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Carrier-free self-assembled nanomedicines from natural small molecules: advances and perspectives for disease treatment

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Carrier-free self-assembled nanomedicines (CFSNs) derived from natural small molecules (NSMs) have garnered significant attention in the field of nanomedicine due to their unique properties and potential therapeutic applications. This review provides an in-depth analysis of the recent advances in the development and application of CFSNs for disease treatment. We discuss the self-assembly mechanisms of NSMs, such as polyphenols, alkaloid, and terpenoid, which form stable and biocompatible nanoscale structures without the need for synthetic carriers. The fundamental forces driving self-assembly, including hydrogen bonding, π–π stacking interactions, electrostatic interactions, and coordination interactions, are elucidated in the first section. These CFSNs exhibit enhanced solubility, improved pharmacokinetics, and reduced toxicity compared to their bulk counterparts. The therapeutic potential of CFSNs is evaluated across various disease models, including cancer, infection, inflammation, cardiovascular diseases, and neurodegenerative disorders. We also address the challenges associated with the clinical translation of CFSNs, such as scalability, reproducibility, and regulatory approval. Finally, we offer perspectives on future research directions, emphasizing the need for interdisciplinary collaboration to fully harness the therapeutic potential of CFSNs. This comprehensive overview aims to provide a foundation for further exploration and development of CFSNs as a promising platform for next-generation nanotherapeutics.

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1 Introduction

Inflammation, infectious diseases, and cancer are among the most significant global public health challenges of the 21st century.[1,2] The World Health Organization reports that over 500 million individuals are affected by chronic inflammatory conditions, such as rheumatoid arthritis, atherosclerosis, and inflammatory bowel disease. Concurrently, bacterial, viral, and fungal infections account for approximately 13 million deaths annually, with antimicrobial resistance (AMR) increasingly undermining the efficacy of existing treatments. Cancer further exacerbates this burden, with nearly 19 million new cases and approximately 10 million deaths reported each year.[3,4] These conditions are epidemiologically interconnected: chronic inflammation can elevate cancer risk, while the tumor microenvironment (TME) often promotes immunosuppression and secondary infections. Traditional treatments for these conditions face several limitations, including high lesion heterogeneity, poor drug penetration, systemic toxicity, and rapid emergence of drug resistance. These challenges are compounded by the poor solubility of hydrophobic agents, short plasma half-life, off-target toxicity, and biological barriers that restrict drug penetration into pathological sites. In this context, carrier-free self-assembled nanomedicines (CFSNs) have emerged as a promising approach. These systems utilize intrinsic non-covalent interactions, such as π–π stacking, hydrogen bonding, hydrophobic effects, and metal coordination to form uniform and stable nanoparticles under physiological conditions, without requiring additional carriers such as liposomes, polymers, or inorganic materials,[5] CFSNs offer high drug loading (50–100%) with minimal excipient toxicity, alongside capabilities for surface engineering and microenvironment-responsive release (*e.g.*, to pH, reactive oxygen species (ROS), enzymes, or glutathione (GSH)), which significantly enhance targeted accumulation.[6,7] They also provide markedly improved solubility (10^2–10^3 fold) without traditional solubilizers, support multi-component co-assembly for synergistic anti-inflammatory, anticancer, or antibacterial

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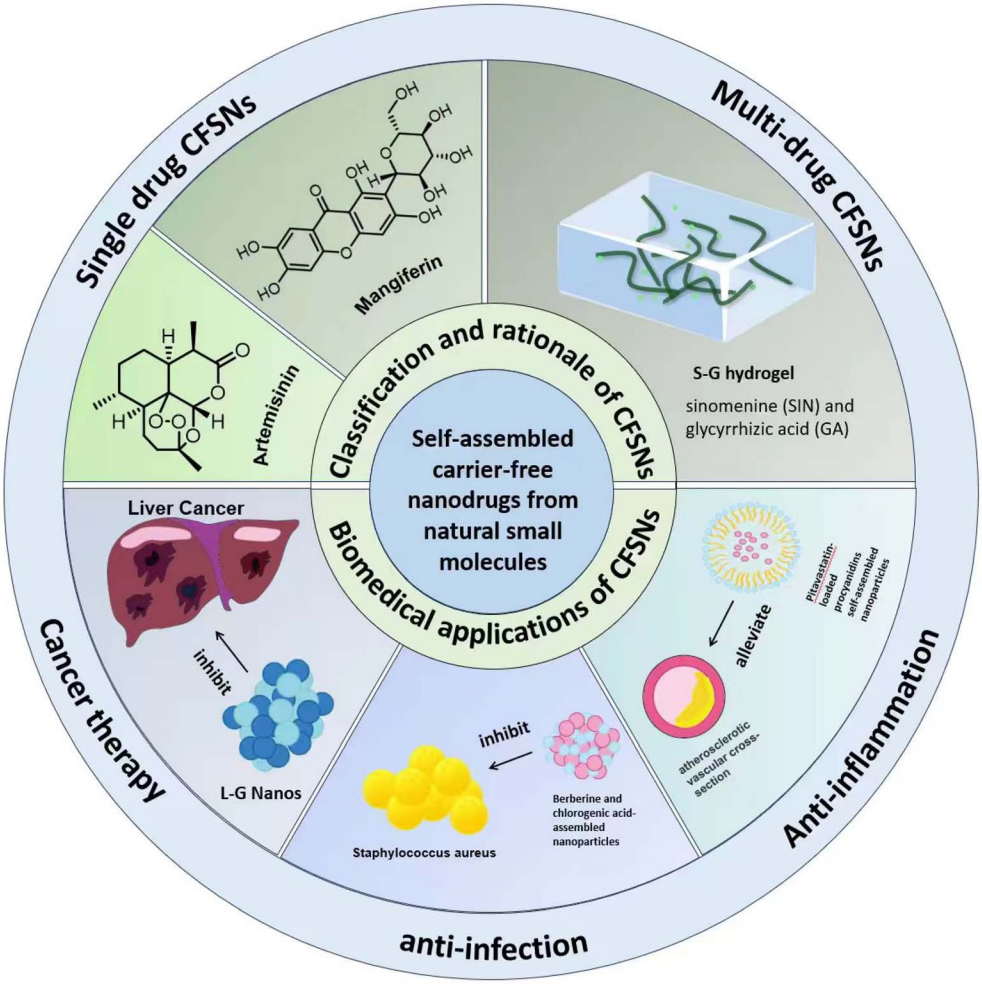

Scheme 1 Classification, rationale and biomedical applications of CFSNs.

effects while delaying resistance, and feature a simple, one-step preparation process that enables scalability and aligns with green pharmaceutical principles.[8,9] Therefore, elucidating the assembly mechanisms and clinical translation pathways of CFSNs for treating inflammation, infection, and cancer is of urgent and high significance.[10]

Natural small molecules (NSMs) represent an invaluable resource for anti-inflammatory, anti-infective, and anticancer therapies.[11] Approximately 60% of marketed small-molecule drugs are directly or indirectly derived from natural sources such as plants, fungi, and marine organisms.[12] For instance, curcumin (Cur), triptolide, and quercetin potently inhibit pro-inflammatory pathways including NF-κB, NLRP3 inflammasome, and COX-2.[13–18] Similarly, compounds such as huangqin glycoside, andrographolide, artemisinin and its derivatives demonstrate strong efficacy against drug-resistant *Staphylococcus aureus*, malaria parasites, and viral replication.[19,20] Additionally, paclitaxel, camptothecin, ursolic acid, and triptolide are widely used as first-line or adjuvant chemotherapeutic agents for breast, colorectal, and hepatocellular cancers.[21–23] Nevertheless, these molecules often face limitations including poor solubility, rapid metabolism, lack of target specificity, and insufficient synergistic effects, which collectively restrict their full therapeutic potential.[24] CFSNs address the aforementioned bottlenecks through a "drug-as-carrier" strategy, in which π–π stacking and hydrophobic interactions drive the formation of a closely packed core framework, creating high-drug-loading hydrophobic microdomains. Furthermore, hydrogen-bond networks among polyphenols, flavonoids, or triterpenoids provide structural stability while enabling rapid dissociation under disease-specific stimuli, facilitating precise drug release.[25] While metal–ligand coordination (*e.g.*, Fe^{3+}–polyphenols, Zn^{2+}–quinoline) further enhances assembly stability and can introduce photothermal or photodynamic synergistic effects.[26] Notably, multicomponent co-assemblies, such as paclitaxel–guggulsterone or Cur–quercetin—integrate multiple mechanisms to achieve synergistic efficacy where "1 + 1>2".[27] By leveraging the self-assembly potential of NSMs and systematically elucidating the intrinsic "composition–structure–efficacy" relationship, this approach aims to surpass the performance limits of traditional formulations, thereby laying the theoretical and experimental groundwork for the next generation of green, efficient, and multifunctional nanomedicines.[28] The utilization of self-assembling NSMs for drug

delivery has garnered considerable research interest, with significant advances achieved over the past several years. Some excellent reviews on the fabrication and biomedical applications CFSNs have been recently published to summarize these advances and achievements, few have specifically focused on the CFSNs based on NSMs. Given the rapid progress in this area, a timely and comprehensive review is warranted to synthesize these developments and highlight future directions in related fields.

In this review, we provide a comprehensive analysis of the recent advances in the development and application of CFSNs based on NSMs for disease treatment (Scheme 1). We begin by discussing the self-assembly mechanisms of NSMs, focusing on the underlying forces that drive the formation of stable and biocompatible nanoscale structures. We then discussed the therapeutic potential of CFSNs across various disease models, including cancer, anti-infection, anti-inflammation, cardiovascular diseases, and neurodegenerative disorders. Additionally, we addressed the challenges associated with the clinical translation of CFSNs, such as scalability, reproducibility, and regulatory approval. Finally, we offer perspectives on future research directions, emphasizing the need for interdisciplinary collaboration to fully harness the therapeutic potential of CFSNs. This comprehensive overview aims to provide a foundation for further exploration and development of CFSNs as a promising platform for next-generation nanotherapeutics. By integrating insights from materials science, chemistry, and biology, we hope to advance the understanding and application of CFSNs in clinical settings, ultimately improving patient outcomes and expanding the therapeutic arsenal available for the treatment of complex diseases.

2 Definition and characteristics of NSMs

2.1 Definition

NSMs are low-molecular-weight compounds (typically < 900 Da) derived from natural sources such as plants, animals, and microorganisms. They possess well-defined chemical structures and are produced through natural biosynthetic pathways. Examples include plant-derived polyphenols (*e.g.*, resveratrol and quercetin),[29] alkaloids (*e.g.*, berberine),[30] and saponins (*e.g.*, ginsenosides);[31] animal-based amino acid derivatives and peptides; as well as microbial metabolites. These molecules are widely distributed across biological systems and play significant roles in various physiological and therapeutic applications.

2.2 Chemical structure

SNMs typically possess low molecular weights, contributing to favorable solubility and permeability. This enables efficient traversal across biological membranes and cellular uptake, offering distinct advantages for drug delivery applications. Their chemical structures are highly diverse and rich in functional groups, including hydroxyl, carbonyl, carboxyl, and amino moieties, which facilitate various interaction modes with drug molecules. These interactions, including hydrogen bonding, hydrophobic effects, electrostatic forces, and coordination interactions, enable efficient drug loading, facilitate targeted delivery, confer new functionalities, and enhance synergistic therapeutic efficacy.[32] Moreover, many NSMs exhibit intrinsic bioactivities, such as antioxidant, anti-inflammatory, antimicrobial, and anticancer properties.[33–35] These functional groups not only enhance the therapeutic performance of the delivery system but may also exert synergistic effects during drug release, further improving treatment outcomes.

The structural diversity of NSMs encompasses a broad spectrum of chemical classes, each with distinct structural features and self-assembly behaviors.[36] Flavonoids, characterized by the C_6–C_3–C_6 skeleton, represent one of the most abundant classes of NSMs.[37] Compounds such as quercetin, kaempferol, and epigallocatechin gallate (EGCG) possess multiple phenolic hydroxyl groups that enable extensive hydrogen bonding networks and metal coordination, facilitating the formation of stable nanoparticles with antioxidant[38] and anticancer activities.[39] Alkaloids, including berberine, camptothecin, and paclitaxel, contain nitrogen-containing heterocycles and complex polycyclic architectures.[40] These planar aromatic structures favor π–π stacking interactions, while their ionizable nature imparts pH-responsive properties to the resulting assemblies.[41] Terpenoids, such as artemisinin and paclitaxel (diterpenoid), are built from isoprene units and exhibit high hydrophobicity due to their extensive hydrocarbon frameworks.[42] Their low aqueous solubility drives strong hydrophobic interactions, promoting micelle-like or core–shell nanoparticle formation. Quinones, exemplified by emodin[43] and aloe-emodin, feature redox-active quinoid structures capable of participating in electron transfer reactions and coordination with metal ions. These properties enable the construction of stimuli-responsive delivery systems with intrinsic therapeutic activities. Lignans, such as sesamin and schisandrin are derived from phenylpropanoid dimerization and display unique stereochemical complexity.[44] Their rigid bicyclic or tricyclic frameworks contribute to specific molecular recognition and ordered packing in supramolecular assemblies. Furthermore, coumarins (*e.g.*, esculetin[45]), stilbenes (*e.g.*, resveratrol[46]), and anthraquinones (*e.g.*, rhein[47]) represent additional structural classes with distinct photophysical properties and biological activities that have been increasingly exploited for multifunctional CFSNs. This vast structural repertoire not only provides abundant building blocks for self-assembly but also enables the rational design of CFSNs with tailored physicochemical properties and therapeutic functionalities through strategic selection and combination of different NSM classes.

2.3 Inherent biological activity for drug delivery

NSMs derived from living organisms generally exhibit high biocompatibility and low immunogenicity, reducing the risk of immune reactions and systemic toxicity.[48] This profile makes them suitable as safe building blocks for constructing carrier-free nanomedicine delivery systems, thereby minimizing adverse effects.[49] Additionally, many NSMs possess inherent

biological targeting properties. For instance, certain polyphenolic compounds can be recognized and metabolized by enzymes overexpressed in tumor cells, enabling tumor-specific delivery.[50] Similarly, some carbohydrate-based small molecules bind selectively to receptors abundant at inflammatory sites, facilitating targeted treatment of inflammation.[51] This targeting capability enhances drug accumulation at disease sites while minimizing distribution in healthy tissues, thereby improving therapeutic efficacy and reducing systemic side effects. Furthermore, the chemical structure of NSMs can be readily modified through straightforward chemical derivatization to tailor drug release kinetics and mechanisms. For instance, by introducing specific functional groups or modulating molecular hydrophobicity, it is possible to design drug release systems that respond to specific physiological stimuli, such as pH, temperature, or enzymatic activity, enabling precise and controlled drug release.[52–54] The characteristics of NSMs make them important materials for constructing self-assembling drug delivery systems without carriers, providing abundant resources and possibilities for developing efficient and safe drug delivery systems.

3 The principle of self-assembly of NSMs

This article provides a comprehensive analysis of the self-assembly mechanisms and delivery principles governing NSMs, particularly bioactive alkaloids and polyphenols. These compounds exhibit characteristic structural features, including hydroxyl/carboxyl groups, alkyl side chains, and rigid benzene rings that collectively enable sophisticated supramolecular organization through synergistic non-covalent interactions. The polar functional groups (hydroxyl and carboxyl moieties) establish hydrogen bonding networks (K_d = 10–100 μM) while simultaneously conferring pH-responsive behavior, allowing dynamic assembly/disassembly in biological environments. Concurrently, hydrophobic alkyl chains (C_4–C_{18}) drive entropy-dominated micellization ($\Delta G = -3$ to -20 kJ mol^{-1}), working in concert with aromatic systems that provide structural stability *via* π–π stacking (3.4–4.0 Å interplanar spacing) and van der Waals interactions. The orchestrated interplay between enthalpy-driven hydrogen bonding and entropy-dominated hydrophobic effects enables the spontaneous self-assembly of stable, carrier-free nanomedicines. These systems exhibit exceptional drug loading capacity (exceeding 20 wt% through optimized molecular packing) along with TME-responsive release behavior and inherent synergistic functionality originating from the intrinsic bioactivity of NSMs. Furthermore, the geometric complementarity among key structural motifs enhances targeting precision, exemplified by the tissue-specific affinity mediated through the rigid backbones of alkaloids and the redox-responsive payload release enabled by polyphenols' aromatic systems. These advantageous properties are fundamentally rooted in the self-assembly principles inherent to NSMs. Governed by a combination of non-covalent interactions, NSMs spontaneously organize into well-ordered nanoaggregates. Among these, hydrogen bonding and π–π stacking frequently serve as the primary driving forces, enabling the formation of stable, carrier-free nanodrug delivery systems. This assembly process arises from both directional and non-directional affinities among functional groups, resulting in nanostructures that efficiently encapsulate drugs and facilitate targeted delivery. Owing to these inherent self-organizing properties, NSM-based nanodrug systems present considerable potential for improving therapeutic outcomes and minimizing adverse effects across a wide range of treatments. In this section, we elucidate five key intermolecular forces, such as hydrogen bonding, π–π stacking, electrostatic interactions, metal coordination and hydrophobic interaction that govern the formation of CFSNs derived from NSMs (Table 1).

3.1 Hydrogen bonding

NSMs commonly contain functional groups, including amino, hydroxyl, and carboxyl, that offer multiple hydrogen-bonding sites.[65,66] These interactions, formed between hydrogen donors and electronegative acceptors (*e.g.*, oxygen, nitrogen), constitute a fundamental driving force in the construction of CFSNs.[67] Recent studies have identified numerous self-assembling NSMs such as alkaloids and polyphenols, whose characteristic structural motifs (hydroxyl, carboxyl, amino groups; alkyl side chains; rigid aromatic frameworks) facilitate the organization of well-ordered nanoaggregates through hydrogen bonding and other non-covalent interactions.[68–71] Due to their typical hydrophobicity, NSMs often undergo self-assembly *via* hydrogen

Table 1 The principle of self-assembly of NSMs

Intermolecular forces	Representative natural small molecule	Applications in disease treatment
Hydrogen bonding	Rhein	Treat neural inflammation[55]
	Magnolol	Cancer treatment[56]
	Berberine (BBR) and cinnamic acid (CA)	Antibiosis[57]
π–π stacking	Rhubarb acid and doxorubicin (DOX)	Cancer treatment[58]
	Piperine (Pip), tannic acid (TA), and Cur	Cancer treatment[59]
Electrostatic interactions	Camptothecin	Cancer treatment[60]
	Baicalin and berberine	Antibiosis[61]
Coordination interaction	DOX and the natural polyphenol quercetin	Cancer treatment[62]
Hydrophobic interaction	Ginsenoside Rb1	Treat cardiovascular diseases[63]
	Berberine (BBR), baicalin (BA) and wogonoside (WOG)	Antibiosis[64]

bonding, particularly under anhydrous conditions where such interactions are favored.[72] For treating neural inflammation, a representative example is provided by Zheng *et al.*,[55] who reported that rhein (Rh), a polyphenol derived from rhubarb can stable hydrogels in phosphate buffered saline (PBS, pH 8.0–9.4) upon sonication or heating. The observed redshift in the IR absorption peaks of hydroxyl and carbonyl groups provided direct evidence of hydrogen bonding participation in the assembly process. Similarly, Ji and colleagues engineered carrier-free nanoparticles derived from magnolol, demonstrating enhanced tumor-targeting capability and colloidal stability.[56] Comprehensive characterization through binding energy analysis, infrared spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy conclusively identified hydrogen bonding as the dominant intermolecular force governing nanoparticle self-assembly.[73,74] In the self-assembly mechanism of the nanomedicine (CA-BBR NPs) studied by Huang and his team,[57] hydrogen bonding is one of the core driving forces. Through single-crystal X-ray diffraction, the research revealed that berberine (BBR) and cinnamic acid (CA) form butterfly-like one-dimensional units *via* hydrogen bonding: BBR acts as the "wings," while CA serves as the "body." The hydrogen bonds between them, such as the interaction between the carboxyl group of CA and the nitrogen atom of BBR, directly induce the formation of the basic assembly units. This hydrogen bonding serves as the foundation for the assembly of nanoparticles into ordered structures at the molecular level, providing building blocks for the subsequent formation of three-dimensional layered configurations through π–π stacking. These collective findings substantiate the pivotal role of hydrogen bonding in orchestrating molecular self-organization processes.[75]

3.2 π–π stacking interaction

π–π stacking is a key non-covalent interaction that occurs between aromatic rings through the overlap of π orbitals.[76] This interaction typically manifests in two primary geometries: face-to-face (parallel) and edge-to-face (T-shaped) configurations, which collectively contribute to the stability and directionality of molecular assemblies.[77,78] These interactions play a significant role in molecular recognition and are increasingly applied in self-assembled drug delivery systems due to their contributions to drug loading, molecular organization, and the formation of three-dimensional networks.[79] Many anticancer drugs contain complex π-conjugated hydrophobic moieties, which facilitate the assembly of NSMs into nanoparticles *via* π–π interactions.[80] Through molecular dynamics simulations, Bai *et al.* demonstrated that π–π interactions predominated over hydrogen bonding in the co-assembly of rhubarb acid and doxorubicin (DOX) for cancer therapy.[58] Lei *et al.* constructed a carrier-free oral delivery system using a one-pot method with piperine (Pip), tannic acid (TA), and Cur. They demonstrated that the co-assembly was driven by both hydrogen bonding and π–π stacking between Cur and Pip, while TA can enhance and stabilize these π–π interactions through its multi-hydroxyl and phenolic groups for promising oral chemotherapy formulations.[59] The disappearance of the TA diffraction peak in X-ray spectra further confirmed this mechanism.

3.3 Electrostatic interactions

Electrostatic interactions, arising from the balance of attraction and repulsion between charged groups, constitute a pivotal driving force in the construction of CFSNs.[81] Molecules involved in such assemblies commonly feature ionizable moieties such as NH_3^+ and COO^- that enable charge-directed association. While intermolecular interactions among drug molecules fundamentally underlie the assembly process, the electrostatic components exhibit pronounced sensitivity to environmental conditions, including ionic strength, pH, and surface charge density.[82] Notably, the strength of electrostatic attraction governs the stability, drug release profiles, and ultimately the therapeutic efficacy of the resulting nanostructures,[83] rendering the controlled assembly of CFSNs *via* electrostatic interactions both a significant challenge and an opportunity for rational design. In a study by Perumal *et al.* reported the self-assembly of camptothecin with antisense DNA to form a nanodrug delivery system through electrostatic interactions.[60] In this system, the cationic ammonium group of the camptothecin prodrug attracted the negatively charged phosphate backbone of the antisense DNA, driving the organization of hydrophobic camptothecin along the hydrophilic DNA strand to form nanoparticles. This strategy significantly enhanced anticancer efficacy and provides compelling evidence for constructing functional carrier-free nanodrug systems *via* electrostatic assembly of NSMs. Moreover, Li and colleagues demonstrated that electrostatic attraction between the carboxyl group of baicalin and the quaternary ammonium ion of berberine drives the self-assembly with flavonoid glycosides.[61] This interaction forms one-dimensional composite units that subsequently aggregate into three-dimensional nanoparticles through hydrophobic effects, exhibiting excellent water solubility and bacterial affinity. In contrast, although wogonoside likewise engages in electrostatic interaction with berberine, the binding force is relatively weaker, and steric hindrance from the 8-methoxy group prevents amphiphilic nanostructure formation, resulting only in fibrous precipitates. These findings reveal that electrostatic interactions provide the common foundation for assembly, while synergistic differences in hydrophobic interaction strength and molecular spatial configuration dictate the final morphology and biological activity.

3.4 Coordination interactions

Coordination interactions represent a class of intermolecular forces with strength intermediate between hydrogen bonds and covalent bonds.[84] They are commonly employed to drive the self-assembly of catechol-containing flavonoids or polyphenolic compounds with metal ions into carrier-free nanoparticles.[85] These coordination bonds exhibit stability under physiological conditions yet responsiveness to the tumor microenvironment (TME) spurred growing interest in fabricating CFSNs *via* metal–drug coordinative self-assembly.[86,87] For instance, Shang *et al.*[62] developed a novel self-assembled nanodrug termed *p*-QDF@M

for combined therapy against triple-negative breast cancer (TNBC). This system incorporates the chemotherapeutic agent DOX, the natural polyphenol quercetin, and a red blood cell membrane coating. Quercetin contains multiple phenolic hydroxyl groups can form a three-dimensional metal-phenolic network (MPN) with Fe^{2+} ions under alkaline conditions *via* coordinative crosslinking, thereby encapsulating DOX. Subsequent coating with a red blood cell membrane enhances the biocompatibility and delivery efficiency of the nanoparticles. Within the TME, the coordination bonds between quercetin and Fe^{2+} dissociate, releasing both quercetin and DOX. Simultaneously, the liberated Fe^{2+} ions act as Fenton reaction catalysts, elevating intracellular ROS levels to induce tumor cell apoptosis. This strategy facilitates synergistic integration of chemotherapy and chemodynamic therapy, demonstrating significant potential for advancing multifunctional theranostic platforms.

3.5 Hydrophobic interaction

Hydrophobic interactions play a pivotal role in the self-assembly of natural small molecules. These interactions occur when hydrophobic groups, such as polycyclic alkyl skeletons containing multiple methyl groups aggregate to minimize contact with water molecules.[88] Amphiphilic natural molecules, characterized by distinct hydrophilic and hydrophobic domains, spontaneously organize into ordered nanostructures driven primarily by the hydrophobic effect, which is entropically favorable as water molecules are released from the structured hydration shell around hydrophobic regions.[89] For instance, terpenoids with hydrophobic skeletons and alkyl side chains rely predominantly on hydrophobic interactions as the main driving force for self-assembly in aqueous solution.[90] A representative example applied in the treatment of cardiovascular diseases is ginsenoside Rb1, a dammarane-type triterpenoid saponin whose molecular structure features hydrophobic fatty acid moieties. In an aqueous environment, the aggregation of these hydrophobic groups creates a core, thereby initiating the self-assembly of GRb1 into nanoparticles with a particle size of approximately 200–300 nm.[63] In the study by Li and colleagues, berberine (BBR) self-assembled with flavonoid glycosides (baicalin BA and wogonoside WOG) into nanoparticles (NPs) and nanofibers (NFs) through electrostatic and hydrophobic interactions.[64] Electrostatic forces primarily drove the formation of one-dimensional composite units, while hydrophobic interactions further directed their assembly into three-dimensional architectures: BA-BBR units assembled into NPs *via* hydrophobic core association, with hydrophilic glucuronic acid moieties facing outward to enhance bacterial affinity and significantly improve antibacterial activity; conversely, WOG-BBR units adopted an I-type planar configuration due to steric hindrance and assembled into NFs solely through strong hydrophobicity, whose hydrophobic surface resulted in weak bacterial binding capacity and diminished antibacterial efficacy. These dual interactions collectively governed the morphological disparities and differential antibacterial performance of the nanostructures.

3.6 Characterization techniques for molecular interactions

Accurate identification of molecular interactions is crucial for revealing assembly mechanisms. This section introduces five commonly used characterization techniques and their typical applications in detecting various interactions.

3.6.1 Infrared spectroscopy. Infrared spectroscopy reflects changes in chemical environment by detecting molecular vibration frequency shifts, serving as the most direct means for identifying hydrogen bonds. Hydrogen bond formation causes red shifts (30–100 cm^{-1}) in X–H stretching vibration frequencies accompanied by peak broadening, with the magnitude of red shift positively correlated with hydrogen bond strength.[91,92]

3.6.2 Nuclear magnetic resonance. Nuclear magnetic resonance (NMR) provides atomic-level structural information through chemical shifts and relaxation times. Hydrogen-bonded protons exhibit significant downfield shifts (δ often >10 ppm) with smaller temperature coefficients (<5 ppb K^{-1}), distinguishable from exposed protons.[93] DOSY NMR[94] calculates aggregation numbers by measuring diffusion coefficients, assisting in studying aggregation behavior; paramagnetic relaxation enhancement (PRE) can be used for locating paramagnetic metal binding sites.[95]

3.6.3 Single-crystal X-ray diffraction. Single-crystal X-ray diffraction (SC-XRD) resolves geometric structures of interactions by precisely determining atomic coordinates,[96] serving as the "gold standard" for characterizing hydrogen bonds and π–π stacking. It directly measures D–H···A distances (2.5–3.5 Å) and angles (>120°) for hydrogen bonds, as well as ring plane distances (<3.8 Å) and slip angles for π–π stacking. For metal complexes, coordination geometry and bond lengths can be precisely determined (precision ± 0.01–0.02 Å). For samples unsuitable for single-crystal analysis (*e.g.*, solutions, amorphous solids), X-ray absorption spectroscopy (XAS, particularly EXAFS) can provide information on the local coordination environment of central atoms.

3.6.4 Ultraviolet-Visible spectroscopy. UV-Vis reflects molecular aggregation states by detecting changes in electronic transition energies.[97] π–π stacking of aromatic molecules causes significant absorption shifts: H-aggregates (face-to-face) typically exhibit blue shifts, while J-aggregates (head-to-tail offset) typically show red shifts.[98,99] Metal coordination may produce characteristic d–d transitions or ligand-to-metal charge transfer (LMCT/MLCT) absorption bands.[100]

3.6.5 Fluorescence spectroscopy. Fluorescence spectroscopy is highly sensitive to microenvironment changes. Hydrophobic probes such as ANS exhibit weak fluorescence in aqueous solution ($\lambda_{max} \approx 520$ nm), but show significantly enhanced fluorescence with blue shifts (~480 nm) upon binding to hydrophobic regions, serving as a common method for detecting hydrophobic interactions.[101] pH control (typically 7.0–8.0) is required to avoid probe dimerization interference. π–π stacking typically causes fluorescence quenching (ACQ); certain molecules exhibit aggregation-induced emission (AIE) through restricted intramolecular motion, which differs fundamentally from the ACQ mechanism.[102]

3.6.6 Complementary strategies for interaction analysis. Given that single techniques often yield ambiguous results. For instance, IR peak shifts may originate from hydrogen bonding, π–π stacking, or electrostatic effects, it is recommended to employ multiple methods for orthogonal validation.[103] Therefore, combining IR spectroscopy (vibrational modes) with NMR (distance constraints) enables definitive characterization of hydrogen bonds, integrating UV-Vis spectroscopy (aggregation type) with concentration-dependent NMR (diffusion coefficients) clarifies π–π stacking mechanisms. For hydrophobic interactions, coupling ANS fluorescence (site localization) with isothermal titration calorimetry (ITC, for thermodynamic parameters) provides both structural information and thermodynamic data.[104] This multi-technique strategy ensures the reliability of conclusions regarding molecular interactions in complex systems.

4 Classification and rationale of CFSNs

CFSNs can be fundamentally classified into single-drug and multi-drug systems based on their composition of NSMs.[105,106] This classification reflects not only structural differences but also distinct therapeutic strategies. Single-drug CFSNs utilize individual bioactive compounds that inherently possess both therapeutic and self-assembling properties, where the drug molecules function as both active pharmaceutical ingredients (API) and structural building blocks. The development of multi-drug CFSNs represents a significant advancement in combinatorial therapy, addressing several critical limitations of conventional drug delivery. First, these systems enable precise spatial organization of multiple therapeutic agents with complementary mechanisms of action, thereby enhancing synergistic effects.[107,108] For instance, the co-assembly of alkaloids and polyphenols can simultaneously target different cellular pathways, achieving superior therapeutic outcomes compared to monotherapies.[109] Second, multi-drug CFSNs effectively overcome drug resistance by concurrently inhibiting compensatory signaling pathways that often develop during treatment.[110] A notable example includes the combination of metabolic modulators with traditional chemotherapeutic agents, which has shown remarkable efficacy in resistant cancer models.[111] Third, these systems optimize the pharmacokinetic profiles of individual drugs by balancing their physicochemical properties, such as hydrophobicity and ionization potential, ensuring synchronized biodistribution and targeted delivery.[112] The rational design of multi-drug CFSNs requires careful consideration of molecular compatibility, including geometric complementarity and interaction patterns. Successful systems typically feature NSMs with complementary functional groups that engage in stable non-covalent interactions, such as hydrogen bonding, π–π stacking, and electrostatic forces. These interactions must be thermodynamically favorable ($\Delta G < -20$ kJ mol^{-1}) to ensure robust nanostructure formation under physiological conditions.[113] Emerging research has further expanded the scope of multi-drug CFSNs to include immunotherapeutic combinations and triple-action systems, which integrate photodynamic agents with dual chemotherapeutics for multimodal therapy.[114] Such innovations highlight the versatility and potential of CFSNs in addressing complex disease mechanisms while minimizing systemic toxicity. In summary, the classification of CFSNs into single-drug and multi-drug systems underscores their adaptability to diverse therapeutic needs. While single-drug CFSNs offer simplicity and intrinsic bioactivity, multi-drug CFSNs provide a powerful platform for synergistic, resistance-proof, and pharmacokinetically optimized therapy. These advancements position CFSNs as a transformative approach in precision medicine. The following section provides a detailed illustration of single-drug CFSNs and multi-drug CFSNs (Table 2).

Table 2 Classification and rationale of CFSNs

Classification	Category	Key features	Mechanism of action	Representative examples
Single-drug CFSNs	Terpenoids	• 100% drug loading • Amphiphilic character • Hydrophobic carbon skeletons with polar functional groups	Hydrophobic interactions, π–π stacking, hydrogen bonding	Paclitaxel hydrogel (Luo *et al.*)[115] Dihydroartemisinin NPs (Zhu *et al.*)[116] Glycyrrhetinic acid spray hydrogel (Ma *et al.*)[117]
	Polyphenols	• Multiple phenolic hydroxyl groups • High capacity for multi-point hydrogen bonding • Extensive π–π stacking capabilities	Multi-point hydrogen bonding, π–π stacking	Honokiol NPs (Gao *et al.*)[118] Mangiferin hydrogel (Wang *et al.*)[119]
Multi-drug CFSNs	Dual-drug systems	• Homogeneous nanoscale architectures • Concurrent encapsulation of multiple agents • Synchronized release	Non-covalent interactions (hydrogen bonding, electrostatic attraction, π–π stacking)	Sinomenine-glycyrrhizic acid nanohydrogel (Xu *et al.*)[120]

4.1 Single drug CFSNs

Single-drug CFSNs represent an advanced class of drug delivery platforms in which the API spontaneously self-assembles into well-defined nanostructures.[121] These systems achieve 100% drug loading, eliminate excipient-related toxicity and immunogenicity risks, and benefit from straightforward and scalable fabrication processes.[122,123] Based on their molecular architecture, the primary compounds exploited for single-drug CFSNs can be classified into two major categories: terpenoids and polyphenols. Each class exhibits distinct structural motifs that dictate unique self-assembly pathways and resultant nanostructure properties.[90,124]

Terpenoids, built from isoprene (C5) units, feature hydrophobic aliphatic or alicyclic carbon skeletons that are frequently modified with polar functional groups such as hydroxyl, carbonyl, or carboxyl moieties.[125] This molecular design confers an amphiphilic character, which is the fundamental driver for their spontaneous self-organization in aqueous environments.[126] The assembly is primarily governed by hydrophobic interactions that minimize the exposure of non-polar domains to water, complemented by π–π stacking of aromatic systems and hydrogen bonding between functional groups.[127] For instance, Zhang *et al.* demonstrated that natural triterpenoids, including betulinic acid, oleanolic acid, and ursolic acid can self-assemble into stable nanostructures through hydrophobic interactions and hydrogen bonding, enabling the co-delivery of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors for enhanced cancer chemoimmunotherapy.[128] Moreover. Zhang *et al.* developed an injectable hydrogel formed solely through the self-assembly of pure paclitaxel molecules *via* hydrogen bonding and π–π stacking interactions, without requiring any carriers or additives.[115] The carrier-free system achieves 100% drug loading, exhibits thermosensitive properties and prolonged *in situ* retention (>40 days). In a 4T1 breast cancer model, it demonstrated superior tumor suppression and metastasis inhibition while significantly reducing systemic toxicity, offering a simple yet effective novel strategy for localized tumor therapy. Artemisinin, a natural sesquiterpene lactone derived from *Artemisia annua*, has demonstrated remarkable antimalarial and anticancer properties. Building upon this foundation, Li *et al.* developed carrier-free dihydroartemisinin nanoparticles (DHA NPs) through molecular self-assembly driven by hydrogen bonding and hydrophobic interactions.[116] These pure nanodrugs exhibit excellent stability, near-spherical morphology with narrow size distribution, and >92% drug loading efficiency. Both *in vitro* and *in vivo* studies confirmed superior therapeutic efficacy compared to free DHA, with mechanistic analysis revealing crucial involvement of the p53 signaling pathway in tumor growth inhibition and apoptosis induction. This work not only presents a green strategy for developing pure nanodrugs from natural compounds but also provides novel insights into DHA's anticancer mechanism, offering significant potential for clinical translation. Glycyrrhetinic acid (GA), a natural bioactive triterpenoid derived from licorice, has garnered significant attention for its remarkable anti-inflammatory, antibacterial, and antitumor properties. However, its poor solubility and potential cytotoxicity at high concentrations have limited its biomedical applications. In a recent report, Ma [117]and colleagues developed a novel degradable, carrier-free spray hydrogel based on the self-assembly of GA molecules (GAG) for preventing postoperative peritoneal adhesion (PPA). This hydrogel was prepared through a simple process involving heating and cooling a mixture of GA and a low-concentration sodium carbonate solution, without any additional chemical cross-linking agents. The resulting GAG exhibited excellent injectability and sprayability, allowing for precise application and complete coverage of irregular wound surfaces. It demonstrated superior biocompatibility, biodegradability, and potent anti-inflammatory and antibacterial activities. In a rat model of side wall defect-cecum abrasion, the sprayed GAG effectively served as a physical barrier, reduced collagen deposition, and slowly released GA to mitigate the inflammatory response, thereby significantly preventing postoperative adhesion formation. This work presents a promising and transformative strategy for preventing PPA and highlights the potential of self-assembled NSMs in advanced biomedical applications.

In contrast, polyphenols are defined by the presence of multiple phenolic hydroxyl groups attached to aromatic rings. This structure endows them with a high capacity for multipoint hydrogen bonding and extensive π-π stacking capabilities. Many polyphenols, such as Cur, epigallocatechin-3-gallate (EGCG), mangiferin (MF), and TA *etc.* have been reported for the self-assembly to preparation of different CFSNs for various biomedical applications. Honokiol (HK), a natural bioactive biphenolic compound derived from *Magnolia officinalis*, has demonstrated remarkable pharmacological properties including anti-inflammatory, antioxidant, and antitumor activities.[129] However, its poor water solubility and low bioavailability have hindered its clinical applications. Recently, Ji *et al.* developed a novel carrier-free nanomedicine system through the self-assembly of HK molecules, forming stable nanoparticles (HK NPs) with high drug loading capacity (>90%).[118] The HK NPs exhibited excellent colloidal stability and pH-responsive drug release behavior. Both *in vitro* and *in vivo* studies demonstrated that the HK NPs could effectively accumulate in tumor tissues *via* EPR effects and significantly enhance the antitumor efficacy compared to free HK. This work presents a simple yet effective strategy for constructing CFNs from NSMs while overcoming their inherent pharmaceutical limitations, offering promising potential for improved cancer therapy. The self-assembly approach eliminates the need for synthetic carriers, thereby reducing potential toxicity concerns while maintaining the intrinsic therapeutic properties of HK. A quintessential example is MF, a natural xanthone glucoside known for its potent anti-inflammatory and antioxidant activities. Hao *et al.* reported the development of a multifunctional hydrogel (MF-gel) through the direct self-assembly of the natural herbal small molecule MF, specifically for the treatment of diabetic wounds.[119] The carrier-free hydrogel was synthesized *via* a heating/cooling treatment, primarily governed by hydrogen bonds and intermolecular π–π stacking interactions. The

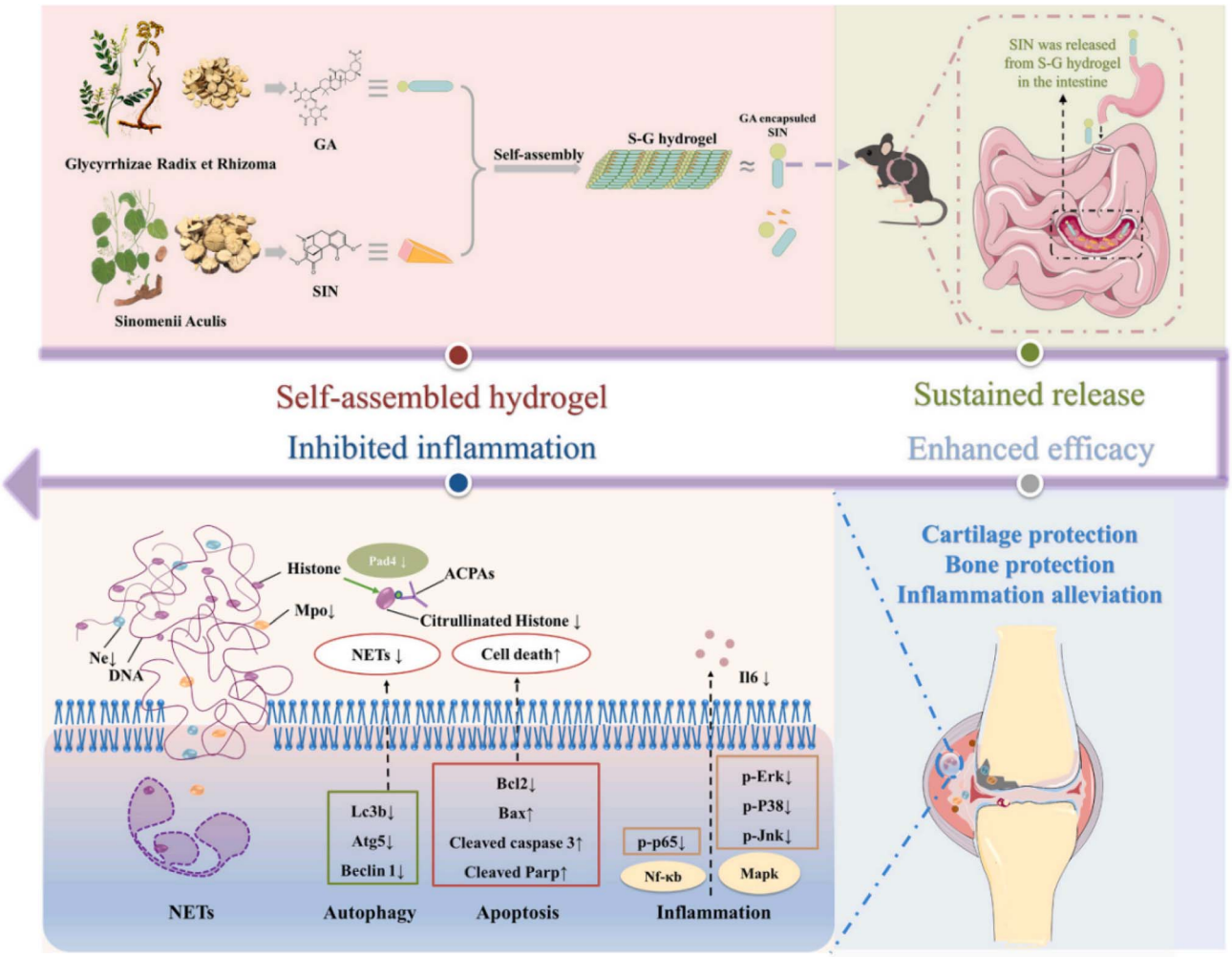

Fig. 1 Schematic illustration of the formation of S–G hydrogel and its mechanism in alleviating rheumatoid arthritis. The natural herbal compounds SIN and GA, both possessing anti-inflammatory properties, are capable of self-assembling into hydrogels. These hydrogels exhibit synergistic anti-inflammatory effects. Specifically, the S–G hydrogel mitigates rheumatoid arthritis by modulating the activity of neutrophils (this figure has been adapted/reproduced from ref. 120 with permission from Elsevier, copyright 2025).

resultant MF-gel exhibits injectable and self-healing properties, along with excellent biocompatibility, continuous release ability, and reversible stimuli-responsive behaviors. *In vitro* studies demonstrated that MF-gel promotes cell migration, angiogenesis, and inflammation regulation by scavenging intracellular ROS. *In vivo* experiments on a diabetic rat model further confirmed its efficacy in accelerating wound contraction and healing through collagen deposition and angiogenesis. This research provides a facile and effective method for diabetic wound management and underscores the potential of natural herbal small molecules in direct self-assembly hydrogels.

4.2 Multi-drug CFSNs

In contrast to single-drug CFSNs, multi-drug CFSNs are homogeneous nanoscale architectures that spontaneously self-assemble *via* non-covalent interactions between multiple therapeutic agents and carrier materials. These systems facilitate the concurrent encapsulation and synchronized release of drugs with disparate physicochemical attributes within a singular particle, thereby simplifying formulation processes, augmenting drug stability, and diminishing batch-to-batch variability. In clinical settings, they are progressively being investigated for the combination therapy of intricate diseases (*e.g.*, cancer, infections, and inflammatory conditions) by enabling spatiotemporally coordinated delivery, enhancing synergistic efficacy, surmounting drug resistance, and alleviating the toxicities and logistical challenges associated with sequential administration. Their modular design further provides a scalable technological platform for personalized and precision medicine. For example, a recent study by Jiang *et al.* presented an innovative approach utilizing the self-assembly of sinomenine (SIN) and glycyrrhizic acid (GA) to create a nanohydrogel (S–G hydrogel) for improved RA management (Fig. 1).[120] This carrier-free hydrogel leverages noncovalent interactions, such as hydrogen bonding and electrostatic attraction, to form a stable and homogeneous structure. *In vitro* studies demonstrated that the S–G hydrogel effectively protected SIN from degradation in acidic conditions, thereby

enhancing its absorption and reducing the required dosage. Mechanistically, the hydrogel significantly suppressed LPS-induced inflammation *via* the NF-κb and MAPK pathways and inhibited PMA-induced neutrophil extracellular traps (NETs) through autophagy inhibition. *In vivo* experiments in a mouse model of RA revealed that the S–G hydrogel markedly reduced joint swelling and NET formation at lower doses compared to free SIN, while also regulating neutrophil activity. This study underscores the potential of self-assembled hydrogels as a platform for developing more effective and safer treatments for chronic inflammatory diseases like RA, highlighting the importance of exploring natural compounds for enhanced drug delivery systems.

5 Biomedical applications of CFSNs

The evolution of CFSNs from an intriguing concept to a revolutionary therapeutic platform is most evident in its diverse biomedical applications (Table 3). By fundamentally reengineering drug delivery, such as eliminating inert carriers and enabling API to self-assemble into nanostructures, this strategy overcomes critical limitations of traditional nanomedicine. The resultant ultra-high drug loading, inherent biocompatibility, and capacity for precise co-delivery of synergistic agents are not merely theoretical advantages; they are driving tangible progress across multiple medical fields. These nanodrugs are demonstrating powerful versatility, from achieving targeted cancer combination therapy and penetrating resistant bacterial biofilms to delivering anti-inflammatory drugs with precision. The following sections detail how this innovative approach is being harnessed to develop next-generation treatments for some of the most pressing challenges in medicine today.

5.1 Applications for cancer therapy

Cancer continues to pose one of the most significant challenges in contemporary medicine, marked by uncontrolled cellular proliferation, invasion, and metastasis. Despite substantial progress in diagnostic techniques and therapeutic strategies, the high mortality rate and considerable morbidity associated with cancer highlight the urgent need for more effective and targeted treatments. Traditional cancer therapies, including chemotherapy, radiotherapy, and surgery, are often limited by non-specific targeting, severe side effects, and the development of drug resistance.[142,143] These limitations underscore the necessity for innovative approaches that can enhance therapeutic efficacy while minimizing adverse effects. In this context, the application of nanotechnology in oncology has emerged as a transformative field, offering promising solutions to overcome the limitations of conventional treatments. Nanomaterials, particularly those derived from NSMs, have garnered significant attention due to their unique properties and potential for improving cancer therapy. NSMs, such as polyphenols, flavonoids, and terpenoids, possess inherent bioactivities, including anti-inflammatory, antioxidant, and anti-cancer properties. However, their clinical application is often hindered by rapid clearance from systemic circulation, potential adverse reactions, and a narrow therapeutic window. CFSNs represent a novel and innovative approach to leveraging the therapeutic potential of NSMs. These nanomaterials spontaneously self-assemble into well-defined nanostructures through non-covalent interactions without the need for synthetic polymers or other inert carriers. In this section, we will introduce the applications of NSM-based CFSNs for cancer treatment, highlighting their potential to revolutionize oncological therapeutics by addressing some of the most pressing challenges in the field. Specifically, these carrier-free nanomaterials offer a unique combination of enhanced solubility, bioavailability, and targeted delivery, which can significantly improve the efficacy and safety of anti-cancer treatments. One notable example of this approach is the recent study by Zong *et al.*, which demonstrated the synergistic anti-tumor effects of luteolin (LUT) and GA when self-assembled into carrier-free nanoparticles (LG-Nanos) for the treatment of liver cancer.[130] These LG-Nanos exhibited enhanced solubility, bioavailability, and tumor-targeting capabilities, significantly inhibiting the proliferation of liver cancer cells while sparing normal liver cells. The self-assembly process involved π–π stacking and hydrogen bonding, resulting in stable and effective drug delivery. *In vivo* studies in a mouse model of liver cancer further confirmed the superior therapeutic efficacy and safety profile of LG-Nanos.

Table 3 Biomedical applications of CFSNs

Application field	Specific category/Disease	Representative examples
Cancer therapy	—	• LG-nanos for the treatment of liver cancer[130] • MSBNAs[131] • ICG@UA/PTX NPs[132] • Cap-p@Cur for the treatment of TNBC[108]
Anti-infection	—	• Photothermal therapy with E-Au NPs[133] • LGG@ZR1 for vulvovaginal candidiasis therapy[134] • BBR/CGA nanocomposite for combating MRSA[135]
Anti-Inflammation	Application for treatment osteoarthritis Application for treatment ulcerative colitis Application for treatment atherosclerosis	• Rh gel@SP-EVs for OA therapy[136] • GA-BBR hydrogel for the treatment of UC[137] • HA@PC@Pita NP for the treatment of atherosclerosis[138]
Treatment of other diseases	Retinal ischemia–reperfusion Treatment of sepsis Acute kidney injury therapy	• PLBP nanoparticles for IR-induced retinal diseases[139] • R–I NPs for the treatment of sepsis[140] • Cur-NPs for the treatment of AKI[141]

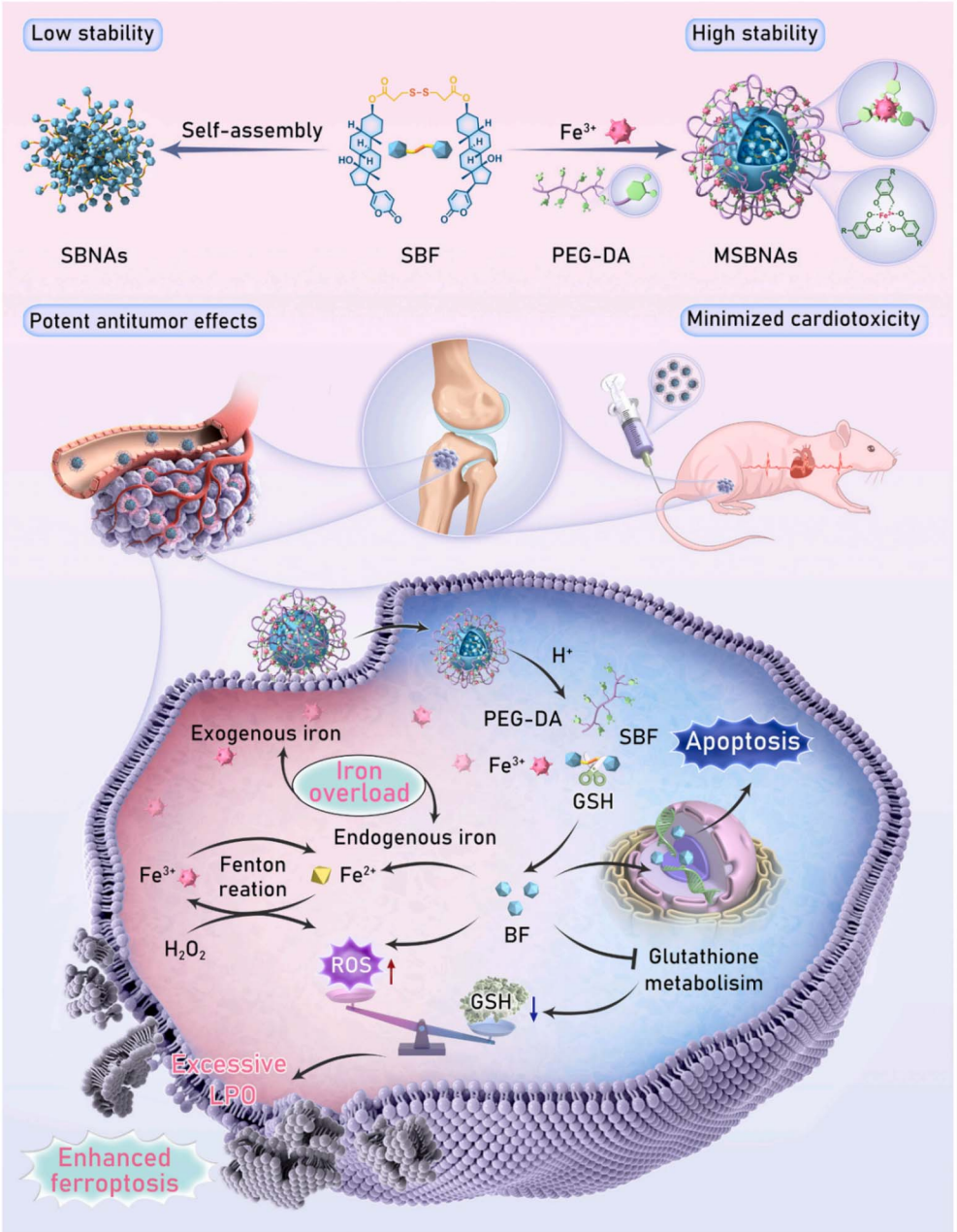

Fig. 2 Illustration of the synthetic methods and therapeutic mechanisms of MSBNAs. Bufalin homodimeric prodrugs are integrated into metal-phenolic networks to form MSBNAs. These nanoparticles exhibit high drug-loading efficiency, long-term stability, extended circulation time, and pH/GSH-responsive drug release, enabling deep tumor penetration. MSBNAs reduce BF-induced cardiotoxicity and enhance antitumor efficacy through iron overload-induced ferroptosis. (This figure has been adapted/reproduced from ref. 131 with permission from Elsevier, copyright 2025.).

This innovative approach not only enhances the therapeutic index of natural compounds but also provides a scalable and biocompatible platform for the development of next-generation cancer therapies. The identification of molecular targets such as estrogen receptor 1 (ESR1) and cyclin-dependent kinase 1 (CDK1) further underscores the potential of carrier-free drug delivery systems to revolutionize cancer treatment.

Ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation, has emerged as a promising therapeutic strategy for cancer treatment due to its distinct mechanisms and potential for overcoming resistance to conventional therapies. Unlike apoptosis, ferroptosis is driven by the accumulation of iron and ROS, leading to lipid peroxidation and eventual cell death. This unique pathway offers new opportunities for developing targeted cancer therapies that can selectively induce ferroptosis in tumor cells. Recent advancements have focused on leveraging ferroptosis to enhance the efficacy of anticancer drugs. For instance, the study by Wu *et al.* introduced a novel nanoparticle system, MSBNAs, which combines disulfide-linked bufalin homodimeric prodrugs with

metal-phenolic networks (Fig. 2).[131] This synergistic assembly not only improves the stability and drug-loading capacity of bufalin but also amplifies its antitumor effects through iron overload and disruption of antioxidant defenses, thereby inducing ferroptosis. This approach contrasts with previous strategies, such as the self-assembly of LUT and GA into carrier-free nanoparticles, which primarily targeted inflammation and cell cycle regulation without specifically leveraging ferroptosis.

Photodynamic therapy (PDT) and the self-assembly of NSMs into tumor-targeting nanoplatforms represent innovative strategies in cancer theranostics. A recent study by Guo *et al.* presents a novel carrier-free, small molecule nanodrug (ICG@UA/PTX NPs) that integrates PDT with the anticancer properties of ursolic acid (UA) and paclitaxel (PTX) through self-assembly.[132] This nanoplatform leverages the photostability and near-infrared (NIR) imaging capabilities of indocyanine green (ICG) to enhance tumor targeting and therapeutic efficacy. The ICG@UA/PTX NPs are formed through electrostatic, π–π stacking, and hydrophobic interactions, resulting in a stable and efficient drug delivery system. These nanoparticles exhibit enhanced water solubility for UA and PTX, prolonged circulation time, and pH-responsive drug release, which are crucial for effective tumor accumulation and reduced systemic toxicity. *In vitro* studies demonstrate that the nanoplatform significantly inhibits cancer cell viability under NIR laser irradiation, highlighting its potent chemophototherapy effects. *In vivo* experiments further confirm the tumor-targeting ability and therapeutic efficacy of ICG@UA/PTX NPs, with nearly complete tumor suppression and no recurrence observed in tumor-bearing mice. This study underscores the potential of integrating PDT with NSMs in a self-assembled nanoplatform, offering a promising strategy for synergistic cancer theranostics. The carrier-free design and enhanced photostability of ICG in the nanoplatform provide a robust foundation for future clinical applications, addressing challenges associated with traditional nanocarriers and advancing the field of cancer treatment. Cur, a natural polyphenol derived from turmeric, exhibits notable potential in PDT. As a photosensitizer, it generates cytotoxic ROS upon light irradiation, inducing apoptosis in cancer cells. Its inherent fluorescence also allows for real-time imaging during treatment. Recent advances in nanoformulations, including liposomes, polymeric nanoparticles, and carrier-free self-assembled systems have significantly enhanced its stability, bioavailability, and targeted delivery, making Cur a promising candidate for image-guided PDT in oncology.[144] In a recent study from our group, we explored the self-assembly of phosphorylated capsaicin (Cap-p) and Cur to develop a novel carrier-free drug delivery system for the treatment of TNBC.[108] Herein, the Cap-p was synthesized through a one-step phosphorylation process, which imparts amphiphilic properties to the molecule, enabling it to self-assemble into nanovesicles with high water dispersibility. These nanovesicles were further utilized to encapsulate the hydrophobic drug Cur, forming Cap-p@Cur. The study demonstrates that Cap-p@Cur exhibits significantly enhanced cell-killing efficacy against MDA-MB-231 cells compared to free Cur or Cap-p alone. Notably, the anticancer effects of Cap-p@Cur are further amplified under light irradiation, highlighting its potential for synergistic chemotherapy and PDT. Additionally, Cap-p displays favorable biocompatibility and

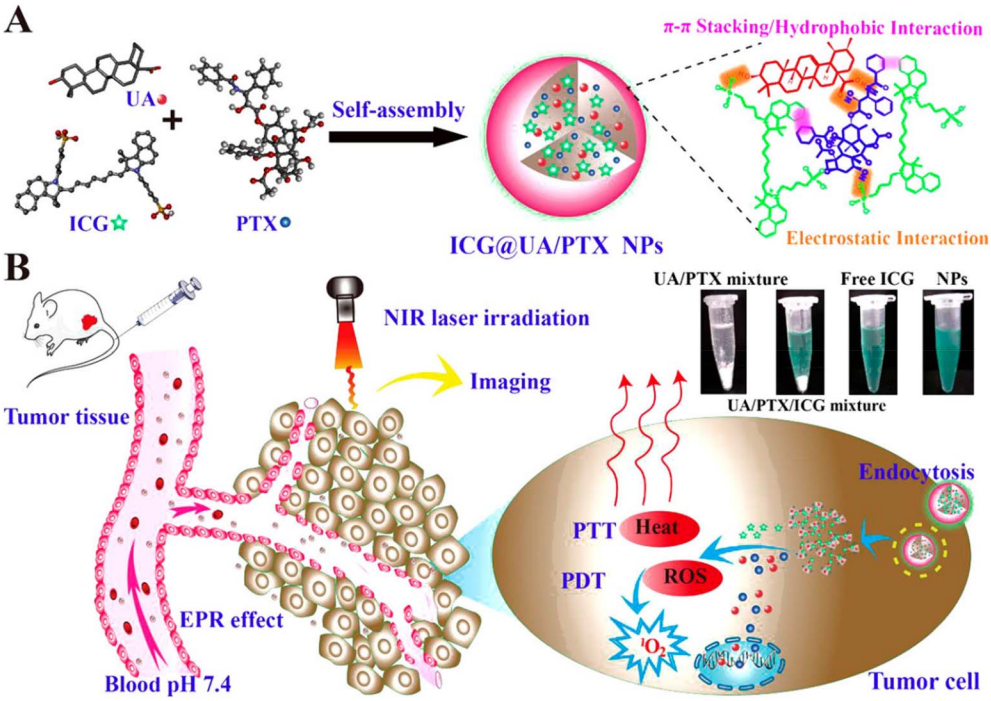

Fig. 3 Schematic illustration of a carrier-free small molecule theranostic nanoplatform. Panel (A) details the self-assembly mechanism, whereas panel (B) highlights the platform's application for *in vivo* tumor imaging and chemo-phototherapy. (This figure has been adapted/reproduced from ref. 132 with permission from American Chemical Society, copyright 2017).

bone-targeting capabilities, suggesting its potential for treating bone metastasis of TNBC (Fig. 3). This work provides valuable insights into the development of natural product-based, self-assembled nanoplatforms for cancer treatment, offering a promising strategy to overcome the limitations of poor water solubility and bioavailability associated with traditional natural compounds.

5.2 Applications for anti-infection

Bacterial infections especially those caused by multidrug-resistance (MDR) strains have become a critical global health threat.[145] The formation of bacterial biofilms significantly exacerbates microbial tolerance and resistance to conventional antimicrobial agents, presenting a formidable challenge in infection management. In response, nanotechnology-enabled approaches and phototherapeutic strategies have emerged as promising alternatives, offering distinct advantages such as localized action and reduced propensity for resistance development.[146] Notably, polyphenolic compounds with their inherent antioxidant, anti-inflammatory, and broad-spectrum antimicrobial properties have garnered increasing attention as multifaceted therapeutic agents capable of simultaneously addressing biofilm-associated infections and oxidative stress.[147–149] Wei and co-workers[133] exploited these advantages by developing E-Au NPs through a one-step aqueous self-assembly of epigallocatechin gallate (EGCG) and $HAuCl_4$ (Fig. 4). E-Au NPs display broad-spectrum antibacterial efficacy against both Gram-positive and Gram-negative pathogens, which is markedly amplified by NIR laser irradiation. They not only prevent MRSA biofilm formation but also effectively dismantle established biofilms. Photothermal therapy with E-Au NPs demonstrates robust activity against multiple bacterial strains, including MDR-MRSA, and shows impressive therapeutic outcomes in skin wounds and keratitis complicated by MRSA biofilms. Mechanistically, the antibacterial action arises from EGCG-mediated quinoprotein generation, NIR-triggered hyperthermia and ROS production, disruption of cellular architecture, and down-regulation of genes governing biofilm formation and virulence. With high efficacy and excellent biocompatibility, E-Au NPs represent a potent nanotherapeutic for combating drug-resistant bacterial infections and hold substantial clinical potential.

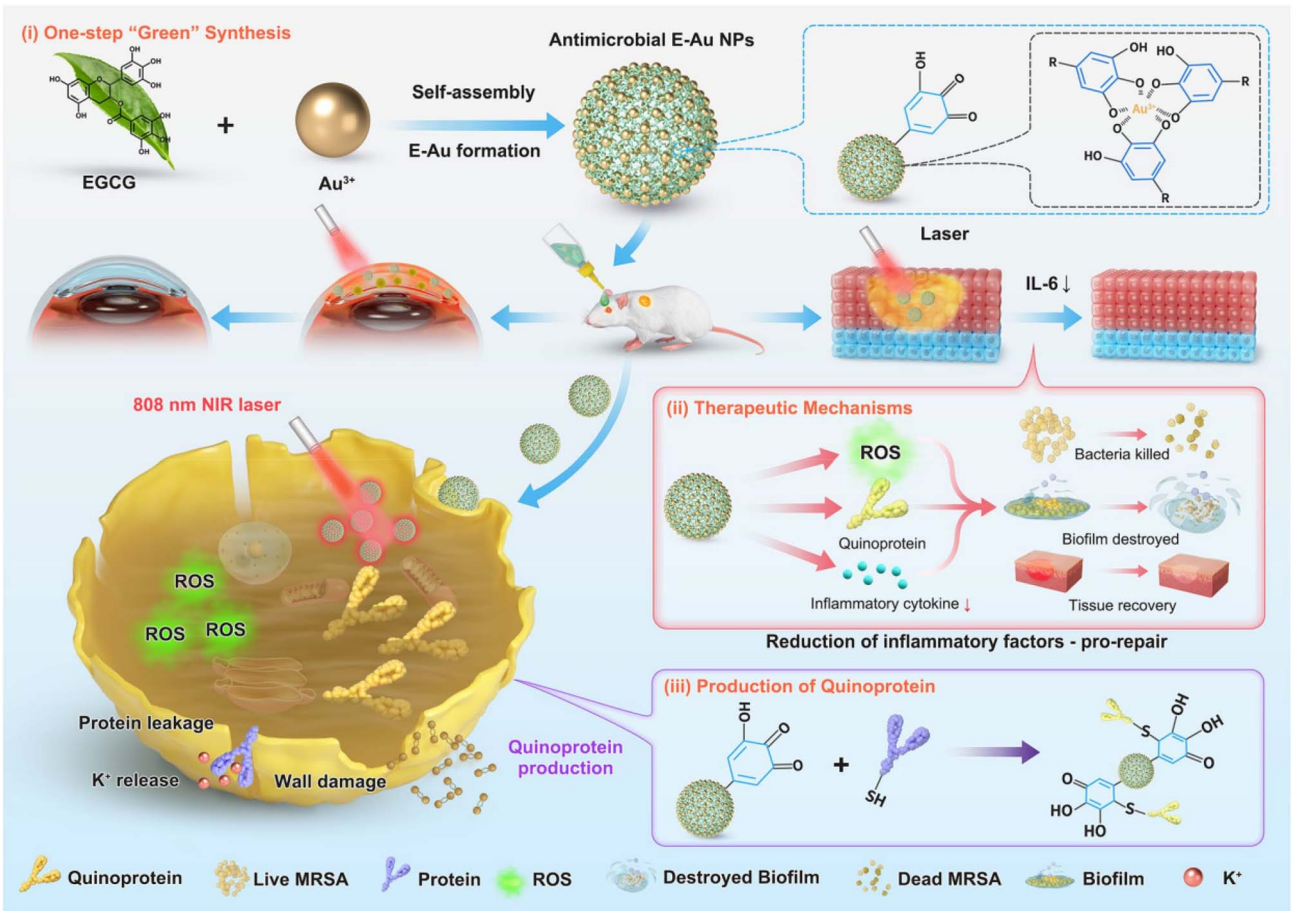

Fig. 4 The diagram illustrates the antimicrobial and biofilm-eradicating capabilities of E-Au nanoparticles. These nanoparticles were synthesized *via* a straightforward, one-step self-assembly technique. Their antibacterial and anti-inflammatory effects were demonstrated in skin wounds infected with methicillin-resistant *Staphylococcus aureus* (MRSA) and in keratitis. The exceptional antibacterial activity is attributed to mild photothermal effects, the generation of ROS, modulation of virulence-associated genes, and the formation of quinoproteins. (This figure has been adapted/reproduced from[133] licensed under CC BY-NC-ND 4.0).

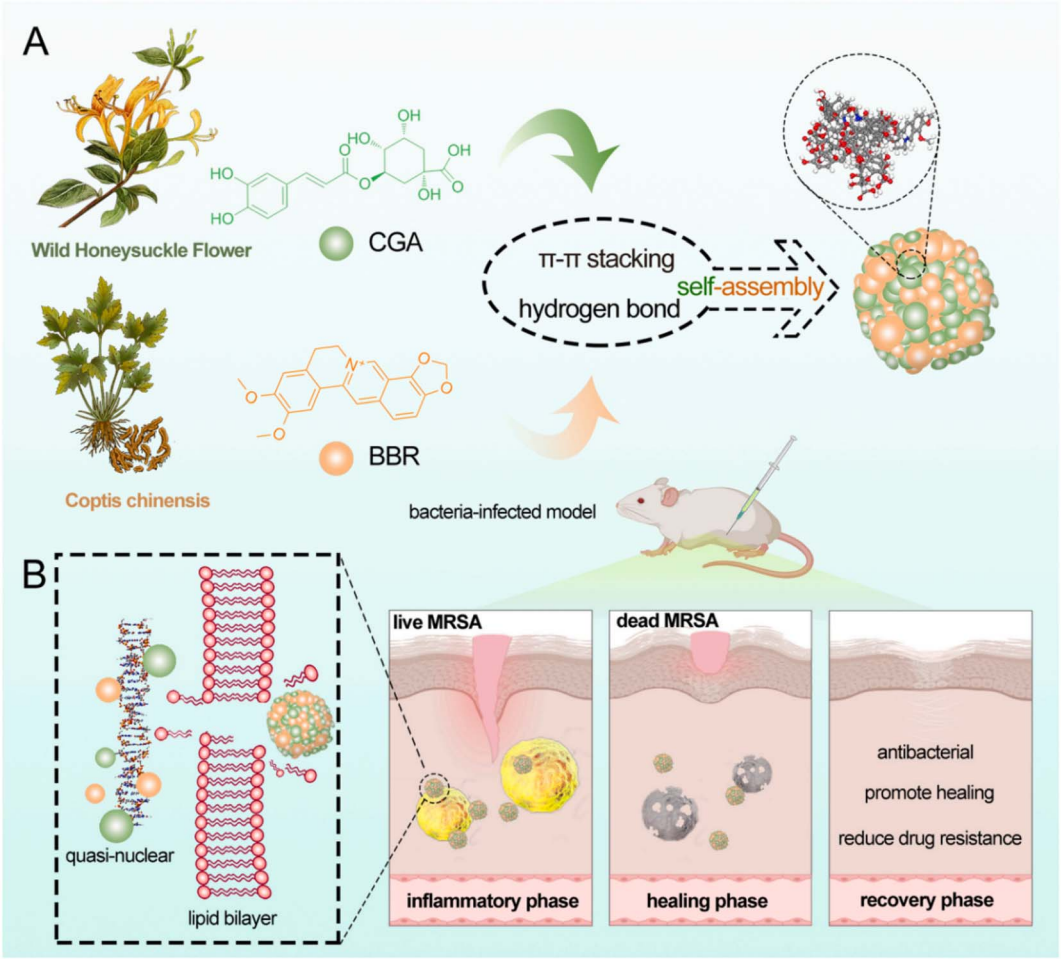

Fig. 5 Schematic representations of (A) the formation process of BBR/CGA nanoparticles and (B) the cellular uptake mechanism, highlighting the ensuing stages of inflammation, tissue repair, and recovery. (This figure has been adapted/reproduced from ref. 135 with permission from Elsevier, copyright 2024).

Simple side-chain modifications or the incorporation of pH- or enzyme-responsive elements enable precise control over particle size and surface chemistry, facilitating passive accumulation at infection sites.[150,151] Upon arrival, stimuli prevalent in the bacterial microenvironment, such as acidic pH, elevated GSH, or overexpressed enzymes trigger rapid disassembly, releasing a burst of active compounds that act synergistically to disrupt membrane potential and destabilize biofilms, thereby overcoming MDR.[114] Recent advancements have expanded this concept from single-mode antimicrobial action to integrated strategies that combine antibacterial, anti-inflammatory, and immune-activating effects. Dynamic covalent bonds or supramolecular cross-linking have also been introduced to confer self-healing and prolonged retention capabilities. These innovations provide a scalable, green platform for addressing drug-resistant infections and biofilm-associated diseases. Ginsenoside R1 (ZR1), a triterpene saponin extracted from the Notoginseng plant, is reported to have potential anti-tumor and anti-angiogenic effects. However, its poor solubility limits its bioavailability, restricting the exploration of its biological activity and clinical applications. In a recent study, Peng *et al.*[152] prepared a ZR1 hydrogel using a simple heat–cool cycle, achieving a minimum gelation concentration of only 2.0 wt%. This ZR1 hydrogel exhibits potent antifungal activity against *Candida albicans* by compromising membrane integrity and driving cell death. This efficacy is critically underpinned by the self-assembly of ZR1 into nanofibrils, where hydrogen bonding stabilizes the fibers, arranging hydrophobic segments in the core while exposing hydrophilic groups to the surface for optimal interaction with fungal membranes. Strong hydrogen bonding between ZR1 and β-1,3-glucans in the Candida cell wall allows the hydrogel to adhere to the membrane surface and disrupt its integrity. Moreover, the hydrogel serves as a probiotic carrier, enabling synergistic suppression of *C. albicans* and restoration of the vaginal microbiota. Thus, LGG@ZR1 offers a dual-action strategy for vulvovaginal candidiasis therapy, simultaneously inhibiting fungal growth and rebalancing microbial communities, heralding broad clinical promise.

The escalating threat of antibiotic resistance has made the development of potent antibacterial strategies an urgent necessity.[153] Although berberine (BBR) and chlorogenic acid (CGA), derived from traditional Chinese medicine, possess intrinsic antimicrobial activity, their clinical utility is limited by poor bioavailability. To address this challenge, Fu *et al.*[135]

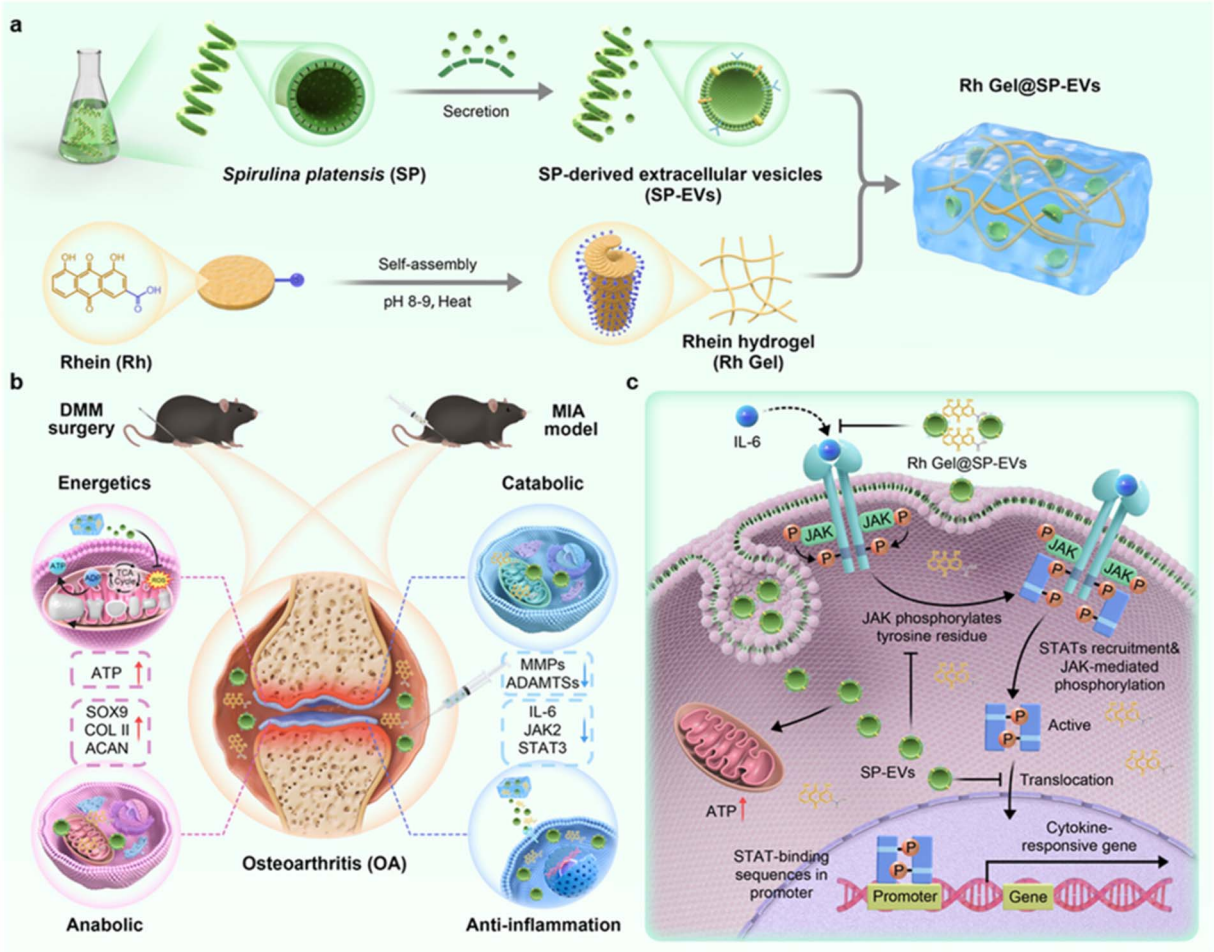

Fig. 6 Self-assembled microalgae extracellular vesicles/herb-based hydrogel for osteoarthritis therapy. (a) Rhein (Rh) molecules self-assemble into nanofibers through non-covalent interactions, forming a 3D bioactive hydrogel (Rh Gel) that can encapsulate extracellular vesicles from *Spirulina platensis* (SP-EVs). The resultant Rh Gel@SP-EVs integrate the therapeutic effects of Rh and microalgae EVs. (b) In mouse models of osteoarthritis (OA) induced by destabilization of the medial meniscus (DMM) or monoiodoacetate (MIA), Rh Gel@SP-EVs effectively slow OA progression by enhancing ATP production, inhibiting catabolic processes, promoting anabolic metabolism, and reducing inflammation. (c) Rh Gel@SP-EVs exhibit potent anti-inflammatory effects *via* the IL-6/JAK2/STAT3 signaling pathway, modulating cytokine production and contributing to OA regression. (This figure has been adapted/reproduced from ref. 136 with permission from American Chemical Society, copyright 2025).

engineered self-assembling BBR/CGA nanoparticles designed to effectively suppress MDR *Staphylococcus aureus* (MRSA) (Fig. 5). Molecular dynamics simulations confirmed that BBR and CGA spontaneously co-assemble through synergistic supramolecular interactions. At a 1 : 1 molar ratio, the resulting nanoparticles exhibit minimal, narrowly distributed diameters, robust colloidal stability, and pH-responsive release profiles. Compared with ampicillin, oxacillin, the individual components, or their physical mixture, the BBR/CGA nanocomplex demonstrates superior bacteriostatic potency, achieving a minimum inhibitory concentration of only 1.5 μM against both *S. aureus* and MRSA. The mechanism involves inhibiting biofilm formation, disrupting membrane integrity, and down-regulating genes implicated in biofilm development and nucleotide metabolism. When co-administered with β-lactam antibiotics, the nanocomplex exerts a pronounced synergistic effect, fully reversing MRSA resistance to these agents. *In vivo* studies confirm the nanocomplex's excellent biocompatibility and safety: topical application significantly reduces bacterial burden, accelerates inflammation resolution, expedites wound closure, and enhances immune responses in murine skin-infection models. Collectively, the BBR/CGA nanocomposite offers a promising alternative for combating MRSA and holds significant translational potential in the fight against antimicrobial resistance. However, personalized nanomedicine design and rigorous clinical efficacy assessment remain essential next steps.

5.3 Applications for anti-inflammation

5.3.1 Application for treatment osteoarthritis. Osteoarthritis (OA) is a degenerative joint disease characterized by the progressive degradation of articular cartilage, subchondral bone changes, and synovial inflammation.[154–156] It is one of the leading causes of chronic pain and disability worldwide. The pathogenesis of OA involves a complex interplay of mechanical,

biochemical, and inflammatory factors, with dysregulated energy metabolism emerging as a key driver of disease progression. Current therapeutic options for OA are limited, primarily focusing on symptom relief rather than disease modification. The advent of naturally derived extracellular vehicles (EVs) has opened new avenues for OA treatment; however, their short intra-articular residence time poses a significant challenge. Hydrogel-based delivery systems offer a promising solution by prolonging retention and enhancing bioavailability. Guided by this rationale, Liang and colleagues[136] engineered a multifunctional platform—rhein-gel-encapsulated *Spirulina platensis*–derived EVs (Rh Gel@SP-EVs) for OA therapy (Fig. 6). SP-EVs were isolated from the culture medium of *Spirulina platensis* using differential ultracentrifugation and sequential filtration. Rhein (Rh) was dissolved in sodium bicarbonate, cooled to induce a sol-to-gel transition, and then loaded with SP-EVs to form Rh Gel@SP-EVs. Comprehensive microscopic and spectroscopic analyses revealed that SP-EVs are nanodisc-shaped, measuring 50–100 nm in diameter, and are enriched in proteins associated with ATP-dependent processes and metabolic regulation—properties that enable modulation of joint homeostasis and OA pathophysiology. The hydrogel exhibits pH-responsive behavior: at pH 5.5, Rh is released more slowly and sustainably. The construct displays excellent biocompatibility and is readily internalized by chondrocytes. *In vitro*, Rh Gel@SP-EVs effectively scavenge ROS, restore mitochondrial function, boost ATP synthesis, rebalance anabolic and catabolic activities in chondrocytes, and suppress the IL-6/JAK/STAT3 signaling axis. *In vivo* studies in a murine OA model demonstrate marked attenuation of disease progression, improved cartilage and subchondral bone integrity, and an excellent safety profile. By orchestrating energy metabolism and exerting anti-inflammatory effects, Rh Gel@SP-EVs offer a promising therapeutic strategy for OA with significant translational potential.

5.3.2 Application for treatment ulcerative colitis. Ulcerative colitis (UC) continues to pose significant therapeutic challenges, with existing treatments often falling short of ideal outcomes.[157] This highlights the urgent need for safe and effective hydrogel-based drug delivery systems. GA and berberine (BBR) have shown potential in treating UC, but their clinical application is limited by poor bioavailability. To address this, Lei and colleagues[158] developed a GA-BBR hydrogel through molecular self-assembly. They systematically characterized its morphology and rheological properties, simulated the self-assembly process, and evaluated its drug release, *in vitro* degradation, cytotoxicity, and anti-inflammatory efficacy both *in vitro* and *in vivo*. The hydrogel forms spontaneously through a synergistic interplay of hydrogen bonding, π–π stacking, and electrostatic interactions. This endows it with injectability, strong mucosal adhesion, and fluorescence enhancement. It is stable in highly acidic conditions (pH 1.5), making it suitable for oral administration, while providing sustained drug release for up to 140 h at pH 4.5, which is particularly advantageous for

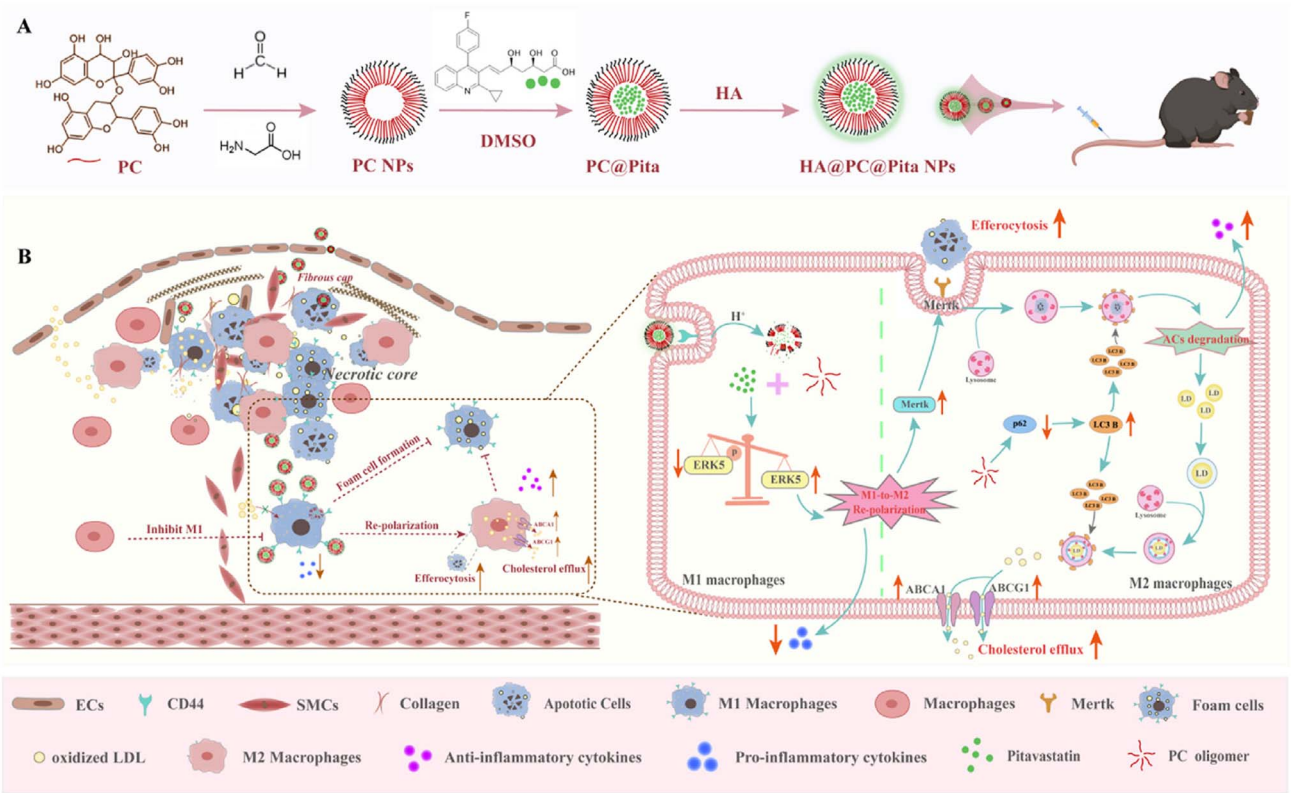

Fig. 7 Schematic preparation of HA@PC@Pita NPs and the strategy for advanced atherosclerosis treatment. (A) Preparation scheme of HA@PC@Pita NPs. (B) HA@PC@Pita NPs alleviate advanced atherosclerosis by restoring efferocytosis and promoting cholesterol efflux (reproduced without modification from[138] Licensed under CC BY-NC-ND 4.0).

treating moderate-to-severe UC. Both *in vitro* and *in vivo* studies confirm the hydrogel's excellent safety profile and superior anti-inflammatory activity compared to mesalamine or GA and BBR monotherapies. The GA-BBR hydrogel thus represents a powerful therapeutic strategy for UC, offering broad prospects for drug development and clinical management of the disease.

5.3.3 Application for treatment atherosclerosis. Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids and fibrous elements in the arterial wall, leading to the formation of plaques that can rupture and cause acute cardiovascular events.[159] Advanced atherosclerosis remains a leading global cause of death, with a hallmark feature being the accumulation of apoptotic cells (ACs) within necrotic cores. Central to this pathology are two macrophage dysfunctions: impaired efferocytosis (the clearance of apoptotic cells) and defective cholesterol efflux. These dysfunctions contribute to plaque instability and progression, making them critical targets for therapeutic intervention. Pitavastatin (Pita) accelerates AC clearance *via* ERK5 activation, while proanthocyanidins (PC) up-regulate the cholesterol-export proteins ABCA1/G1. Wu and co-workers[138] capitalized on these complementary mechanisms by fabricating a hierarchical nano-therapeutic. Through polyphenol condensation and benzoxazine chemistry, PC first self-assembles into monodisperse nanoparticles (PC NPs) that encapsulate Pita with an exceptional efficiency of 97.12% and a drug-loading content of 6.45%. Subsequent hyaluronic acid (HA) surface conjugation yields HA@PC@Pita NPs (Fig. 7). The construct exhibits pH-responsive release, accelerated at pH 5.4 and remains colloidally stable in both PBS and 10% FBS. HA-mediated CD44 targeting directs the nanocarrier to activated macrophages, where it simultaneously enhances efferocytosis, suppresses foam-cell formation, and drives M1-to-M2 repolarization. Intracellularly, the particles reactivate lipophagy, restore cholesterol efflux, and potentiate hepatic lipid metabolism, thereby shrinking necrotic cores system-wide. Despite their robust biological activity, HA@PC@Pita NPs display negligible cytotoxicity, minimal hemolysis, and no significant alterations in blood counts or serum biochemistry. Histological evaluation confirms the absence of injury to heart, liver, spleen, lung, or kidney, underscoring the platform's translational safety and its promise for precision therapy in late-stage atherosclerosis. This innovative approach addresses key pathological mechanisms in atherosclerosis, offering a potential breakthrough for treating this complex and deadly disease.

5.4 Applications for treatment of other diseases

5.4.1 Retinal ischemia–reperfusion. Retinal ischemia–reperfusion (IR) injury is a critical pathological process that triggers oxidative stress and neuro-inflammation, ultimately leading to the irreversible loss of retinal ganglion cells (RGCs) and vision.[160] This condition is particularly challenging due to the lack of effective neuroprotective therapies currently available in clinical practice. Lycium barbarum polysaccharide (LBP) is known for its potent antioxidant properties, but its therapeutic efficacy is significantly limited by poor bioavailability. To address this limitation, Ni *et al.* devised an innovative method by covalently attaching phenylboronic acid pinacol ester (PBA), a powerful ROS scavenger, to LBP, thereby creating an amphiphilic conjugate (PLBP) that self-assembles into nanoparticles.[161] The successful grafting of PBA to LBP was confirmed by 1H NMR and FTIR spectroscopy. The resulting PLBP nanoparticles exhibit a hydrodynamic diameter of 294.6 nm and a zeta potential of −19.2 mV. Compared to native LBP, PLBP nanoparticles demonstrate enhanced efficacy in quenching intracellular ROS, up-regulating antioxidant enzymes, and robustly activating the NRF2 pathway. Additionally, PLBP nanoparticles effectively dampen microglial phagocytosis, migration, and the release of pro-inflammatory cytokines, while suppressing NF-κB signaling. By acting both directly on RGCs and indirectly *via* microglia, PLBP significantly reduces RGC death. Mechanistically, PLBP lowers intracellular Fe^{3+} levels, attenuates lipid peroxidation, and modulates the expression of ferroptosis-related proteins. *In vivo* studies in IR-challenged mice demonstrate that PLBP preserves optic nerve axonal integrity and markedly improves visual function. This multimodal strategy, which combines antioxidant, anti-inflammatory, and anti-ferroptotic actions, offers a promising new therapeutic avenue for IR-induced retinal diseases.

5.4.2 Treatment of sepsis. Sepsis is a life-threatening condition characterized by a dysregulated immune response to infection, leading to organ dysfunction and potentially multiple organ failure. It is a major cause of mortality in intensive care units, with high morbidity and significant economic burden. Current treatments for sepsis are largely supportive, focusing on managing symptoms and complications rather than directly targeting the underlying pathophysiology. Therefore, there is an urgent need for innovative therapeutic strategies to improve outcomes in sepsis patients. Xing *et al.* reported a novel approach to treating sepsis using carrier-free, small molecule-assembled nanoparticles derived from traditional Chinese medicine (TCM).[140] The researchers identified bioactive compounds in the decoction of rhubarb and epimedium that can self-assemble into nanoparticles without the need for additional carriers. Among these compounds, rhein and icariin were selected for their anti-inflammatory and metabolic disorder treatment potentials. The researchers synthesized rhein–icariin nanoparticles (R–I NPs) through a nanoprecipitation process. These NPs exhibited good stability, with an average hydrodynamic diameter of approximately 103 nm and a zeta potential of 35.7 mV, indicating excellent colloidal stability. The R–I NPs were characterized using various techniques, including UV-Vis spectroscopy, fluorescence spectroscopy, and transmission electron microscopy (TEM). The results confirmed the successful self-assembly of rhein and icariin into nanoparticles. *In vitro* experiments demonstrated that R–I NPs effectively reduced the production of ROS and inhibited the expression of pro-inflammatory cytokines such as TNF-α and IL-6. The NPs also showed potential in alleviating ferroptosis, a form of cell death characterized by iron-dependent lipid peroxidation. These findings suggest that R–I NPs have significant anti-inflammatory and antioxidant properties, which are crucial for mitigating the effects of sepsis. To evaluate the therapeutic potential of R–I NPs *in vivo*, the

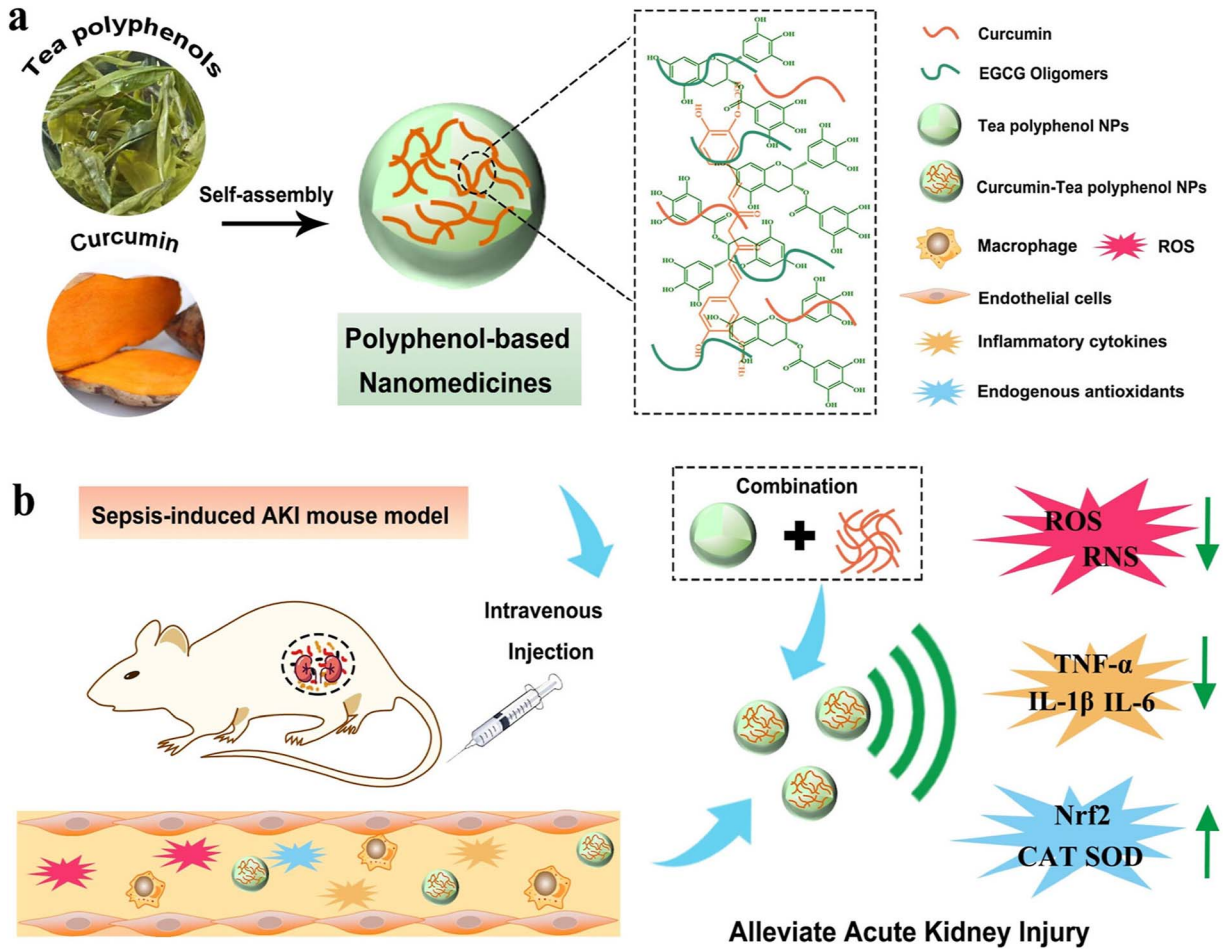

Fig. 8 (a) Diagrammatic representation of the eco-friendly synthesis of polyphenol-derived nanotherapeutics and (b) their synergistic efficacy in targeted AKI treatment. (This figure has been adapted/reproduced from ref. 141 with permission from American Chemical Society, copyright 2023).

researchers used a cecal ligation and puncture (CLP) model in mice, which mimics the pathophysiology of sepsis. The results showed that R–I NPs significantly prolonged the survival time of septic mice by maintaining kidney function. The treatment reduced the levels of blood serum inflammatory cytokines and improved renal function markers, as evidenced by histopathological analysis and immunohistochemical staining. The study concludes that R–I NPs derived from TCM show great potential for the treatment of sepsis. The carrier-free, self-assembled nanoparticles offer a safe and effective drug delivery system, leveraging the anti-inflammatory and antioxidant properties of TCM compounds. This research provides a novel strategy for sepsis treatment and highlights the potential of integrating modern nanotechnology with traditional medicinal practices to address contemporary health challenges.

5.4.3 Acute kidney injury therapy. Acute kidney injury (AKI) is a severe clinical condition characterized by a rapid decline in kidney function, often leading to life-threatening complications.[162] It is particularly prevalent among intensive care unit patients, with sepsis being a major cause. AKI is associated with significant morbidity and mortality, and current treatments are largely supportive, lacking specific therapies to prevent or mitigate kidney damage. In a recent study, Chen *et al.* explored a novel approach to AKI treatment using natural polyphenol-based nanomedicines (Fig. 8).[141] The researchers developed a nanocarrier system using tea polyphenol oligomers to deliver the poorly water-soluble drug Cur, aiming to enhance its bioavailability and therapeutic efficacy. The nanomedicines were synthesized through a disassembly/reassembly process, resulting in Cur-loaded nanoparticles (Cur-NPs) with improved aqueous dispersity and stability. *In vitro* experiments demonstrated that Cur-NPs effectively scavenged free radicals, protected cells from oxidative damage, and suppressed pro-inflammatory factors. The nanoparticles exhibited superior antioxidant and anti-inflammatory activities compared to free Cur. In an *in vivo* sepsis-induced AKI mouse model, intravenous administration of Cur-NPs significantly alleviated kidney injury by reducing oxidative stress, suppressing inflammation, and restoring antioxidant defenses. The treatment decreased levels of acute injury biomarkers (KIM-1 and NGAL), inflammatory cytokines (TNF-α and IL-6), and oxidative stress markers (MDA), while enhancing endogenous antioxidants (Nrf2, CAT, and

SOD). These findings highlight the potential of polyphenol-based nanomedicines as a targeted and effective therapy for AKI, offering a promising strategy to address the limitations of current treatments and improve outcomes for patients with this debilitating condition.

6 Conclusions and prospects

In summary, this review provides an in-depth analysis of the recent advances in CFSNs derived from NSMs for disease treatment. CFSNs, which form stable and biocompatible nanoscale structures through non-covalent interactions without synthetic carriers, have shown significant potential in various disease models, including cancer, infection, inflammation, cardiovascular diseases, and neurodegenerative disorders. These nanomedicines offer unique advantages such as high drug loading, enhanced solubility, and improved pharmacokinetics. Compared with conventional chemotherapeutic, anti-inflammatory, or anti-infective agents, self-assembling natural small molecules (NSMs) offer several distinct advantages. First, the absence of excipients and the high drug loading capacity significantly reduce systemic toxicity. Second, the passive targeting enabled by nanoparticles in the 20–200 nm range, combined with microenvironment-responsive release, enhances drug concentrations at the lesion sites while minimizing off-target effects. Third, the dual role of these molecules as both therapeutic agents and carriers facilitates multimodal synergy, simplifies formulations, and lowers costs. Moreover, plant-derived active ingredients exhibit superior biocompatibility and lower toxicity, further enhancing the therapeutic potential of self-assembling NSMs. The clinical translation of CFSNs still faces several significant challenges that must be addressed to realize their full therapeutic potential. One of the primary obstacles is scalability. The self-assembly processes that work efficiently in the laboratory often struggle to maintain consistency and quality when scaled up for industrial production. Ensuring that the nanoscale structures remain stable and uniform across larger batches is crucial for the reliability and efficacy of the final product. Reproducibility is another critical issue. The formation of CFSNs is highly sensitive to environmental conditions such as pH, temperature, and ionic strength. Variations in these parameters can lead to differences in the size, shape, and drug loading of the nanoparticles, which in turn affect their therapeutic performance. Achieving consistent results across different batches and laboratories is essential for clinical applications. The regulatory approval also poses a significant hurdle. As a novel drug delivery system, CFSNs must meet stringent safety and efficacy standards set by regulatory bodies. Demonstrating the biocompatibility and non-toxicity of these nanomaterials, especially when derived from natural sources, requires extensive preclinical and clinical testing. Ensuring that the self-assembled structures do not elicit adverse immune responses or cause off-target effects is paramount. Ensuring biocompatibility and targeting efficiency is also a major challenge. While many NSMs are inherently biocompatible, some may exhibit cytotoxicity at higher concentrations. Optimizing the concentration and formulation of these molecules to maximize therapeutic benefits while minimizing potential harm is essential. Additionally, enhancing the targeting capabilities of CFSNs to ensure that they specifically accumulate at disease sites while avoiding healthy tissues is crucial for reducing side effects and improving treatment outcomes.

Despite these challenges, the future of CFSNs is highly promising, particularly with the advent of interdisciplinary collaboration. By bringing together expertise from material science, chemistry, biology, and clinical medicine, researchers can develop comprehensive strategies to overcome the limitations of CFSNs and unlock their full therapeutic potential. One promising direction is the exploration of novel NSMs, especially those from underutilized sources such as marine organisms. Marine natural products are known for their unique chemical structures and diverse bioactivities, which could provide new opportunities for developing CFSNs with enhanced therapeutic properties. These novel NSMs could offer improved stability, targeting efficiency, and synergistic effects when combined with existing therapeutic agents. Developing smart, stimuli-responsive CFSNs is another key area of future research. These nanomaterials can be designed to release their payload in response to specific physiological cues, such as changes in pH, temperature, or the presence of certain enzymes. For instance, pH-responsive CFSNs can release drugs in the acidic microenvironment of tumors, while temperature-sensitive nanoparticles can be triggered by hyperthermia treatments. This targeted release mechanism ensures that the drug is delivered precisely where it is needed, maximizing therapeutic efficacy while minimizing systemic toxicity. Integrating CFSNs with emerging treatments like immunotherapy and phototherapy is also a promising strategy. Combining CFSNs with immune checkpoint inhibitors could enhance the immune response against cancer cells, while PDT could be used to generate ROS at the tumor site, leading to synergistic therapeutic effects. This multimodal approach leverages the unique properties of CFSNs to improve the overall treatment outcome. Standardizing production processes and establishing robust quality control measures are essential for ensuring the stability and reproducibility of CFSNs. Developing standardized protocols for the synthesis and characterization of CFSNs will facilitate consistent production and enable reliable clinical trials. Implementing rigorous quality control measures, including real-time monitoring and validation, will help maintain the integrity and performance of these nanomaterials. Personalized medicine approaches, tailored to individual patient needs, could further optimize treatment outcomes. By considering factors such as genetic profiles, disease stage, and patient-specific physiological conditions, CFSNs can be customized to provide the most effective therapy for each patient. This personalized approach could significantly enhance the therapeutic efficacy and safety of CFSNs, making them a powerful tool in the fight against complex diseases. While the clinical translation of CFSNs faces several challenges, ongoing research and interdisciplinary collaboration are paving the way for innovative solutions. By addressing issues related to scalability, reproducibility, regulatory approval, biocompatibility, and targeting efficiency, CFSNs

have the potential to revolutionize disease treatment and improve patient outcomes.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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