently self-assemble into vesicular nanoparticles and load drugs (Figure 3B). Furthermore, changes in the pH of the medium can result in lysis of the vesicular morphology with concomitant release of the entrapped doxorubicin [50]. In addition, recent reports have unveiled that triterpenoid-based carbon dots exhibit self-assembly capabilities and possess unique biological properties [54–61]. For instance, using three triterpenoids (oleanolic acid, glycyrrhetinic acid, and ursolic acid) as precursors, novel triterpenoid-carbon dots were fabricated using a one-step solvothermal approach for effective cancer therapy (Figure 3C) [56]. In two other examples ursolic acid–carbon dots [55] and ginsenoside Rg1–carbon dots [59] were successfully prepared using similar methods. Both nanoparticles functioned as multi-model anticancer therapeutic agents, resulting in improved therapeutic efficiency and reduced adverse effects [55, 59].

The co-assembling of multiple terpenoids [65–68] or with other compounds (e.g., flavonoids [69–71], carotenoids [72], polyphenols [73], bilins [74], and quinones [75, 76]) greatly improves the aqueous solubility and bioavailability of drugs and achieves high drug loading. Besides, through some specific chemical modifications, the introduction of various stimuli-responsive linkers or targeting moieties can benefit the smart delivery and controlled release of therapeutics [62, 77–81]. In one example termed TK-GA_2-Rh2 NPs, a carrier-free triterpenoid-based co-assembled prodrug consisting of ginsenoside Rh2 and TK-GA_2 (two glycyrrhetinic acid molecules conjugated with a thioketal linker) was fabricated [62]. These glucosyl group-equipped nanoparticulate prodrugs were competitively taken up by oral squamous cell carcinoma cells through glucose transporters (GLUTs). The reactive oxygen species (ROS) endogenously generated by glycyrrhetinic acid triggered the ROS-specific bond cleavage for self-boosted drug release and synergistically induced strong cell apoptosis with ginsenoside Rh2 (Figure 3D).

Furthermore, owing to the combination of various functional components, it is often feasible to fabricate carrier-free nanodrugs. This innovative approach leverages the synergistic properties of multiple constituents, allowing the development of nanodrugs that do not rely on traditional carrier systems. Compared with single treatments, triterpenoid-based carrier-free nanodrugs exhibit outstanding synergistic therapeutic effects and fewer side effects [62, 66–71, 75, 77, 78, 82–92]. Noncovalent interactions between triterpenoids and other types of compounds (such as sonosensitizers and photosensitizers) often participate in the construction and stability maintenance of the self-assembled carrier-free prodrug systems. For example, oleanolic acid could self-assemble with heptamethine cyanine (Cy7) and hematoporphyrin (Hp) via hydrogen bonds and hydrophobic interactions [84]. This prodrug showed deep tumor penetration and generated multiple long-lived hypertoxic reactive species, thus achieving effective chemo-sonodynamic combination therapy. The absence of carriers can enhance the pharmacokinetic profiles of triterpenoid-based nanodrugs, potentially improving their therapeutic efficacy and reducing their side effects. Consequently, triterpenoid-based carrier-free nanodrugs are highly promising for facilitating the translation of triterpenoid-based therapeutics from the bench to the bedside.

Triterpenoids can also serve as multifunctional platforms for delivering biomacromolecules (e.g., peptides) in addition to small molecules [63, 93–95]. In one example of triterpenoid–peptide complexes, a lanostane-type triterpenoid acid, dehydrotrametenolic acid (DTA), was used to encapsulate GLP-1 (Figure 3E) [63]. The resulting GLP-1-NPs exhibited a rod-like morphology akin to that of DTA-NPs without encapsulation. During intraperitoneal glucose tolerance tests, mice received an intraperitoneal injection of glucose followed by oral delivery of GLP-1-NPs and showed a significant decrease in their glucose levels compared with the free GLP-1 oral group. To address the low solubility and poor permeability in the transdermal delivery of peptide drugs, bioactive self-assembled nano-micellar ionic liquids were successfully prepared using oleanane-type triterpenoid glycyrrhizic acid and oxymatrine in another example [95]. The amphiphilic nature of glycyrrhizic acid, combined with the presence of carboxyl groups, enhances the strong electron-donating capabilities of the N^+–O^- and C=O bonds in the chemical structure of oxymatrine, thereby facilitating the formation of stable nano-micellar ionic liquids. After loading with palmitoyl pentapeptide-4 in the absence of additional auxiliary materials, permeation, and subcutaneous retention were significantly increased. Furthermore, the exceptional anti-inflammatory properties of glycyrrhizic acid, combined with the antiphotoaging capabilities of oxymatrine and palmitoyl pentapeptide-4, collectively contributed to an unprecedented antiphotoaging effect. These results suggest that triterpenoids are promising peptide drug delivery vehicles for both oral and transdermal delivery.

The assembly of triterpenoids with biomacromolecules significantly facilitates the delivery of active biomolecules as discussed above, while certain biomacromolecules can also participate in and regulate the formation of triterpenoid self-assemblies. These biomacromolecules typically exhibit excellent molecular

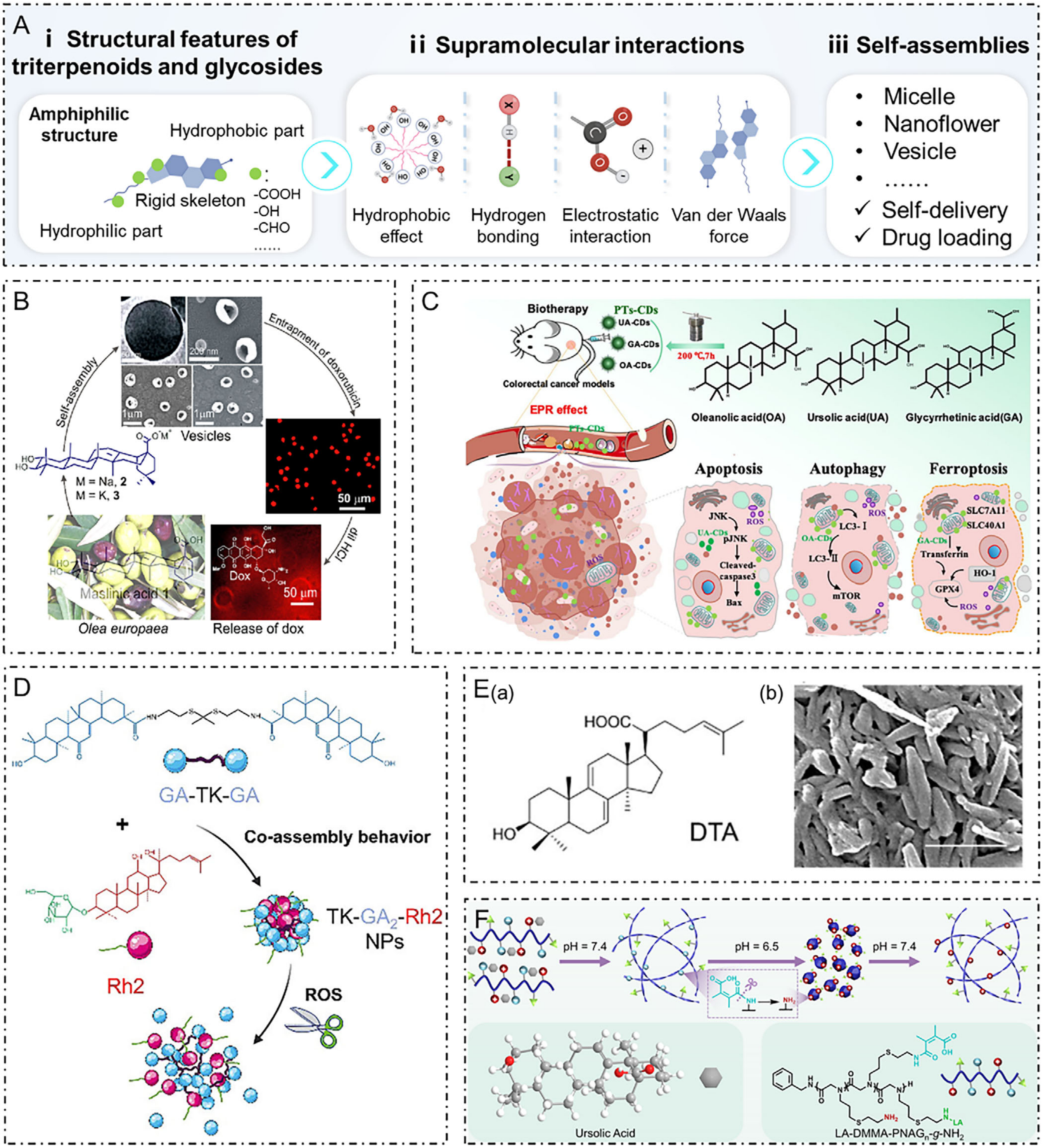

FIGURE 3 | (A) Schematic of self-assembly strategies for triterpenoids. (B) Self-assemblies of sodium and potassium salts of maslinic acid and their applications on drug loading. Reproduced with permission [50]. Copyright 2023, Elsevier. (C) Triterpenoid-based carbon dots exert anticancer activity through a multimodel approach. Reproduced with permission [56]. Copyright 2023, Elsevier. (D) Triterpenoid-based prodrug fabricated with ROS self-supplied TK-GA_2 and ginsenoside Rh2 for self-boosted drug release and synergistic oral squamous cell carcinoma chemotherapy. Reproduced with permission [62]. Copyright 2024, American Chemical Society. (E_a) Molecular structure of DTA and (E_b) SEM images of GLP-1-NPs, scale bar: 500 nm. Reproduced with permission [63]. Copyright 2019, Springer Nature. (F) Schematic design of pH-responsive cofactor-assisted ursolic acid helix. Reproduced with permission [64]. Copyright 2025, American Chemical Society.

flexibility and tunable intermolecular interactions, demonstrating significant potential in the construction of functional triterpenoid nanomaterials. Inspired by the dynamic regulatory mechanisms of molecular chaperones, Lin et al. innovatively designed an active polypeptoid as an assembly facilitator for ursolic acid compounds (Figure 3F) [64]. To do so, the team simulated the precise assembly process of biomacromolecules, utilizing bioactive polypeptoids to regulate the in situ dynamic self-assembly of ursolic acid, successfully constructing a pH-responsive helical nanofiber structure. This self-assembly process exhibited a distinct three-stage evolution: initially forming nanoscale subunits, followed by assembly into virus-like nanoparticles, and ultimately organizing into stable helical nanofibers (Figure 3F). The stability of this assembly system was synergistically regulated by multiple factors, particularly critical parameters such as charge ratio, salt concentration, degree of polymerization, and solution pH. Notably, this system demonstrated excellent reversible pH-responsive behavior, maintaining a stable fibrous morphology under neutral pH conditions while spontaneously transforming into virus-like nanoparticles in acidic environments at the tumor site. This intelligent morphological transformation significantly enhanced the penetration efficiency of the nanodrug in tumor tissues, thus inhibiting tumor growth and metastasis.

4.2.2 | Improved Intracellular Delivery and Endosomal/Lysosomal Escape through Triterpenoid-Induced Lipid Reintegration

In 1962, Bangham et al. [96] first reported triterpenoid saponin-induced membrane permeabilization after observing hexagonal structures on cholesterol-containing planar membranes treated with triterpenoid saponin. They suggested the formation of a hexagonal micellar structure by saponins and cholesterol, which generated transient pores in the membrane plane. This observation was subsequently confirmed ex vivo when isolated human erythrocyte cell membranes were treated with saponin, resulting in the formation of pores that were large enough to permit the diffusion of substantial 450 kDa proteins [97]. The membrane disruption and reintegration caused by the sophisticated interaction between triterpenoid saponins and phospholipid membranes have been applied to enhance the intracellular delivery of drugs and improve lysosomal escape, particularly for peptides and nucleic acid therapeutics (Figure 4A). For example, based on these findings, α-hederin, a pentacyclic triterpenoid saponin, was utilized as a drug carrier for intracellular delivery (Figure 4B) [98]. The distinctive permeabilization and amphiphilic characteristics of triterpenoid saponins enabled the successful delivery of large nanoparticles in less than 5 min, which is approximately 20 times faster than that of previously reported nanoparticle delivery systems.

To access the cellular transcription machinery, nucleic acids must escape from the endosomes/lysosomes into the cytosol. Several innovative strategies have been developed to augment the endosomal/lysosomal escape of nucleic acids and avoid therapeutic failures [102]. Owing to their excellent fusogenic properties with cell lipid membranes, triterpenoid saponins have been explored as powerful tools for increasing the endosomal/lysosomal escape of peptide or nucleic acid-containing nanocarriers. Weng et al. first demonstrated that certain triterpenoid saponins specifically facilitated the release of saporins from late endosomes and lysosomes into the cytosol while preserving the integrity of the plasma membrane [103]. Since then, considering the major obstacle of efficient gene delivery and the membrane-active properties of triterpenoid saponins, studies have focused on a series of triterpenoid saponins isolated from plants as endosomal/lysosomal escape-enhancing agents for improved gene delivery [99, 100, 104, 105]. Among these, SO1861, a natural triterpenoid glycoside, has been shown to efficiently augment the escape of the genetic cargo from endosomes and lysosomes into the cytosol via its membrane-activated properties (Figure 4C) [99]. A strategy has been developed by Kolster et al., who described a gene delivery vector consisting of plasmid DNA, a poly-*L*-lysine (PLL) cationic peptide, and the triterpenoid SO1861 (Figure 4D) [100]. Transfection efficiency assay on multiple cell lines showed superior susceptibility to transfection in various tissues and organisms of origin. Corresponding in vivo tests showed inhibited tumor growth and improved survival rate for the SO1861-equipped gene delivery vector compared with the control group.

In addition, the independent construction of triterpenoid saponin-functionalized nanoparticles, combined with targeted drug delivery systems, has been shown to be an effective strategy for enhancing endosomal escape. An example of a modified superparamagnetic iron oxide nanoparticle (SPION) incorporated dianthin-epidermal growth factor (a targeted toxin) and SO1881, allowing for a comparison of the toxicity and targeting efficacy of the dianthin-epidermal growth factor in the presence or absence of SO1861-SPION (Figure 4E) [101]. The results demonstrated that SO1861-SPION significantly enhanced the toxicity (by 2000-fold) and targeting efficacy (by 6.7-fold) of dianthin-epidermal growth factor-SPION when used alone.

4.2.3 | Triterpenoids for Immune Stimulating and Fabricating Vaccine Adjuvant System

Quillaja saponaria-21 (QS-21, Figure 5A), a triterpenoid saponin present in the chromatographic fractions of the Chilean soapbark tree, is well known for its role as an immunostimulatory adjuvant in vaccines. This is especially important in subunit vaccines, where the immune system may not respond sufficiently strongly to the isolated antigens without an adjuvant. QS-21 is a potent adjuvant currently used in both exploratory and licensed vaccines. Compared with classical vaccine adjuvants, such as aluminum hydroxide [106], QS-21 can boost the effectiveness of vaccines by enhancing the immunogenicity of antigens via the activation of immune cells. QS-21 has been utilized as an integral component of advanced/licensed vaccines against malaria [107, 108], respiratory syncytial virus [109, 110], severe acute respiratory syndrome coronavirus 2 [111, 112], rabies virus [113], cancers [114], and many more [115, 116].

Several hypotheses suggest that QS-21 enhances the antigen uptake by the antigen-presenting cells (APCs) by binding to cell surface lectins via its carbohydrate domains. This interaction can result in specific cytokine profiles that boost the responses of T and/or B cells [117–119]. Additionally, a proposed mechanism indicates that QS-21 (and other related QS triterpenoid saponin

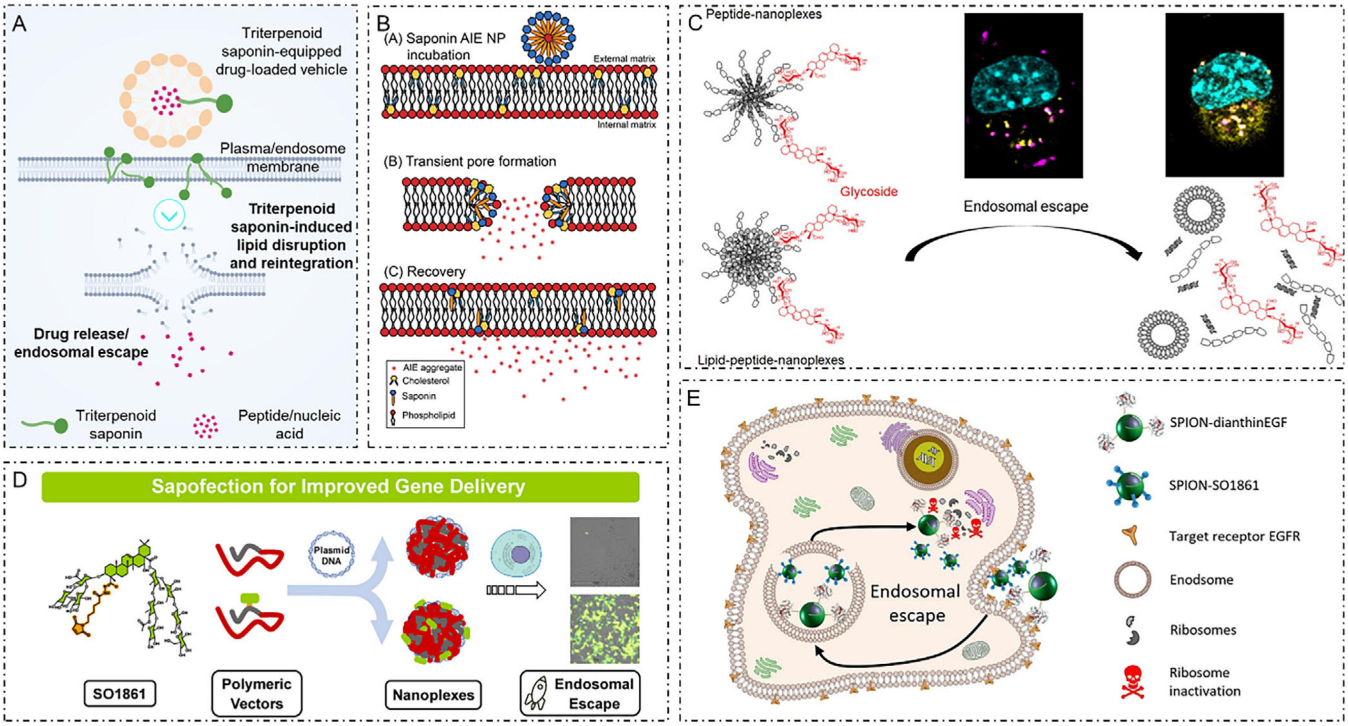

FIGURE 4 | (A) Improved intracellular delivery and endosomal/lysosomal escape through triterpenoid saponin-induced lipid disruption and reintegration. (B) Schematic of the cell permeabilization mechanism of triterpenoid saponin micelles for the ultrafast delivery of nanoparticles. Reproduced with permission [98]. Copyright 2017, American Chemical Society. (C) Triterpenoid aglycon SO1861 mediates the enhanced endosomal/lysosomal escape of the genetic cargo. Reproduced with permission [99]. Copyright 2015, Elsevier. (D) Cationic peptide-triterpenoid conjugates with superior transfection efficiency and cell viability mediated by SO1861. Reproduced with permission [100]. Copyright 2024, American Chemical Society. (E) SO1861-functionalized superparamagnetic iron oxide nanoparticles as endosomal escape enhancers for the delivery of targeted toxins. Reproduced with permission [101]. Copyright 2021, MDPI.

adjuvants) acts effectively on both dendritic cells (DCs) and T cells [117–119]. Most importantly, the strong affinity of QS-21 for lipid bilayer membranes destabilizes the membrane [96, 97], leading to membranous pore formation as discussed above. This process facilitates the escape of antigens into the cytosol where they are further processed into peptides. These peptides are then loaded onto major histocompatibility complex molecules and present on the surface of DCs to naïve CD8$^+$ T cells, resulting in the generation of cytotoxic T lymphocytes (CTLs) and the secretion of the corresponding cytokines (Figure 5C) [115, 117–119]. In a recent representative example (Figure 5D) [112], a highly modular triterpenoid saponin-based nanoparticle platform has been developed, incorporating Toll-like receptor agonists (TLRas) such as TLR1/2a, TLR4a, and TLR7/8a adjuvants, along with their mixtures. These diverse TLRa-triterpenoid saponin nanoparticle adjuvant constructs elicited distinct acute cytokine and immune-signaling profiles, resulting in specific T helper responses. Overall, this work highlighted a modular TLRa-triterpenoid saponin nanoparticle adjuvant platform that has the potential to enhance vaccine design and influence modern vaccine development.

QS-18 is the most abundant QS saponin fraction, exhibiting a subtle structural difference (an additional β-D-glucopyranosyl unit) in the oligosaccharide domain of the quillaic acid moiety (Figure 5B). However, the applications of QS-18 are limited due to toxicity concerns, according to some preclinical studies [122]. Compared with QS-21 liposomes, recent studies revealed that QS-18 formulated in liposomes (Figure 5E) generated higher levels of CD8$^+$ T cells specific to cancer neoepitopes and tumor-associated antigens. This study comprehensively evaluated the adjuvanticity and toxicity of QS-18 and QS-21 to determine the feasibility of replacing QS-21 with QS-18 in vaccine development [120].

Macrophages, as a crucial component of the innate immune system, heavily rely on specific metabolic reprogramming to perform their immune functions [123]. Therefore, the development of adjuvants that can reprogram macrophages is equally important. Most recently, a polysaccharide nanoparticle adjuvant termed MPSNPr has been developed (Figure 5F) [121]. This innovative study directly conjugated dextran with betulinic acid to create an engineered nanoparticle adjuvant. Compared with free betulinic acid, dextran-betulinic acid enhanced cancer immunotherapy by inducing M1 polarization in macrophages, promoting DC maturation, and activating CTLs, leading to significant inhibition of tumor growth in the mouse model.

Collectively, QS-21 together with the related QS fractions (such as QS-18, QS-17, and QS-7) [122, 124] and other potential immunomodulatory triterpenoids play crucial roles in the fields of immunotherapy and vaccine development. Their ability to enhance immune responses and act as effective adjuvants makes them promising candidates for improving vaccine formulations and overall public health outcomes. Particularly in the context of liposomal vaccines, the incorporation of these triterpenoids may enhance the stability and delivery of antigens, thereby affording

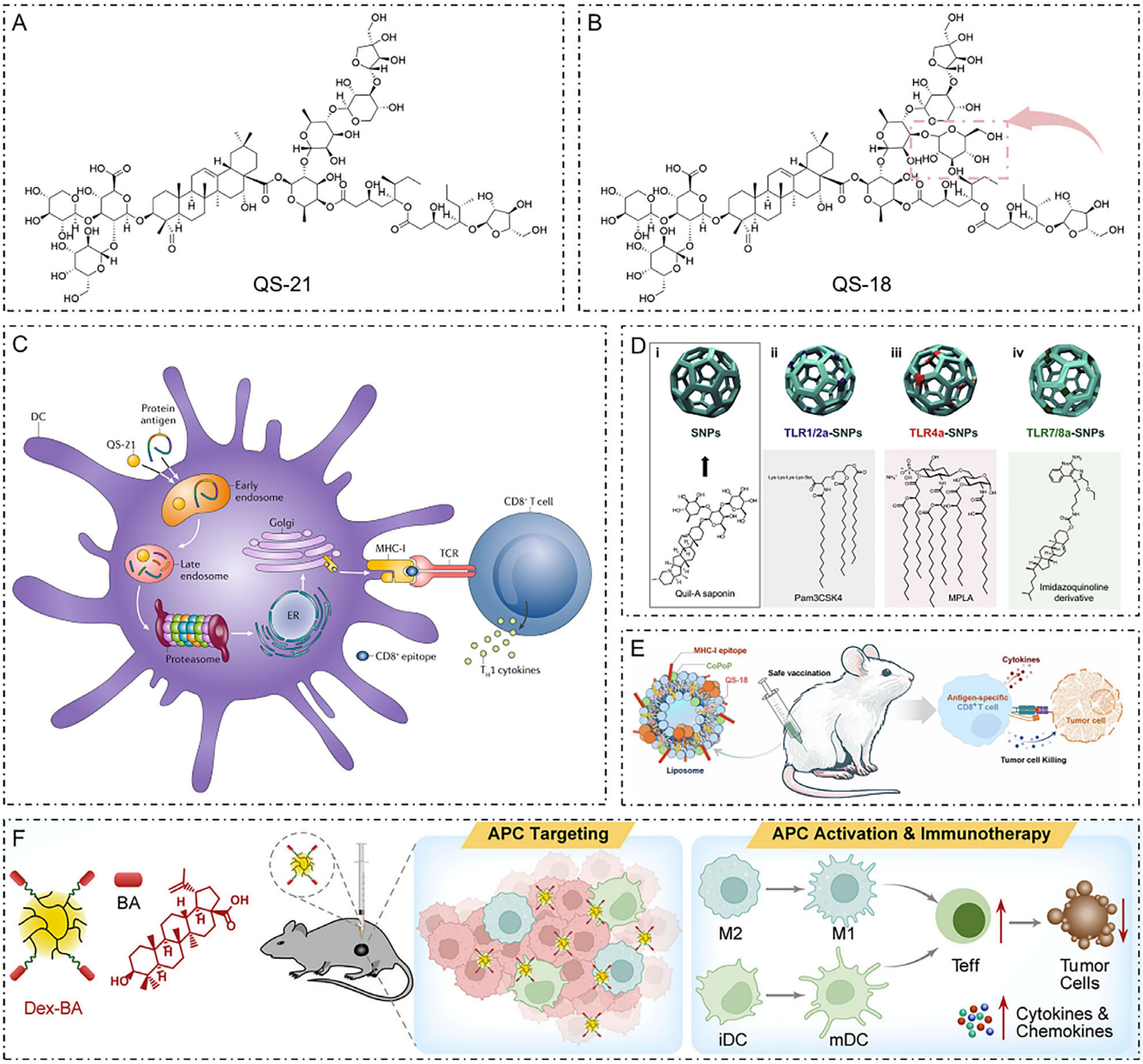

FIGURE 5 | Chemical structures of (A) QS-21 and (B) QS-18. (C) Proposed mechanism of action for QS-21-related saponin adjuvants. Reproduced with permission [119]. Copyright 2021, Springer Nature. (D) Schematic representation of triterpenoid saponin nanoparticles and different formulations. Reproduced with permission [112]. Copyright 2024, The American Association for the Advancement of Science. (E) QS-18 formulated liposomal vaccines. Reproduced with permission [120]. Copyright 2024, Elsevier. (F) Activation of APCs by proinflammatory polysaccharide nanoadjuvant (dextran-betulinic acid) for enhanced cancer immunotherapy [121]. Reproduced with permission. Copyright 2025, The Authors.

a more robust immune response. With ongoing research delving deeper into the mechanisms of action and optimal formulations of immune-stimulating triterpenoids, their potential applications in immunotherapy and vaccine technologies are likely to expand significantly. This could pave the way for innovative therapeutic interventions and ultimately contribute to advancements in disease prevention and treatment strategies in public health.

4.2.4 | Enhanced Active Targeting Drug Delivery by Triterpenoid Modification

In the 1990s, studies [125–127] revealed that glycyrrhetinic acid and glycyrrhizic acid bound specifically and reversibly to a particulate fraction of rat livers, suggesting, for the first time, the higher affinity of these two triterpenoids toward the liver compared with other organs, through their specific binding proteins. Since then, several studies have reported the presence of a large number of glycyrrhetinic acid receptors in human hepatocyte membranes, especially hepatocellular carcinoma cells [128]. Receptor-mediated endocytosis facilitates the selective uptake of drugs conjugated with glycyrrhetinic acid, enhancing their accumulation in liver tissues and minimizing systemic side effects. These studies have paved the way for the development of hepatoma-targeted therapy with the fabrication of glycyrrhizic acid and glycyrrhetinic acid-modified liposomes [129–132], polymeric nanoparticles [133–137], recombinant human serum albumin nanoparticles [138], extracellular vesicles [139], metal-organic frameworks [140], and others [141–143] (Figure 6A). As shown in Figure 6B, a drug carrier was

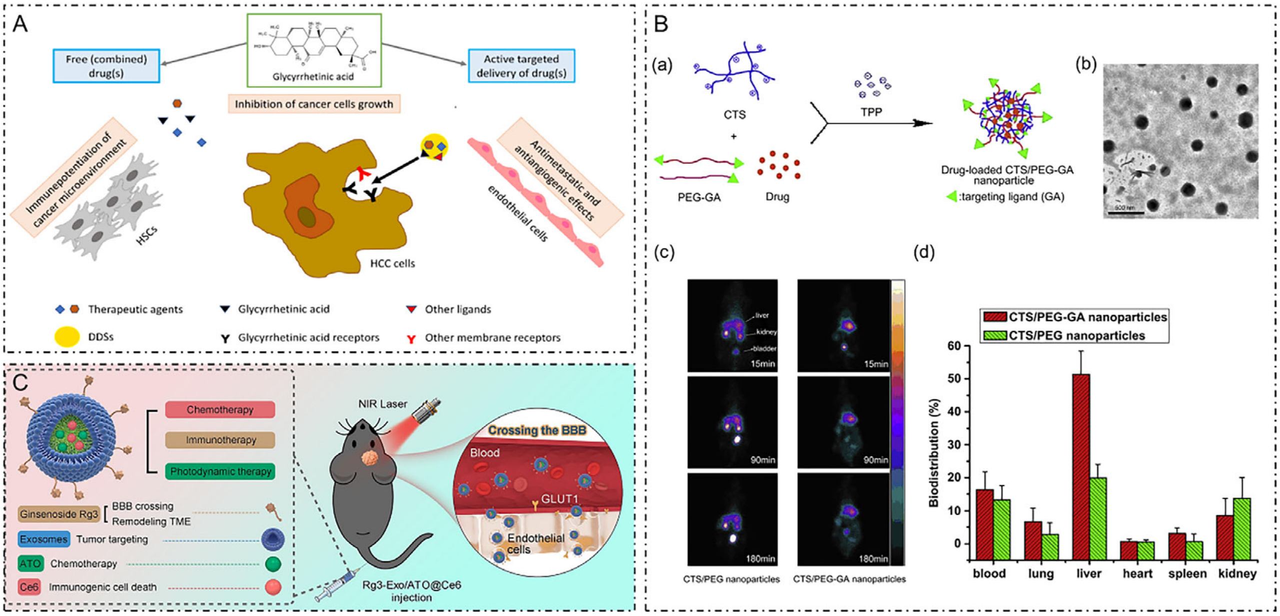

FIGURE 6 | (A) Chemical structures of glycyrrhetinic acid and modified delivery systems with hepatocyte-targeting effects. Reproduced with permission [143]. Copyright 2022, MDPI. (B_a) Preparation of the CTS/PEG-GA nanoparticles. (B_b) TEM image of the CTS/PEG-GA nanoparticles. (B_c) Single-photon emission computed tomography images of the mice after injections with the CTS/PEG and CTS/PEG-GA nanoparticles at 15, 90, and 180 min. (B_d) Tissue distribution of radiolabeled CTS/PEG and CTS/PEG-GA nanoparticles 180 min after intravenous injection. Reproduced with permission [133]. Copyright 2010, Elsevier. (C) Schematic depiction of ginsenoside Rg3-engineered exosomes for potent and orthotopic glioblastoma-specific synergistic therapy. Reproduced with permission [144]. Copyright 2023, Elsevier.

fabricated using chitosan/poly(ethylene glycol)-glycyrrhetinic acid (CTS/PEG-GA, Figure $6B_a$) and characterized (Figure $6B_b$). After injection, single-photon emission computed tomography was used to evaluate the liver-targeting ability of the CTS/PEG-GA nanoparticles. Real-time biodistribution analysis revealed consistently high radioactivity in the liver within 180 min, with no significant decrease observed until the end of the measurement (Figure $6B_c$,B_d) [133].

Considering the critical role of targeting performance in pharmacology, glycyrrhizic acid, and glycyrrhetinic acid is highly promising as targeting ligands in liver-targeted drug delivery systems. Their inherent ability to bind selectively to specific liver receptors significantly enhances the efficacy and safety of therapeutic agents. This selective binding mechanism not only facilitates the precise delivery of drugs to liver tissues but also minimizes off-target effects, thereby improving the overall therapeutic index of the administered agents. Incorporation of these ligands into advanced drug delivery strategies represents a substantial advancement in the field of targeted therapy. By leveraging their natural affinity for liver receptors, more effective delivery systems can be developed, that optimize drug concentration at the site of action, while reducing systemic exposure. This is particularly beneficial for the treatment of liver-related diseases, in which localized delivery can lead to improved patient outcomes. Ongoing research is actively investigating the full potential of glycyrrhizic acid and glycyrrhetinic acid for various therapeutic applications. As the knowledge in this area expands, it is anticipated that these compounds will play a pivotal role in the development of innovative treatment modalities for liver diseases, ultimately contributing to enhanced clinical management and therapeutic success.

Glycosylation strategies have been a focal point of research in the field of pharmacology owing to their potential to facilitate carrier-mediated transport across the blood–brain barrier through specific binding to the GLUTs on endothelial cells [145]. Numerous triterpenoid glycosides, such as ginsenoside Rg3 and Rh2, have been shown to contribute to the development of targeted drug delivery systems via the interaction between the glycones and GLUTs. Notably, many tumor cells exhibit high expression of GLUTs due to their abnormal proliferation phenotype and significant energy demands, providing an opportunity for triterpenoid glycoside-modified drug delivery systems [62, 144, 146]. Consequently, they are particularly well-suited for the treatment of brain tumors, such as glioblastoma. Li et al. recently reported a ginsenoside Rg3-functionalized homologous glioblastoma cell-derived exosomes encapsulated with arsenic trioxide and chlorin e6 (Figure 6C). The presence of glucosyl residues in ginsenoside Rg3 was shown to significantly enhance the ability to cross the blood–brain barrier and target glioma sites of the drug system, thereby exerting a potentiated synergistic antitumor effect [144]. It is noteworthy that the application of glycosylation strategies, combined with the use of triterpenoids as cholesterol substitutes, significantly enhances the construction and optimization of lipid-based nanoplatforms. This topic will be further discussed in Section 4.4.

4.3 | Triterpenoids as Potential Gelators for Rational Hydrogel Design

Self-assembled triterpenoid hydrogels have attracted considerable attention in payload-free hydrogel [147–151] and the delivery of small-molecule drugs [152–162], TCM extracts [163], or pharmacological nanoparticles [157, 164–166]. These hydrogels are formed through the spontaneous assembly of triterpenoid molecules into a 3D network [3–5, 22, 167, 168], offering excellent biocompatibility, biodegradability, and sustained drug release. By incorporating specific additional materials and employing tailored preparation methods, triterpenoid hydrogels can be endowed with tunable viscoelasticity, injectability, and thermoresponsiveness, which are required for various biological applications [3–5]. The three main approaches for designing functional triterpenoid-based hydrogels are summarized and emphasized in the following sections.

4.3.1 | Triterpenoid Derivative Development

Triterpenoids and their derivatives have been widely used as gelators, owing to their structural versatility, which allows for tailored modifications for enhanced solubility, mechanical strength, and biocompatibility.

Many triterpenoid compounds can spontaneously assemble into stable hydrogel systems under specific experimental conditions without the need for additional crosslinking agents or any chemical modification. These hydrogel systems often exhibit greater structural stability compared with poorly soluble monomeric triterpenoids. For instance, while the water solubility of sodium aescinate is relatively low, a simple process of heating, dissolving, cooling to gel, and freeze-drying results in a sodium aescinate powder that demonstrated excellent self-gelling properties (Figure 7A), making it suitable for effective wound sealing and rapid hemostasis [149]. Furthermore, these hydrogel systems also display enhanced biological activity in most cases, largely attributed to the unique interactions between their nanofibril structures and biological membrane interfaces following gel formation. A recent study reported a hydrogel network formed from a triterpenoid saponin zingibroside R1 extracted from *Panax notoginseng* (Figure 7B$_a$) [150]. In solution, zingibroside R1 exhibits poor solubility and limited antifungal activity; however, after a straightforward heating-cooling process, zingibroside R1 could form a 3D hydrogel network composed of tubular nanofibrils (Figure 7B$_b$), significantly enhancing its stability and antifungal properties. Studies on the interaction between the fibril structure and fungal cell walls revealed that zingibroside R1's nanofiber structure can specifically recognize the glucan components of fungal cell walls, thereby compromising their structural integrity (Figure 7B$_c$).

Triterpenoid derivatives can also be engineered to exhibit enhanced gelation properties, leading to hydrogels with desirable characteristics such as controlled release and biodegradability, together with an unprecedented hierarchical self-assembly behavior [169–177]. For instance, using glycyrrhetinic acid (Figure 7C$_a$) as the mother nucleus, the derivative GN-Bn (Figure 7C$_b$) was designed and synthesized. Governed by π–π stacking, hydrogen bonding, and van der Waals forces, GN-Bn could self-assemble into a hydrogel in water containing 10–30% ethanol. Micromorphology analyses showed that its 3D network skeleton was composed of nanofibers [169]. To explore novel bacteriostatic agents based on glycyrrhetinic acid hydrogels, Guo et al. developed a glycyrrhetinic acid derivative, GA-O-20 (Figure 7C$_c$), which exhibited exceptional bactericidal ability and was two to four times more effective than the glycyrrhetinic acid hydrogel [173]. Similarly, functionalized with an aromatic pyridinium cation (Figure 7C$_d$), both the molecular hydrophilicity and the origin of π–π stacking methyl glycyrrhetate conjugates were significantly enhanced, resulting in well-ordered supramolecular helical nanofibers [170].

Building on the structure of MGP, Gao et al. [178] substituted pyridine with bipyridine to design and synthesize a glycyrrhetinic acid amphiphile containing a π-chromophore (MGB, Figure 7D). This study demonstrated multiple strategies for modulating the supramolecular assembly structure of MGBP by adjusting solvent polarity and counterions. Depending on the solvent's polarity, MGBP could assemble into nanofibers, helices, pentagonal, and hexagonal microplates. Furthermore, by introducing counterions of varying sizes and valences, nanofibers in a methanol/water mixture could be transformed into ribbon-like robust fibers and fiber bundles. This work offers a straightforward approach to control the assembly structure of a natural triterpenoid amphiphile, thereby expanding the applications of natural products to supramolecular materials [178].

Glycyrrhizic acid (Figure 7E$_a$), a glycoside compound of glycyrrhetinic acid, stands as one of the most extensively studied triterpenoid hydrogel gelators. Low-molecular-weight glycyrrhizic acid can dissolve rapidly in hot water, forming a clear solution that transitions into a flowable, shape-moldable hydrogel upon cooling (Figure 7E$_b$,F) [22, 154], Derivatives of glycyrrhizic acid, such as GL-An [176] and AGA [171], have also been designed to form hydrogels with distinct properties. In the following sections, glycyrrhizic acid, this star triterpenoid, plays a pivotal role in synergizing with other compounds to create multifunctional materials with tailored properties for specific biomedical applications.

4.3.2 | Metal Ion Complexation

Metal ions tend to adopt diverse geometries for coordinating with molecules in supramolecular chemistry and yield different stable coordinated complexes. The functional groups present in triterpenoids, such as hydroxyl, carboxyl, and carbonyl groups can interact with metal ions (e.g., Na^+ [147, 149, 179, 180], K^+ [179–181], Ag^+ [182, 183], Mn^{2+} [184, 185], Mg^{2+} [186, 187], Zn^{2+} [188–192], Cu^{2+} [181, 193–195], Fe^{2+} [196–198], Sr^{2+} [199], and Ga^{3+} [200, 201]), which play crucial roles in the structural integrity and functional regulation of the metal ion-complexed triterpenoid hydrogel.

Glycyrrhizic acid is a naturally occurring edible chiral triterpenoid saponin capable of undergoing hierarchical self-assembly in water, thus forming supramolecular hydrogels. To customize the properties of glycyrrhizic acid supramolecular hydrogels for wider biomedical applications, Yu et al. introduced several metal ions with different valence states (Na^+, K^+, Ca^{2+}, Zn^{2+}, and Al^{3+}) and concentrations (5 and 50 mM) for glycyrrhizic supramolecular hydrogel fabrication (Figure 8A). They revealed that monovalent metal ions at low concentrations exerted minor effects on the linear/nonlinear rheological and network properties of the glycyrrhizic acid hydrogels. Conversely, when complexed with high concentrations of monovalent metal ions,

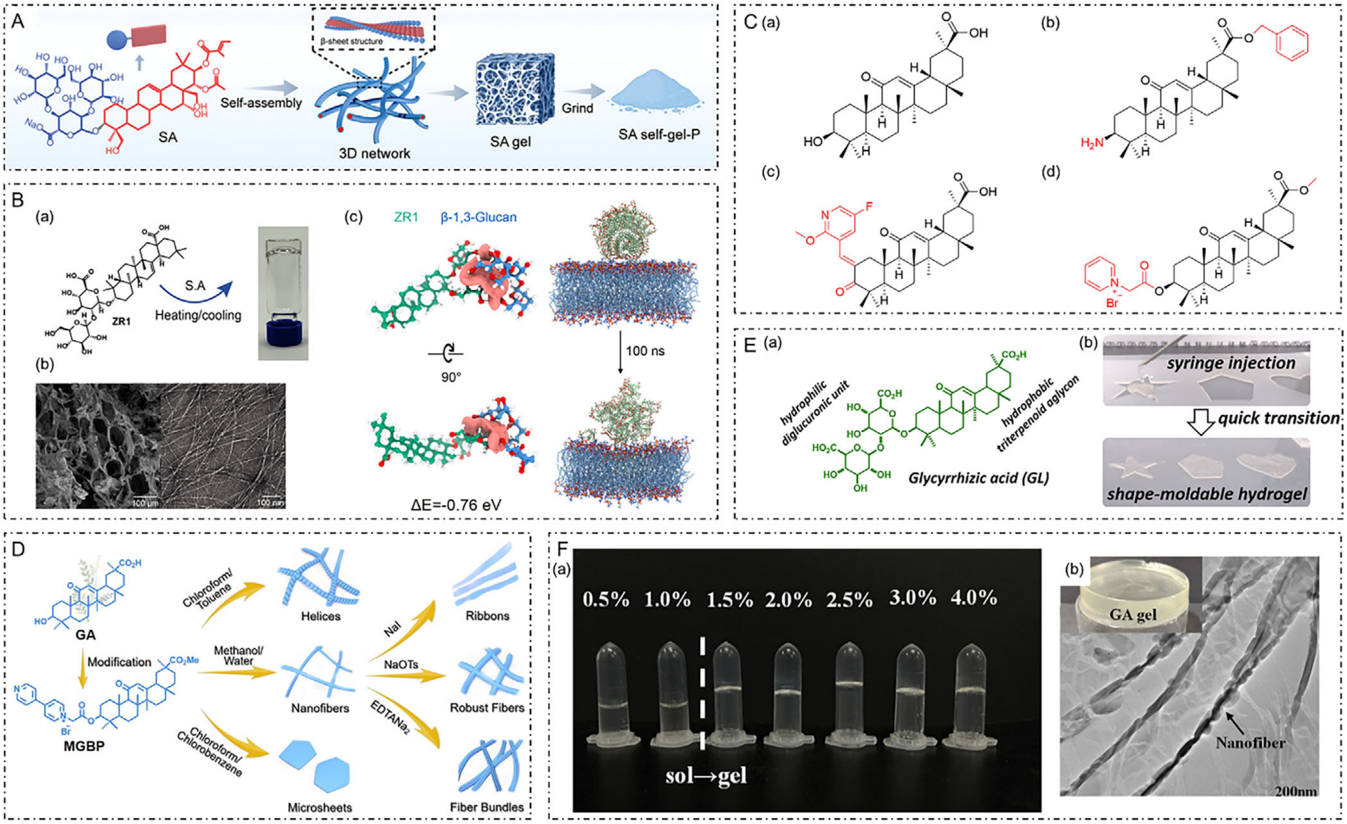

FIGURE 7 | (A) Schematic diagram of the self-assembly mechanism of sodium aescinate self-gelling powder. Reproduced with permission [149]. Copyright 2025, Wiley-VCH GmbH. (B_a) Hydrogel formation of zingibroside R1. (B_b) SEM (left) and TEM (right) images of zingibroside R1 gel. (B_c) Density functional theory calculations (left) and molecular dynamics simulation (right) of the potential interactions between zingibroside R1 nanofibril and fungal cell membrane. Reproduced with permission [150]. Copyright 2025, Wiley-VCH GmbH. Chemical structures of (C_a) glycyrrhetinic acid and its derivatives (C_b) GN-Bn, (C_c) GA-O-20, and (C_d) MGP. (D) Schematic of hierarchical assembly of MGBP regulated by solvents and counterions. Reproduced with permission [178]. Copyright 2021, Elsevier. (E_a) Chemical structure of glycyrrhizic acid and (E_b) its shape-moldable property. Reproduced with permission [22]. Copyright 2019, American Chemical Society. (F_a) The transition of glycyrrhizic acid from sol to gel and (F_b) the transmission electron microscope image of glycyrrhizic acid hydrogel. Reproduced with permission [154]. Copyright 2023, American Chemical Society.

the glycyrrhizic acid hydrogels exhibited prominent nonlinear rheological properties, featuring a distinct transition from elastic to viscous behavior. Owing to their higher charge density and stronger binding with glycyrrhizic acid, polyvalent metal ions greatly enhanced the network strength of the hydrogel at low concentrations, whereas unstable fibrillar structures and discrete gel networks were observed at higher concentrations [179]. Based on these findings, a novel hierarchical supramolecular hydrogel composed of glycyrrhizic acid and carrageenan was fabricated using Na^+ and K^+ [180].

Metal ions can significantly influence the properties of the resulting hydrogel, including its swelling behavior, mechanical strength, and bioactivity. Among the polyvalent metal ions, Zn^{2+} proved more effective in promoting glycyrrhizic acid hydrogel formation even at a glycyrrhizic acid concentration of 0.5 wt% [188, 189]. However, considering the special functions of some metal ions themselves, studies have focused on finding a balance between physical properties and biological functions when selecting ion modules for triterpenoid hydrogel preparation (Figure 8B). For example, given the multiple effects of Mg^{2+} in soft tissue repair [202], Zhang et al. [186] reported a Mg^{2+}-complexed betulinic acid self-stacked hydrogel for wound healing (Figure 8C). The sustained release and synergistic pharmacological effects of Mg^{2+} and betulinic acid endowed this wound dressing with excellent mechanical properties that can be applied to chronic wounds to accelerate scar-free healing. Zn^{2+} serves as a crucial structural and catalytic factor, playing important roles in maintaining homeostasis, immune function, and oxidative stress response [203]. Wang et al. [191] complexed Zn^{2+} with glycyrrhizic acid to form a primary network, which was then mixed with hyaluronic acid methacrylate and polyvinyl alcohol to create a robust cross-linked hydrogel network. This low-swelling and moisturizing hydrogel demonstrated excellent therapeutic efficacy in a rat model of infected wounds (Figure 8D). In another study, a Cu^{2+}-complexed dual-triterpenoid hydrogel composed of glycyrrhizic acid and celastrol was developed that exerted a formidable antitumor effect [193]. In addition to participating in the construction of the gel, Cu^{2+}, as a redox-active metal ion, can dynamically regulate the tumor microenvironment through chemodynamic therapy and stimulate cuproptosis (Figure 8E) [193]. Table 1 summarizes the composition and biological application of triterpenoid hydrogels complexed with different metal ions.

TABLE 1 | Prominent examples of metal ion-complexed triterpenoid hydrogels.

Metal ions	Triterpenoids	Payloads	Other cross-linked networks	Bioapplications	References
Na^+	Glycyrrhetinic acid	/	/	Postoperative peritoneal adhesion	[147]
	β-Aescin	/	/	Traumatic brain injury	[149]
Ag^+	Glycyrrhizic acid	/	Silk fibroin	Bacteria-infected wound healing	[182]
	Glycyrrhizic acid	/	Silk sericin	Bacteria-infected wound healing	[183]
Mn^{2+}	Glycyrrhizic acid	*Kansui Radix* ethyl acetate extract	/	Cancer	[184]
	Glycyrrhizic acid	/	/	Degenerated intervertebral discs	[185]
Mg^{2+}	Betulinic acid	/	Bacterial cellulose	Wound healing	[186]
	Asiatic acid	/	Bacterial cellulose	Wound healing	[187]
Zn^{2+}	Glycyrrhizic acid	/	Methacrylate silk fibroin	Diabetic wound healing	[188]
	Glycyrrhizic acid	/	/	Respiratory syncytial virus	[189]
	Glycyrrhizic acid	/	Methacrylate konjac glucomannan	Diabetic wound healing	[190]
	Glycyrrhizic acid	/	Methacrylate silk fibroin	Bone defects	[192]
	Glycyrrhizic acid	Epigallocatechin-3-gallate	Hyaluronic acid methacrylate, polyvinyl alcohol	Bacteria-infected wound healing	[191]
Cu^{2+}	Glycyrrhizic acid	Celastrol	/	Cancer	[193]
	Glycyrrhizic acid	Norcantharidin	/	Cancer	[194]
	Glycyrrhizic acid	Protocatechuic acid	/	Wound healing	[195]
Fe^{2+}	Glycyrrhizic acid	/	/	Bacteria-infected wound healing	[197]
	Glycyrrhizic acid	/	Carboxymethyl chitosan	Bacteria-infected wound healing	[198]
	Glycyrrhizic acid	Iron sulfide	/	Diabetic wound healing	[196]
Sr^{2+}	Glycyrrhizic acid ammonium salt	Pectin	/	Wound healing	[199]
Ga^{3+}	Glycyrrhizic acid	/	/	Pressure ulcers	[200]
	Glycyrrhizic acid	/	Gelatin methacryloyl	Bacteria-infected diabetic foot ulcers	[201]

/: nil or not mentioned.

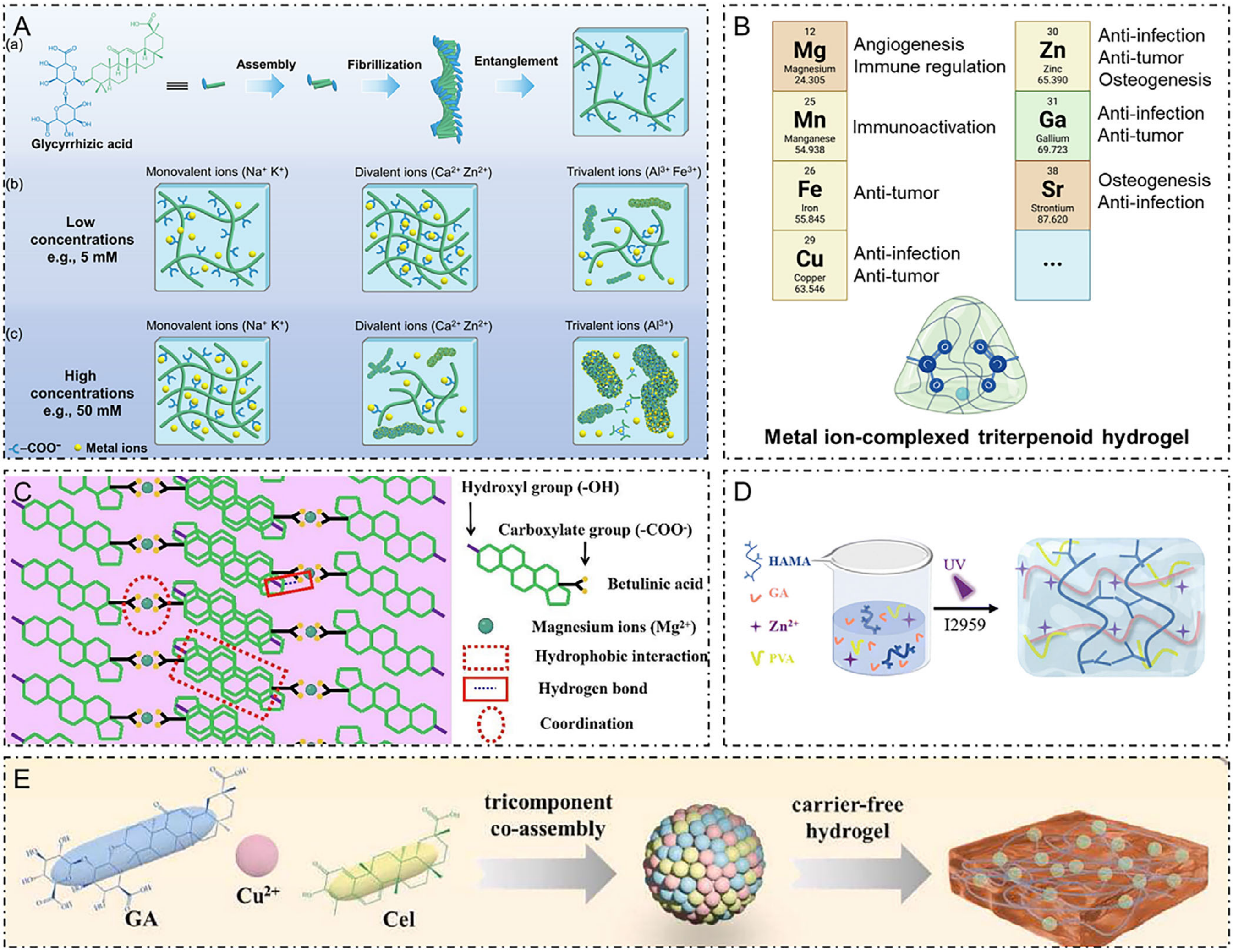

FIGURE 8 | (A) Schematic of the metal ion-modulated glycyrrhizic acid supramolecular hydrogel networks. Reproduced with permission [179]. Copyright 2024, Elsevier. (B) Hydrogel fabricated with multiple biological function-equipped metal ions and triterpenoids. (C) Schematic of the preparation and self-assembly mechanism of Mg^{2+}-complexed betulinic acid supramolecular hydrogel networks. Reproduced with permission [186]. Copyright 2024, Elsevier. (D) Schematic of Zn^{2+}-complexed glycyrrhizic acid supramolecular hydrogel networks. Reproduced with permission [191]. Copyright 2025, Royal Society of Chemistry. (E) Schematic of the preparation of Cu^{2+}-complexed glycyrrhizic acid supramolecular hydrogel loaded with celastrol. Reproduced with permission [193]. Copyright 2025, Elsevier.

In summary, metal-ion complexation represents a valuable approach for fabricating triterpenoid-based hydrogels with improved properties and diverse applications. Future research should prioritize the optimization of both triterpenoid and metal ion selection to maximize the beneficial effects of complexation. A thorough investigation of the underlying mechanisms of complexation is essential to elucidate the ways the different metal ions interact with triterpenoids at the molecular level. This will provide insights into the formation of hydrogels with tailored properties suitable for specific applications.

4.3.3 | Interpenetrating Multinetwork Hydrogel With Other Gelators

Another innovative approach to enhance the properties of triterpenoid hydrogels is the development of multiple interpenetrating networks by cross-linking with other macromolecules/small molecules. Interpenetrating multinetwork hydrogels involves the simultaneous presence of two or more polymer networks in a single hydrogel system. In the context of triterpenoid-based hydrogels, this can entail integrating natural or artificially synthetic macromolecules (e.g., hyaluronic acid [204], chitosan [205], polyvinyl alcohol [206], carrageenan [180, 207], silk fibroin [182, 208, 209], sodium alginate [210–213], gelatin [214], bacterial cellulose [187, 215], gellan gum [216], mussel adhesive protein [181], soy protein isolate [217–219], astragalus polysaccharide [220], and synthetic polymers [53, 188, 221–230]) and other small-molecule gelators (e.g., puerarin [231]). The interpenetration network strategy often affords synergistic effects in which the combined properties of different networks can lead to enhanced performance.

By varying the composition and ratio of the interpenetrating networks, several mechanical properties (e.g., swelling behavior, tensile strength, elasticity, and adhesion) can be fine-tuned and

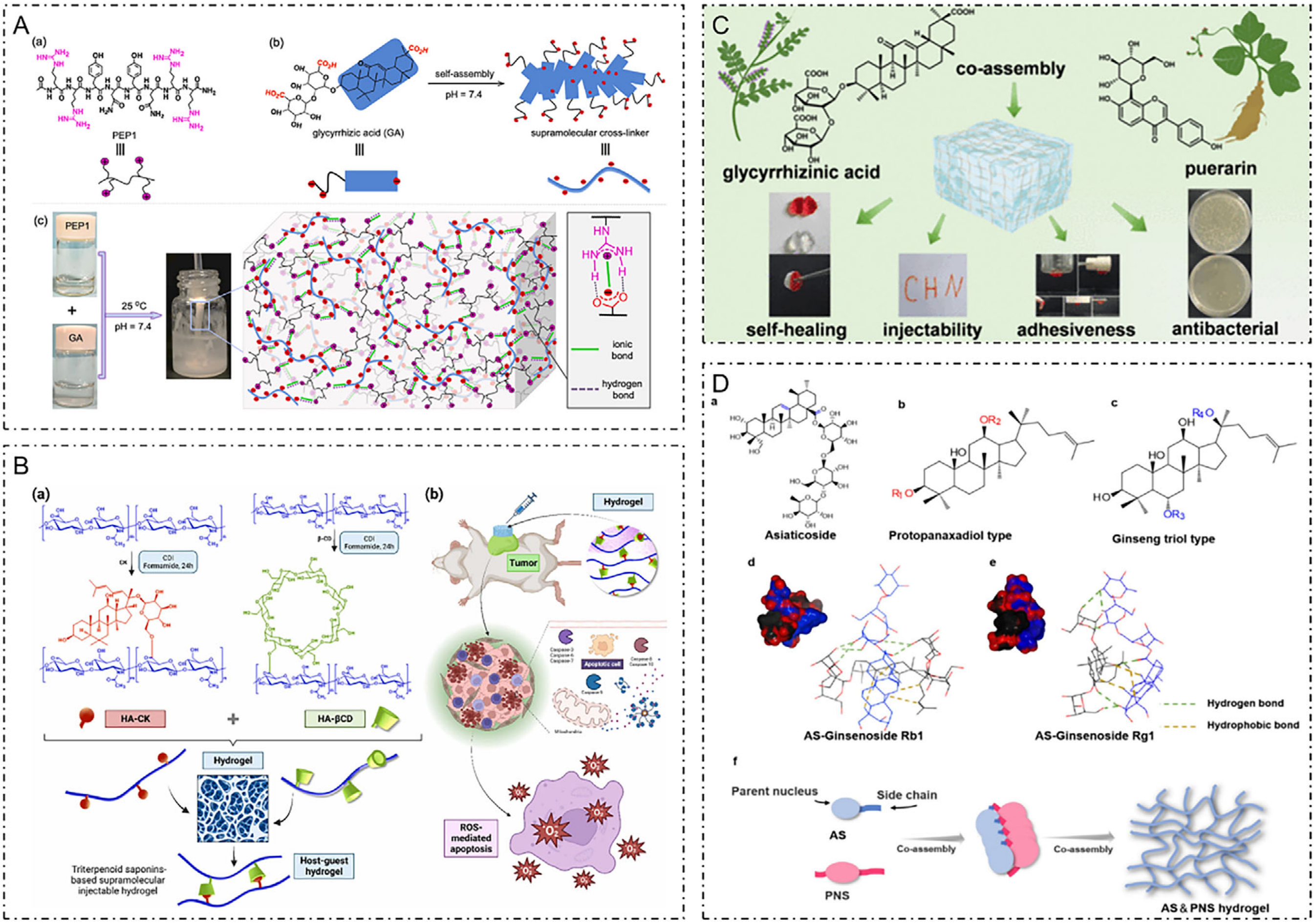

FIGURE 9 | (A) Primary sequence of the peptide PEP1, the chemical structure of glycyrrhizic acid, and schematic of the peptide/glycyrrhizic acid supramolecular hydrogel networks. Reproduced with permission [223]. Copyright 2023, Elsevier. (B_a) Chemical structures of the ginsenoside compound K-hyaluronic acid conjugates and β-cyclodextrin-hyaluronic acid conjugates and the fabrication of triterpenoid-based host-guest hydrogel. (B_b) ROS-mediated apoptosis induced by triterpenoid-based supramolecular host–guest hydrogel for cancer therapy. Reproduced with permission [232]. Copyright 2024, Elsevier. (C) Schematic for the preparation of two-component small-molecule hydrogel built from triterpenoid gelator and puerarin gelator. Reproduced with permission [231]. Copyright 2025, American Chemical Society. (D) Molecular docking simulation of asiaticoside and *Panax notoginseng* saponins hydrogel and proposed co-assembly mechanism. Reproduced with permission [233]. Copyright 2024, Elsevier.

the biocompatibility of hydrogels can be enhanced. For example, 3D hydrogel networks composed solely of glycyrrhizic acid often exhibit low adhesion, morphological instability, and low mechanical strength. Furthermore, self-assembled glycyrrhizic acid can induce cytotoxicity at certain concentrations, rendering it unsuitable for most biomedical applications. However, when cross-linked with other gel materials, these interpenetrating networks typically demonstrate superior mechanical strength and biological functionality compared with single gel networks. For instance, the supramolecular hydrogel formed by crosslinking the peptide PEP1 with glycyrrhizic acid demonstrated strong tissue adhesion on wet surfaces [223]. This adhesion was attributed to the bidentate hydrogen-bond-associated salt bridges between the guanidinium groups of arginine residues in PEP1 and the deprotonated carboxylic groups of glycyrrhizic acid, along with additional driving forces such as hydrogen bonding (Figure 9A). Animal experiments revealed that this interpenetrating network hydrogel can serve as a reliable medical adhesive for dural sealing and repair.

Self-assembling polymers based on β-cyclodextrin as noncovalent host–guest modules have attracted attention owing to the ease of modification, the capability of β-cyclodextrin to form complexes with different guest molecules (such as adamantane), and the reversible nature of this complexation [234]. Alternatively, triterpenoids have been explored recently as a novel guest molecule for the fabrication of supramolecular self-healable materials, with the host-guest interaction being based on β-cyclodextrin [232, 235–239]. In a previous study, the ginsenoside compound K was employed as a novel guest molecule to fabricate an injectable supramolecular hydrogel [232]. This hydrogel was obtained by straightforward mixing ginsenoside compound K and β-cyclodextrin complexes with different molar ratios, with both components being previously attached to hyaluronic acid (Figure 9B). The obtained hydrogel showed enhanced antitumor efficacy and immune responses compared with single-drug treatment, which can be attributed to the prolonged release of the ginsenoside compound K to the tumor tissues from the hydrogel.

Small molecule gelators are not exclusive to triterpenoid compounds; other small molecules with different chemical frameworks, such as rhein and puerarin, also exhibit significant hydrogel-forming capabilities at low concentrations [240, 241]. Therefore, the co-assembly strategy of triterpenoid compounds with other low molecule weight gelators, alongside polymeric materials, provides a new research direction for constructing stable hydrogel systems. This approach establishes a novel research paradigm of "component interactions-supramolecular structure-biological activity," significantly advancing the development of functional hydrogels. Notably, many of these natural small-molecule gelators are derived from active components of TCM. Investigating their molecular interaction mechanisms not only offers scientific support for the combination of TCM theories but also inspires innovative hydrogel design based on these principles. Research by Ji et al. [231] demonstrated that glycyrrhizic acid can form stable two-component hydrogels with puerarin through a simple heating-cooling process, exhibiting notable antibacterial activity (Figure 9C).

Furthermore, it has been observed that certain triterpenoids, which exhibit weak or no gelation properties when isolated, can form stable hydrogel systems when blended with other triterpenoid molecules. This synergistic effect significantly enhances the stability and bioavailability of triterpenoids, especially showcasing important application prospects in transdermal delivery systems and oral formulations. For instance, Huang et al. successfully developed a hydrogel dressing with wound-healing properties by optimizing the ratio of the poorly soluble triterpenoid asiaticoside and nongel-forming TCM extracts (*Panax notoginseng* saponins), achieving significant therapeutic effects in animal models (Figure 9D) [233].

Collectively, exploring innovative fabrication and processing techniques is crucial for enhancing the physical properties of triterpenoid hydrogels, including their mechanical strength, elasticity, and stability, as well as their biological performance. While conventional crosslinking methods remain fundamental for hydrogel formation, advanced techniques such as microfluidic fabrication, freeze-thaw cycling, and photopolymerization can be employed to create triterpenoid-based hydrogels with tailored architectures and functionalities [242–244]. Additionally, post-processing approaches including 3D printing and electrospinning of hydrogel composites enable the creation of sophisticated constructs with precise structural features [245, 246]. By advancing these research areas, the efficacy and applicability of triterpenoid-based hydrogels can be significantly improved, ultimately contributing to the development of next-generation biomaterials with transformative potential for biomedical applications.

4.4 | Triterpenoids as Cholesterol Alternatives for Optimizing Lipid-Based Nanoparticles

The majority of clinically approved nanoparticle-mediated therapeutics are lipid-based nanoparticles, such as liposomes and lipid nanoparticles (LNPs). In particular, with the advent of COVID-19 vaccines, LNPs have been more widely recognized since 2020 [247, 248]. Most lipid-based nanoparticles contain cholesterol [248, 249]. As an amphiphilic compound, cholesterol can interact with the phospholipids and embed itself within phospholipid molecules during lipid-based nanoparticle preparation, thereby regulating the structure and properties of the liposomal membrane [250, 251]. Additionally, cholesterol modulates the fluidity of the phospholipid bilayer, reduces membrane permeability, and minimizes drug leakage. Another reason for the widespread use of cholesterol is its ability to impart flexibility to the lipid membranes and prevent phospholipid oxidation [251]. Therefore, lipid-based nanoparticles containing cholesterol help combat variations in external conditions, owing to their dual-phase regulatory effect on the phase transition of phospholipids [250, 252].

However, safety concerns regarding the use of cholesterol in lipid-based nanoparticle formulations have been reported recently [253]. First, excess exogenous cholesterol is metabolized in the body and is partially converted to oxysterols, which can affect the immune system and potentially promote immune evasion and tumor growth in the tumor microenvironment [253–255], as well as exacerbate inflammatory diseases [253]. Second, cholesterol-dependent complement activation has been suggested as a potential factor that influences the pathogenesis of atherosclerosis [256] and the occurrence of complement-mediated pseudoallergic reactions [257–259]. Third, cholesterol may be detrimental in certain patients. For instance, as a precursor of testosterone biosynthesis, cholesterol can increase the levels of testosterone and dihydrotestosterone in the body, leading to follicular damage and hair loss. Therefore, cholesterol-free ginsenoside Rg3 liposomes [260] and dutasteride-loaded cholesterol-free protopanaxadiol liposomes [261] have been developed to treat alopecia.

Steroids [262–273] and triterpenoids [274–282] have a skeletal portion that closely resembles that of cholesterol and possess certain pharmacological activities. Several studies have reported that they can partially or completely substitute cholesterol in lipid-based nanoparticle formulations (Figure 10A). Moreover, cationic amphiphilic drugs have also been reported to improve cytosolic nucleic acid delivery and serve as cholesterol alternatives [283–285]. Numerous studies have shown that triterpenoid-based cholesterol-free lipid-based nanoparticle formulations often exhibit comparable or even superior biological performance compared with traditional cholesterol-containing lipid-based nanoparticle formulations [274, 277–281], particularly in the context of diseases associated with cholesterol homeostasis imbalance.

Triterpenoids possess the ability to regulate membrane fluidity and stability akin to cholesterol, while additionally providing a variety of other functionalities, such as pharmacological activity and immunomodulatory properties. This multiple functionality positions triterpenoids as a compelling strategy to enhance LNP performance. For instance, a study comparing doxorubicin-loaded liposomes composed of corosolic acid and cholesterol revealed that corosolic acid liposomes exhibited higher stability, lower drug leakage (Figure $10B_a$), and better tumor spheroid penetration characteristics (Figure $10B_b$) than traditional liposomes [275].

Notably, compared with traditional cholesterol-containing LNPs, triterpenoid saponins with glycosyl ligands often expose glucose moieties on the surface of LNPs due to their amphiphilicity during LNP preparation, providing new insights for blood-brain

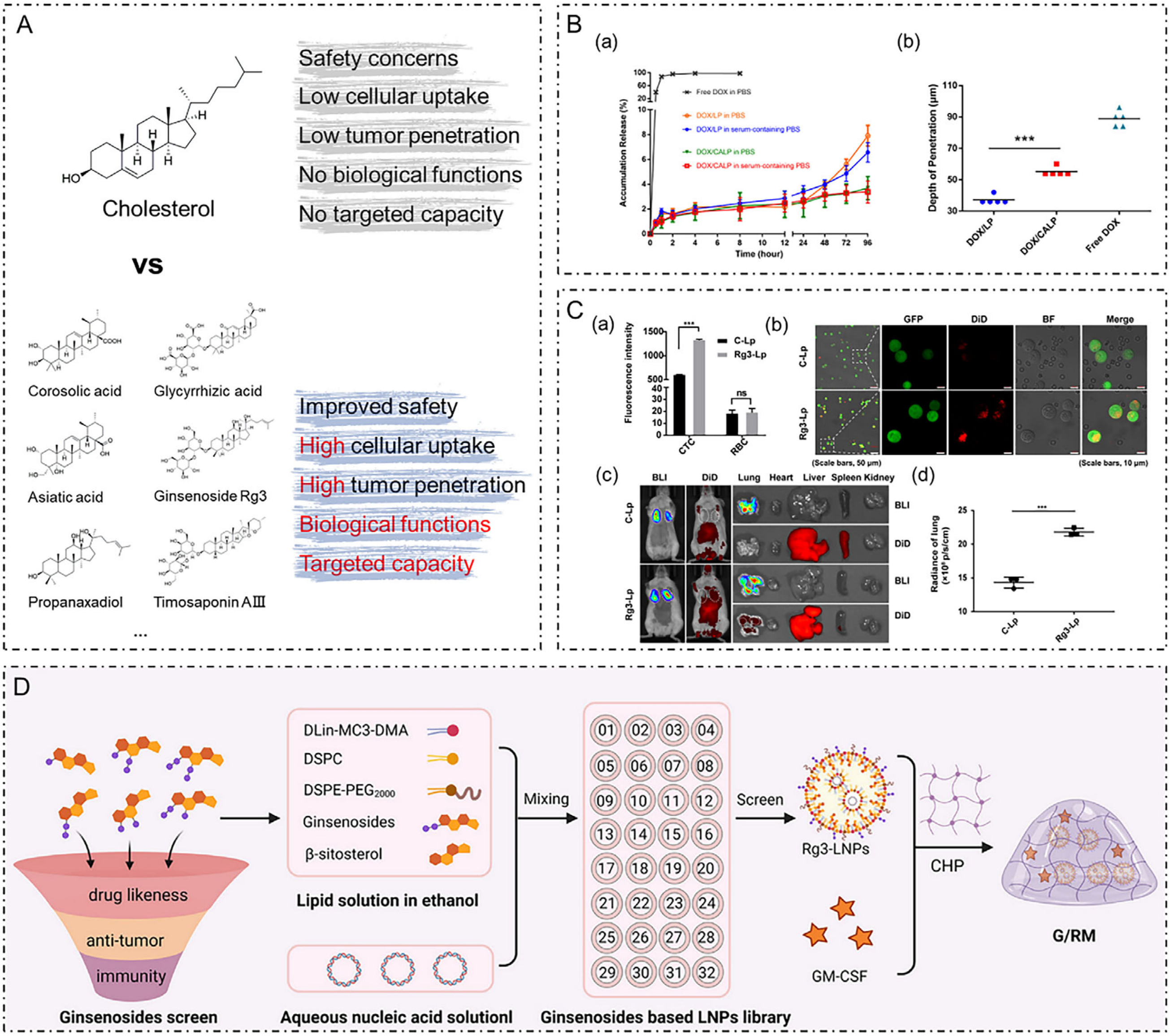

FIGURE 10 | (A) Comparison of cholesterol and triterpenoids for the fabrication of lipid-based nanoparticles. (B_a) Drug release profile from cholesterol-/corosolic acid-containing liposomes. (B_b) Penetration depth in 3D tumor spheroids of cholesterol-/corosolic acid-containing liposomes. Reproduced with permission [275]. Copyright 2020, Elsevier. (C_a) Quantitative analysis of the cellular uptake of cholesterol-/ginsenoside Rg3-containing liposomes by circulating tumor cells and red blood cells. (C_b) Representative confocal laser scanning microscope images of the cellular uptake of cholesterol-/ginsenoside Rg3-liposomes by circulating tumor cells. (C_c) In vivo fluorescent and bioluminescent images of mice and various organs and (C_d) Semi-quantification of the fluorescent signals in lung tissues. Reproduced with permission [288]. Copyright 2022, The American Association for the Advancement of Science. (D) Screening ginsenosides to assemble self-adjuvant lipid nanoparticles for antigens tagging guided therapeutic tumor vaccine. Reproduced with permission [296]. Copyright 2025, Wiley-VCH GmbH.

barrier transport and tumor targeting. Considering the high demand for glucose in tumors, active targeting can be achieved via the interaction between the glycosyl moiety-enriched triterpenoids and glucose transporters (GLUTs) overexpressed in tumors. Several actively targeting cholesterol-free triterpenoid lipid-based nanoparticles based on GLUT targeting have been successfully fabricated [280, 281, 286–295]. For example, Xia et al. [288] compared Rg3-containing liposomes with traditional cholesterol-containing liposomes and validated the specific internalization capability of Rg3-containing liposomes into circulating tumor cells in vitro, which was not observed in normal cells (red blood cells) (Figure 10C_a,C_b). In vivo experiments further demonstrated that the Rg3-containing liposomes could be extensively captured by tumor cells after injection compared with cholesterol-containing liposomes (Figure 10C_c,C_d). Furthermore, Rg3-GLUT1 docking and surface plasmon resonance experiments demonstrated the strong affinity of Rg3 for GLUT1 through its glycosyls, suggesting that it could serve as a promising active targeting ligand for GLUT overexpressed tumor therapy.

LNPs, as nonviral carriers, demonstrate remarkable efficacy in the delivery of nucleic acid vaccines [297]. Traditional vaccines activate CTLs by delivering antigens to DCs to kill tumor cells; however, tumor cells can evade the immune response by downregulating surface antigens. Conventional LNPs often require adjuvants to enhance immune responses, making the development of self-adjuvant tumor vaccine platforms that can simultaneously target tumor cell antigens and activate DCs particularly important. The role of triterpenoids is becoming increasingly prominent for enhancing nucleic acid vaccine delivery owing to their multifunctional properties as cholesterol analogs, GLUT targeting groups, immune adjuvants, and pharmacological agents. Liang et al. screened various ginsenosides and identified ginsenoside Rg3-LNPs as the most effective formulation, capable of efficiently loading nucleic acids and promoting gene transfection (Figure 10D) [296]. Co-loading ginsenoside Rg3-LNPs with GM-CSF (granulocyte-macrophage colony-stimulating factor) in a porous hydrogel allowed for localized delivery around tumors, facilitating accumulation in both the tumor and lymph nodes. Ginsenoside Rg3-LNPs mediated targeting through GLUT1 on tumor cell surfaces, anchoring antigens to enhance CTL recognition while simultaneously activating DCs in lymph nodes to improve antigen presentation. Additionally, ginsenoside Rg3 inhibited the infiltration of immunosuppressive cells and angiogenesis, working synergistically with GM-CSF to remodel the tumor microenvironment and significantly enhance antitumor immune responses. This strategy has shown potent immune activation and antitumor activity in breast cancer and melanoma models, offering a novel approach for the clinical application of tumor nucleotide vaccines.

The structural similarities between triterpenoids and cholesterol, their exceptional efficiency as membrane modulators, unique biological functions, targeting capabilities, and, most importantly, the growing concerns regarding cholesterol safety, render the substitution of cholesterol by triterpenoids in the development of lipid-based nanoparticles for drug delivery systems a promising strategy. This approach is especially important for treating diseases associated with cholesterol homeostasis imbalance, such as alopecia and cardiovascular conditions. Table 2 summarizes the prominent examples of triterpenoid-substituted cholesterol-free lipid-based nanoparticles.

Nevertheless, it is crucial to acknowledge that, despite the extensive clinical research supporting traditional lipid-based nanoparticle formulations, significant challenges remain in the pursuit of establishing triterpenoids as viable alternatives to cholesterol within these systems. Although triterpenoids exhibit promising properties that can enhance the performance of lipid-based nanoparticle formulations, the transition from theoretical applications to practical and clinically relevant alternatives necessitates rigorous investigation and validation. Furthermore, a comprehensive evaluation of the potential biotoxicity of triterpenoids is imperative. Understanding the safety profiles of these compounds is essential for ensuring their suitability for pharmaceutical applications. This requires an assessment of their cytotoxic effects on various cell types and research on the potential immunogenic responses and long-term biocompatibility.

5 | Conclusion and Future Perspectives

Research on triterpenoids and their derivatives has revealed their promising clinical potential, particularly as lead compounds for new anticancer and antiviral drugs. Triterpenoids have been employed in a wide range of functional nano-sized biomaterials and multitasking hydrogels, with the design of triterpenoid-based assembly materials being an emerging frontier in supramolecular chemistry. The triterpenoid unit is not only a superb assembling motif but also an excellent therapeutic agent with extensive biofunctions, exemplifying promising avenues for future biomedical applications.

Although significant milestones have been achieved, the full potential of triterpenoid-based supramolecular assemblies remains unclear. Consequently, considerable efforts have been dedicated to investigating the self-assembly of naturally derived/artificially synthesized triterpenoids, facilitating the development of more functionally complex biomaterials. In recent years, the rapid advancement of multiscale modeling—particularly through density functional theory calculations and molecular dynamics simulations—has provided valuable tools for studying the self-assembly structures and evolutionary processes of triterpenoid assemblies. These approaches complement experimental results and enhance our understanding of noncovalent interactions within these assemblies. Moreover, with the advancement of artificial intelligence, deep learning has demonstrated significant potential in the structural design and performance research of co-assembled nanodrugs [295, 318–322]. By utilizing deep learning, the relationship between drug structure and co-assembly performance can be elucidated, enabling the prediction of co-assembled drug molecules and the further construction of co-assembled nanodrugs. This approach provides potential support for analyzing the influence of molecular local structures in the co-assembly process of triterpenoid assemblies and for designing novel triterpenoid-based drug formulations.

Notably, as prominent natural products, triterpenoids are the primary active components of various commonly used TCMs, such as ginseng, hoelen, and astragalus. Research on the supramolecular chemistry of triterpenoid compounds has greatly aided the development of new drug formulations and shed light on the theories and principles underlying TCM preparations [323–325]. Supramolecular self-assembly in TCMs, characterized by specific structures, can afford distinct pharmacological effects compared with the simple additive properties of monomer compounds, serving as an essential theoretical foundation for TCM practices. Further studies on the supramolecular assembly of triterpenoids, such as the hierarchical structure of the assemblies, assembly process, and potential mechanisms, could provide breakthroughs in theoretical research on TCM compatibility, processing, and the intrinsic properties of medicinal substances.

In our opinion, future research on the enhancement and optimization of triterpenoid-based supramolecular chemistry and biomedical applications should focus on the following areas:

1. The supramolecular assembly of triterpenoids faces a significant challenge due to their inherent hydrophobicity—most triterpenoids are soluble in organic solvents but exhibit negligible water solubility, confining their assembly processes predominantly to organic media and severely limiting biomedical applications. To overcome this, strategic structural modifications of the triterpenoid scaffold have emerged as a promising solution. Introducing hydrophilic groups (e.g., PEG chains or ionic moieties) to create prodrugs or derivatives [326], or incorporating stimuli-responsive linkers

TABLE 2 | Prominent examples of triterpenoid-substituted cholesterol-free lipid-based nanoparticles.

Triterpenoids	Payloads	Compositions	Bioapplications	References
Asiatic acid (**AA**)	Doxorubicin	S100 : **AA** (10 : 3, mass ratio)	Cancer	[282]
Corosolic acid (**CA**)	Doxorubicin	HSPC : **CA** : DSPE-PEG$_{2000}$ (56.3 : 38.4 : 5.3, molar ratio)	Cancer	[275]
	Paclitaxel	SPC : **CA** (/)	Cancer	[276]
	pDNA	DLin-MC3-DMA : DSPC : **CA** : DSPE-PEG$_{2000}$(/)	Avian influenza	[298]
Corosolic acid derivative (**CAβ**)	mRNA/siRNA	ALC-0315 : **CAβ** : DSPC : DMG-PEG (50 : 38.5 : 10 : 1.5, molar ratio)	Cancer	[299]
Ginsenoside Compound K (**CK**)	Dexamethasone	EYPC : **CK** (10 : 3, mass ratio)	Rheumatoid arthritis	[300]
Ilexgenin A (**IA**)	Docetaxel	EYPC : **IA** (10 : 3, mass ratio)	Cancer	[295]
Ginsenoside Rg3 (**Rg3**)	Docetaxel	EYPC : **Rg3** (10 : 3, mass ratio)	Cancer	[288, 301]
	Paclitaxel	EYPC : **Rg3** (10 : 3, mass ratio)	Cancer	[289, 290]
	Paclitaxel	EYPC : **Rg3** (5 : 2, mass ratio)	Cancer	[292]
	Garcinic acid	EYPC : **Rg3** (5 : 2, molar ratio)	Cancer	[287]
	Oxaliplatin and calcium peroxide	EYPC : **Rg3** (4 : 1, molar ratio)	Cancer	[293]
	Celastrol	SPC : **Rg3** (7 : 1, mass ratio)	Cancer	[294]
	Celastrol	SPC : **Rg3** (10 : 3, mass ratio)	Cancer	[302]
	Rivastigmine hydrogen tartrate	PL-100M : **Rg3** (/)	Alzheimer's disease	[303]
	/	EYPC : **Rg3** (10 : 3, mass ratio)	Psoriasis	[304]
	/	EYPC : **Rg3** (10 : 3, mass ratio)	Alopecia	[260]
	Berberine	EYPC : **Rg3** (10 : 3, mass ratio)	Infectious wound healing	[305]
	/	EYPC : **Rg3** : DSPE-PEG$_{2000}$ (3 : 1 : 0.15, molar ratio)	Corneal alkali burn	[306]
Ginsenoside Rg5 (**Rg5**)	siRNA	DOTAP : DOPE : **Rg5** (5 : 5 : 1, mass ratio)	Cancer	[274]
	siRNA/DNA	DOTAP : DOPE : **Rg5** (5 : 5 : 4, mass ratio)	Cancer	[307]
Ginsenoside Rh2 (**Rh2**)	Paclitaxel	EYPC : **Rh2** (10 : 3, mass ratio)	Cancer	[286]
	Docetaxel	EYPC : **Rh2** : DSPE-PEG$_{2000}$ (24 : 6.5 : 2.8, mass ratio)	Cancer	[308]
	Paclitaxel	EYPC : **Rh2** (10 : 3, mass ratio)	Cancer	[291]

(Continues)

TABLE 2 | (Continued)

Triterpenoids	Payloads	Compositions	Bioapplications	References
	Paclitaxel	EYPC : **Rh2** : DSPE-PEG$_{2000}$ (22 : 5 : 4, mass ratio)	Cancer	[309]
	Annonaceous acetogenins	SPC : **Rh2** (45 : 12, mass ratio)	Cancer	[310]
Ginsenoside Rk1 (**Rk1**)	Cabazitaxel	EYPC : **Rk1** (5 : 1, mass ratio)	Cancer	[311]
Ginsenoside Rb1 (**Rb1**)	/	SPC : **Rb1** : DSPE-PEG$_{2000}$ (56 : 6 : 1, mass ratio)	Atherosclerosis	[312]
Glycyrrhetinic acid (**GA**)	Carthamin yellow	DOPG : **GA** (/)	Diabetic nephropathy	[313]
Glycyrrhizic acid (**GL**)	Triptolide	EYPC : **GL** (5 : 1, mass ratio)	Cancer	[314]
	Kaempferol	SPC : CTAB : **GL** (/)	*Helicobacter pylori* infection	[315]
	Cantharidin	EYPC : **GL** (20 : 7, mass ratio)	Cancer	[131]
Protopanaxadiol (**PPD**)	Dutasteride	SPC : **PPD** (3 : 1, mass ratio)	Alopecia	[261]
	Cisplatin prodrug	EYPC : **PPD** (5 : 1, mass ratio)	Cancer	[316]
Tubeimoside I (**TubI**)	Gemcitabine	SPC : **TubI** (10 : 3, mass ratio)	Cancer	[317]

Abbreviations: /, nil or not mentioned; HSPC, (hydrogenated soybean phosphotidylcholine, 1,2-diacyl-*sn*-glycero-3-phosphocholine); DSPE-PEG$_{2000}$, (1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]); SPC, (soybean phosphatidylcholine, soybean lecithin); DSPC, (distearoylphosphatidylcholine, 1,2-distearoyl-*sn*-glycero-3-phosphacholine); EYPC, (egg yolk lecithin, egg yolk phosphatidylcholine); DOTAP, (1,2-dioleoyl-3-trimethylammonium-propane); DOPE, (1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine); DOPG, (dioleoylphosphatidylglycerol, 1,2-dioleoyl-*sn*-glycero-3-phosphoglycerol); CTAB, (cetyltrimethylammonium bromide).

(e.g., ROS-/pH-/enzyme-cleavable bonds) [62, 77, 78], can markedly enhance aqueous stability and enable controlled assembly in physiological environments. Future research should further focus on expanding their assembly in aqueous systems and utilizing these assemblies to better leverage the excellent pharmacological activities of triterpenoids and broaden the scope of triterpenoid-based supramolecular systems.

2. An in-depth exploration of the relationship between the molecular structure, functional groups, and assembly patterns of triterpenoids, as well as the impact of chiral selection during the assembly process, is essential for regulating the assembly process and reliably predicting their supramolecular structures. Such a study will facilitate the development of more self-assembled systems with specific functions, thereby establishing a solid theoretical foundation for supramolecular assemblies and supporting extensive future research.
3. Given the abundance and variety of triterpenoid compounds in TCM, the assembly behavior of triterpenoids is very important for the modernization and globalization of TCM. Emphasis should be therefore placed on the ways the assembly behavior of triterpenoids with exogenous or endogenous components contributes to solubilization enhancement, toxicity reduction, efficacy improvement, and other beneficial effects of TCM formulations. This will provide a research foundation for the modernization of the fundamental theories of TCM.
4. Although the preparation of most triterpenoid supramolecular assemblies is relatively straightforward, enhancing their stability poses a significant challenge for clinical translation because of the weak noncovalent forces driving the self-assembly process. Particularly, in complex physiological environments, triterpenoid assemblies may interact with various biomolecules, potentially interfering with their specific biological functions. To address this issue, research should focus on promoting the clinical application of triterpenoid bioactive materials, ensuring their biocompatibility, biodegradability, and environmental friendliness, while advancing the study of their stability in both in vivo and in vitro complex environments.
5. Another important avenue for future research is the systematic investigation of the pharmacokinetics and pharmacodynamics of triterpenoid-containing lipid-based nanoparticle formulations, including thorough toxicological studies. By addressing these critical factors, the feasibility of incorporating triterpenoids as cholesterol alternatives in lipid-based nanoparticle formulations can be ascertained, ultimately paving the way for the development of safer and more effective drug delivery systems. This comprehensive approach is vital for advancing the field and ensuring that the

new lipid-based nanoparticle formulations meet the stringent safety and efficacy standards required for clinical use.

This review summarizes the ongoing supramolecular assembled research that involves the use of triterpenoids as an assembled module to produce organized functional supramolecular biomaterials with tunable physicochemical and biological parameters. With advancements in pharmaceutical technologies, the design and development of novel triterpenoid-based supramolecular therapeutics with tailored functionalities have emerged as a critical challenge for future research. Achieving this goal requires a deeper and more nuanced understanding of the underlying assembly mechanisms governing the formation of these supramolecular structures. As researchers strive to create effective and customizable therapeutics to meet specific clinical needs, the integration of triterpenoids into supramolecular frameworks is highly promising.

Taken together, triterpenoid-based supramolecular therapeutics are poised to revolutionize drug delivery and treatment modalities, offering innovative solutions to complex medical challenges. Addressing the above multifaceted issues is essential for harnessing the full potential of triterpenoids for the development of advanced biomaterials and therapeutics, ultimately contributing to improved health outcomes and enhanced therapeutic efficacy.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, "Zur Kenntnis der Triterpene. 190. Mitteilung. Eine stereochemische Interpretation der biogenetischen Isoprenregel bei den Triterpenen," *Helvetica Chimica Acta* 38, no. 7 (1955): 1890–1904.

2. A. Eschenmoser and D. Arigoni, "Revisited After 50 Years: The 'Stereochemical Interpretation of the Biogenetic Isoprene Rule for the Triterpenes'," *Helvetica Chimica Acta* 88, no. 12 (2005): 3011–3050.

3. Z. Özdemir, Nonappa, and Z. Wimmer, "Triterpenoid Building Blocks for Functional Nanoscale Assemblies: A Review," *ACS Applied Nano Materials* 5, no. 11 (2022): 16264–16277.

4. B. G. Bag and R. Majumdar, "Self-Assembly of Renewable Nano-Sized Triterpenoids," *Chemical Record* 17, no. 9 (2017): 841–873.

5. H. Zhang, J. Guo, J. Hu, and M. Zhou, "Terpenoid-Based Supramolecular Materials: Fabrications, Performances, Applications," *Supramolecular Chemistry* 34, no. 2 (2023): 105–131.

6. B. G. Bag, C. Garai, R. Majumdar, and M. Laguerre, "Natural Triterpenoids as Renewable Nanos," *Structural Chemistry* 23, no. 2 (2012): 393–398.

7. B. G. Bag, G. C. Maity, and S. R. Pramanik, "Arjunolic Acid: A Promising New Building Block for Nanochemistry," *Pramana* 65, no. 5 (2005): 925–929.

8. B. G. Bag, S. K. Dinda, P. P. Dey, V. A. Mallia, and R. G. Weiss, "Self-Assembly of Esters of Arjunolic Acid Into Fibrous Networks and the Properties of Their Organogels," *Langmuir* 25, no. 15 (2009): 8663–8671.

9. J. Hu, M. Zhang, and Y. Ju, "A Simple Oleanlic Acid Derivative as Potent Organogelator," *Soft Matter* 5, no. 24 (2009): 4971.

10. J. Lu, Y. Gao, J. Wu, and Y. Ju, "Organogels of Triterpenoid–Tripeptide Conjugates: Encapsulation of Dye Molecules and Basicity Increase Associated With Aggregation," *RSC Advances* 3, no. 45 (2013): 23548.

11. J. Lu, J. Wu, and Y. Ju, "Tuning the Aggregation Mode to Induce Different Chiralities in Organogels of Mono- and Bis-Triterpenoid Derivatives and the Preparation of Gold Nanoparticles for Use as a Template," *New Journal of Chemistry* 38, no. 12 (2014): 6050–6056.

12. P. Dzubak, M. Hajduch, D. Vydra, et al., "Pharmacological Activities of Natural Triterpenoids and Their Therapeutic Implications," *Natural Product Reports* 23, no. 3 (2006): 394.

13. T. Moses, J. Pollier, J. M. Thevelein, and A. Goossens, "Bioengineering of Plant (tri)Terpenoids: From Metabolic Engineering of Plants to Synthetic Biology in Vivo and in Vitro," *New Phytologist* 200, no. 1 (2013): 27–43.

14. S. G. Hillier and R. Lathe, "Terpenes, Hormones and Life: Isoprene Rule Revisited," *Journal of Endocrinology* 242, no. 2 (2019): R9–R22.

15. J. M. Augustin, V. Kuzina, S. B. Andersen, and S. Bak, "Molecular Activities, Biosynthesis and Evolution of Triterpenoid Saponins," *Phytochemistry* 72, no. 6 (2011): 435–457.

16. X. Lin, X. Huang, W. Pi, et al., "Self-assembly Variation of Glycyrrhetinic Acid Epimers: Assembly Mechanism and Antibacterial Efficacy Between 18 α-GA and 18 β-GA," *Colloids and Surfaces B* 242 (2024): 114120.

17. B. G. Bag and R. Majumdar, "Self-Assembly of a Renewable Nano-Sized Triterpenoid 18β-Glycyrrhetinic Acid," *RSC Advances* 2, no. 23 (2012): 8623–8626.

18. B. C. Stephenson, A. Goldsipe, and D. Blankschtein, "Molecular Dynamics Simulation and Thermodynamic Modeling of the Self-Assembly of the Triterpenoids Asiatic Acid and Madecassic Acid in Aqueous Solution," *Journal of Physical Chemistry B* 112, no. 8 (2008): 2357–2371.

19. J. Liu, "Oleanolic Acid and Ursolic Acid: Research Perspectives," *Journal of Ethnopharmacology* 100, no. 1 (2005): 92–94.

20. L. Fan, B. Zhang, A. Xu, et al., "Carrier-Free, Pure Nanodrug Formed by the Self-Assembly of an Anticancer Drug for Cancer Immune Therapy," *Molecular Pharmaceutics* 15, no. 6 (2018): 2466–2478.

21. Z. Li, Y. Zheng, H. Shi, et al., "Convenient Tuning of the Elasticity of Self-Assembled Nano-Sized Triterpenoids to Regulate Their Biological Activities," *ACS Applied Materials & Interfaces* 13, no. 37 (2021): 44065–44078.

22. X. Zhao, H. Zhang, Y. Gao, Y. Lin, and J. Hu, "A Simple Injectable Moldable Hydrogel Assembled From Natural Glycyrrhizic Acid With Inherent Antibacterial Activity," *ACS Applied Bio Materials* 3, no. 1 (2020): 648–653.

23. Z. Sun, Y. Hou, X. Xu, et al., "A Novel Nonreversible Heat-Induced Low-Molecular-Weight Gel Based on Naturally-Occurring Self-Assembled Fupenzic Acid for Tumor Therapy," *Colloids and Surfaces B* 228 (2023): 113392.

24. J. Lu, X. Wu, L. Liu, H. Chen, and Y. Liang, "First Organogelation Study of Ursolic Acid, a Natural Ursane Triterpenoid," *Chemistry Letters* 45, no. 8 (2016): 860–862.

25. Y. Liu, H. Zhang, X.-W. Chen, T. Yang, C. Sun, and S.-D. Sun, "Fabrication and Characterization of Novel Thermoresponsive Emulsion Gels and Oleogels Stabilizied by Assembling Nanofibrous From Dual Natural Triterpenoid Saponins," *Food Chemistry: X* 18 (2023): 100751.

26. X.-W. Chen, H. Zhang, X.-X. Li, and S.-D. Sun, "Edible HIPE-Gels and Oleogels Formed by Synergistically Combining Natural Triterpenoid Saponin and Citrus Dietary fiber," *Carbohydrate Polymers* 305 (2023): 120499.

27. S. Li, P. Li, Y. Chen, et al., "Camellia Saponin Based Oleogels by Emulsion-Templated Method: Preparation, Characterization, and in Vitro Digestion," *ACS Food Science & Technology* 3, no. 12 (2023): 2085–2093.

28. L. Du, S. Zhou, Y. Huang, and Z. Meng, "Investigation on the Structure Characteristics, Stability Evaluation, and Oral Tribology of Natural Oleanolic Acid-Based Water-in-Oil High Internal Phase and Multiple Pickering Emulsions as Realistic Fat Analogues," *Food Chemistry* 465 (2025): 142121.

29. E. M. Ahmed, "Hydrogel: Preparation, Characterization, and Applications: A Review," *Journal of Advanced Research* 6, no. 2 (2015): 105–121.

30. A. S. Hoffman, "Hydrogels for Biomedical Applications," *Advanced Drug Delivery Reviews* 64 (2012): 18–23.

31. H. Zhang, W. Jianqiao, G. Junbo, and J. Hu, "Natural Terpenoid-Based Sustainable Thermoplastics, Cross-Linked Polymers, and Supramolecular Materials," *Polymer Reviews* 64, no. 1 (2024): 119–161.

32. W. Teng, Z. Zhou, J. Cao, and Q. Guo, "Recent Advances of Natural Pentacyclic Triterpenoids as Bioactive Delivery System for Synergetic Biological Applications," *Foods* 13, no. 14 (2024): 2226.

33. Y. Chen, J. W. Y. Lam, R. T. K. Kwok, B. Liu, and B. Z. Tang, "Aggregation-Induced Emission: Fundamental Understanding and Future Developments," *Materials Horizons* 6, no. 3 (2019): 428–433.

34. X. Yu, Y. Meng, H. Zhang, et al., "Trans/Cis-Stereoisomers of Triterpenoid-Substituted Tetraphenylethene: Aggregation-Induced Emission, Aggregate Morphology, and Mechano-Chromism," *Nanoscale* 13, no. 36 (2021): 15257–15266.

35. X. Yu, J. Li, H. Zhang, M.-H. Li, and J. Hu, "Glycyrrhetinic Acid and Polyethylene Glycol-Disubstituted Trans/Cis-Tetraphenylethene Stereoisomers Showing Thermoresponsive Fluorescent Self-Assembly," *ACS Applied Polymer Materials* 5, no. 9 (2023): 7467–7476.

36. X. Wang, X. Zhang, G. Zheng, et al., "Mitochondria-Targeted Pentacyclic Triterpene NIR-AIE Derivatives for Enhanced Chemotherapeutic and Chemo-Photodynamic Combined Therapy," *European Journal of Medicinal Chemistry* 264 (2024): 115975.

37. B. Zhang, X. Yu, J. Li, K. Wei, L. Gao, and J. Hu, "Four-Armed Biobased Glycyrrhizic Acid-Tailored AIE Fluorescent Gelator," *Journal of Molecular Structure* 1258 (2022): 132684.

38. J. Liu, F. Yin, J. Hu, and Y. Ju, "Isomerism and Silver Ion-Regulated Triterpenoid-Based Nanostructures for in Situ Synthesis of Ag Nanoparticles With Plasmonic Chirality," *ACS Applied Nano Materials* 5, no. 8 (2022): 10735–10743.

39. Y. Gao, J. Hao, J. Liu, et al., "Imprinting Supramolecular Chirality on Silica From Natural Triterpenoid-Regulated Helical Ribbons," *Materials Chemistry Frontiers* 3, no. 2 (2019): 308–313.

40. F. Han, F. Shi, H. Li, Y. Yang, and Y. Li, "Facile Fabrication of Helical Hybrid Silica Ribbons With High-Efficiency Circularly Polarized Luminescence," *Materials Letters* 327 (2022): 133026.

41. Y. Meng, Z. Li, C. Xie, et al., "Natural Triterpenoid-Tailored Self-Assembled Chiral Helical Ribbons for Regulating Droplet Bounce," *Cell Reports Physical Science* 3, no. 4 (2022): 100810.

42. J. Mei, Y. Hong, J. W. Lam, A. Qin, Y. Tang, and B. Z. Tang, "Aggregation-Induced Emission: The Whole Is More Brilliant Than the Parts," *Advanced Materials* 26, no. 31 (2014): 5429–5479.

43. C. Zhang, S. Cheng, Q. Zhuang, A. Xie, and W. Dong, "18α-Glycyrrhetinic Acid Aggregation-Induced Emission Probes for Visual Fluorescence Detection of Explosive as Well Multi-Functional Applications," *New Journal of Chemistry* 46, no. 4 (2022): 1896–1904.

44. Y. Xiao, A. Ouyang, L. Fan, et al., "Precision Delivery of Binary Cooperative Nanodrugs Self-Assembled by Berberine Glycyrrhetinic Acid Salts for Hepatocellular Carcinoma Treatment," *ACS Applied Materials & Interfaces* 16, no. 43 (2024): 58489–58505.

45. J. Sun, C. Lv, T. Zhang, J. Zang, and G. Zhao, "Sprayable, Washable, and Light-Perceptible Hydrogels With AIE Activity Constructed by Co-assembly of Natural Glycyrrhizic Acid and Berberine for Fruit Preservation," *Food Chemistry* 467 (2025): 142260.

46. B. G. Bag, S. N. Hasan, S. Ghorai, and S. K. Panja, "First Self-Assembly of Dihydroxy Triterpenoid Maslinic Acid Yielding Vesicles," *ACS Omega* 4, no. 4 (2019): 7684–7690.

47. B. G. Bag and K. Paul, "Vesicular and Fibrillar Gels by Self-Assembly of Nanosized Oleanolic Acid," *Asian Journal of Organic Chemistry* 1, no. 2 (2012): 150–154.

48. B. G. Bag, S. Das, S. N. Hasan, and A. Chandan Barai, "Nanoarchitectures by Hierarchical Self-Assembly of Ursolic Acid: Entrapment and Release of Fluorophores Including Anticancer Drug Doxorubicin," *RSC Advances* 7, no. 29 (2017): 18136–18143.

49. B. G. Bag and S. S. Dash, "Hierarchical Self-Assembly of a Renewable Nanosized Pentacyclic Dihydroxy-Triterpenoid Betulin Yielding Flower-Like Architectures," *Langmuir* 31, no. 51 (2015): 13664–13672.

50. S. N. Hasan, J. Banerjee, S. Patra, et al., "Self-Assembled Renewable Nano-Sized Pentacyclic Triterpenoid Maslinic Acids in Aqueous Medium for Anti-Leukemic, Antibacterial and Biocompatibility Studies: An Insight Into Targeted Proteins-Compound Interactions Based Mechanistic Pathway Prediction Through Molecular Docking," *International Journal of Biological Macromolecules* 245 (2023): 125416.

51. X. Gao, X. Tang, Z. Tu, et al., "Tertiary Amine Modification Enables Triterpene Nanoparticles to Target the Mitochondria and Treat Glioblastoma via Pyroptosis Induction," *Biomaterials* 317 (2025): 123035.

52. M. Vágvölgyi, E. Kocsis, B. A. Tayeb, et al., "Ecdysteroid-Containing Squalenoylated Self-Assembling Nanoparticles Exert Tumor-Selective Sensitization to Reactive Oxygen Species (ROS)-Induced Oxidative Damage While Protecting Normal Cells: Implications for Selective Radiotherapy," *Journal of Medicinal Chemistry* 68, no. 7 (2025): 7197–7212.

53. F. Yin, Q. Liu, J. Hu, and Y. Ju, "Natural Oleanolic Acid-Tailored Eutectogels Featuring Multienvironment Shape Memory Performance," *ACS Applied Materials & Interfaces* 16, no. 5 (2024): 6424–6432.

54. T. Tong, H. Hu, J. Zhou, et al., "Glycyrrhizic-Acid-Based Carbon Dots With High Antiviral Activity by Multisite Inhibition Mechanisms," *Small* 16, no. 13 (2020): e1906206.

55. C.-M. Lai, J. Xu, B.-C. Zhang, S.-H. He, and J.-W. Shao, "A Natural Product-Derived Nanozyme Regulator Induced Chemo-Ferroptosis Dual Therapy in Remodeling of the Tumor Immune Microenvironment of Hepatocellular Carcinoma," *Chemical Engineering Journal* 482 (2024): 148976.

56. L. Tian, H. Ji, W. Wang, et al., "Mitochondria-Targeted Pentacyclic Triterpenoid Carbon Dots for Selective Cancer Cell Destruction via Inducing Autophagy, Apoptosis, as Well as Ferroptosis," *Bioorganic Chemistry* 130 (2023): 106259.

57. S. Zhang, B. Li, J. Zhou, et al., "Kill Three Birds With One Stone: Mitochondria-Localized Tea Saponin Derived Carbon Dots With AIE Properties for Stable Detection of HSA and Extremely Acidic pH," *Food Chemistry* 405 (2023): 134865.

58. Y. Jiang, L. Xiao, J. Wang, et al., "Carbon Nanodots Constructed by Ginsenosides and Their High Inhibitory Effect on Neuroblastoma," *Journal of Nanobiotechnology* 21, no. 1 (2023): 244.

59. J. Wang, N. Tian, T. Tian, et al., "Low Toxicity Ginsenoside Rg1-Carbon Nanodots as a Potential Therapeutic Agent for Human Non-Small Cell Lung Cancer," *Colloids and Surfaces B* 246 (2025): 114392.

60. J. Wang, E. Xu, H. Wang, et al., "Carbon Nanodots-Integrated Multifunctional Nanomedicine Establishes a Regenerative Feedback Loop Between Vascular-Immune-Muscle Systems for Comprehensive Therapy of Critical Limb Ischemia," *ACS Applied Materials & Interfaces* 17, no. 17 (2025): 24977–24993.

61. P. Sheng, C. Bu, T. Hui, L. Zhou, H. Chen, and G. Zhou, "Polydopamine-Activated Celastrol Carbon Dots for Synergistic Chemotherapy-Photothermal Therapy of Tumors," *International Journal of Pharmaceutics: X* 6 (2023): 100218.

62. J. Zhong, G. He, X. Ma, et al., "Triterpene-Based Prodrug for Self-Boosted Drug Release and Targeted Oral Squamous Cell Carcinoma Chemotherapy," *ACS Applied Materials & Interfaces* 16, no. 32 (2024): 41960–41972.

63. X. Yang, C. Ma, Z. Chen, et al., "Single Small Molecule-Assembled Nanoparticles Mediate Efficient Oral Drug Delivery," *Nano Research* 12, no. 10 (2019): 2468–2476.

64. M. Lin, D. Liu, Y. Gong, et al., "Bioactive Assembly Cofactor-Assisted Ursolic Acid Helix for Enhanced Anticancer Efficacy via in Situ Virus-Like Transition," *Journal of the American Chemical Society* 147 (2025): 17010–17021.

65. W. Zhang, Y. Huang, J. Li, et al., "Carrier-Free Poly(glycyrrhetinic acid)-Facilitated Celastrol-Loaded Nanoparticle for High-Efficiency Low-Toxicity Treatment of Rheumatoid Arthritis," *Materials and Design* 241 (2024): 112951.

66. S. Zuo, J. Wang, X. An, Z. Wang, X. Zheng, and Y. Zhang, "Fabrication of Ginsenoside-Based Nanodrugs for Enhanced Antitumor Efficacy on Triple-Negative Breast Cancer," *Frontiers in Bioengineering and Biotechnology* 10 (2022): 945472.

67. J. Wang, H. Zhao, W. Qiao, J. Cheng, Y. Han, and X. Yang, "Nanomedicine-Cum-Carrier by Co-Assembly of Natural Small Products for Synergistic Enhanced Antitumor With Tissues Protective Actions," *ACS Applied Materials & Interfaces* 12, no. 38 (2020): 42537–42550.

68. Y. Han, X. Yang, S. Fu, et al., "Co-assembly of Abietic Acid and Oleanolic Acid Into Nanoparticles Encapsulating Proanthocyanidin B2 to Improve Pac B2 Bioavailability and Thermal Stability," *Food Chemistry* 485 (2025): 144512.

69. L. Zong, Y. Dai, J. Xu, et al., "Luteolin and Glycyrrhetinic Exert Cooperative Effect on Liver Cancer by Selfassembling Into Carrier-Free Nanostructures," *Chinese Chemical Letters* (2025): 111325.

70. G. You, T. Feng, G. Zhang, et al., "Preparation, Optimization, Characterization and in Vitro Release of Baicalein-Solubilizing Glycyrrhizic Acid Nano-Micelles," *International Journal of Pharmaceutics* 601 (2021): 120546.

71. G. Li, Z. Song, Y. Ru, et al., "Small-Molecule Nanoprodrug With High Drug Loading and EGFR, PI3K/AKT Dual-Inhibiting Properties for Bladder Cancer Treatment," *Exploration* 3, no. 5 (2023): 20220141.

72. S. Liu, J. Zhang, R. Fu, et al., "Improved Stability and Aqueous Solubility of *β*-Carotene via Encapsulation in Self-assembled Bioactive Oleanolic Acid Nanoparticles," *Food Chemistry* 373, no. Pt B (2022): 131498.

73. C. Liu, W. Du, L. Zhang, and J. Wang, "Natural Synergy: Oleanolic Acid-Curcumin Co-assembled Nanoparticles Combat Osteoarthritis," *Colloids and Surfaces B* 245 (2025): 114286.

74. Y. Su, R. Chen, B. Wang, et al., "Erythrocyte Membrane Camouflaged Celastrol and Bilirubin Self-Assembly for Rheumatoid Arthritis Immunotherapy Based on STING Inhibition and RONS Clearance," *Journal of Nanobiotechnology* 23, no. 1 (2025): 318.

75. T. Liang, Y. Wu, Q. Zeng, et al., "Development of a Self-Assembled Micelles Based on Cryptotanshinone and Glycyrrhizic Acid: An Efficient Strategy for Acne Treatment," *International Journal of Pharmaceutics* 674 (2025): 125411.

76. J. Cui, X. Wang, J. Li, et al., "Immune Exosomes Loading Self-Assembled Nanomicelles Traverse the Blood–Brain Barrier for Chemoimmunotherapy Against Glioblastoma," *ACS Nano* 17, no. 2 (2023): 1464–1484.

77. J. Cheng, X. Li, S. Wang, Y. Han, H. Zhao, and X. Yang, "Carrier-Free Triterpene Prodrugs With Glutathione Response and Biosafety for Synergistically Enhanced Photochemotherapy," *ACS Applied Materials & Interfaces* 13, no. 1 (2021): 245–256.

78. J. Cheng, S. Wang, H. Zhao, Y. Liu, and X. Yang, "Exploring the Self-Assembly Mechanism and Effective Synergistic Antitumor Chemophototherapy of a Biodegradable and Glutathione Responsive Ursolic Acid Prodrug Mediated Photosensitive Nanodrug," *Biomaterials Science* 9, no. 10 (2021): 3762–3775.

79. R. P. Shukla, P. Tiwari, A. Sardar, et al., "Alendronate-Functionalized Porous Nano-Crystalsomes Mitigate Osteolysis and Consequent Inhibition of Tumor Growth in a Tibia-Induced Metastasis Model," *Journal of Controlled Release* 372 (2024): 331–346.

80. L. Kang, X. Chang, S. Ma, et al., "Redox-Responsive Self-Assembled HG-type Pectin Nanomicelles for Alleviating Chronic Alcoholic Liver Injury in Mice," *Carbohydrate Polymers* 361 (2025): 123619.

81. L. Fu, Z. Su, S. Wu, Y. Cheng, C. Hu, and J. Zhang, "Redox-responsive Hyaluronic Acid-Celastrol Prodrug Micelles With Glycyrrhetinic Acid Co-delivery for Tumor Combination Therapy," *Chinese Chemical Letters* 36, no. 5 (2025): 110227.

82. Y. Zhang, Y. Lian, C. Zhou, et al., "Self-Assembled Natural Triterpenoids for the Delivery of Cyclin-Dependent Kinase 4/6 Inhibitors to Enhance Cancer Chemoimmunotherapy," *Journal of Controlled Release* 378 (2025): 791–802.

83. X. Zhang, Y. Chen, X. Li, et al., "Carrier-Free Self-Assembled Nanomedicine Based on Celastrol and Galactose for Targeting Therapy of Hepatocellular Carcinoma via Inducing Ferroptosis," *European Journal of Medicinal Chemistry* 267 (2024): 116183.

84. Z. Li, H. Xie, H. Shi, et al., "Triterpenoids and Ultrasound Dual-Catalytic Nanoreactor Ignites Long-Lived Hypertoxic Reactive Species Storm for Deep Tumor Treatment," *Chemical Engineering Journal* 453 (2023): 139938.

85. J. Cheng, H. Zhao, B. Li, et al., "Photosensitive Pro-Drug Nanoassemblies Harboring a Chemotherapeutic Dormancy Function Potentiates Cancer Immunotherapy," *Acta Pharmaceutica Sinica B* 13, no. 2 (2023): 879–896.

86. Z. Li, H. Shi, H. Xie, et al., "Tri-Component Programmable Nanoregulator With Three-Pronged Penetration Boosts Immunotherapy of Triple-Negative Breast Cancer," *Chemical Engineering Journal* 439 (2022): 135712.

87. Y. Zheng, Z. Li, Y. Yang, H. Shi, H. Chen, and Y. Gao, "A Nanosensitizer Self-Assembled From Oleanolic Acid and Chlorin e6 for Synergistic Chemo/Sono-Photodynamic Cancer Therapy," *Phytomedicine* 93 (2021): 153788.

88. Y. Bao, S. Zhang, Z. Chen, et al., "Synergistic Chemotherapy for Breast Cancer and Breast Cancer Brain Metastases via Paclitaxel-Loaded Oleanolic Acid Nanoparticles," *Molecular Pharmaceutics* 17, no. 4 (2020): 1343–1351.

89. S. Fu, M. Wang, B. Li, et al., "Bionic Natural Small Molecule Co-assemblies Towards Targeted and Synergistic Chemo/PDT/CDT," *Biomaterials Research* 27, no. 1 (2023): 43.

90. J. Wang, W. Qiao, X. Li, et al., "A Directed Co-assembly of Herbal Small Molecules Into Carrier-Free Nanodrugs for Enhanced Synergistic Antitumor Efficacy," *Journal of Materials Chemistry B* 9, no. 4 (2021): 1040–1048.

91. J. Cheng, H. Zhao, J. Wang, Y. Han, and X. Yang, "Bioactive Natural Small Molecule-Tuned Coassembly of Photosensitive Drugs for Highly

Efficient Synergistic and Enhanced Type I Photochemotherapy," *ACS Applied Materials & Interfaces* 12, no. 39 (2020): 43488–43500.

92. Z. Li, H. Xie, H. Shi, H. Chen, and Y. Gao, "Photosensitizers Dispersed on Nanosized Triterpenoid Matrix With Deaggregation-Enhanced Singlet Oxygen Production," *ACS Applied Materials & Interfaces* 15, no. 4 (2023): 4973–4983.

93. S. Zhu, Z. Qiu, X. Qiao, et al., "Creating Burdock Polysaccharide-Oleanolic Acid-Ursolic Acid Nanoparticles to Deliver Enhanced Anti-Inflammatory Effects: Fabrication, Structural Characterization and Property Evaluation," *Food Science and Human Wellness* 12, no. 2 (2023): 454–466.

94. B.-C. Zhang, C.-M. Lai, B.-Y. Luo, and J.-W. Shao, "Triterpenoids-Templated Self-Assembly Nanosystem for Biomimetic Delivery of CRISPR/Cas9 Based on the Synergy of TLR-2 and ICB to Enhance HCC Immunotherapy," *Acta Pharmaceutica Sinica B* 14, no. 7 (2024): 3205–3217.

95. Z. Wang, J. Liu, Q. Chen, et al., "Bioactive Glycyrrhizic Acid Ionic Liquid Self-Assembled Nanomicelles for Enhanced Transdermal Delivery of Anti-Photoaging Signal Peptides," *Advanced Science* 12 (2025): e2412581.

96. W. S. Bertaud and R. H. Hedley, "Hexagonal Patterns in Cell Membranes," *Nature* 200, no. 4901 (1963): 89–90.

97. P. Seeman, D. Cheng, and G. H. Iles, "Structure of Membrane Holes in Osmotic and Saponin Hemolysis," *Journal of Cell Biology* 56, no. 2 (1973): 519–527.

98. A. Nicol, R. T. K. Kwok, C. Chen, et al., "Ultrafast Delivery of Aggregation-Induced Emission Nanoparticles and Pure Organic Phosphorescent Nanocrystals by Saponin Encapsulation," *Journal of the American Chemical Society* 139, no. 41 (2017): 14792–14799.

99. A. Weng, M. D. Manunta, M. Thakur, et al., "Improved Intracellular Delivery of Peptide- and Lipid-Nanoplexes by Natural Glycosides," *Journal of Controlled Release* 206 (2015): 75–90.

100. M. Kolster, A. Sonntag, C. Weise, et al., "Broadening the Scope of Sapofection: Cationic Peptide-Saponin Conjugates Improve Gene Delivery in Vitro and in Vivo," *ACS Applied Materials & Interfaces* 16, no. 28 (2024): 36095–36105.

101. A. Zarinwall, M. Asadian-Birjand, D. A. Seleci, et al., "Magnetic Nanoparticle-Based Dianthin Targeting for Controlled Drug Release Using the Endosomal Escape Enhancer SO1861," *Nanomaterials* 11, no. 4 (2021): 1057.

102. I. M. S. Degors, C. Wang, Z. U. Rehman, and I. S. Zuhorn, "Carriers Break Barriers in Drug Delivery: Endocytosis and Endosomal Escape of Gene Delivery Vectors," *Accounts of Chemical Research* 52, no. 7 (2019): 1750–1760.

103. A. Weng, M. Thakur, B. von Mallinckrodt, et al., "Saponins Modulate the Intracellular Trafficking of Protein Toxins," *Journal of Controlled Release* 164, no. 1 (2012): 74–86.

104. S. Sama, G. Jerz, P. Schmieder, E. Woith, M. F. Melzig, and A. Weng, "Sapofectosid—Ensuring Non-Toxic and Effective DNA and RNA Delivery," *International Journal of Pharmaceutics* 534, no. 1-2 (2017): 195–205.

105. J. Clochard, G. Jerz, P. Schmieder, et al., "A New Acetylated Triterpene Saponin From Agrostemma githago L. modulates Gene Delivery Efficiently and Shows a High Cellular Tolerance," *International Journal of Pharmaceutics* 589 (2020): 119822.

106. I. Welsby, S. Detienne, F. N'Kuli, et al., "Lysosome-Dependent Activation of Human Dendritic Cells by the Vaccine Adjuvant QS-21," *Frontiers in immunology* 7 (2016): 663.

107. A. Y. Nadeem, A. Shehzad, S. U. Islam, E. A. Al-Suhaimi, and Y. S. Lee, "Mosquirix™ RTS, S/AS01 Vaccine Development, Immunogenicity, and Efficacy," *Vaccines* 10, no. 5 (2022): 713.

108. M. B. Laurens, "RTS,S/AS01 Vaccine (Mosquirix™): An Overview," *Human Vaccines & Immunotherapeutics* 16, no. 3 (2020): 480–489.

109. G. E. Hancock, D. J. Speelman, P. J. Frenchick, M. M. Mineo-Kuhn, R. B. Baggs, and D. J. Hahn, "Formulation of the Purified Fusion Protein of respiratory Syncytial Virus With the Saponin QS-21 Induces Protective Immune Responses in Mice That Are Similar to Those Generated by Experimental Infection," *Vaccine* 13, no. 4 (1995): 391–400.

110. A. D. Robert and A. K. Ruth, "Respiratory Syncytial Virus Vaccines," *Clinical Microbiology Reviews* 11, no. 3 (1998): 430–439.

111. B. L. Ober Shepherd, P. T. Scott, J. N. Hutter, et al., "SARS-CoV-2 Recombinant Spike Ferritin Nanoparticle Vaccine Adjuvanted With Army Liposome Formulation Containing Monophosphoryl Lipid A and QS-21: A Phase 1, Randomised, Double-Blind, Placebo-Controlled, First-in-Human Clinical Trial," *The Lancet Microbe* 5, no. 6 (2024): e581–e593.

112. B. S. Ou, J. Baillet, M. V. Filsinger Interrante, et al., "Saponin Nanoparticle Adjuvants Incorporating Toll-Like Receptor Agonists Drive Distinct Immune Signatures and Potent Vaccine Responses," *Science Advances* 10, no. 32 (2024): eadn7187.

113. C. Wang, Y. Geng, H. Wang, et al., "A Broadly Applicable Protein-Polymer Adjuvant System for Antiviral Vaccines," *EMBO Molecular Medicine* 16, no. 6 (2024): 1451–1483.

114. L. Derré, V. Cesson, I. Lucca, et al., "Intravesical Bacillus Calmette Guerin Combined With a Cancer Vaccine Increases Local T-Cell Responses in Non-Muscle–Invasive Bladder Cancer Patients," *Clinical Cancer Research* 23, no. 3 (2017): 717–725.

115. M.-A. Lacaille-Dubois, "Updated Insights Into the Mechanism of Action and Clinical Profile of the Immunoadjuvant QS-21: A Review," *Phytomedicine* 60 (2019): 152905.

116. P. Yousefpour, Y. J. Zhang, L. Maiorino, et al., "Modulation of Antigen Delivery and Lymph Node Activation in Nonhuman Primates by Saponin Adjuvant Saponin/Monophosphoryl Lipid A Nanoparticle," *PNAS Nexus* 3, no. 12 (2024): 529.

117. D. J. Marciani, "Vaccine Adjuvants: Role and Mechanisms of Action in Vaccine Immunogenicity," *Drug Discovery Today* 8, no. 20 (2003): 934–943.

118. D. J. Marciani, "Elucidating the Mechanisms of Action of Saponin-Derived Adjuvants," *Trends in Pharmacological Sciences* 39, no. 6 (2018): 573–585.

119. C. Pifferi, R. Fuentes, and A. Fernández-Tejada, "Natural and Synthetic Carbohydrate-Based Vaccine Adjuvants and Their Mechanisms of Action," *Nature Reviews Chemistry* 5, no. 3 (2021): 197–216.

120. S. Zhou, Y. Song, A. Nilam, et al., "The Predominant Quillaja Saponaria Fraction, QS-18, Is Safe and Effective When Formulated in a Liposomal Murine Cancer Peptide Vaccine," *Journal of Controlled Release* 369 (2024): 687–695.

121. X. Mo, A. Shen, Y. Han, et al., "Polysaccharide Nanoadjuvants Engineered via Phenotype-Specific Nanoprobe-Assisted Phenotypic Screen Reprogram Macrophage Cell Functions for Cancer and Rheumatoid Arthritis Therapy," *ACS Nano* 19, no. 13 (2025): 12920–12936.

122. C. R. Kensil, U. Patel, M. Lennick, and D. Marciani, "Separation and Characterization of Saponins With Adjuvant Activity From *Quillaja saponaria* Molina Cortex," *Journal of Immunology* 146, no. 2 (1991): 431–437.

123. R. Jin, L. Neufeld, and T. L. McGaha, "Linking Macrophage Metabolism to Function in the Tumor Microenvironment," *Nature Cancer* 6, no. 2 (2025): 239–252.

124. M. H. den Brok, C. Büll, M. Wassink, et al., "Saponin-Based Adjuvants Induce Cross-Presentation in Dendritic Cells by Intracellular Lipid Body Formation," *Nature Communications* 7, no. 1 (2016): 13324.

125. T. Ichikawa, S. Ishida, Y. Sakiya, Y. Sawada, and M. Hanano, "Biliary Excretion and Enterohepatic Cycling of Glycyrrhizin in Rats," *Journal of Pharmaceutical Sciences* 75, no. 7 (1986): 672–675.

126. M. Negishi, A. Irie, N. Nagata, and A. Ichikawa, "Specific Binding of Glycyrrhetinic Acid to the Rat Liver Membrane," *Biochimica Et Biophysica Acta* 1066, no. 1 (1991): 77–82.

127. S. Osaka, H. Tsuji, and H. Kiwada, "Uptake of Liposomes Surface-Modified With Glycyrrhizin by Primary Cultured Rat Hepatocytes," *Biological & Pharmaceutical Bulletin* 17, no. 7 (1994): 940–943.

128. Y.-Q. Sun, C.-M. Dai, Y. Zheng, S.-D. Shi, H.-Y. Hu, and D.-W. Chen, "Binding Effect of Fluorescence Labeled Glycyrrhetinic Acid With GA Receptors in Hepatocellular Carcinoma Cells," *Life Sciences* 188 (2017): 186–191.

129. Z. Y. He, X. Zheng, X. H. Wu, et al., "Development of Glycyrrhetinic Acid-Modified Stealth Cationic Liposomes for Gene Delivery," *International Journal of Pharmaceutics* 397, no. 1-2 (2010): 147–154.

130. L. F. Zhang, W. Q. Deng, Q. W. Huang, et al., "Vicious Cycle-Breaking Lipid Nanoparticles Remodeling Multicellular Crosstalk to Reverse Liver Fibrosis," *Advanced Materials* 36, no. 16 (2024): e2311474.

131. Y. Wang, W. Wang, H. Yao, et al., "Glycyrrhizic Acid-Based Liposome for Tumor-Targeted Delivery of Cantharidin," *ACS Applied Nano Materials* 7, no. 1 (2024): 1030–1044.

132. M. Qiu, J. Wang, J. Bai, et al., "Dual-Ligand-Functionalized Liposomes Based on Glycyrrhetinic Acid and cRGD for Hepatocellular Carcinoma Targeting and Therapy," *Molecular Pharmaceutics* 20, no. 4 (2023): 1951–1963.

133. Q. Tian, C.-N. Zhang, X.-H. Wang, et al., "Glycyrrhetinic Acid-Modified Chitosan/Poly(ethylene glycol) Nanoparticles for Liver-Targeted Delivery," *Biomaterials* 31, no. 17 (2010): 4748–4756.

134. X. Zhang, X. Xu, X. Wang, et al., "Hepatoma-Targeting and Reactive Oxygen Species-Responsive Chitosan-Based Polymeric Micelles for Delivery of Celastrol," *Carbohydrate Polymers* 303 (2023): 120439.

135. W. Huang, W. Wang, P. Wang, et al., "Glycyrrhetinic Acid-Modified Poly(ethylene glycol)–b-poly(γ-benzyl l-glutamate) Micelles for Liver Targeting Therapy," *Acta Biomaterialia* 6, no. 10 (2010): 3927–3935.

136. X. Su, H. Zhong, Y. Zeng, et al., "Dual-Ligand-Functionalized Nanostructured Lipid Carriers as a Novel Dehydrocavidine Delivery System for Liver Fibrosis Therapy," *Colloids and Surfaces B* 246 (2025): 114376.

137. T. Yan, J. Cheng, Z. Liu, et al., "Acid-Sensitive Polymeric Vector Targeting to Hepatocarcinoma Cells via Glycyrrhetinic Acid Receptor-Mediated Endocytosis," *Materials Science & Engineering, C: Biomimetic and Supramolecular Systems* 87 (2018): 32–40.

138. W. W. Qi, H. Y. Yu, H. Guo, et al., "Doxorubicin-Loaded Glycyrrhetinic Acid Modified Recombinant human Serum Albumin Nanoparticles for Targeting Liver Tumor Chemotherapy," *Molecular Pharmaceutics* 12, no. 3 (2015): 675–683.

139. C. Wu, S. Xiang, H. Wang, et al., "Orally Deliverable Sequence-Targeted Fucoxanthin-Loaded Biomimetic Extracellular Vesicles for Alleviation of Nonalcoholic Fatty Liver Disease," *ACS Applied Materials & Interfaces* 16, no. 8 (2024): 9854–9867.

140. L. Cui, X. Wang, Z. Liu, et al., "Metal-organic Framework Decorated With Glycyrrhetinic Acid Conjugated Chitosan as a pH-Responsive Nanocarrier for Targeted Drug Delivery," *International Journal of Biological Macromolecules* 240 (2023): 124370.

141. Y. Cai, Y. Xu, H. F. Chan, X. Fang, C. He, and M. Chen, "Glycyrrhetinic Acid Mediated Drug Delivery Carriers for Hepatocellular Carcinoma Therapy," *Molecular Pharmaceutics* 13, no. 3 (2016): 699–709.

142. L. A. Stecanella, A. P. R. Bitencourt, G. R. Vaz, E. Quarta, J. O. C. Silva Júnior, and A. Rossi, "Glycyrrhizic Acid and Its Hydrolyzed Metabolite 18β-Glycyrrhetinic Acid as Specific Ligands for Targeting Nanosystems in the Treatment of Liver Cancer," *Pharmaceutics* 13, no. 11 (2021): 1792.

143. A. Speciale, C. Muscarà, M. S. Molonia, M. Cristani, F. Cimino, and A. Saija, "Recent Advances in Glycyrrhetinic Acid-Functionalized Biomaterials for Liver Cancer-Targeting Therapy," *Molecules* 27, no. 6 (2022): 1775.

144. J. Li, X. Wang, Y. Guo, et al., "Ginsenoside Rg3-engineered Exosomes as Effective Delivery Platform for Potentiated Chemotherapy and Photoimmunotherapy of Glioblastoma," *Chemical Engineering Journal* 471 (2023): 144692.

145. G. C. Terstappen, A. H. Meyer, R. D. Bell, and W. Zhang, "Strategies for Delivering Therapeutics Across the Blood–Brain Barrier," *Nature Reviews Drug Discovery* 20, no. 5 (2021): 362–383.

146. I. Zare, S. Zirak Hassan Kiadeh, A. Varol, et al., "Glycosylated Nanoplatforms: From Glycosylation Strategies to Implications and Opportunities for Cancer Theranostics," *Journal of Controlled Release* 371 (2024): 158–178.

147. L. Zou, Y. Hou, J. Zhang, et al., "Degradable Carrier-Free Spray Hydrogel Based on Self-assembly of Natural Small Molecule for Prevention of Postoperative Adhesion," *Materials Today Bio* 22 (2023): 100755.

148. H. Yu, G. Zhang, M. You, et al., "Herbal Small Molecule-Based Low/Medium Internal Phase Supramolecular Gel Emulsion for Diabetic Wound Healing," *Journal of Colloid & Interface Science* 671 (2024): 270–282.

149. T. Li, J. Zheng, M. Xia, et al., "In Situ Sprayed Self-Gelling Powder Self-Assembled by a Pure Molecular Drug From Herbal Extract for Rapid Hemostasis and Neuroprotection in Traumatic Brain Injury," *Advanced Functional Materials* 35 (2025): e2419613.

150. M. Peng, Q. Peng, W. Li, et al., "Atomic Insights into Self-Assembly of Zingibroside R1 and Its Therapeutic Action against Fungal Diseases," *Advanced Materials* (2025): e2503283.

151. K. Zhi, Y. Sun, H. Zhao, C. Zhang, H. Peng, and X. Yang, "Self-Assembled Supramolecular Material Derived From Traditional Chinese Medicine: Injectable Self-Assembled Natural Product Gel for Drug Delivery With Biological Activity," *Materials Today Communications* 23 (2020): 101149.

152. K. Zhi, J. Wang, H. Zhao, and X. Yang, "Self-Assembled Small Molecule Natural Product Gel for Drug Delivery: A Breakthrough in New Application of Small Molecule Natural Products," *Acta Pharmaceutica Sinica B* 10, no. 5 (2020): 913–927.

153. X. Zhao, M. Liu, Z. Ma, et al., "Constructing a Hydrogel Based on Self-Assembly Properties of Glycyrrhizic Acid: A Drug Delivery System With Digestive Tract Responsive," *Colloids and Surfaces A* 697 (2024): 134497.

154. W. Liu, Z. Li, Z. Wang, et al., "Functional System Based on Glycyrrhizic Acid Supramolecular Hydrogel: Toward Polymorph Control, Stabilization, and Controlled Release," *ACS Applied Materials & Interfaces* 15, no. 6 (2023): 7767–7776.

155. J. Zheng, X. Song, Z. Yang, et al., "Self-Assembling Glycyrrhizic Acid Micellar Hydrogels as Encapsulant Carriers for Delivery of Curcumin," *Colloids and Surfaces A* 658 (2023): 130680.

156. S. K. Panja, S. Patra, and B. G. Bag, "Self-Assembly of the Monohydroxy Triterpenoid Lupeol Yielding Nano-Fibers, Sheets and Gel: Environmental and Drug Delivery Applications," *RSC Advances* 11, no. 53 (2021): 33500–33510.

157. W. Luo, Z. Yang, J. Zheng, et al., "Small Molecule Hydrogels Loading Small Molecule Drugs From Chinese Medicine for the Enhanced Treatment of Traumatic Brain Injury," *ACS Nano* 18, no. 42 (2024): 28894–28909.

158. C. Lei, J. Wen, Y. Sun, M. Ren, R. Qiao, and C. Li, "Self-Assembled Herbal Hydrogel for Rectal Administration Therapy in Ulcerative Colitis," *Chemical Engineering Journal* 503 (2025): 158477.

159. H. Jiang, Q. Lu, X. Huang, et al., "Sinomenine-Glycyrrhizic Acid Self-Assembly Enhanced the Anti-Inflammatory Effect of Sinomenine in the Treatment of Rheumatoid Arthritis," *Journal of Controlled Release* 382 (2025): 113718.

160. W. Y. He, X. C. Wang, W. Gong, et al., "Construction of an Antibacterial Hydrogel Based on Diammonium Glycyrrhizinate and Gallic Acid for Bacterial-Infected Wound Healing," *Colloids and Surfaces B* 222 (2023): 112975.

161. Q. Li, Y. Liu, S. Liu, et al., "All-Natural Aggregation-Induced Emission-Active Glycyrrhizic Acid Hydrogels for Drug-Resistant

Bacteria-Infected Wound Healing," *Chemical Engineering Journal* 512 (2025): 162677.

162. D. Song, C. Lu, C. Chang, et al., "Natural Binary Herbal Small Molecules Self-Assembled Nanogel for Synergistic Inhibition of Respiratory Syncytial Virus," *ACS Biomaterials Science & Engineering* 10, no. 10 (2024): 6648–6660.

163. Y. Yang, D. Cai, Y. Shu, et al., "Natural Small Molecule Self-Assembled Hydrogel Inhibited Tumor Growth and Lung Metastasis of 4T1 Breast Cancer by Regulating the CXCL1/2-S100A8/9 Axis," *Materials and Design* 225 (2023): 111435.

164. M. Zhan, D. Zhou, L. Lei, et al., "Glycyrrhizic Acid and Glycyrrhetinic Acid Loaded Cyclodextrin MOFs With Enhanced Antibacterial and Anti-Inflammatory Effects for Accelerating Diabetic Wound Healing," *Colloids and Surfaces B* 245 (2025): 114200.

165. X. Fu, Y. Ni, G. Wang, et al., "Synergistic and Long-Lasting Wound Dressings Promote Multidrug-Resistant Staphylococcus Aureus-Infected Wound Healing," *International Journal of Nanomedicine* 18 (2023): 4663–4679.

166. C. Zhang, S. Sun, T. Zhu, et al., "NIR-Activating Glycyrrhizic Acid/Carbon Nanozyme Injectable Polysaccharides-Based Hydrogels for Promoting Polymicrobial Infected Wound Healing," *International Journal of Biological Macromolecules* 307 (2025): 142082.

167. Y. Hou, M. Chen, H. Ruan, et al., "A New Supramolecular Natural Product Gel Based on Self-Assembled Pomolic Acid From Traditional Chinese Medicine," *Colloid and Interface Science Communications* 46 (2022): 100583.

168. B. G. Bag and S. S. Dash, "First Self-Assembly Study of Betulinic Acid, a Renewable Nano-Sized, 6-6-6-6-5 Pentacyclic Monohydroxy Triterpenic Acid," *Nanoscale* 3, no. 11 (2011): 4564.

169. D. Cai, Y. Yang, J. Lu, et al., "Injectable Carrier-Free Hydrogel Dressing With Anti-Multidrug-Resistant *Staphylococcus aureus* and Anti-Inflammatory Capabilities for Accelerated Wound Healing," *ACS Applied Materials & Interfaces* 14, no. 38 (2022): 43035–43049.

170. Y. Gao, J. Hao, J. Wu, X. Zhang, J. Hu, and Y. Ju, "Supramolecular Helical Nanofibers Assembled From a Pyridinium-Functionalized Methyl Glycyrrhetate Amphiphile," *Nanoscale* 7, no. 32 (2015): 13568–13575.

171. Q. Li, S. Zhang, R. Du, et al., "Injectable Self-Healing Adhesive Natural Glycyrrhizic Acid Bioactive Hydrogel for Bacteria-Infected Wound Healing," *ACS Applied Materials & Interfaces* 15, no. 14 (2023): 17562–17576.

172. J.-P. Fan, F.-H. Tao, X.-H. Zhang, et al., "Synthesis of an Ursolic Acid Organic Salt Based Low-Molecular-Weight Supramolecular Hydrogel With Unique Thermo-Responsiveness Behavior," *Colloids and Surfaces A* 652 (2022): 129839.

173. S. Guo, S. Chen, N. Cao, et al., "A Novel 18β-Glycyrrhetinic Acid Derivative Supramolecular Self-Assembly Hydrogel With Antibacterial Activity," *Journal of Materials Science* 56, no. 30 (2021): 17254–17267.

174. J.-P. Fan, H. Zhong, X.-H. Zhang, T.-T. Yuan, H.-P. Chen, and H.-L. Peng, "Preparation and Characterization of Oleanolic Acid-Based Low-Molecular-Weight Supramolecular Hydrogels Induced by Heating," *ACS Applied Materials & Interfaces* 13, no. 24 (2021): 29130–29136.

175. Z. Özdemir, D. Šaman, K. Bertula, et al., "Rapid Self-Healing and Thixotropic Organogelation of Amphiphilic Oleanolic Acid–Spermine Conjugates," *Langmuir* 37, no. 8 (2021): 2693–2706.

176. L. Zhao, H. Zhang, Z. Guo, et al., "Natural Glycyrrhizic Acid-Tailored Homogeneous Conductive Polyaniline Hydrogel as a Flexible Strain Sensor," *ACS Applied Materials & Interfaces* 14, no. 45 (2022): 51394–51403.

177. L. Zou, Y. Hou, X. Nie, et al., "All-Small-Molecule Supramolecular Hydrogel Combining Self-Delivery and ROS-Responsive Release for Inhibiting Tumor Growth and Postoperative Recurrence," *ACS Applied Materials & Interfaces* 17, no. 9 (2025): 13494–13512.

178. Y. Gao, K. Zhao, X. Yu, et al., "Multiple Modulations of Supramolecular Assemblies From a Natural Triterpenoid-Tailored Bipyridinium Amphiphile," *Journal of Colloid & Interface Science* 584 (2021): 92–102.

179. X. Yu, M. Xu, J. Cai, et al., "Tunable Glycyrrhizic Acid Supramolecular Hydrogels via Metal Ion Complexation," *Giant* 17 (2024): 100240.

180. X. Yu, J. Cai, M. Xu, et al., "A Natural Food-Grade Supramolecular Self-Assembly System for Creation of Hierarchically Structured Hydrogels," *Nanoscale* 16, no. 30 (2024): 14261–14268.

181. Z. Wang, J. Liu, Y. Zheng, et al., "Copper Ion-Inspired Dual Controllable Drug Release Hydrogels for Wound Management: Driven by Hydrogen Bonds," *Small* 20, no. 34 (2024): e2401152.

182. F. Zhang, C. Yin, X. Qi, C. Guo, and X. Wu, "Silk Fibroin Crosslinked Glycyrrhizic Acid and Silver Hydrogels for Accelerated Bacteria-Infected Wound Healing," *Macromolecular Bioscience* 22, no. 4 (2022): 2100407.

183. X. Li, Y. Li, A. Tehoungue, et al., "An Antibacterial Hydrogel Based on Silk Sericin Cross-Linking Glycyrrhizic Acid and Silver for Infectious Wound Healing," *Biomacromolecules* 26, no. 4 (2025): 2356–2367.

184. X. Zhang, L. Yang, W. Pi, et al., "Natural Diterpene Carrier-Free Hydrogel Enhances Antigen Presentation and Intensifies T Cell Activation for Tumor Immunotherapy," *Chemical Engineering Journal* 500 (2024): 156383.

185. Y. Fu, H. Sun, Y. Jin, et al., "Self-Assembled Antioxidant Enzyme-Mimicking Hydrogel: Targeting Oxidative Stress and Macrophage Organization for Improving Degenerated Intervertebral Discs," *Materials Today Bio* 31 (2025): 101586.

186. W. Zhang, S. Zhao, H. Zhang, et al., "A Simple and Universal Approach for Fabricating Bioactive Self-Stacked Hydrogels With Enhanced Therapeutic Efficacy," *Chemical Engineering Journal* 496 (2024): 154316.

187. W. Zhang, S. Zhao, Q. Guan, P. Li, and Y. Fan, "Enhancing Chronic Wound Healing Through Engineering Mg 2+ -Coordinated Asiatic Acid/Bacterial Cellulose Hybrid Hydrogels," *ACS Applied Materials & Interfaces* 16, no. 7 (2024): 8238–8249.

188. Y. Qian, Y. Zheng, J. Jin, et al., "Immunoregulation in Diabetic Wound Repair With a Photoenhanced Glycyrrhizic Acid Hydrogel Scaffold," *Advanced Materials* 34, no. 29 (2022): e2200521.

189. C. Lu, C. Chang, Y. Zheng, et al., "Supramolecular Self-Assembled Hydrogel for Antiviral Therapy Through Glycyrrhizic Acid-Enhanced Zinc Absorption and Intracellular Accumulation," *ACS Applied Materials & Interfaces* 16, no. 44 (2024): 60027–60044.

190. J. Li, D. Wu, Z. Su, et al., "Zinc-Induced Photocrosslinked Konjac Glucomannan/Glycyrrhizic Acid Hydrogel Promotes Skin Wound Healing in Diabetic Mice Through Immune Regulation," *Carbohydrate Polymers* 348 (2025): 122780.

191. J. Wang, W. Wang, K. Li, et al., "A Functional Hydrogel Dressing Based on Glycyrrhizic Acid With Low-Swelling and Moisturizing Properties for Enhancing Infected Wound Repair," *Journal of Materials Chemistry B* 13, no. 2 (2025): 656–667.

192. R. Huang, C. Hu, S. Xu, et al., "3D-Printed Bifunctional Scaffold for Treatment of Critical Bone Defects Based on Osteoimmune Microenvironment Regulation and Osteogenetic Effects," *ACS Applied Materials & Interfaces* 16, no. 46 (2024): 63345–63357.

193. L. Wu, W. Pi, X. Huang, et al., "Orchestrated Metal-Coordinated Carrier-Free Celastrol Hydrogel Intensifies T Cell Activation and Regulates Response to Immune Checkpoint Blockade for Synergistic Chemo-Immunotherapy," *Biomaterials* 312 (2025): 122723.

194. W. Pi, L. Wu, J. Lu, et al., "A Metal Ions-Mediated Natural Small Molecules Carrier-Free Injectable Hydrogel Achieving Laser-Mediated Photo-Fenton-Like Anticancer Therapy by Synergy Apoptosis/Cuproptosis/Anti-Inflammation," *Bioactive Materials* 29 (2023): 98–115.

195. X. Jia, Y. Dong, J. Lu, et al., "A Self-Assembly Enzyme-Like Hydrogel With ROS Scavenging and Immunomodulatory Capability for

Microenvironment-Responsive Wound Healing Acceleration," *International Journal of Pharmaceutics* 675 (2025): 125529.

196. Z. Xu, Z. Xu, J. Gu, et al., "In Situ Formation of Ferrous Sulfide in Glycyrrhizic Acid Hydrogels to Promote Healing of Multi-Drug Resistant Staphylococcus aureus-Infected Diabetic Wounds," *Journal of Colloid & Interface Science* 650, no. Pt B (2023): 1918–1929.

197. Z. Xu, Z. Gao, J. Lu, et al., "Ferrous Iron-Induced Formation of Glycyrrhizic Acid Hydrogels for *Staphylococcus aureus*-Infected Wound Healing," *Colloids and Surfaces B* 221 (2023): 112977.

198. Y. Wu, Z. Gu, T. Chen, et al., "Effect of Different Crosslinking Agents on Carboxymethyl Chitosan-Glycyrrhizic Acid Hydrogel: Characterization and Biological Activities Comparison," *International Journal of Biological Macromolecules* 298 (2025): 139977.

199. C. Lu, Q. Sun, Z. Li, et al., "Injectable Glycyrrhizinate-Pectin Hydrogel Wound Dressing Based on Natural Ingredients," *Carbohydrate Polymers* 359 (2025): 123562.

200. C. Zhang, E. Cai, X. Qi, et al., "Immunomodulatory Gallium/Glycyrrhizic Acid Hydrogels for Treating Multidrug-Resistant Pseudomonas Aeruginosa-Infected Pressure Ulcers," *Chemical Engineering Journal* 487 (2024): 150756.

201. X. Qi, Y. Shi, C. Zhang, et al., "A Hybrid Hydrogel With Intrinsic Immunomodulatory Functionality for Treating Multidrug-Resistant *Pseudomonas aeruginosa* Infected Diabetic Foot Ulcers," *ACS Materials Letters* 6, no. 7 (2024): 2533–2547.

202. B. Dalisson and J. Barralet, "Bioinorganics and Wound Healing," *Advanced Healthcare Materials* 8, no. 18 (2019): e1900764.

203. P. Bonaventura, G. Benedetti, F. Albarède, and P. Miossec, "Zinc and Its Role in Immunity and Inflammation," *Autoimmunity Reviews* 14, no. 4 (2015): 277–285.

204. Y. Yuan, H. Zhao, X. Yin, D. Wang, X. Mei, and P. Zhang, "Alloy Nanozyme-Reinforced Hyaluronic Acid-Based Hydrogel With Wound Environment-Responsive Properties for Synergistically Accelerating Infectious Wound Healing," *International Journal of Biological Macromolecules* 269 (2024): 131896.

205. M. Saeedi, M. R. Moghbeli, and O. Vahidi, "Chitosan/Glycyrrhizic Acid Hydrogel: Preparation, Characterization, and Its Potential for Controlled Release of Gallic Acid," *International Journal of Biological Macromolecules* 231 (2023): 123197.

206. H. Zhang, N. Tang, X. Yu, et al., "Natural Glycyrrhizic Acid-Tailored Hydrogel With In-Situ Gradient Reduction of AgNPs Layer as High-Performance, Multi-Functional, Sustainable Flexible Sensors," *Chemical Engineering Journal* 430 (2022): 132779.

207. Z. Zheng, Z. Wu, C. Li, et al., "Enhanced Immunoregulation in Traumatic Urethral Stricture Repair Utilizing a Glycyrrhizic Acid-Infused Antiswelling Biogel Scaffold," *RSC Advances* 15, no. 18 (2025): 14217–14226.

208. B. Zhang, W. Wang, P. Gao, et al., "Injectable, Electroconductive, Free Radical Scavenging Silk Fibroin/Black Phosphorus/Glycyrrhizic Acid Nanocomposite Hydrogel for Enhancing Spinal Cord Repair," *Advanced Healthcare Materials* 13, no. 18 (2024): e2304300.

209. H. Wu, Z. Xue, Z. Wang, et al., "Injectable Glycyrrhizic Acid-Based Hydrogel With Immunoregulatory and Angiogenic Properties for Diabetic Wound Healing," *Materials and Design* 253 (2025): 113928.

210. X. F. Tong, F. Q. Zhao, Y. Z. Ren, Y. Zhang, Y. L. Cui, and Q. S. Wang, "Injectable Hydrogels Based on Glycyrrhizin, Alginate, and Calcium for Three-Dimensional Cell Culture in Liver Tissue Engineering," *Journal of Biomedical Materials Research, Part A* 106, no. 12 (2018): 3292–3302.

211. J. Ge, C. Fang, H. Tan, et al., "Endogenous Zinc-Ion-Triggered in Situ Gelation Enables Zn Capture to Reprogram Benign Hyperplastic Prostate Microenvironment and Shrink Prostate," *Advanced Materials* 36, no. 11 (2024): e2307796.

212. Q. Li, X. Yu, S. Zhang, et al., "All-Natural, Robust, and pH-Responsive Glycyrrhizic Acid-Based Double Network Hydrogels for Controlled Nutrient Release," *ACS Appl Mater Interfaces* 15, no. 37 (2023): 43633–43647.

213. F.-Q. Zhao, G.-F. Wang, D. Xu, H.-Y. Zhang, Y.-L. Cui, and Q.-S. Wang, "Glycyrrhizin Mediated Liver-Targeted Alginate Nanogels Delivers Quercetin to Relieve Acute Liver Failure," *International Journal of Biological Macromolecules* 168 (2021): 93–104.

214. J. Sun, M. Sun, J. Zang, T. Zhang, C. Lv, and G. Zhao, "Highly Stretchable, Transparent, and Adhesive Double-Network Hydrogel Dressings Tailored With Fish Gelatin and Glycyrrhizic Acid for Wound Healing," *ACS Applied Materials & Interfaces* 15, no. 36 (2023): 42304–42316.

215. L. Tan, S. Wu, L. Liu, et al., "Bacterial Cellulose Based Gel of Glycyrrhizic Acid Gel for Atopic Dermatitis: Design, Optimization, in Vitro and in Vivo Investigation," *International Journal of Biological Macromolecules* 286 (2025): 138425.

216. S. Qin, H. Li, X. Liu, et al., "Supramolecular Nanofiber Network Hydrogel Dressing for Promoting Wound Healing With Low Swelling and Mechanical Stability Properties," *Colloids and Surfaces B* 245 (2025): 114345.

217. W.-J. Yin, X.-W. Chen, C.-G. Ma, and J.-M. Wang, "Fabrication and Characterization of Tunable High Internal Phase Emulsion Gels (HIPE-Gels) Formed by Natural Triterpenoid Saponin and Plant Soy Protein," *ACS Food Science & Technology* 2, no. 7 (2022): 1103–1113.

218. Q. Cui, X. Song, L. Zhou, et al., "Fabrication of Resveratrol-Loaded Soy Protein Isolate-Glycyrrhizin Nanocomplex for Improving Bioavailability via pH-Responsive Hydrogel Properties," *International Journal of Biological Macromolecules* 258 (2024): 128950.

219. Z. Cui, X. Zhang, L. Zhou, et al., "A Carrier-Free Injectable Hydrogel Self-Assembled Using Natural Thymol and Glycyrrhizin for MRSA-Infected Wound Healing in Rats," *Chemical Engineering Journal* 489 (2024): 151418.

220. H. Zheng, S. Gao, Y. Liu, et al., "Bioactive Glycyrrhizic Acid–Astragalus Polysaccharide Hydrogel Facilitates Gastric Ulcer Healing via ROS Scavenging and Anti-Apoptotic Effects," *Carbohydrate Polymers* 362 (2025): 123685.

221. H. Sun, Z. Dong, X. Kou, et al., "Herbal Molecule-Mediated Dual Network Hydrogels With Adhesive and Antibacterial Properties for Strain and Pressure Sensing," *RSC Advances* 13, no. 9 (2023): 5762–5769.

222. D. Y. Zhu, Z. P. Chen, Z. P. Hong, et al., "Injectable Thermo-Sensitive and Wide-Crack Self-Healing Hydrogel Loaded With Antibacterial Anti-Inflammatory Dipotassium Glycyrrhizate for Full-Thickness Skin Wound Repair," *Acta Biomaterialia* 143 (2022): 203–215.

223. X. Liu, X. Cheng, Y. Sun, et al., "Peptide/Glycyrrhizic Acid Supramolecular Polymer: An Emerging Medical Adhesive for Dural Sealing and Repairing," *Biomaterials* 301 (2023): 122239.

224. L. Zhang, Z. Luo, H. Chen, X. Wu, and Y. Zhao, "Glycyrrhizic Acid Hydrogel Microparticles Encapsulated With Mesenchymal Stem Cell Exosomes for Wound Healing," *Research* 7 (2024): 0496.

225. X. Li, L. Guan, X. Li, et al., "A Hierarchical Hydrogel Dressing With Continuous Biochemical Gradient for Immunoregulation, Nerve Repair and Angiogenesis of Refractory Diabetes Wounds," *Chinese Chemical Letters* (2024): 110661.

226. Q. Guo, R. Li, Y. Zhao, et al., "An Injectable, Self-Healing, Anti-Infective, and Anti-Inflammatory Novel Glycyrrhizic Acid Hydrogel for Promoting Acute Wound Healing and Regeneration," *Frontiers in Bioengineering and Biotechnology* 12 (2025): 1525644.

227. Y. Fan, Z. Niu, L. Yin, et al., "Membrane Biomimetic Nanoenzyme-Incorporated Hybrid Glycyrrhizic Acid Hydrogel for Precise Mitochondrial ROS Scavenging for Osteoarthritis Treatment," *Materials Today Bio* 32 (2025): 101778.

228. X. Wang, H. Huo, Y. Zhong, et al., "Synergistic Antimicrobial Glycyrrhizic Acid-Based Functional Biosensing Composite for Sensitive Glucose Monitoring and Collaborative Wound Healing," *Advanced Healthcare Materials* 13, no. 20 (2024): e2400580.

229. S. Bao, A. Jiang, L. Peng, et al., "Injectable Dual-Network Hydrogel for Phototherapy and Immunomodulation in the Treatment of MRSA-Infected and Diabetic Wound," *Chemical Engineering Journal* 513 (2025): 163026.

230. Y. Zheng, L. Fu, Z. Zhang, et al., "Three-Dimensional Bioprinting of Growth Differentiation Factor 5-Preconditioned Mesenchymal Stem Cell-Derived Exosomes Facilitates Articular Cartilage Endogenous Regeneration," *ACS Nano* 19, no. 16 (2025): 15281–15301.

231. Y. Ji, Y. Yuan, F. Peng, et al., "Two-Component Hydrogels Built From Chinese Herbal Medicine-Derived Glycyrrhizic Acid and Puerarin: Assembly Mechanism, Self-Healing Properties, and Selective Antibacterial Activity," *ACS Applied Materials & Interfaces* 17, no. 3 (2025): 5223–5231.

232. R. Mathiyalagan, M. Murugesan, Z. M. Ramadhania, et al., "Triterpenoid Saponin-Based Supramolecular Host-Guest Injectable Hydrogels Inhibit the Growth of Melanoma via ROS-Mediated Apoptosis," *Materials Science and Engineering R: Reports* 160 (2024): 100824.

233. H. Huang, X. Yang, X. Qin, et al., "Co-Assembled Supramolecular Hydrogel of Asiaticoside and Panax Notoginseng Saponins for Enhanced Wound Healing," *European Journal of Pharmaceutics and Biopharmaceutics* 207 (2025): 114617.

234. F. Topuz and T. Uyar, "Advances in the Development of Cyclodextrin-Based Nanogels/Microgels for Biomedical Applications: Drug Delivery and Beyond," *Carbohydrate Polymers* 297 (2022): 120033.

235. Y. Li, J. Li, X. Zhao, et al., "Triterpenoid-Based Self-Healing Supramolecular Polymer Hydrogels Formed by Host–Guest Interactions," *Chemistry— A European Journal* 22, no. 51 (2016): 18435–18441.

236. G. Xu, J. Li, J. Wu, H. Zhang, J. Hu, and M.-H. Li, "Tough Polymeric Hydrogels Formed by Natural Glycyrrhetinic Acid-Tailored Host–Guest Macro-Cross-Linking Toward Biocompatible Materials," *ACS Applied Polymer Materials* 1, no. 10 (2019): 2577–2581.

237. J. Hao, Y. Gao, Y. Li, Q. Yan, J. Hu, and Y. Ju, "Thermosensitive Triterpenoid-Appended Polymers With Broad Temperature Tunability Regulated by Host–Guest Chemistry," *Chemistry Asian Journal* 12, no. 17 (2017): 2231–2236.

238. Y. Zhang, F. Li, G. Guo, et al., "Preparation and Characterization of Betulin/Methyl-Beta-Cyclodextrin Inclusion Complex Electrospun Nanofiber: Improving the Properties of Betulin," *Industrial Crops and Products* 209 (2024): 117974.

239. M. Li, S. Wang, Y. Li, et al., "An Integrated All-Natural Conductive Supramolecular Hydrogel Wearable Biosensor With Enhanced Biocompatibility and Antibacterial Properties," *ACS Applied Materials & Interfaces* 16, no. 38 (2024): 51618–51629.

240. J. Zheng, R. Fan, H. Wu, et al., "Directed Self-Assembly of Herbal Small Molecules Into Sustained Release Hydrogels for Treating Neural Inflammation," *Nature Communications* 10, no. 1 (2019): 1604.

241. Y. Cai, J. Zhang, Y. He, et al., "A Supramolecular Hydrogel of Puerarin," *Journal of Biomedical Nanotechnology* 14, no. 2 (2018): 257–266.

242. K. J. De France, F. Xu, and T. Hoare, "Structured Macroporous Hydrogels: Progress, Challenges, and Opportunities," *Advanced Healthcare Materials* 7 (2018): e1700927.

243. D. Zhao, L. Qian, Q. Yang, et al., "Microfluidic Synthesis of Stimuli-Responsive Hydrogel Particles," *Applied Materials Today* 42 (2025): 102571.

244. L. Li, J. M. Scheiger, and P. A. Levkin, "Design and Applications of Photoresponsive Hydrogels," *Advanced Materials* 31, no. 26 (2019): e1807333.

245. A. P. Dhand, M. D. Davidson, and J. A. Burdick, "Lithography-Based 3D Printing of Hydrogels," *Nature Reviews Bioengineering* 3, no. 2 (2025): 108–125.

246. M. Zhang, S. Xu, R. Wang, et al., "Electrospun Nanofiber/Hydrogel Composite Materials and Their Tissue Engineering Applications," *Journal of Materials Science and Technology* 162 (2023): 157–178.

247. G. Guerrini, D. Magrì, S. Gioria, D. Medaglini, and L. Calzolai, "Characterization of Nanoparticles-Based Vaccines for COVID-19," *Nature Nanotechnology* 17, no. 6 (2022): 570–576.

248. R. Tenchov, R. Bird, A. E. Curtze, and Q. Zhou, "Lipid Nanoparticles─From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement," *ACS Nano* 15, no. 11 (2021): 16982–17015.

249. T. M. Allen and P. R. Cullis, "Liposomal Drug Delivery Systems: From Concept to Clinical Applications," *Advanced Drug Delivery Reviews* 65, no. 1 (2013): 36–48.

250. W. W. Sułkowski, D. Pentak, K. Nowak, and A. Sułkowska, "The Influence of Temperature, Cholesterol Content and pH on Liposome Stability," *Journal of Molecular Structure* 744-747 (2005): 737–747.

251. S. Kaddah, N. Khreich, F. Kaddah, and C. Charcosset, "Cholesterol Modulates the Liposome Membrane Fluidity and Permeability for a Hydrophilic Molecule," *Food and Chemical Toxicology* 113 (2018): 40–48.

252. M.-L. Briuglia, C. Rotella, A. McFarlane, and D. A. Lamprou, "Influence of Cholesterol on Liposome Stability and on in Vitro Drug Release," *Drug Delivery and Translational Research* 5, no. 3 (2015): 231–242.

253. P. I. Back, M. Yu, S. Modaresahmadi, et al., "Immune Implications of Cholesterol-Containing Lipid Nanoparticles," *ACS Nano* 18, no. 42 (2024): 28480–28501.

254. A. Kloudova, F. P. Guengerich, and P. Soucek, "The Role of Oxysterols in Human Cancer," *Trends in Endocrinology and Metabolism* 28, no. 7 (2017): 485–496.

255. X. Ma, E. Bi, Y. Lu, et al., "Cholesterol Induces CD8+ T Cell Exhaustion in the Tumor Microenvironment," *Cell Metabolism* 30, no. 1 (2019): 143–156.e145.

256. G. M. Swartz, M. K. Gentry, L. M. Amende, E. J. Blanchette-Mackie, and C. R. Alving, "Antibodies to Cholesterol," *Proceedings National Academy of Science USA* 85, no. 6 (1988): 1902–1906.

257. S. Moein Moghimi, I. Hamad, R. Bünger, et al., "Activation of the Human Complement System by Cholesterol-Rich and PEGylated Liposomes—Modulation of Cholesterol-Rich Liposome-Mediated Complement Activation by Elevated Serum LDL and HDL Levels," *Journal of Liposome Research* 16, no. 3 (2006): 167–174.

258. J. Szebeni, L. Baranyi, S. Savay, et al., "Liposome-Induced Pulmonary Hypertension: Properties and Mechanism of a Complement-Mediated Pseudoallergic Reaction," *American Journal of Physiology* 279, no. 3 (2000): H1319–H1328.

259. F. Zahednezhad, M. Saadat, H. Valizadeh, P. Zakeri-Milani, and B. Baradaran, "Liposome and Immune System Interplay: Challenges and Potentials," *Journal of Controlled Release* 305 (2019): 194–209.

260. Q. Yang, P. Guo, P. Lei, et al., "Dissolvable Microneedles Loaded Ginsenoside Rg3 Liposome: A Transdermal Delivery Approach for Alopecia Treatment," *Regenerative Biomaterials* 11 (2024): rbae086.

261. X. Zhang, S. Li, Y. Dong, H. Rong, J. Zhao, and H. Hu, "A Multifunctional Cholesterol-Free Liposomal Platform Based on Protopanaxadiol for Alopecia Therapy," *Nano Research* 15, no. 10 (2022): 9498–9510.

262. Y. Eygeris, S. Patel, A. Jozic, and G. Sahay, "Deconvoluting Lipid Nanoparticle Structure for Messenger RNA Delivery," *Nano Letters* 20, no. 6 (2020): 4543–4549.

263. K. Tai, M. Rappolt, X. He, et al., "Effect of β-Sitosterol on the Curcumin-Loaded Liposomes: Vesicle Characteristics, Physicochemical Stability, in Vitro Release and Bioavailability," *Food Chemistry* 293 (2019): 92–102.

264. A. A. Jovanović, B. D. Balanč, A. Ota, et al., "Comparative Effects of Cholesterol and β-Sitosterol on the Liposome Membrane Characteristics," *European Journal of Lipid Science and Technology* 120, no. 9 (2018): 1800039.

265. M. Cui, W. Wu, L. Hovgaard, Y. Lu, D. Chen, and J. Qi, "Liposomes Containing Cholesterol Analogues of Botanical Origin as Drug Delivery

Systems to Enhance the Oral Absorption of Insulin," *International Journal of Pharmaceutics* 489, no. 1 (2015): 277–284.

266. C. Zhong, T. Liu, J. Diao, X. Li, M. Liu, and Y. Wang, "Preparation and Characterization of Astaxanthin-Loaded Liposomes by Phytosterol Oleate Instead of Cholesterol," *Food Chemistry* 462 (2025): 141008.

267. S. Patel, N. Ashwanikumar, E. Robinson, et al., "Naturally-Occurring Cholesterol Analogues in Lipid Nanoparticles Induce Polymorphic Shape and Enhance Intracellular Delivery of mRNA," *Nature Communications* 11, no. 1 (2020): 983.

268. X. Xiao, X. Wu, Z. Yu, and J. He, "Incorporation of the Sterol From Camellia Oil Deodorant Distillate Into Vitamin C Liposomes: Vesicle Characteristics, Stability, Release, and Bioavailability," *Food Biophysics* 18, no. 1 (2023): 10–22.

269. G. Liu, P. Sun, J. Yan, P. Shao, and S. Feng, "Regulation of Nanoliposome Rigidity and Bioavailability of Oligomeric Proanthocyanidin With Phytosterols Containing Different C3 Branches," *ACS Applied Materials & Interfaces* 15, no. 37 (2023): 43414–43430.

270. S. K. Patel, M. M. Billingsley, A. J. Mukalel, et al., "Bile Acid-Containing Lipid Nanoparticles Enhance Extrahepatic mRNA Delivery," *Theranostics* 14, no. 1 (2024): 1–16.

271. M. Jiang, L. Chen, C. Hong, et al., "A Novel Polyphyllin I-Based Liposome Delivery System Sensitizes Hepatic Carcinoma to Doxorubicin via Cholesterol Modulation," *Journal of Drug Delivery Science and Technology* 78 (2022): 103925.

272. L. Chen, J. Lan, Z. Li, et al., "A Novel Diosgenin-Based Liposome Delivery System Combined With Doxorubicin for Liver Cancer Therapy," *Pharmaceutics* 14, no. 8 (2022): 1685.

273. G. Liu, J. Liu, P. Shao, et al., "Novel Nanoliposomes Synergistically Modulated by Sitogluside and Dioscin: Stability, Bioavailability, and Capacity To Alleviate Hyperuricaemia," *Journal of Agricultural and Food Chemistry* 73, no. 4 (2025): 2596–2612.

274. M. Z. Wang, Y. Xu, J. F. Xie, Z. H. Jiang, and L. H. Peng, "Ginsenoside as a New Stabilizer Enhances the Transfection Efficiency and Biocompatibility of Cationic Liposome," *Biomaterials Science* 9, no. 24 (2021): 8373–8385.

275. X. Li, A. S. Widjaya, J. Liu, X. Liu, Z. Long, and Y. Jiang, "Cell-Penetrating Corosolic Acid Liposome as a Functional Carrier for Delivering Chemotherapeutic Drugs," *Acta Biomaterialia* 106 (2020): 301–313.

276. A. S. Widjaya, Y. Liu, Y. Yang, W. Yin, J. Liang, and Y. Jiang, "Tumor-Permeable Smart Liposomes by Modulating the Tumor Microenvironment to Improve the Chemotherapy," *Journal of Controlled Release* 344 (2022): 62–79.

277. R. Li, L. Y. Zhang, Z. J. Li, et al., "Characterization and Absorption Kinetics of a Novel Multifunctional Nanoliposome Stabilized by Sea Cucumber Saponins Instead of Cholesterol," *Journal of Agricultural and Food Chemistry* 68, no. 2 (2020): 642–651.

278. J. Xia, C. Chen, M. Dong, et al., "Ginsenoside Rg3 Endows Liposomes With Prolonged Blood Circulation and Reduced Accelerated Blood Clearance," *Journal of Controlled Release* 364 (2023): 23–36.

279. J. Zhou, B. Gao, H. Zhang, et al., "Ginsenoside Modified Lipid-Coated Perfluorocarbon Nanodroplets: A Novel Approach to Reduce Complement Protein Adsorption and Prolong in Vivo Circulation," *Acta Pharmaceutica Sinica B* 14, no. 4 (2024): 1845–1863.

280. C. Hong, D. Wang, J. Liang, et al., "Novel Ginsenoside-Based Multifunctional Liposomal Delivery System for Combination Therapy of Gastric Cancer," *Theranostics* 9, no. 15 (2019): 4437–4449.

281. X. Wang, W. Zheng, Q. Shen, et al., "Identification and Construction of a Novel Biomimetic Delivery System of paclitaxel and Its Targeting Therapy for Cancer," *Signal Transduction and Targeted Therapy* 6, no. 1 (2021): 33.

282. Y. Zhang, Y. Wang, H. Zhang, et al., "Replacing Cholesterol With Asiatic Acid to Prolong Circulation and Enhance Anti-Metastatic Effects of Non-PEGylated Liposomes," *Journal of Controlled Release* 366 (2024): 585–595.

283. T. Van de Vyver, B. Bogaert, L. De Backer, et al., "Cationic Amphiphilic Drugs Boost the Lysosomal Escape of Small Nucleic Acid Therapeutics in a Nanocarrier-Dependent Manner," *ACS Nano* 14, no. 4 (2020): 4774–4791.

284. C. Muntean, E. Blondeel, L. Harinck, et al., "Repositioning the Antihistamine Ebastine as an Intracellular siRNA Delivery Enhancer," *International Journal of Pharmaceutics* 644 (2023): 123348.

285. B. Bogaert, A. Debisschop, T. Ehouarne, et al., "Selective Replacement of Cholesterol With Cationic Amphiphilic Drugs Enables the Design of Lipid Nanoparticles With Improved RNA Delivery," *Nano Letters* 24, no. 10 (2024): 2961–2971.

286. C. Hong, J. Liang, J. Xia, et al., "One Stone Four Birds: A Novel Liposomal Delivery System Multi-Functionalized With Ginsenoside Rh2 for Tumor Targeting Therapy," *Nanomicro Letters* 12, no. 1 (2020): 129.

287. J. Lan, L. Chen, Z. Li, et al., "Multifunctional Biomimetic Liposomes With Improved Tumor-Targeting for TNBC Treatment by Combination of Chemotherapy, Antiangiogenesis and Immunotherapy," *Advanced Healthcare Materials* 13 (2024): e2400046.

288. J. Xia, S. Ma, X. Zhu, et al., "Versatile Ginsenoside Rg3 Liposomes Inhibit Tumor Metastasis by Capturing Circulating Tumor Cells and Destroying Metastatic Niches," *Science Advances* 8, no. 6 (2022): eabj1262.

289. Y. Zhu, J. Liang, C. Gao, et al., "Multifunctional Ginsenoside Rg3-Based Liposomes for Glioma Targeting Therapy," *Journal of Controlled Release* 330 (2021): 641–657.

290. Y. Zhu, A. Wang, S. Zhang, et al., "Paclitaxel-loaded Ginsenoside Rg3 Liposomes for Drug-Resistant Cancer Therapy by Dual Targeting of the Tumor Microenvironment and Cancer Cells," *Journal of Advanced Research* 49 (2023): 159–173.

291. C. Hong, A. Wang, J. Xia, et al., "Ginsenoside Rh2-Based Multifunctional Liposomes for Advanced Breast Cancer Therapy," *International Journal of Nanomedicine* 19 (2024): 2879–2888.

292. Y. Shen, B. Zhong, W. Zheng, et al., "Rg3-Lipo Biomimetic Delivery of Paclitaxel Enhances Targeting of Tumors and Myeloid-Derived Suppressor Cells," *Journal of Clinical Investigation* 134, no. 22 (2024): e178617.

293. Y. Xie, M. Zhu, H. Bao, et al., "Enhanced Antitumor Efficacy and Reduced Toxicity in Colorectal Cancer Using a Novel Multifunctional Rg3- Targeting Nanosystem Encapsulated With Oxaliplatin and Calcium Peroxide," *International Journal of Nanomedicine* 20 (2025): 1021–1046.

294. J. Huang, J. Shi, N. Ma, et al., "Celastrol-Loaded Ginsenoside Rg3 Liposomes Enhance Anti-Programmed Death Ligand 1 Immunotherapy by Inducing Immunogenic Cell Death in Triple-Negative Breast Cancer," *Phytomedicine* 139 (2025): 156514.

295. J. Xia, Z. Gan, J. Zhang, et al., "Geometric-Aware Deep Learning Enables Discovery of Bifunctional Ligand-Based Liposomes for Tumor Targeting Therapy," *Nano Today* 61 (2025): 102668.

296. S. Liang, S. Gao, S. Fu, et al., "Screening Natural Cholesterol Analogs to Assemble Self-Adjuvant Lipid Nanoparticles for Antigens Tagging Guided Therapeutic Tumor Vaccine," *Advanced Materials* (2025): e2419182, https://doi.org/10.1002/adma.202419182.

297. E. J. Sayour, D. Boczkowski, D. A. Mitchell, and S. K. Nair, "Cancer mRNA Vaccines: Clinical Advances and Future Opportunities," *Nature Reviews Clinical Oncology* 21, no. 7 (2024): 489–500.

298. Z. Guo, Q. Jing, Z. Xu, D. Zhang, W. Zheng, and F. Ren, "Corosolic Acid-Modified Lipid Nanoparticles as Delivery Carriers for DNA Vaccines Against avian Influenza," *International Journal of Pharmaceutics* 638 (2023): 122914.

299. Y. Liu, R. Zhang, Y. Yang, X. Liu, and Y. Jiang, "Corosolic Acid Derivative-Based Lipid Nanoparticles for Efficient RNA Delivery," *Journal of Controlled Release* 378 (2025): 1–17.

300. M. Zhang, R. Zhang, C. Feng, X. Jiang, X. Xu, and J. Wang, "Ginsenoside Compound K-Based Multifunctional Liposomes for the Treatment of Rheumatoid Arthritis," *Drug Delivery* 32, no. 1 (2025): 2464190.

301. J. Xia, S. Zhang, R. Zhang, et al., "Targeting Therapy and Tumor Microenvironment Remodeling of Triple-Negative Breast Cancer by Ginsenoside Rg3 Based Liposomes," *Journal of Nanbiotechnology* 20, no. 1 (2022): 414.

302. H. Zhang, J. Huang, Y. Li, et al., "Celastrol-Loaded Ginsenoside Rg3 Liposomes Boost Immunotherapy by Remodeling Obesity-Related Immunosuppressive Tumor Microenvironment in Melanoma," *Acta Pharmaceutica Sinica B* 15, no. 5 (2025): 2687–2702.

303. X. Yue, H. Guo, G. Wang, et al., "A Tailored Phytosomes Based Nose-to-brain Drug Delivery Strategy: Silver Bullet for Alzheimer's Disease," *Bioactive Materials* 44 (2025): 97–115.

304. C. Huang, K. Gou, X. Yue, et al., "A Novel Hyaluronic Acid-Based Dissolving Microneedle Patch Loaded With Ginsenoside Rg3 Liposome for Effectively Alleviate Psoriasis," *Materials and Design* 224 (2022): 111363.

305. W. Yang, M. Cao, W. Wang, et al., "Multifunctional Composite Soluble Microneedle Patch Based on "One Stone, Three Birds" Strategy for Promoting the Healing of Infectious Wounds," *Colloids and Surfaces B* 241 (2024): 114049.

306. H. Tang, X. Li, C. Li, et al., "Sequential Delivery of Anti-Inflammatory and Anti-Scar Drugs by Rg3 Liposome-Embedded Thiolated Chitosan Hydrogel Eye Drops for Corneal Alkali Burn," *Carbohydrate Polymers* 361 (2025): 123626.

307. M.-Z. Wang, T.-W. Gu, Y. Xu, L. Yang, Z.-H. Jiang, and L.-H. Peng, "Mechanical Stretching of Cells and Lipid Nanoparticles for Nucleic Acid Delivery," *Journal of Controlled Release* 339 (2021): 208–219.

308. M. Liu, S.-T. Li, J.-H. Wang, et al., "Methotrexate-Modified Docetaxel Liposome Targeting With Ginsenoside Rh2 as a Membrane Stabilizer for the Treatment of Ovarian Cancer," *Journal of Drug Delivery Science and Technology* 98 (2024): 105917.

309. S. Hu, D. Sun, L. Tang, et al., "Follicle-Stimulating Hormone Peptide-Conjugated Liposomes in the Treatment of Epithelial Ovarian Cancer Through the Induction of M2-to-M1 Macrophage Repolarization," *International Journal of Pharmaceutics* 672 (2025): 125334.

310. H. Ao, H. Song, J. Li, and X. Wang, "Enhanced Anti-Glioma Activity of Annonaceous Acetogenins Based on a Novel Liposomal Co-delivery System With Ginsenoside Rh2," *Drug Delivery* 31, no. 1 (2024): 2324716.

311. D. Huang, Z. Tang, X. Pu, T. Wang, F. Gao, and C. Li, "A Novel Cabazitaxel Liposomes Modified With Ginsenoside Rk1 for Cancer Targeted Therapy," *Acupuncture and Herbal Medicine* 4, no. 1 (2024): 113–121.

312. F. Gong, Z. Wang, R. Mo, et al., "Nano-Sponge-Like Liposomes Remove Cholesterol Crystals for Antiatherosclerosis," *Journal of Controlled Release* 349 (2022): 940–953.

313. Y. Wang, W. He, P. Ren, L. Zhao, D. Zheng, and J. Jin, "Carthamin Yellow-Loaded Glycyrrhetinic Acid Liposomes Alleviate Interstitial Fibrosis in Diabetic Nephropathy," *Renal Failure* 47, no. 1 (2025): 2459356.

314. Z. Xu, Y. Huang, Y. Wu, et al., "Glycyrrhizic Acid-Lipid Framework Nanovehicle Loading Triptolide for Combined Immunochemotherapy," *ACS Applied Materials & Interfaces* 15, no. 35 (2023): 41337–41350.

315. S. Zhang, S. Ma, S. Hao, et al., "Fucoidan-Modified Antibiotic-Free Nanovesicles: A Multidimensional Approach to Eradicate Intracellular and Extracellular Helicobacter pylori and Restore Gastrointestinal Homeostasis," *International Journal of Biological Macromolecules* 307 (2025): 141786.

316. A. Prakash, T. Gates, and E. Lou, "Senescence-Associated Secretory Phenotype Regulation by Dual-drug Delivery Biomimetic Nanoplatform for Enhanced Tumor Chemotherapy," *Molecular Therapy: Oncology* 32, no. 4 (2024): 200869.

317. S. Li, Y. Liu, X. Sui, et al., "Novel Tubeimoside I Liposomal Drug Delivery System in Combination With Gemcitabine for the Treatment of Pancreatic Cancer," *Nanomedicine* 19, no. 24 (2024): 1977–1993.

318. K. Wang, L. Yang, X. Lu, et al., "Construction of Sonosensitizer-Drug Co-Assembly Based on Deep Learning Method," *Small* (2025): e2502328.

319. C. Zhang, Y. Yuan, Q. Xia, et al., "Machine Learning-Driven Prediction, Preparation, and Evaluation of Functional Nanomedicines via Drug–Drug Self-Assembly," *Advanced Science* 12, no. 9 (2025): e2415902.

320. J.-J. Zheng, Q.-Z. Li, Z. Wang, X. Wang, Y. Zhao, and X. Gao, "Computer-Aided Nanodrug Discovery: Recent Progress and Future Prospects," *Chemical Society Reviews* 53, no. 18 (2024): 9059–9132.

321. P. Tan, X. Chen, H. Zhang, Q. Wei, and K. Luo, "Artificial Intelligence Aids in Development of Nanomedicines for Cancer Management," *Seminars in Cancer Biology* 89 (2023): 61–75.

322. L. Rao, Y. Yuan, X. Shen, G. Yu, and X. Chen, "Designing Nanotheranostics With Machine Learning," *Nature Nanotechnology* 19, no. 12 (2024): 1769–1781.

323. Y.-L. Wang, Y. Mu, Y.-L. Zhang, et al., "Accessible and Effective Nanomedicines: Self-Assembly Products from Chinese Herbal Medicines (CHMs)," *Advanced Functional Materials* 35, no. 9 (2025): e2416151.

324. X. Guo, W. Luo, L. Wu, et al., "Natural Products From Herbal Medicine Self-Assemble Into Advanced Bioactive Materials," *Advanced Science* 11, no. 35 (2024): e2403388.

325. Y.-L. Zhang, Y.-L. Wang, K. Yan, et al., "Nanostructures in Chinese Herbal Medicines (CHMs) for Potential Therapy," *Nanoscale Horiz* 8, no. 8 (2023): 976–990.

326. M. Zhou, R.-H. Zhang, M. Wang, G.-B. Xu, and S.-G. Liao, "Prodrugs of Triterpenoids and Their Derivatives," *European Journal of Medicinal Chemistry* 131 (2017): 222–236.