

Supramolecular self-assembly of natural herb extracts: From molecular interactions to functional biomaterials

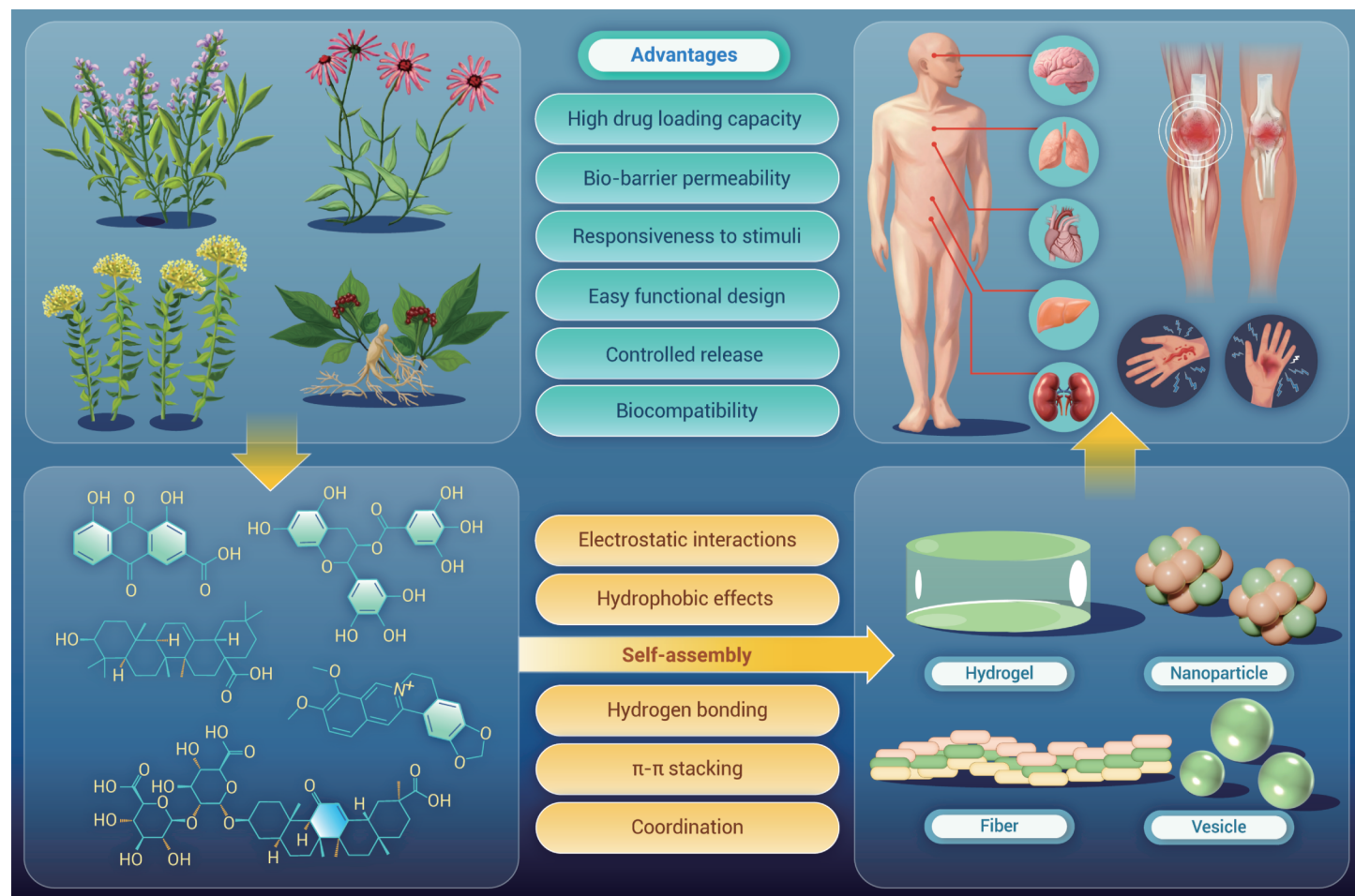
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- The types of natural herb extracts and their self-assembly driving forces were reviewed.
- The relationship between the structure of natural herb extracts and self-assembled products was discussed.
- The development directions in the natural herb extracts self-assembly were analyzed.

Supramolecular self-assembly of natural herb extracts: From molecular interactions to functional biomaterials

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In recent years, supramolecular self-assembly has garnered increasing attention as a versatile strategy for materials design, offering novel opportunities in the development of functional biomaterials. Among these, natural herb extracts (NHEs) have emerged as promising building blocks due to their intrinsic ability to self-assemble through diverse noncovalent interactions. Compared with conventional polymer-based medical materials, NHE-derived assemblies possess distinctive advantages, including high drug-loading capacity, controlled-release behavior, permeability across biological barriers, and excellent biocompatibility. Notably, NHE self-assembled systems have demonstrated broad therapeutic potential, ranging from wound healing to cancer treatment. This review summarizes recent progress in the field of NHE-based supramolecular self-assembly. We first introduce the fundamental concepts of supramolecular self-assembly, highlighting the advantages and driving forces underlying NHE-derived assemblies. The major types of NHE molecules, their dominant interactions, and the resulting supramolecular architectures, particularly nanoparticles and hydrogels, are systematically reviewed, with emphasis on structure-function relationships and biomedical applications. In addition, advances in integrating NHE self-assembly with emerging technologies such as microneedles, photodynamic therapy, and photothermal therapy are discussed. Finally, we outline the current challenges and future research directions, aiming to provide insights into the rational design and translational potential of NHE-based supramolecular assemblies in biomedicine.

INTRODUCTION

Supramolecular chemistry has rapidly evolved into a central discipline in chemistry, providing a powerful conceptual framework for understanding and manipulating intermolecular interactions.¹ Among its core principles, supramolecular self-assembly has emerged as a versatile strategy for constructing highly ordered and hierarchically organized molecular architectures through a range of noncovalent interactions, including electrostatic and dipolar interactions, hydrogen bonding, π - π stacking, van der Waals forces, and hydrophobic effects.^{2,3} This design paradigm offers unique opportunities for creating adaptive and multifunctional materials with tunable properties.

Self-assembly is deeply embedded in biological systems, where it underlies the formation of complex structures such as the deoxyribonucleic acid double helix, cytoskeleton filaments, viral capsids, and phospholipid bilayer. Many natural materials, including pearls, seashells, and silk, also owe their hierarchical organization to self-assembly.⁴⁻⁶ These natural examples highlight the universality and efficiency of self-assembly as a molecular programming principle and motivate the development of bioinspired materials that mimic nature's precision and adaptability.

In recent years, increasing attention has been directed toward the self-assembly of bioactive small molecules extracted from natural herbs (NHEs), including phenols, alkaloids, saponins, terpenoids, quinones, etc. NHEs are rich in functional groups, such as carboxyl, amino, hydroxyl, and aromatic moieties, that enable extensive noncovalent interactions and thus facilitate spontaneous organization into supramolecular architectures. This capability provides a promising platform for the advancement of traditional medicine and modern therapeutics, particularly through the development of carrier-free nanostructures and drug delivery systems. Over the past decade, significant progress has been made in utilizing self-assembly to construct NHE-derived

nanomaterials, with applications in cancer therapy, tissue regeneration, and precision medicine.^{7,8} Compared with conventional drug delivery and biomaterial platforms, NHE-based supramolecular self-assemblies offer unique advantages, including high drug loading capacity, controlled release behavior,^{9,10} bio-barrier permeability,¹¹ easy functional design,¹² responsiveness to physiological stimuli,¹³ and excellent biocompatibility and biodegradability (Figure 1).¹⁴

The supramolecular self-assembly of NHEs is governed by multiple noncovalent interactions, with hydrogen bonding, π - π stacking, hydrophobic effects, electrostatic interactions, and coordination serving as the primary driving forces. And in practice, the self-assembly of NHEs rarely depends on a single driving force, but rather synergistic interactions among multiple forces. For example, combinations of electrostatic and hydrophobic interactions or hydrogen bonding and π - π interactions have been shown to direct NHEs into diverse nanostructures, including nanoparticles, nanofibers,¹⁵ and reversible gels¹⁶ with therapeutic functions. Accumulating evidence suggests that supramolecular assemblies are present not only in purified NHEs but also in traditional Chinese medicine decoctions, where they contribute to pharmacological activity. These findings have inspired growing interest in exploring molecular self-assembly as a bridge between traditional medicine and modern supramolecular material science.¹⁷⁻²⁰

Despite these advances, systematic analyses of NHE-based supramolecular assemblies remain limited. This review seeks to provide a comprehensive overview of recent progress in this emerging field, focusing on the typical NHEs, the mechanisms underlying self-assembly, the resulting nanostructures, and their biomedical applications. Furthermore, we highlight challenges and future opportunities to guide the rational design of supramolecular self-assembly derived from NHEs.

SELF-ASSEMBLY OF NATURAL HERB EXTRACTS AND TECHNIQUES

Self-assembly of natural herb extracts

Supramolecular self-assembly of polyphenols. Polyphenols are among the most abundant plant-derived secondary metabolites and possess potent antioxidant properties, conferring immunomodulatory, anti-inflammatory, and antibacterial effects.²¹ Structurally, polyphenols are characterized by multiple aromatic rings, hydroxyl, and carbonyl groups, which provide rich sites for intermolecular interactions. These structural motifs facilitate molecular self-assembly via π - π stacking and hydrogen bonding, while the overall supramolecular organization is also strongly influenced by the amphiphilic balance between hydrophilic and hydrophobic regions.

Curcumin, a well-studied plant polyphenol, was one of the earliest molecules reported to self-assemble into microencapsulated structures upon the addition of fructose, a process primarily driven by strong hydrogen bonding between the two molecules.²² Building on this understanding, Huang et al.²³ demonstrated that gallic acid alone could form hydrogels through cooperative π - π stacking and hydrogen bonding, whereas structurally related analogues, including protocatechuic acid, protocatechualdehyde, pyrogallol, coumalic acid, p-coumaric acid, ellagic acid, cinnamic acid, and sinapic acid, failed to gel under identical conditions. These findings underscored the critical roles of hydroxyl and carboxyl functionalities in mediating supramolecular network formation.

Further investigations have expanded the repertoire of polyphenol-based assemblies. Sun et al.²⁴ developed quercetin-based supramolecular nanorib-

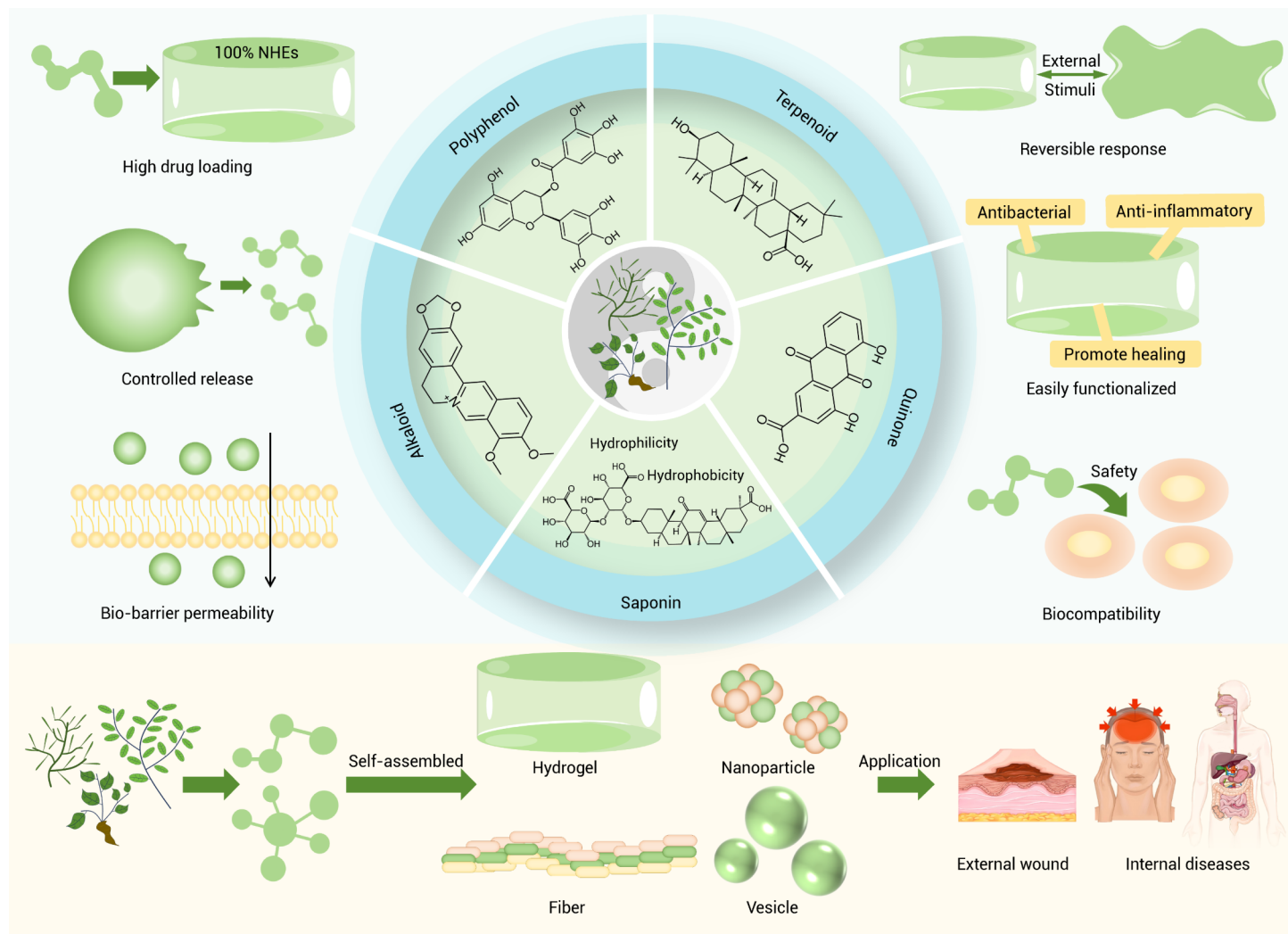


Figure 1. A schematic illustration of the self-assembly of NHEs, depicting the molecular structure of five representative extracts, the advantages of their self-assembled products, as well as their preparation strategies and biomedical applications Illustrations of wound and diseases are provided by Servier Medical Art (<https://smart.servier.com/>) with modifications, licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

bonds, dominated by π - π stacking and hydrophobic interactions, with auxiliary hydrogen bonding, demonstrating therapeutic potential for intestinal inflammation. Similarly, epigallocatechin gallate (EGCG) and curcumin were co-assembled into nanoparticles via hydrogen bonding and π - π stacking, effectively mitigating radiation-induced skin injury.¹⁰ In another example, glabridin and puerarin formed supramolecular hydrogels through cooperative hydrogen bonding and π - π stacking, exhibiting promise in inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding and supporting lung tissue repair.²⁵ Additionally, ellagitannin 1,2,3,4,6-penta-O-galloyl- β -D-glucose was shown to self-assemble into hydrogels with axially stacked architectures, featuring hydrophobic cores and hydrophilic surfaces stabilized by extensive hydrogen bonding and π - π stacking.²⁶

Collectively, these studies highlight π - π stacking as a central driving force in polyphenol-based supramolecular assembly, with hydrogen bonding serving as a key stabilizing interaction. Hydrophobic interactions, although often underappreciated, are equally significant in dictating molecular orientation, particularly in assemblies of relatively hydrophobic compounds such as quercetin. Together, these findings illustrate the interplay of multiple noncovalent interactions in guiding the design of polyphenol-derived supramolecular materials and underscore their broad biomedical potential.

Supramolecular self-assembly of alkaloids. Alkaloids are a class of naturally occurring nitrogen-containing basic organic compounds, typically featuring complex heterocyclic ring structures. Their structural characteristics render them prone to supramolecular self-assembly through various noncovalent interactions, including electrostatic interactions, π - π stacking,

and hydrogen bonding.²⁷ In particular, alkaloids often exhibit strong affinity for phenolic acids or other carboxyl-containing molecules, such as tannic acid, gallic acid, and glycyrrhizic acid, primarily via electrostatic interactions.

Berberine, a major alkaloid extracted from *Coptidis rhizoma*, has been extensively applied in clinical settings for its antibacterial, antiviral, and anti-inflammatory effects. Owing to its unique quaternary ammonium isoquinoline structure and long medicinal history, berberine has also become a model molecule for investigating supramolecular self-assembly. For instance, Fu et al.²⁸ and Huang et al.²⁹ reported co-assembly of berberine with chlorogenic acid and cinnamic acid, respectively, targeting methicillin-resistant *Staphylococcus aureus* (MRSA) infections. In both cases, supramolecular assembly was primarily driven by hydrogen bonding and π - π stacking, with electrostatic interactions facilitating initial molecular recognition. Similarly, berberine self-assembled with tannic acid³⁰ and hesperetin³¹ through comparable noncovalent forces, resulting in supramolecular systems that exhibited therapeutic efficacy against ulcerative colitis. Notably, berberine is also utilized in traditional Chinese medicine to mitigate aristolochic acid toxicity. The detoxification effect arises from the formation of linear heterogeneous supramolecular assemblies between berberine and aristolochic acid, stabilized mainly by electrostatic attraction and π - π stacking.³² Collectively, these studies highlight berberine's versatility as both a therapeutic agent and a supramolecular building block.

Camptothecin, another well-known alkaloid with potent antitumor activity, illustrates the value of self-assembly in overcoming inherent pharmacological limitations. Its clinical application is hindered by a reversible ring-opening

reaction, leading to the generation of toxic carboxylate species. Fortunately, camptothecin's intrinsic planar aromatic structure enables self-assembly into nanostructures, which enhances its stability and functionality. As early as a decade ago, camptothecin was proved to self-assemble into pH-responsive chiral nanostructures through π - π stacking and hydrogen bonding.³³ Building on this, Qin et al.³⁴ designed supramolecular assemblies stabilized primarily by π - π interactions of the quinoline ring, leading to helical nanoribbon structures via J-type self-aggregation, with hydrogen bonding, hydrophobic interactions, and electrostatic repulsion further influencing molecular arrangement. Moreover, the co-assembly of irinotecan, a camptothecin derivative, with curcumin has demonstrated improved tumor targeting and reduced systemic toxicity compared to irinotecan alone. This system leverages the rigid planar structures of both molecules to facilitate π - π stacking, hydrophobic interactions, hydrogen bonding, while electrostatic adsorption further promotes intermolecular attraction and self-assembly.³⁵

Together, these examples underscore the versatility of alkaloids as both therapeutic agents and supramolecular scaffolds. Their intrinsic structural features, such as aromatic rigidity, charge distribution, and functional group diversity, make them ideal candidates for the design of self-assembled drug delivery systems, offering enhanced bioactivity, reduced side effects, and improved stability.

Supramolecular self-assembly of saponins. Saponins are a class of naturally occurring glycoside compounds consisting of a triterpene or spirostanoid glycoside ligand and one or more sugar chains.³⁶ Owing to the inherent lipophilicity of the glycoside ligand and the high hydrophilicity of the sugar chains, saponins exhibit amphiphilic characteristics,³⁷ which underlie their rich potential for supramolecular organization. This amphiphilicity facilitates a range of noncovalent interactions during self-assembly, including hydrophobic interactions, hydrogen bonding, π - π stacking, and electrostatic forces.

Extensive studies have demonstrated that saponins readily undergo self-assembly, often forming micelles or hydrogels with structures highly sensitive to environmental factors such as pH³⁸ and interfacial conditions.³⁹ Subtle variations in the saccharide composition or configuration of the sugar chains profoundly influence hydrophilicity-hydrophobicity balance, thereby modulating self-assembly behavior and the physicochemical properties of the resulting materials.⁴⁰

Among saponins, glycyrrhizic acid, a major bioactive compound extracted from *Glycyrrhiza glabra*, has attracted considerable attention for its diverse pharmacological properties and robust self-assembly capacity. Its amphiphilic molecular structure enables spontaneous aggregation into micelles or supramolecular hydrogels. Leveraging this property, Zhao et al.⁴¹ developed a glycyrrhizic acid-based drug delivery system capable of gastrointestinal pH-responsive release of sixteen bioactive compounds, including flavonoids, alkaloids, anthraquinones, organic acids, coumarins, and saponins. In this system, hydrophobic interaction and hydrogen bonding were the dominant driving forces for gel formation.

Further illustrating its versatility, Cui et al.¹¹ demonstrated that glycyrrhizic acid co-assembles with tanshinone IIA into micelles via hydrophobic interactions and hydrogen bonding. These micelles were subsequently encapsulated into exosomes to enhance blood-brain barrier (BBB) penetration, offering a promising therapeutic platform for glioblastoma treatment. In addition, the multiple carboxyl groups of glycyrrhizic acid confer a strong negative charge, enabling electrostatic interactions with cationic molecules. For instance, glycyrrhizic acid was shown to co-assemble with a cationic short peptide (AC-RRYNYQRR-NH₂) through electrostatic interactions and hydrogen bonding, producing a bio-adhesive suitable for dura mater closure and repair.⁴² Moreover, the gel-forming capacity of glycyrrhizic acid has also been exploited to integrate berberine-rhein nanoparticles via hydrogen bonding and hydrophobic interactions, forming stable hydrogels with potential applications in brain injury repair.⁴³

Beyond glycyrrhizic acid, other saponins also exhibit pronounced self-assembly potential. Li et al.⁴⁴ reported the preparation of a sodium aescinate-based self-assembled powder capable of rapid hemostasis and neural repair following brain injury. In this material, hydrogel formation was primarily driven by intertwining and crosslinking of β -sheet ribbon-like structures stabilized by

intermolecular hydrogen bonding.

Supramolecular self-assembly of quinones. Quinones are a class of aromatic compounds characterized by a six-carbon cyclic diketone structure with conjugated double bonds. Owing to this structural feature, their supramolecular self-assembly is predominantly governed by π - π stacking and hydrogen bonding interactions. Many quinones exhibit diverse biological activities, including antitumor, anti-inflammatory, and bactericidal properties.^{45,46} Despite their pharmacological potential, studies on the self-assembly of quinone-based natural extracts remain limited. Most investigations have focused on rhein, with only a few studies into tanshinone¹¹ and aloe emodin,⁴⁷ which can respectively self-assemble with glycyrrhizic acid to form micelles and function as natural photosensitizers in photodynamic technology. Rhein, an anthraquinone derivative abundantly present in *Rheum palmatum*, *Polygonum multiflorum*, *Aloe barbadensis*, and other traditional medicinal plants, exhibits a wide range of bioactivities, including antimicrobial, anti-inflammatory, neuroprotective, and hepatoprotective effects.^{48,49} In 2019, Zheng et al.⁵⁰ first reported the supramolecular self-assembly of rhein into hydrogel for neuroinflammation therapy. In this system, rhein molecules organized into J-type aggregates and formed dimers via hydrogen bonding and π - π stacking, which subsequently assembled into higher-order nanofibers exhibiting left-handed helicity. These nanofibers crosslinked to create a robust three-dimensional hydrogel network. Building on this foundation, Liao et al.⁵¹ designed a hybrid system in which rhein was conjugated with a peptide sequence (Nap-DFDFG-ss-ERGD) and co-assembled with EGCG. The incorporation of peptide and polyphenol components enhanced intermolecular interactions, promoting more efficient self-assembly. The resulting injectable hydrogel demonstrated therapeutic potential for mitigating myocardial ischemia-reperfusion injury by interrupting reactive oxygen species (ROS)-induced inflammatory cascades.

Supramolecular self-assembly of terpenoids. Terpenoids are a structurally diverse class of natural products composed of multiple isoprene units and are well recognized for their wide range of biological activities.⁵² Owing to their predominantly hydrophobic nature, terpenoids typically contain multiple unsaturated carbon atoms and hydroxyl groups, enabling their spontaneous self-assembly through hydrogen bonding, π - π stacking, hydrophobic forces, and other noncovalent interactions. This intrinsic molecular versatility makes terpenoids an important focus in the study of supramolecular self-assembly.

Research into the self-assembly of terpenoids began relatively early. In 2011, Bag and Dash first investigated the self-assembly of betulinic acid,⁵³ although the underlying molecular driving forces were not elucidated at that time. Building on this work, Dash and colleagues subsequently demonstrated in 2015 the potent anti-leukemic activity of self-assembled betulinic acid nanofibers.⁵⁴ More recently, Li and colleagues⁵⁵ designed betulinic acid nanoparticles for glioblastoma therapy, providing clear evidence that hydrogen bonding is the primary driving force governing its self-assembly.

Oleanolic acid and ursolic acid, two structurally related terpenoids with broad pharmacological activities, have also been extensively studied. For example, Zhou et al.⁵⁶ prepared oleanolic acid nanoparticles for the treatment of subarachnoid hemorrhage, while Luo et al.⁵⁷ developed oleanolic acid nanomicelles that induced cancer cell pyroptosis. Both studies confirmed the synergistic role of hydrogen bonding and hydrophobic interactions in the self-assembly of oleanolic acid. Ursolic acid and its derivatives have attracted similar attention. Its reduction product, uvaol, was shown to assemble into porous wreath-like structures capable of co-loading anticancer drugs, thereby enhancing therapeutic outcomes.⁵⁸ Moreover, Ou et al.⁵⁹ synthesized poly(ursolic acid) via polycondensation, which self-assembled with paclitaxel to form nanoparticles for cancer therapy. Interestingly, due to the consumption of hydroxyl and carboxyl groups during polycondensation, this polymer largely lost its hydrogen-bonding ability, making hydrophobic interactions the dominant force in its self-assembly.

Other terpenoids have also demonstrated unique self-assembly potential. Lutein, for example, was reported to co-assemble with nintedanib, an angiogenesis inhibitor, through a combination of electrostatic interactions, π - π stacking, hydrogen bonding, and hydrophobic interactions. This co-assembly strategy improved lutein stability, effectively inhibited fundus angiogenesis,

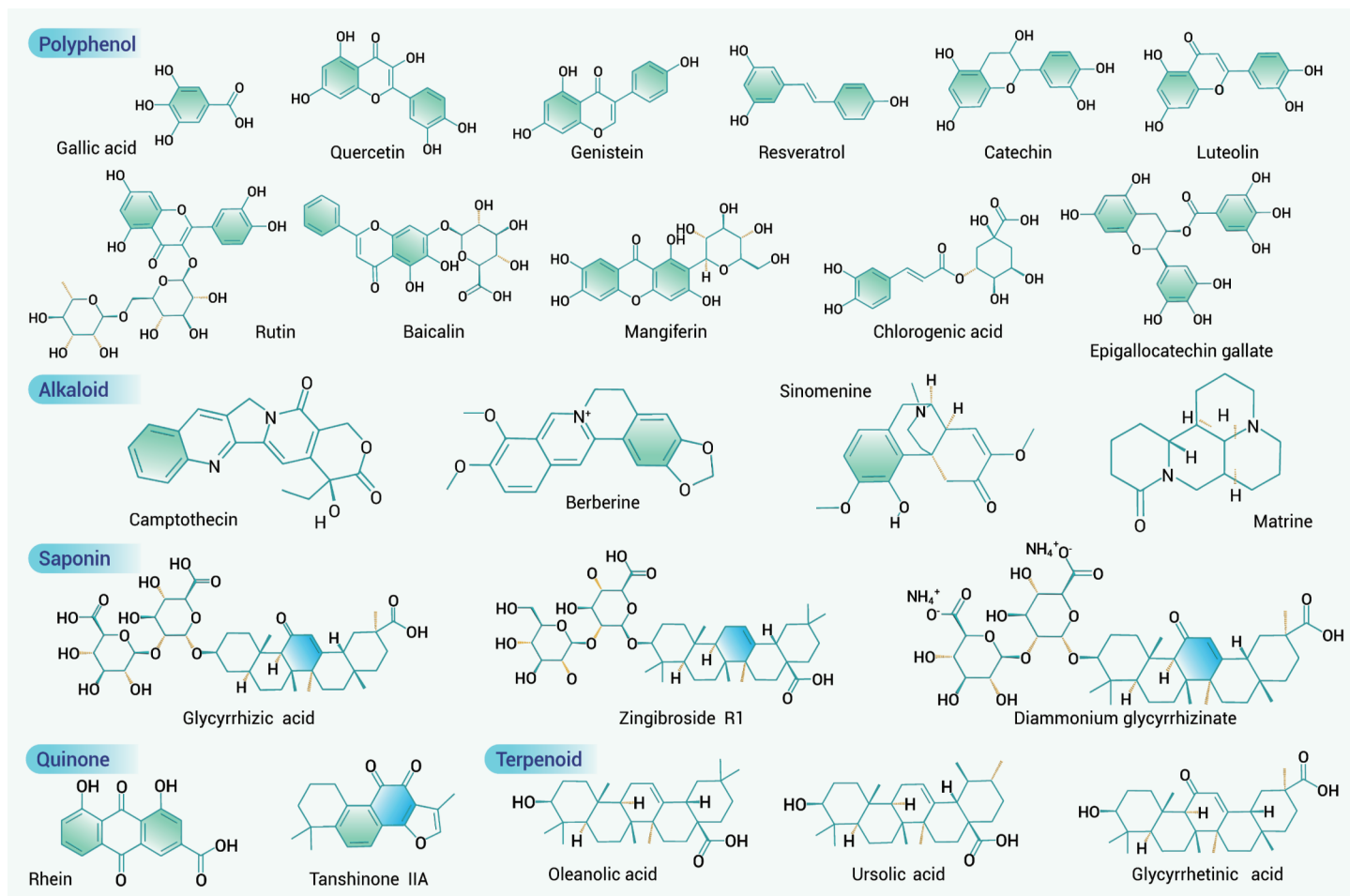


Figure 2. Molecular structure of NHEs, including polyphenols, alkaloids, saponins, quinones, and terpenoids.

and alleviated inflammation for the treatment of age-related macular degeneration.⁶⁰

The above studies illustrate that molecular diversity of NHEs, including polyphenols, alkaloids, saponins, quinones, and terpenoids (Figure 2), leads to distinct dominant intermolecular forces and assembly mechanisms, resulting in a broad spectrum of supramolecular architectures. The varied chemical functionalities of these compounds, such as hydroxyl, carboxyl, amino, and aromatic groups, underpin their ability to engage in hydrogen bonding, π - π stacking, electrostatic interactions, and hydrophobic effects in different combinations, enabling precise control over nanoscale morphology and bioactivity. By systematically analyzing single-component and multi-component assembly patterns of these NHE categories, as summarized in Figure 3 and detailed in Table 1 and 2, this review highlights how subtle structural differences drive unique self-assembly behaviors. This comparative framework lays the foundation for the rational design of bioactive nanomaterials inspired by traditional medicine and provides a basis for future translational applications in drug delivery, regenerative medicine, and targeted therapy.

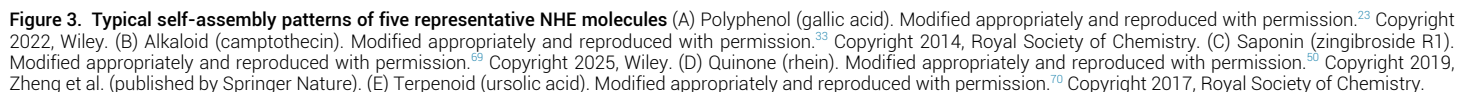
Self-assembly techniques

As discussed, structural diversity across NHE categories generates distinct self-assembly driving forces. Traditional design of NHE self-assembly materials relies on understanding these structures and associated forces, typically dependent on experimental trial-and-error methods supplemented by historical data. This approach emphasizes experimental exploration rather than predictive computational modeling of assembly processes, thereby exhibiting inherent limitations in both design precision and research efficiency.

With the rise of artificial intelligence (AI), it is poised to become an emerging driving force in the design of self-assembling materials, demonstrating significant potential particularly in predicting self-assembly tendencies, forecasting product phase states, simulating molecular interface behavior, and

high-throughput screening and design.^{61,62} Research in the field of supramolecular self-assembly is progressively being driven by AI away from the 'experimental trial-and-error' approach towards the 'computationally driven + experimentally validated + AI-assisted' paradigm, which will significantly shorten the research cycle for self-assembly materials and propel the development of more complex, multifunctional self-assembled structures.⁶¹ Numerous studies have already explored the potential applications of AI in the design and self-assembly prediction of protein and peptide supramolecular materials,^{63,64} and have attempted to introduce the concept of 'AI-guided programmable assembly' into the binary self-assembly of colloidal nanoparticles.⁶⁵

Wang et al.⁶⁶ demonstrated that transformer-based deep learning models effectively predict the aggregation propensity of peptide systems. Their work identified aggregation patterns for designing self-assembling peptides and revealed transferable aggregation propensity relationships across pentapeptides, decapeptides, and mixed pentapeptides. Remarkably, these models exhibit robust scalability even in systems with vast combinatorial spaces, such as decapeptides and mixed pentapeptides with over 10 trillion sequences. Based on these studies, recent advances demonstrate the emerging application of AI in predicting and designing the self-assembly of NHEs. For instance, Zhang et al.⁶⁷ developed a machine learning platform using Food and Drug Administration-approved small-molecule drug carriers. By employing AI to screen drug combinations and predict self-assembly mechanisms, indomethacin-paclitaxel nanomedicines were prepared and exhibited pH-responsive drug release within tumor microenvironments. Similarly, Shan et al.⁶⁸ constructed a deep learning framework that screened 1,800 natural small molecules, enabling the identification of promising drug combinations and the subsequent development of oridonin-cepharantine self-assembled nanoparticles. These nanoparticles demonstrated enhanced immunotherapeutic efficacy against cancer. The above studies highlight that



For instance, Huang et al.⁸⁷ demonstrated the coordination-driven self-assembly of gallic acid with Zn²⁺, producing flower-like nanoparticles with selective targeting of Gram-positive bacteria. Similarly, Zhang et al.⁸⁸ developed ultra-small Fe³⁺-gallic acid MPNs for the treatment of calcium oxalate nephropathies, highlighting the clinical potential of polyphenol-based coordination chemistry. EGCG, another representative polyphenol, has been shown to coordinate with Cu²⁺ to form porous network coatings⁸⁹ and with lanthanide ions such as samarium (Sm³⁺) to generate nanocomplexes.⁹⁰ EGCG-Cu²⁺ coatings, further functionalized with bivalirudin and rapamycin, demonstrated both pro-endothelialization and antithrombotic activity in vascular scaffolds, whereas EGCG-Sm³⁺ complexes effectively inhibited

Table 1. Self-assembled structures derived from single-component natural herb extracts.

Natural herb extract types	Components	Self-assembly products	Driving force	References
Polyphenol	Gallic acid	Hydrogels	π - π stacking, hydrogen bonding	23
	Quercetin	Nanoribbons	π - π stacking, hydrophobic interactions, hydrogen bonding	24
	Genistein	Nanoparticles	π - π stacking, hydrogen bonding	71
Alkaloid	Camptothecin	Helical nanoribbons	π - π stacking, hydrogen bonding	33
Saponin	Zingibroside R1	Hydrogels	Hydrogen bonding, hydrophobic interaction	69
	Glycyrrhizic acid	Nanoclusters, hydrogels	Hydrogen bonding, hydrophobic interaction	72
Quinone	Rhein	Hydrogels	π - π stacking, hydrogen bonding	50
Terpenoid	Oleanolic acid	Nanoparticles, nanogels	π - π stacking, hydrogen bonding, hydrophobic interaction	73
	Ursolic acid	Vesicles, tubes, hydrogels	Hydrogen bonding, hydrophobic interaction	70

Table 2. Co-assembled structures derived from multi-component natural herb extracts.

Natural herb extract types	Components	Self-assembly products	Driving force	References
Polyphenol	Mangiferin; Rutin	Self-gelling powders	π - π stacking, hydrogen bonding	74
	Baicalin; Resveratrol	Nanoparticles	π - π stacking, hydrogen bonding	75
Polyphenol Alkaloid	Catechin; Berberine	Nanoparticles	π - π stacking	76
	Chlorogenic acid; Berberine	Amphiphilic spherical supramolecules	Electrostatic interactions, hydrophobic interactions, π - π stacking	77
Polyphenol Saponin	Gallic acid; Diammonium glycyrrhizinate	Hydrogels	π - π stacking, hydrogen bonding	78
Polyphenol Terpenoid	Epigallocatechin gallate; Ursolic acid	Nanoparticles	Hydrophobic interaction, hydrogen bonding,	79
	Luteolin; Glycyrrhetic acid	Nanoparticles	π - π stacking, hydrogen bonding	80
Alkaloid Saponin	Sinomenine; Glycyrrhizic acid	Hydrogels	Hydrogen bonding, electrostatic interactions, hydrophobic interactions	81
Alkaloid Quinone	Matrine; Rhein	Nanoparticles	π - π stacking, hydrogen bonding	82
	Berberine; Rhein	Nanoparticles	Electrostatic interactions, hydrophobic interactions, π - π stacking	83
Saponin Quinone	Glycyrrhizic acid; Tanshinone IIA	Micelles	Hydrogen bonding, hydrophobic interactions	11

melanocytoma metastasis.

Beyond EGCG, other polyphenols have also been extensively utilized to construct MPNs. Zhu et al.⁹¹ reported copper-piceatannol nanoparticles formed via pH-regulated coordination, followed by hyaluronic acid modification, which enhanced cancer therapy by inducing cellular pyroptosis. Similarly, Zhou et al.⁹² engineered a tannic acid-bleomycin-Fe³⁺ coordination network as a nanocarrier shell, enabling efficient drug delivery and tumor suppression. Furthermore, quercetin was used to assemble with Fe²⁺-based MPNs, with doxorubicin incorporated into the three-dimensional structure through π - π stacking. This approach markedly reduced doxorubicin-induced cardiotoxicity while enhancing antitumor efficacy, offering a promising strategy for treating triple-negative breast cancer.⁸⁵

Collectively, these studies underscore the versatility of polyphenol-metal coordination chemistry in fabricating biofunctional supramolecular systems. By leveraging the intrinsic chelating capability of polyphenols and the tunable physicochemical properties of transition or lanthanide ions, MPNs provide a powerful platform for antibacterial therapy, drug delivery, tissue engineering, and cancer treatment.

Metal-quinone networks and metal-saponin networks. Metal-quinone coordination networks are primarily constructed through the interaction between the carbonyl moieties of quinones and metal ions, with hydroxyl and carboxyl substituents further enhancing coordination stability and diversity. Rhein, one of the most extensively studied quinone derivatives, exemplifies this concept. Its molecular structure contains two para-carbonyl groups, two hydroxyl groups, and one carboxyl group, enabling a wide range of coordination configurations. Liang et al.⁹³ reported the incorporation of Ag⁺ ions into

the self-assembled skeleton of rhein, forming a supramolecular hydrogel designed to accelerate the healing of infected wounds. The coordination between rhein and Ag⁺ ions was attributed to synergistic interactions among its carbonyl, hydroxyl, and carboxyl groups, as confirmed through multi-technique characterization and molecular dynamics simulations. Beyond silver-based systems, rhein has also been employed to coordinate with Al³⁺ ions, yielding hydrogels capable of encapsulating the receptor-binding domain of the SARS-CoV-2 spike protein.⁹⁴ These hydrogels not only retained the adjuvant properties of aluminum salts but also exhibited the intrinsic self-repairing and antigen-display functionalities of supramolecular assemblies. In this system, multiple functional groups on rhein were demonstrated to actively participate in the coordination process.

Similar to the quinone derivatives, saponins are rich in hydroxyl and carboxyl functionalities, conferring a strong potential for metal ion coordination. Several studies have demonstrated that glycyrrhizic acid, a representative saponin, forms coordination-driven hydrogels in the presence of Zn²⁺, Ga³⁺,⁹⁷ or Cu²⁺ ions.⁹⁸ Remarkably, metal coordination significantly reduces the critical gelation concentration, enhancing hydrogel formation efficiency. Detailed mechanistic investigations revealed that the carboxyl group of glucuronic acid residues plays a dominant role in coordination, whereas the abundant hydroxyl groups contribute less critically to network stabilization.

Natural macromolecule-natural herb extract self-assembly

Beyond the self-assembly of small molecules derived from NHEs, numerous natural macromolecules also exhibit intrinsic pharmacological activities and are enriched with diverse functional groups, endowing them with strong

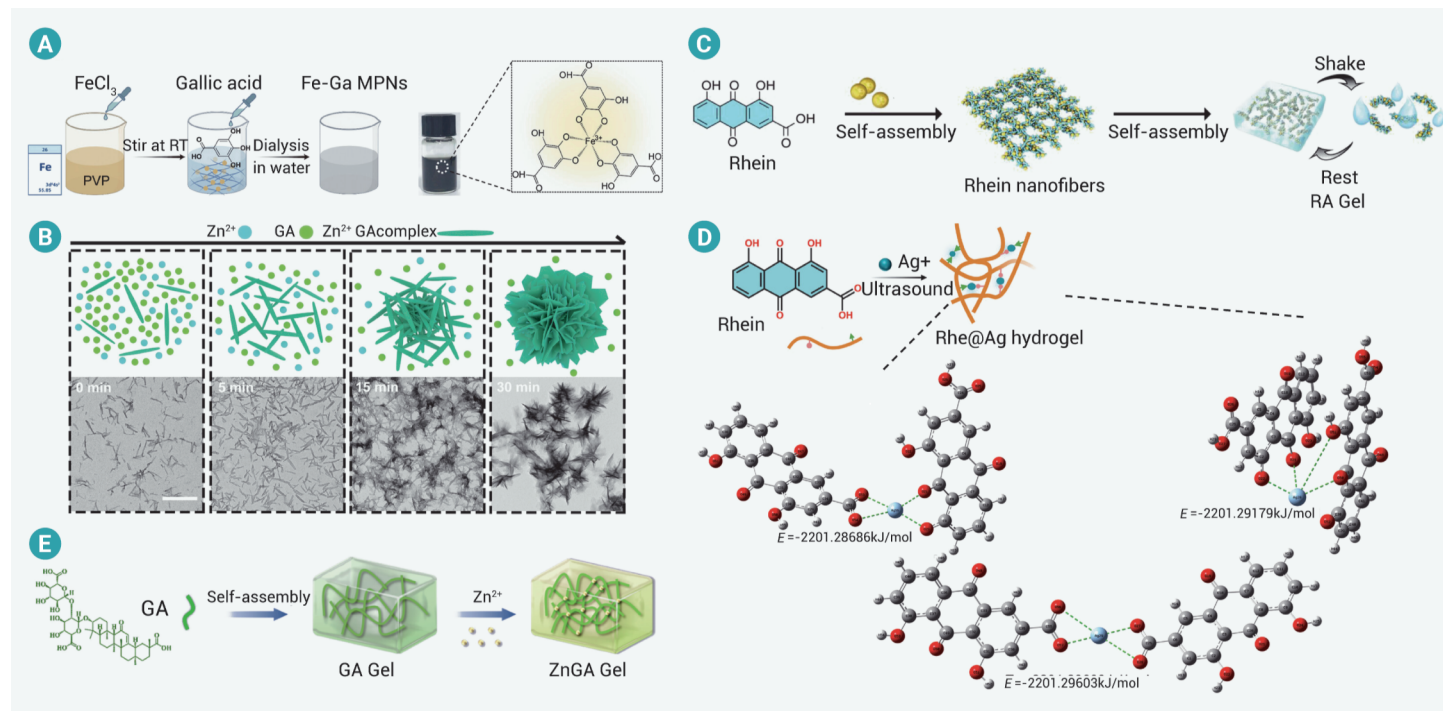


Figure 4. Schematic illustration of coordination-driven self-assembly patterns between various NHEs and metal ions (A) Gallic acid-Fe³⁺ (metal-polyphenol network). Modified appropriately and reproduced with permission.⁸⁸ Copyright 2025, Wiley. (B) Gallic acid-Zn²⁺ (metal-polyphenol network). Modified appropriately and reproduced with permission.⁸⁷ Copyright 2024, Wiley. (C) Rhein-Al³⁺ (metal-quinone network). Modified appropriately and reproduced with permission.⁹⁴ Copyright 2024, American Chemical Society. (D) Rhein-Ag⁺ (metal-quinone network). Modified appropriately and reproduced with permission.⁹³ Copyright 2024, Wiley. (E) Glycyrrhizic acid-Zn²⁺ (metal-saponin network). Modified appropriately and reproduced with permission.⁹⁵ Copyright 2024, American Chemical Society.

self-assembly potential. Integrating NHEs with natural macromolecules thus provides a powerful strategy for designing dual-network materials with expanded functionalities, improved structural stability, and tunable therapeutic effects.

Chen et al.⁹⁹ demonstrated this approach by combining puerarin with the antimicrobial polysaccharide chitosan. Inspired by traditional Chinese medicine grinding techniques, mechanical forces were introduced to enhance molecular collision efficiency, thereby facilitating hydrogel formation. The assembly was primarily driven by extensive hydrogen bonding between puerarin and chitosan molecules.

The incorporation of macromolecules not only introduces bioactivity but also markedly reinforces the mechanical strength of small-molecule self-assembled hydrogels. For instance, methacrylate-modified silk fibroin (SF), which enables photo-crosslinking, was incorporated into a glycyrrhizic acid-Zn²⁺ system to generate a dual-network hydrogel. Upon photo-crosslinking, the hydrogel displayed significantly enhanced mechanical strength compared with single-network hydrogels composed of either glycyrrhizic acid or SF alone.⁹⁶ Similarly, Li et al.¹⁰⁰ oxidized glycyrrhizic acid to produce an aldehyde-functionalized derivative, which subsequently combined with carboxymethyl chitosan. In addition to hydrogen bond-driven self-assembly, Schiff base linkages formed between aldehyde and amino groups, resulting in an injectable dual-network hydrogel with improved mechanical and structural properties. Yang et al.¹⁰¹ further developed quercetin-SF hydrogel, in which hydrogen bonding and Schiff base interactions served as primary crosslinking mechanisms. Incorporation of gallium ions (Ga³⁺) introduced electrostatic attraction and metal coordination effects, fine-tuning the hydrogel microstructure and reinforcing network stability.

Dual-network systems combining NHEs and natural macromolecules also enable programmed and sequential release of bioactive agents, achieving sustained therapeutic effects tailored to different phases of disease or tissue repair. Lin et al.¹⁰² reported a dual-network hydrogel consisting of chlorogenic acid-Zn²⁺ complexes and heparin-grafted gelatin with basic fibroblast growth factor. This hydrogel rapidly released chlorogenic acid and Zn²⁺ during the inflammatory phase of infected wounds, providing antibacterial, anti-inflammatory, and pro-angiogenic effects, followed by gradual release of heparin and basic fibroblast growth factor during the proliferation and

remodeling phases to minimize scar formation.

Collectively, these studies demonstrate that composite assemblies constructed from natural macromolecules and NHEs offer a versatile materials platform. Through the synergistic integration of molecular diversity, noncovalent interactions, and dynamic crosslinking strategies, such systems achieve superior mechanical properties, programmable drug delivery profiles, and multifunctional therapeutic effects, underscoring their potential in precision medicine and bioengineering applications.

MECHANISMS OF DIFFERENT NATURAL HERB EXTRACT SELF-ASSEMBLED MORPHOLOGIES AND THEIR APPLICATIONS

Self-assembly mechanisms

As previously stated, non-covalent intermolecular forces are the fundamental driving forces behind molecular self-assembly. The relative contribution of these forces varies with molecular structure, ultimately dictating the morphology, stability, and functionality of the resulting assemblies. Hydrogen bonding is a fundamental interaction that plays a central role in molecular recognition and self-assembly. Dense hydrogen bonds can approach the strength of covalent bonds, conferring significant structural stability. π - π stacking, another key interaction, arises between aromatic moieties or conjugated systems, profoundly influencing molecular packing and supramolecular organization. Hydrophobic effects are equally critical, as the spatial arrangement of hydrophobic groups drives molecules to minimize water contact, leading to ordered assemblies such as bilayers, vesicles, micelles, and lamellae. These interactions enable precise control of supramolecular architectures and offer opportunities for encapsulating hydrophobic drugs, as exemplified by glycyrrhizic acid micelles for anticancer drug delivery.¹⁰³ Electrostatic interactions, on the other hand, typically induce rapid aggregation of oppositely charged molecules, favoring the formation of nanoparticles or small aggregates rather than extended hydrogel networks. Moreover, coordination with metal ions constitutes a distinct form of non-covalent interaction, whereby metal ions function as crosslinking agents to facilitate the expansion of self-assembled structures.

It should be emphasized that even among molecules with comparable structures and biological activities, subtle differences can lead to the formation of distinct self-assembled architectures, thereby influencing both their

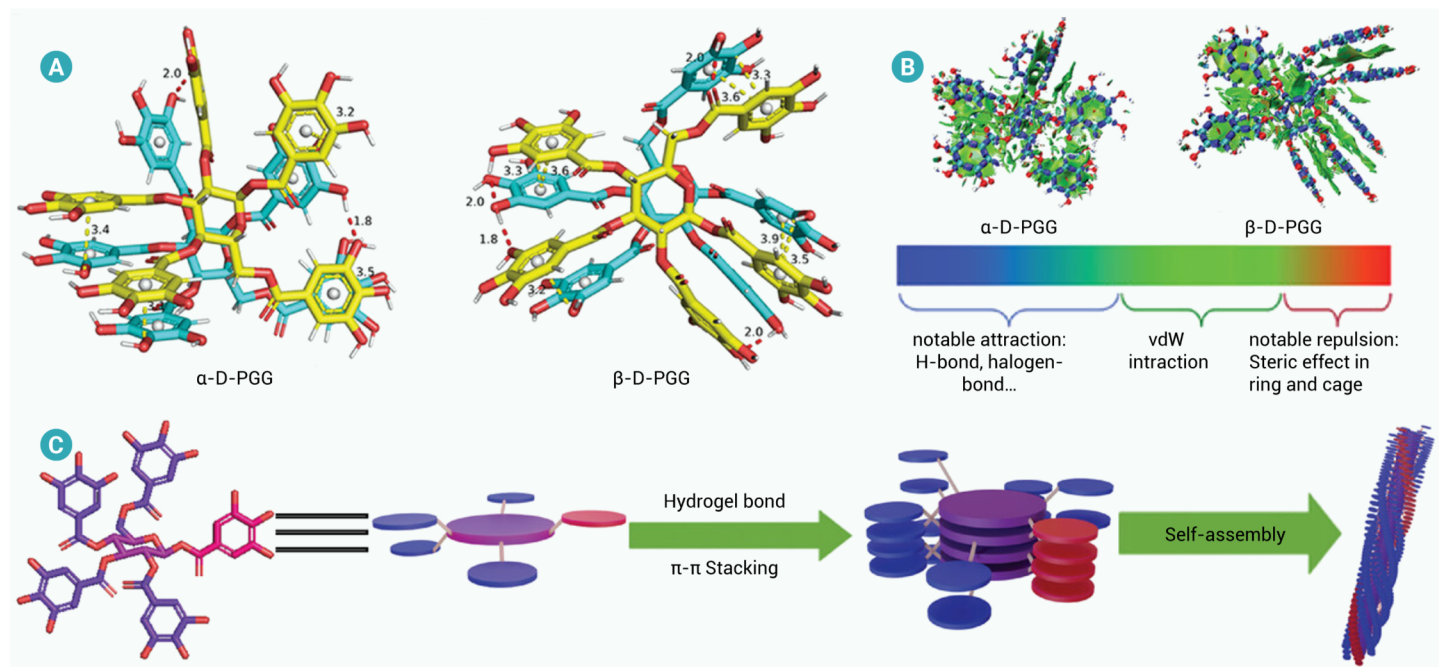


Figure 5. Self-assembly mechanisms of α -D-PGG and β -D-PGG (A) Schematic illustration of intermolecular interactions in α -D-PGG/ α -D-PGG and β -D-PGG/ β -D-PGG pairs. (B) Interaction region indicator analysis of α -D-PGG/ α -D-PGG and β -D-PGG/ β -D-PGG. (C) Proposed self-assembly mechanism of β -D-PGG leading to hydrogel formation. Modified appropriately and reproduced with permission.²⁶ Copyright 2024, Wiley.

bioactivities and potential applications. Therefore, whether in the self-assembly of hydrogels or nanoparticles, the molecular spatial structure is the primary focus that requires attention. The steric hindrance effects arising from molecular structure constitute the foremost factor impeding molecular self-assembly. As shown in Figure 5, the natural ellagitannin epimers 1,2,3,4,6-penta-O-galloyl- α -D-glucose (α -D-PGG) and 1,2,3,4,6-penta-O-galloyl- β -D-glucose (β -D-PGG) exhibit striking different self-assembly behaviors. β -D-PGG readily forms nanofibers through hydrogen bonding and π - π stacking, ultimately leading to hydrogel formation. In contrast, α -D-PGG remains in solution due to its *cis*-configuration at the C1 and C2 positions, which generates steric hindrance that disrupts intermolecular interactions. Moreover, the mutual repulsion of gallic acid acyl groups in α -D-PGG increases its water solubility, further inhibiting its capability for supramolecular self-assembly.²⁶ These structural insights highlight the critical influence of stereochemistry and functional group orientation on the self-assembly potential of herbal molecules.

Similarly, berberine was reported to co-assemble with two structurally similar flavonoid glycosides, forming nanoparticles in one case and nanofibers in the other.¹⁵ This is primarily due to steric hindrance effects altering molecular arrangements, thereby inducing variations in hydrophilicity and hydrophobicity, which in turn result in divergent self-assembly behaviors. Interestingly, the resulting assemblies displayed markedly different antimicrobial activities, with the nanoparticle formulation exhibiting significantly stronger inhibitory effects than the nanofiber system. Such observations underscore the high sensitivity of self-assembly processes to molecular structure and interaction dynamics. The self-assembly patterns of nanoparticles and hydrogels will be detailed in the subsequent sections.

Nanoparticles. In studies of supramolecular self-assembly from NHEs, the assembly of nanoparticles in natural herbal molecular systems is generally simpler and more widely observed. In principle, any herbal component capable of engaging in intermolecular interactions possesses the potential to self-assemble into nanoparticles. As shown in Figure 6A, a widely employed strategy for preparing nanoparticles from NHEs involves co-mixing herbal molecules under suitable concentration and pH conditions, followed by precipitation in different solution systems and subsequent purification steps such as centrifugation,¹⁰⁴ dialysis,²⁸ or lyophilization.¹⁰⁵ Notably, numerous studies have demonstrated that nanoparticles generated through the self-assembly of small drug molecules play an important role in traditional herb decoctions.¹⁰⁶ For example, the presence of co-assembled nanoparticles has

been confirmed in formulations such as the *Astragalus membranaceus*-*Angelica sinensis* pairing,¹⁷ the combination of *Rhei Radix et Rhizoma* with *Coptidis Rhizoma*,¹⁰⁷ and *Coptidis Rhizoma* with *Glycyrrhiza uralensis*.¹⁰⁸ These findings suggest that extraction from herb decoction represents an effective approach for obtaining self-assembled NHE nanoparticles (Figure 6B).

In addition to simple nanoparticles, many amphiphilic herbal-derived molecules can spontaneously organize into higher-order supramolecular assemblies such as vesicles¹⁰⁹ and micelles,¹¹⁰ where hydrophobic moieties oriented inward while hydrophilic groups face outward, primarily driven by hydrophobic interactions. Representative examples include nanocapsules formed from a hydrophobic camptothecin-hydrophilic flouxuridine conjugate,¹¹¹ as well as micelles derived from bioactive ionic liquids synthesized from glycyrrhizic acid and oxymatrine, which have shown promise as efficient carriers for transdermal drug delivery.¹¹²

Hydrogels. Compared with nanoparticle formation, hydrogel formation from NHEs has been relatively less common, largely because it requires a delicate balance among multiple noncovalent interactions. Among NHEs, saponins are the most frequently reported gelators, while certain polyphenols, quinones, and a limited number of terpenoids also demonstrate hydrogel-forming ability. By contrast, alkaloid-derived hydrogels are rarely reported.

Current research indicates two main modes of NHE-derived hydrogel formation (Figure 7). In the first mode, π - π stacking serves as the dominant driving force, enabling continuous aggregation of NHEs into nanofibers, which subsequently entangle and interconnect to yield a hydrogel network (Figure 7A). This means that this type of self-assembly pattern necessitates the molecular structure to be characterized by a planar structure containing aromatic rings, thereby producing a regular stacked microstructure. Representative examples include rhein,⁵⁰ gallic acid,²³ and chlorogenic acid.¹¹³

The second mode involves modulation of the hydrophilic-hydrophobic balance of the molecules, allowing them to self-assemble into nanoparticles, vesicles, tubules, or lamellar structures with hydrophobic groups inside and hydrophilic groups exposed to the solvent (Figure 7B). These supramolecular assemblies then undergo further stacking and crosslinking via noncovalent interactions to form hydrogels. The hydrophobic or amphiphilic components, glycyrrhizic acid,⁷² oleanolic acid,⁷³ and ursolic acid⁷⁰ exemplify this mechanism.

Regardless of the specific assembly pathway, hydrogel formation fundamentally depends on the establishment of a regular and ordered supramolecular network. Disruption of hydrogen-bonding interactions or

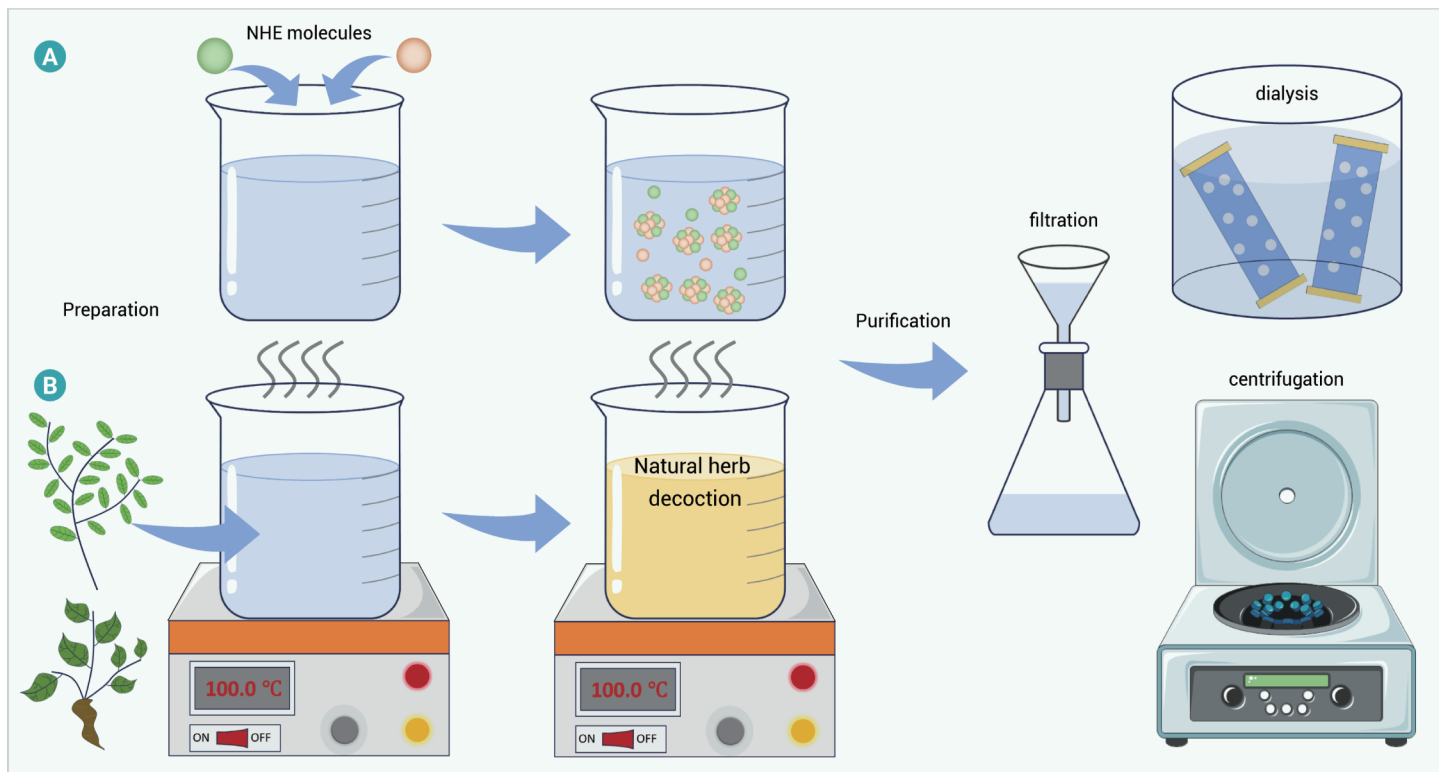


Figure 6. Schematic illustration of nanoparticle preparation method (A) Self-assembled nanoparticles prepared from NHE molecules as raw materials, (B) nanoparticles obtained from herbal decoctions through isolation and purification. The illustration of centrifuge is provided by Servier Medical Art (<https://smart.servier.com/>), licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

perturbations in hydrophilic-hydrophobic balance by other molecules can destabilize this network, preventing gelation and instead giving rise to alternative nanostructures. For instance, chlorogenic acid¹¹³ and rhein⁵⁰ can individually self-assemble into nanofibers and subsequently form hydrogel. However, when co-assembled with berberine, both compounds yielded spherical nanoparticles rather than fibrous gels.^{28,114} These findings highlight the strong influence of molecular co-assembly on the outcome of supramolecular organization.

In addition, environmental parameters such as concentration and pH play decisive roles in the formation and stability of NHE-derived supramolecular hydrogels. The density of intermolecular interactions is closely governed by molecular concentration. At low concentrations, NHE molecules typically assemble into small, dispersed aggregates. Once a critical concentration threshold is exceeded, increased molecular contact promotes the fusion or stacking of these aggregates, leading to the emergence of larger three-dimensional networks characteristic of hydrogels. A representative example is the glycyrrhizic acid-curcumin self-assembly system, in which a concentration of 0.5% serves as the threshold distinguishing micelle formation from hydrogel formation.¹¹⁵ pH exerts a similarly pivotal influence by modulating the ionization state of dissociable groups, including carboxyl and amino moieties, within NHE molecules. Changes in protonation and charge distribution directly affect the strength and nature of intermolecular forces, thereby governing the pH-responsiveness frequently observed in NHE-derived supramolecular hydrogels. Such systems often exhibit reversible structural transitions in response to environment pH fluctuations.¹¹⁶ Examples of pH-responsive NHE assembled hydrogels are discussed in the following section.

Application scenarios of natural herb extract-based self-assembled nanoparticles and hydrogels

Nanoparticles. The primary advantages of NHE nanoparticles include enhancing the bioavailability of poorly soluble drugs,¹¹⁷ enabling synergistic therapeutic effects of multiple agents,³¹ providing sustained and controlled drug release,¹¹⁸ and mitigating the adverse effects associated with single-drug administration.³² Nevertheless, NHE-based nanoparticles generally lack distinct macroscopic morphology and intrinsic adhesion to biological tissues,

which limits their applicability in traumatic wound healing. Instead, they are more suitable for systemic or internal diseases, such as inflammatory disorders, organ injuries,¹¹⁹ and cancers (Figure 8).⁸⁰

A representative example is the co-assembly of berberine and chlorogenic acid into nanoparticles, which not only enhanced their individual anti-inflammatory activities but also synergistically inhibited lipopolysaccharide-induced production of ROS and proinflammatory cytokines (IL-1 β and IL-18), thereby alleviating macrophage pyroptosis.⁷⁷

In the context of organ injury, Ping et al.¹²⁰ extracted nanoparticles from the traditional Chinese herb formula 'Bai-Hu-Tang', which effectively alleviated lipopolysaccharide-induced febrile phenomenon and reduced lung injury. Similarly, Xia et al.¹²¹ enriched nanoparticles rich in flavonoids and terpenoids from *Scutellaria barbata* and *Scleromitrion diffusum*. These nanoparticles protected renal tubular epithelial cells against oxidative stress and ferroptosis by activating the Nrf2 signaling pathway, ultimately mitigating acute kidney injury. Moreover, plant exosomes represent a special type of nanoparticle, which are naturally occurring, self-assembled phospholipid bilayer vesicles derived from plants. Rich in bioactive molecules such as proteins, peptides, nucleic acids, and various small molecules, they inherently encapsulate NHE components. These endogenous constituents contribute to the diverse therapeutic effects exhibited by plant exosomes.¹²² Compared to synthetically prepared liposomes, plant-derived exosomes show negligible cytotoxicity. Importantly, they also possess inherent targeting capabilities, enabling precise drug delivery and therapeutic functions without additional modifications,¹²³ which are mainly determined by their intrinsic composition, including the specific proteins, nucleic acids, and NHE-derived small molecules they encapsulate.¹²⁴⁻¹²⁶ For example, exosome-like nanoparticles directly extracted from *Platycodon grandiflorum* have been demonstrated to exhibit significant therapeutic efficacy in the treatment of acute lung injury.¹²⁷

NHE-based nanoparticles have also demonstrated great promise in oncology. For instance, luteolin and glycyrrhetic acid co-assembled into rod-shaped nanoparticles through hydrogen bonding, electrostatic interactions, and π - π stacking. These nanoparticles exhibited selective tumor-targeting capabilities and induced cell cycle arrest at the G2/M phase in hepatocellular carcinoma cells, thereby enhancing therapeutic efficacy while reducing

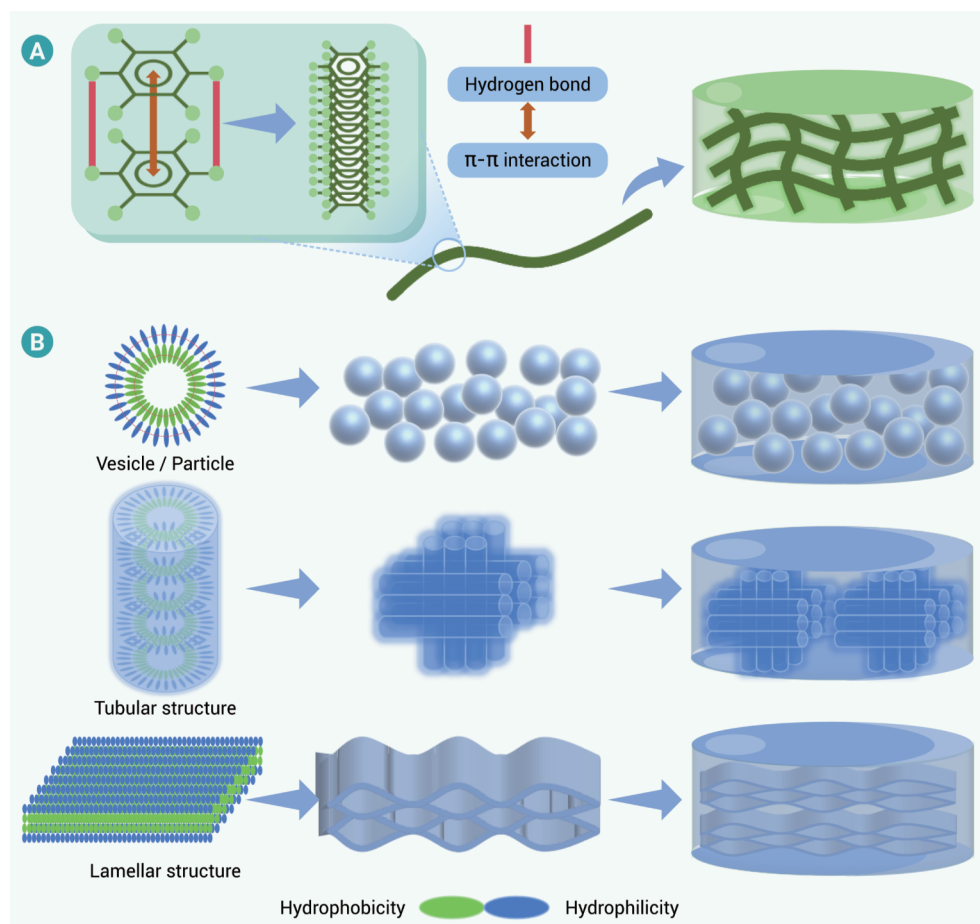


Figure 7. Molecular self-assembly modes of NHE-based hydrogels driven by different interactions. (A) Driven by π - π interactions. (B) Driven by hydrophobic interactions.

trauma management (Figure 9).

In the context of internal diseases and trauma, several studies have demonstrated the therapeutic potential of NHE-derived self-assembled hydrogels. Luo et al.⁴³ developed a glycyrrhizic acid-based hydrogel, mechanically tuned to match the modulus of brain tissue, and further incorporated berberine and rhein nanoparticles. This hydrogel alleviated inflammation and neurological damage in traumatic brain injury models. Meanwhile, the inherent injectability of NHE-based hydrogels has proven advantageous in minimally invasive therapies for arthritis, ensuring localized delivery and sustained bioactivity.⁹¹

Beyond inflammation and tissue injury, NHE self-assembled hydrogels also show promise in combating viral and fungal infections. Qi et al.²⁵ constructed a glabridin-puerarin hydrogel with potent efficacy against SARS-CoV-2-induced lung injury, while Peng et al.⁶⁹ reported a zingibroside R1 hydrogel capable of treating *Candida albicans*-induced vulvovaginal candidiasis, underscoring the enhanced pharmacological benefits conferred by the supramolecular hydrogel framework.

systemic toxicity.⁸⁰

For tumors located in the central nervous system, such as glioblastoma, overcoming the BBB remains a formidable challenge. Li et al.⁵⁵ and Zhao et al.⁷¹ independently designed nanoparticles encapsulating betulinic acid and genistein, respectively. These formulations successfully improved water solubility, prolonged half-life, and enhanced tissue targeting, thereby facilitating drug delivery across the BBB and significantly improving therapeutic outcomes in glioblastoma treatment.

Beyond anti-inflammatory and anticancer applications, numerous NHE-derived nanoparticles exhibit excellent antimicrobial properties. Moreover, synergistic effects can be achieved through the co-assembly of multiple herbal components. Huang and colleagues²⁹ prepared cinnamic acid–berberine nanoparticles, which displayed markedly superior antibacterial activity compared with conventional antibiotics such as norfloxacin, amoxicillin, and tetracycline, as well as their monomeric counterparts. Likewise, self-assembled nanoparticles of berberine and rhein were shown to effectively eradicate *Staphylococcus aureus* biofilms,¹¹⁴ underscoring the potential of NHE-based nanostructures as antibiotic alternatives.

In summary, NHE-derived nanoparticles represent a versatile platform for therapeutic applications, ranging from anti-inflammatory and organ-protective functions to anticancer and antimicrobial activities. Their ability to enhance bioavailability, achieve synergistic therapeutic effects, and overcome biological barriers highlights their promise in modern nanomedicine, although their clinical translation still faces challenges such as stability and large-scale preparation.

Hydrogels. Compared with nanoscale assemblies, hydrogels formed via supramolecular self-assembly of NHEs present distinct macroscopic morphologies and structural integrity. Importantly, the intrinsic reversibility, dynamic responsiveness, and environmental sensitivity of the NHE-based self-assembly process align well with the physicochemical properties of hydrogels. These features facilitate structural modulation, enable spatiotemporal control over bioactivity, and ultimately broaden their therapeutic applicability across diverse scenarios in both internal diseases and external

efficacy of NHE-based hydrogels in wound healing, particularly in infected wound environments. Representative examples include gallic acid hydrogels,²³ glycyrrhetic acid derivative hydrogels (benzyl 3 β -amino-11-oxoolean-12-en-30-oate),¹²⁸ and baicalin-sanguinarine hydrogels,¹²⁹ all of which demonstrated significant antibacterial activity and tissue repair capabilities. Meanwhile, their adaptability has also been validated in specialized applications, such as burn wound care¹³⁰ and chronic diabetic wound healing.¹³¹

In addition to wound and systemic disease management, NHE-derived hydrogels offer opportunities for treating epidermal disorders owing to their high permeability across biological barriers. For example, Zeng et al.¹³² developed a cryptotanshinone derivative-glycyrrhizic acid hydrogel for acne treatment, which demonstrated excellent dermal penetration, biocompatibility, and synergistic antimicrobial and anti-inflammatory effects. These examples collectively highlight the versatile biomaterials platforms for next-generation clinical applications.

Stimulus responsive natural herb extract self-assembly materials. The noncovalent interactions driving NHE self-assembly are sensitive to external environmental conditions, rendering microenvironmental responsiveness a key feature of supramolecular self-assembled hydrogels. Among these stimuli, pH exerts the most direct effect on molecular assembly. Both excessively high and low pH values disrupt noncovalent interaction patterns and consequently affect hydrogel and nanoparticle formation.^{16,133} Therefore, pH responsiveness represents an essential functional attribute of self-assembled materials. Taking rhein as a typical example, a noteworthy property of rhein is its pH-sensitive protonation and deprotonation, which modulates hydrogen bonding and other noncovalent interactions, imparting stimulus-responsive characteristics to rhein-based materials. Rhein-based hydrogels form within a narrow alkaline window (pH 8.0–9.4) and exhibit distinct morphological states depending on pH: rod-like precipitates below pH 6.8, viscous gels between pH 6.8 and 8.0, and a solution state above pH 9.4. This behavior has been attributed to the pH-dependent protonation ratio of rhein molecules, which governs their self-assembly and resultant supramolecular architectures.^{50,134} Leveraging this feature, Zhong et al.¹³⁵ incorporated *Spir-*

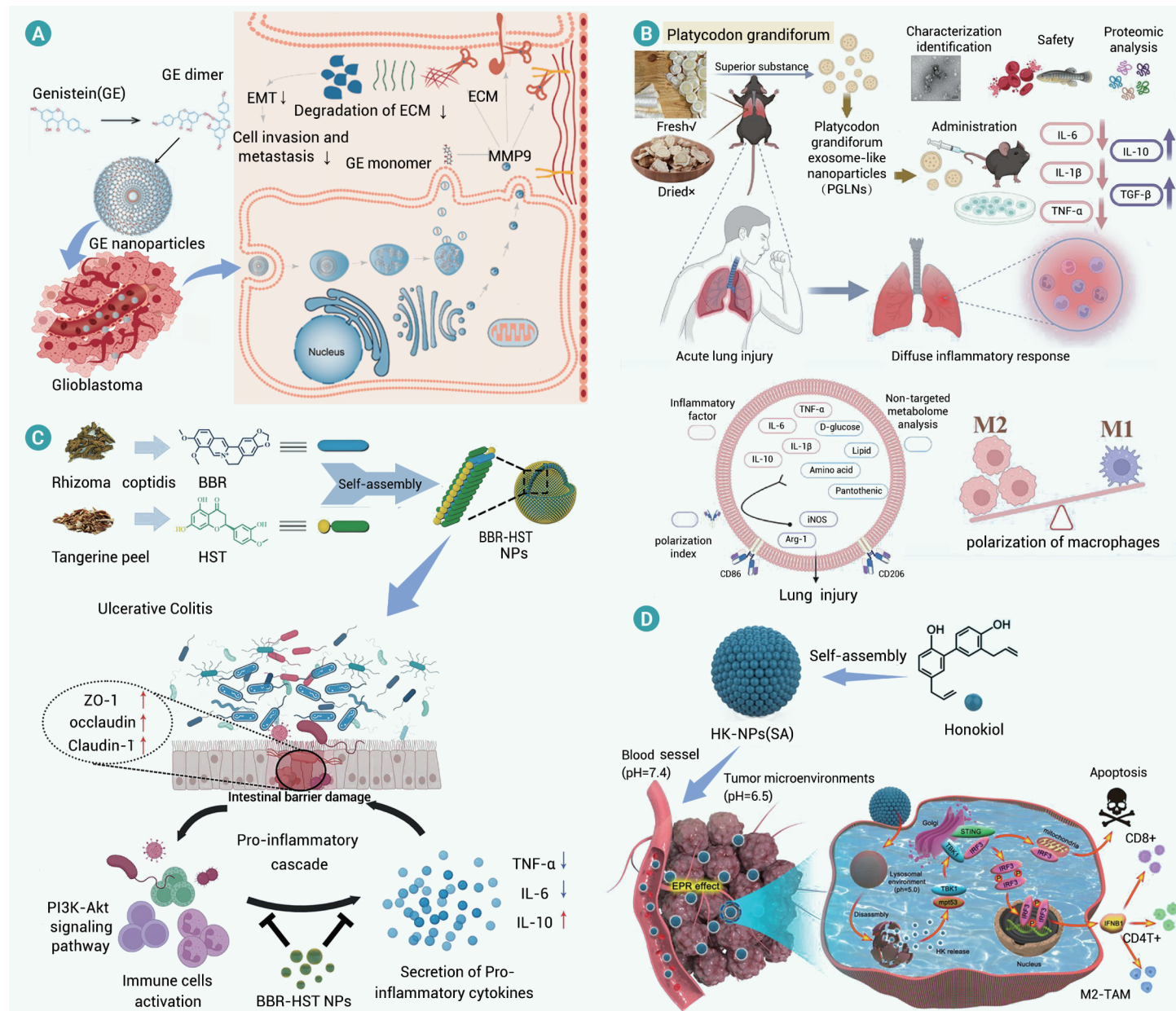


Figure 8. Applications of self-assembled nanoparticles derived from NHEs in disease treatment (A) Genistein nanoparticles for glioblastoma treatment. Modified appropriately and reproduced with permission.¹⁷ Copyright 2024, Zhao et al. (published by Elsevier), licensed under the CC-BY license. (B) *Platycodon grandiflorum* exosome-like nanoparticles in regulating acute lung injury. Modified appropriately and reproduced with permission.¹²⁷ Copyright 2025, Fu et al. (published by Springer Nature), licensed under the CC-BY-NC-ND license. (C) Mechanism of berberine-hesperetin nanoparticles in ulcerative colitis treatment. Modified appropriately and reproduced with permission.³¹ Copyright 2023, Wiley. (D) Honokiol nanoparticles for P53-mutated colorectal cancer treatment. Modified appropriately and reproduced with permission.¹¹⁷ Copyright 2022, American Chemical Society.

ulina platensis biomass into rhein hydrogels for enteritis treatment, while Liang et al.¹³⁶ employed extracellular vesicles derived from *Spirulina platensis* for arthritis therapy. Both systems demonstrated pH-responsive release of bioactive molecules, achieving enhanced therapeutic efficacy and highlighting the potential for rhein-based supramolecular hydrogels as smart delivery platforms. In addition, glycyrrhizic acid is also a typical pH-sensitive NHE. Lei et al.¹³ designed a pH-responsive glycyrrhizic acid-berberine supramolecular hydrogel that enabled site-specific and stimulus-triggered drug release in the colon, demonstrating significant efficacy in the treatment of ulcerative colitis.

Nanoparticles also exhibit pH responsiveness. Jia et al.¹³⁷ developed a pH-responsive nanoparticle for insulin encapsulation via coordination and hydrogen bonding between baicalin and Al³⁺. The nanoparticles display specific pH responsiveness in the gastrointestinal tract, enabling targeted insulin release in the intestinal environment. Conversely, Zhang et al.⁷⁹ developed an acid-responsive nanoparticle through the self-assembly of ursolic acid and EGCG, modified with EpCAM-aptamer for enhanced targeting. Upon binding to tumor tissues, the acidic microenvironment triggers EGCG dissociation,

releasing ursolic acid and achieving responsive anticancer effects.

Differences in molecular oxidation and reduction states also modulate noncovalent interactions. Leveraging this principle, Zhao et al.¹³⁸ utilized the oxidation sensitivity of ferrocene to regulate its self-assembly with β -cyclodextrin, thereby developing an oxidation-responsive self-assembled hydrogel. By integrating this hydrogel with rhein self-assembly products, they constructed a multifunctional dressing suitable for chronic inflammatory wounds. Moreover, temperature and mechanical shear are also determinants of noncovalent interactions, particularly for hydrogen bond formation and dissociation. NHE-based self-assembled hydrogels often undergo temperature-induced sol-gel transitions, involving heat-mediated dissolution followed by cooling-induced gelation. The sol-gel transition can also be regulated by adjusting the shear rate, thereby enabling injectability. Hydrogels derived from rhein,⁵⁰ glycyrrhizic acid,⁴³ and gallic acid²³ commonly exhibit reversible thermo- and shear-responsive sol-gel transitions. In sum, these observations indicate that NHE self-assembled hydrogels are inherently multi-

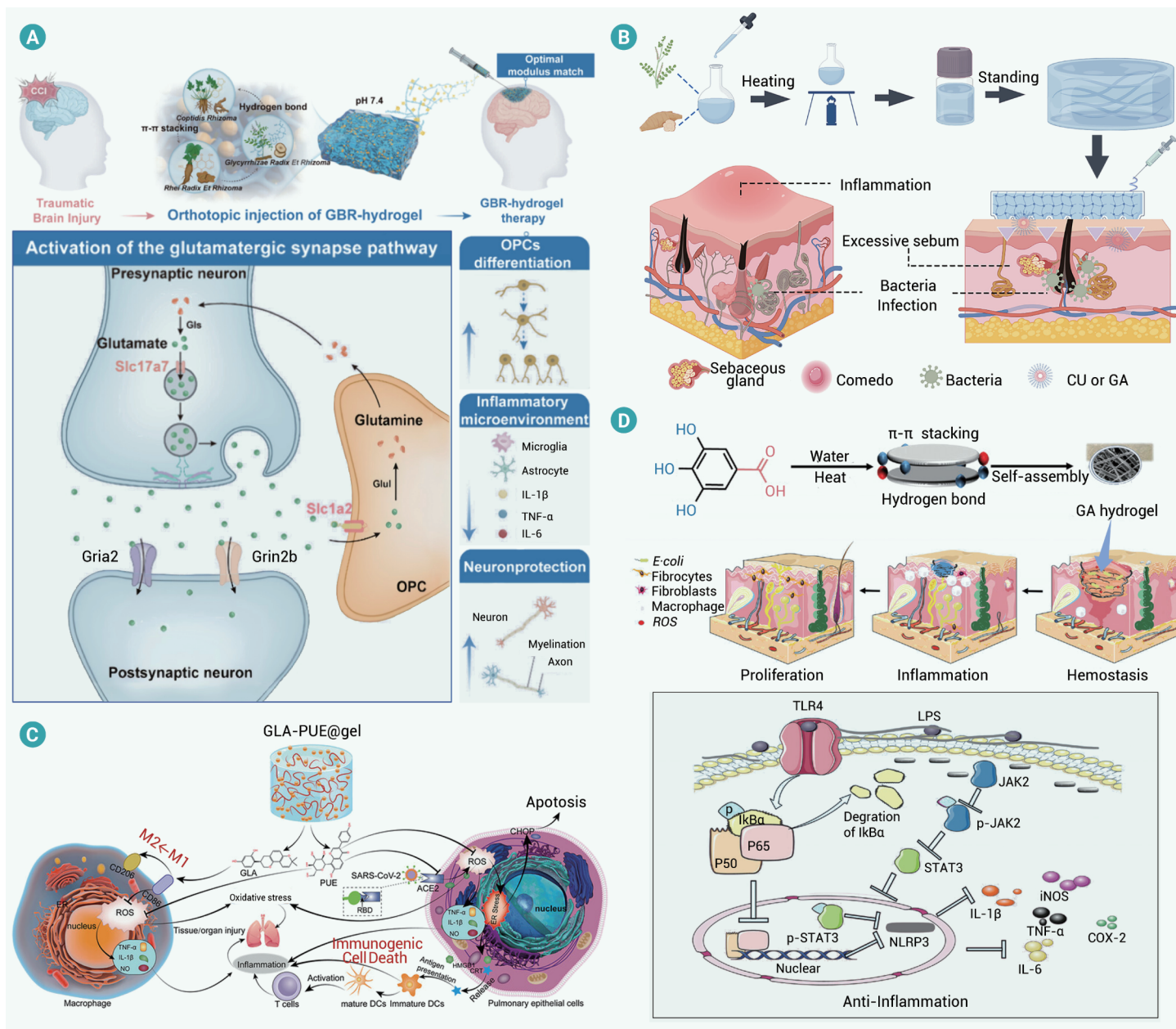


Figure 9. Applications of self-assembled hydrogels derived from NHEs in disease treatment (A) Glycyrrhizic acid-berberine-rhein hydrogel for repairing traumatic brain injury. Modified appropriately and reproduced with permission.⁴⁵ Copyright 2024, American Chemical Society. (B) Glycyrrhizic acid-cryptotanshinone-peptide conjugate hydrogel for acne therapy. Modified appropriately and reproduced with permission.¹³² Copyright 2025, American Chemical Society. (C) Glabridin-puerarin hydrogel for alleviating lung injury. Modified appropriately and reproduced with permission.²⁵ Copyright 2025, Qi et al. (published by Wiley), licensed under the CC-BY license. (D) Gallic acid hydrogel for promoting wound healing. Modified appropriately and reproduced with permission.²³ Copyright 2025, Wiley.

responsive, rather than being limited to a single stimulus.

COMBINATION OF NATURAL HERB EXTRACT SELF-ASSEMBLY PRODUCTS WITH OTHER TECHNOLOGIES

Although self-assembled materials derived from NHEs have demonstrated promising potential across diverse biomedical applications, how to further exploit their intrinsic advantages remains an active area of research. One important strategy involves the integration of NHE-based self-assembled products with advanced delivery platforms or therapeutic technologies, thereby amplifying their efficacy and broadening their scope of application.

Microneedling

Microneedling is an emerging transdermal drug delivery technology capable of penetrating the stratum corneum and delivering bioactive compounds into the dermis and epidermis, thereby enhancing drug permeation with minimal tissue damage.^{139,140} The synergistic combination of microneedling with

NHE-derived self-assembled systems has recently shown considerable therapeutic potential.

For instance, EGCG-curcumin self-assembled nanoparticles delivered via microneedles exhibited improved dermal penetration and demonstrated therapeutic efficacy in treating radiation-induced skin injuries (Figure 10A).¹⁰ Similarly, baicalein-berberine self-assembled ROS-responsive nanoparticles, when combined with microneedles, were found to significantly accelerate the healing of infected diabetic wounds.¹⁴¹

In addition to nanoparticle-assisted delivery, Chi et al.¹⁴² pioneered the development of microneedles entirely composed of herbal components, including *Premna microphylla* juice, *Centella asiatica* extract, and *Lolium perenne* L. ash. These bio-derived microneedles exhibited inherent antibacterial, anti-inflammatory, and tissue-repair properties, underscoring the feasibility of constructing fully herbal microneedle systems. Interestingly, Deng et al.¹⁴³ reported a novel strategy by integrating berberine-ferulic acid self-assembled nanoparticles into negative-pressure microneedles for psoriasis

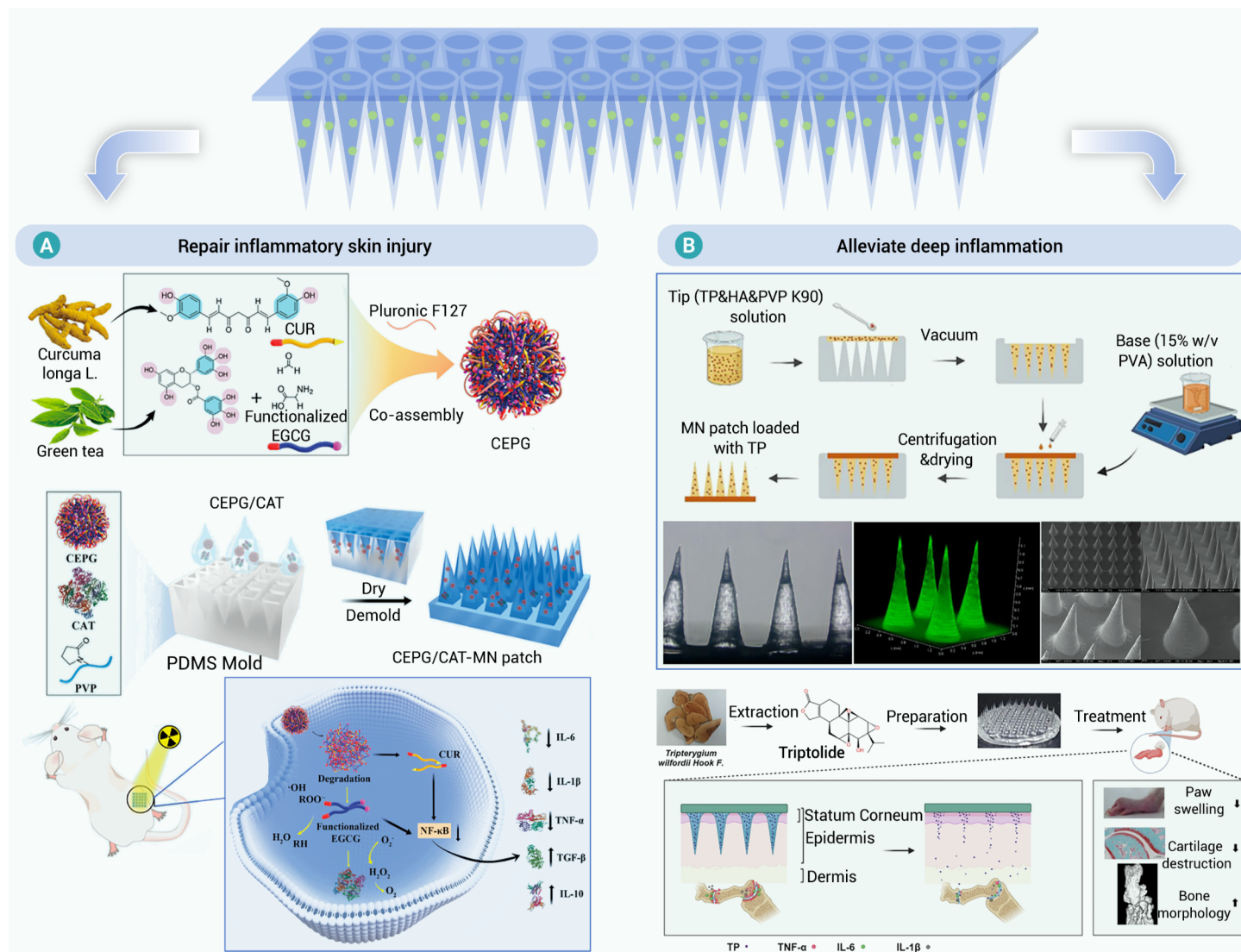


Figure 10. Application of NHE-based self-assembled products in combination with microneedle technology (A) Microneedles loaded with EGCG-curcumin nanoparticles for the treatment of radiation-induced skin injury. Modified appropriately and reproduced with permission.¹⁰ Copyright 2024, American Chemical Society. (B) Microneedle patch-assisted acupoint transdermal delivery of triptolide for rheumatoid arthritis treatment. Modified appropriately and reproduced with permission.¹⁴⁴ Copyright 2024, Li et al. (published by Springer Nature), licensed under the CC-BY-NC-ND license.

treatment. This design facilitated enhanced penetration of nanoparticles through the thickened stratum corneum characteristic of psoriatic lesions, thereby achieving superior antimicrobial and anti-inflammatory outcomes. Moreover, the application of microneedles can also promote the deep release of natural herbal extracts. Li et al.¹⁴⁴ constructed microneedles loaded with triptolide, effectively enhancing its delivery efficiency at joint sites while reducing systemic toxicity (Figure 10B).

Collectively, these studies highlight the promise of combining NHE self-assembled products with microneedling technologies to achieve enhanced transdermal delivery, improved therapeutic precision, and expanded biomedical applications.

Photodynamic therapy and photothermal therapy

Photodynamic therapy (PDT) has emerged as a promising targeted therapeutic strategy, in which photosensitizers are activated by light of specific wavelengths to generate ROS with potent bactericidal and antitumor effects.^{145,146} Despite its therapeutic potential, the clinical application of PDT has been limited by issues such as low selectivity and potential biotoxicity of conventional photosensitizers. Consequently, increasing efforts have been directed toward exploring NHEs as safer, multifunctional alternatives.

Several representative studies have demonstrated the advantages of NHE-based self-assembly in PDT. Yu et al.⁴⁷ reported the fabrication of nanoparti-

cles by combining aloe emodin, a natural photosensitive herbal component, with copper ions under the modification of PEG_{2k}-DSPE-FA. These nanoparticles exhibited effective PDT activity against non-small cell lung cancer while addressing toxicity concerns associated with traditional photosensitizers. In another approach, Li et al.¹⁴⁷ and Lei et al.¹³ independently discovered the aggregation-induced emission effect in hydrogels self-assembled from glycyrrhizic acid and berberine. Interestingly, glycyrrhizic acid significantly enhanced the fluorescence and photodynamic activity of berberine, enabling the hydrogel to achieve nearly complete eradication of MRSA after 60 min of irradiation, while simultaneously accelerating the healing of MRSA-infected wounds.

Beyond enhancing therapeutic efficacy, the integration of NHEs also offers the ability to mitigate PDT-induced side effects. For instance, PDT has been shown to activate the expression of high mobility group box 1 (HMGB1) protein in the psoriasis treatment, which inadvertently triggers innate and adaptive immune responses, thereby aggravating skin inflammation and impeding symptom relief. To counteract this, glycyrrhizic acid was incorporated with the photosensitizer chlorin e6 into nanoparticles. This formulation not only preserved the therapeutic benefits of PDT but also exploited the anti-inflammatory and HMGB1-blocking ability of glycyrrhizic acid, leading to improved treatment outcomes.¹⁴⁸ Meanwhile, it has been proved that the preparation of natural active product-photosensitizer self-assembled

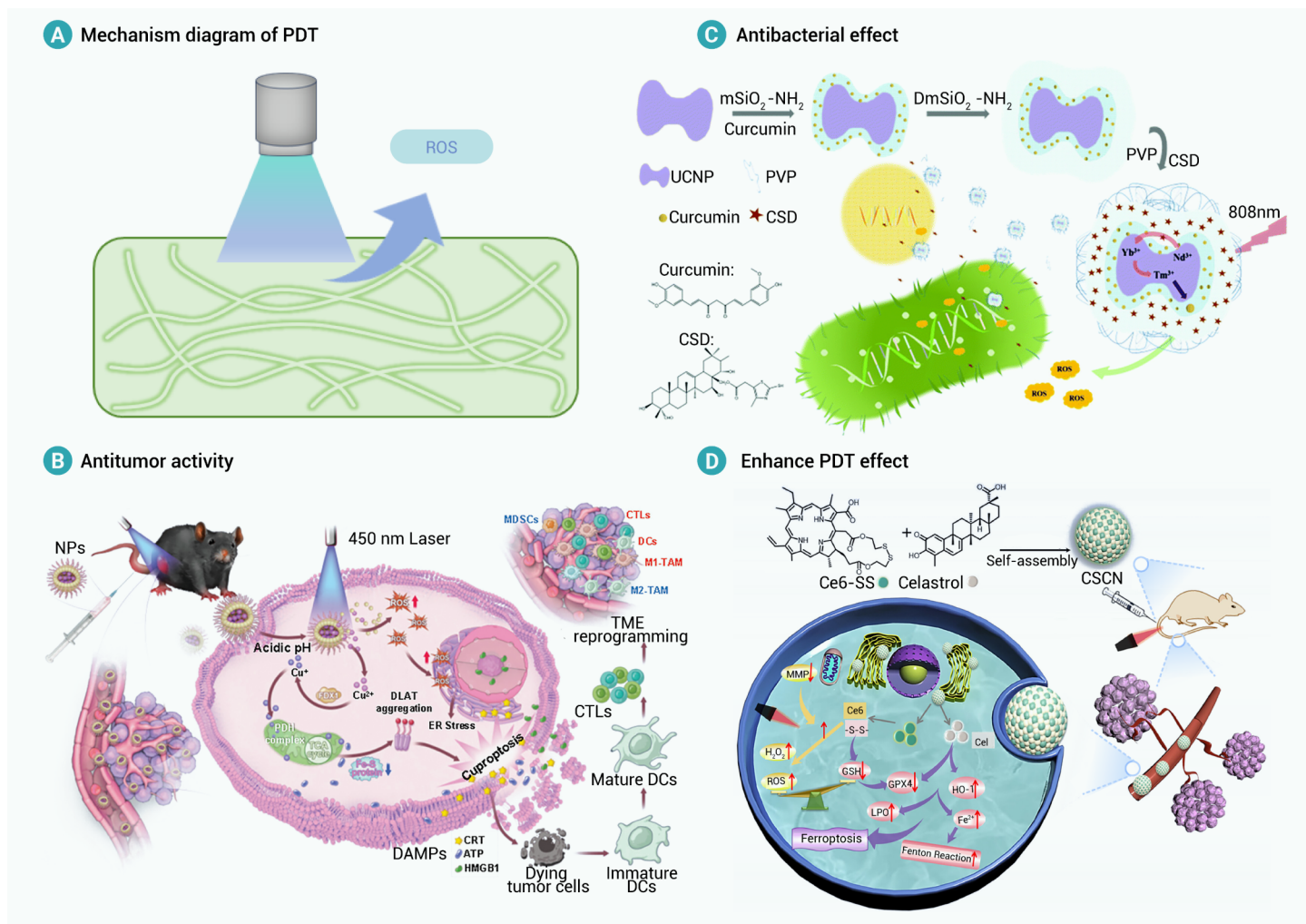


Figure 11. Application of NHE-based self-assembled products in combination with photodynamic therapy (A) Mechanism diagram and application of NHE-based self-assembled products combined with PDT. (B) Aloe emodin-copper ion nanoparticles employing aloe emodin as the photosensitizer for tumor treatment. Modified appropriately and reproduced with permission.¹⁴⁷ Copyright 2025, Wiley. (C) *Camellia* sapogenin/curcumin nanoparticles utilizing curcumin as the photosensitizer for deep-tissue anti-infection treatment. Modified appropriately and reproduced with permission.¹⁴⁶ Copyright 2022, Royal Society of Chemistry. (D) Disulfide-bonded chloride e6-celastrol nanoparticles for triple negative breast cancer therapy, leveraging celastrol inhibiting the activity of peroxisomal enzymes to enhance PDT efficacy. Modified appropriately and reproduced with permission.¹⁴⁹ Copyright 2025, American Chemical Society.

nanoparticles can further enhance the PDT effect while reducing biological toxicity.¹⁴⁹

In sum, these studies highlight the significant potential of NHE-based self-assembled systems in PDT. By enhancing photosensitizer performance, reducing biotoxicity, and mitigating adverse immune response, NHE-derived nanomaterials represent a compelling direction for advancing safer and more effective PDT platforms (Figure 11).

In addition, photothermal therapy (PTT) is a technique similar to PDT, differing primarily in that PTT utilizes photothermal agents to convert light energy into heat to eliminate cancer cells and bacteria.¹⁵⁰ Liu et al.¹⁵¹ synthesized luteolin-Fe³⁺ nanoparticles via coordination self-assembly, introducing a supramolecular photothermal effect that potently suppressed cancer cell growth, demonstrating promising potential for cancer therapy. Subsequently, Liu et al.¹⁵² engineered dihydroartemisinin-loaded luteolin-Fe³⁺ nanoparticles, which enable PTT for cancer therapy and enhance tumor cell killing through amplified Fenton reaction efficiency under photothermal conditions. Overall, these studies demonstrate the tremendous potential of combining phototherapy with NHE self-assembled materials.

Integration with other technologies

Sonodynamic therapy (SDT), also similar to PDT, achieves therapeutic activation through sound waves rather than light irradiation.¹⁵³ Zheng et al.¹⁵⁴ fabricated a self-assembled nanoparticle based on oleanolic acid and photosensitizer/sonosensitizer-chlorin e6 for cancer treatment. This system

achieved synergistic photodynamic and sonodynamic effects while leveraging oleanolic acid's intrinsic anticancer activity. Additionally, it significantly enhanced the bioavailability of both agents, improving therapeutic efficacy and reducing the required drug dosages relative to single-modal therapies.

Moreover, magnetic fields also offer a viable strategy for integration with NHE self-assembly materials.¹⁵⁵ Studies demonstrate that incorporating magnetic components into these NHE-based nanoassemblies enables magnetically guided delivery to target sites, enhancing site-specific accumulation and enabling stimuli-responsive release.^{156,157}

Overall, the above findings demonstrate the versatility of NHE self-assembly materials when combined with advanced therapeutic modalities, underscoring their broad application potential. Nonetheless, research on the synergistic integration of NHE self-assembly materials with other emerging technologies remains insufficient, highlighting substantial opportunities for future exploration.

SUMMARY AND PROSPECT

Although herb medicine has a long history in clinical use, the lack of precise analytical tools for identifying and characterizing active components has historically constrained its systematic development. With the advancement of modern technologies, key bioactive molecules such as glycyrrhizic acid,¹⁵⁸ rehin,¹⁵⁹ and berberine¹⁶⁰ have been increasingly recognized, and their therapeutic targets in disease contexts gradually elucidated. Importantly, supramolecular self-assembly of NHEs has revealed unique advantages over

conventional drugs and traditional biomaterials, including higher permeability across biological barriers, facile preparation, excellent biocompatibility, and abundant natural availability.

This review has summarized the driving forces underlying NHE self-assembly, the diversity of their supramolecular architectures, and the corresponding biomedical applications. Overall, NHE-based supramolecular self-assemblies represent an emerging class of bioactive materials with considerable potential for advancing therapeutic strategies. Nonetheless, several fundamental challenges continue to restrict their broader development and clinical translation.

(1) Limitations of characterization techniques for NHE self-assembly processes: Self-assembly of NHEs in solution is governed exclusively by dynamic noncovalent interactions, which are inherently weak, reversible, and difficult to capture experimentally. Current analytical technologies provided limited resolution to dissect the contributions of individual interactions, forcing reliance on theoretical simulations for mechanistic insight. Meanwhile, the occurrence of NHE self-assembly remains highly contingent, and the influence of distinct functional groups on the self-assembly process has not been systematically elucidated. Establishing clear correlations between molecular structure, self-assembly behavior, and resultant supramolecular products therefore constitutes a pressing research need.

(2) Limited understanding of pharmacological mechanisms: Despite extensive research on the tissue- and cell-level targets of NHEs, the complex diversity of NHEs prevents a comprehensive understanding of each molecule's pharmacological mechanisms. Meanwhile, elucidating synergistic or antagonistic interactions among components in multi-component co-assembled materials presents another major challenge. In addition, while current studies focus on structure-interaction relationships, research on the structure-activity relationships of drug molecules remains limited, which is also a critical issue impeding the development of advanced NHE self-assembled materials.

(3) Challenges in industrial production and clinical applications: Current preparation techniques for NHE self-assembled materials, primarily based on simple blending, temperature variations, solution modifications, and decoc-tion enrichment extraction, often fail to guarantee product uniformity. Furthermore, noncovalent interactions represent long-term interactions. Consequently, achieving long-term storage and transportation presents a major challenge, hindering the clinical translation of these materials from laboratory research. In addition, the relatively small molecular size of NHEs, coupled with weak cohesive interactions, often results in assemblies with inferior mechanical strength and structural stability compared to macro-molecular biomaterials. Enhancing the robustness and durability of NHE-based assemblies, particularly hydrogel systems, remains a critical challenge for their practical application.

Alongside these challenges, several promising development prospects are emerging:

(1) Material development: To address the limited temporal resolution for self-assembly processes, future research should prioritize in situ and continuous monitoring strategies. The integrating of high-resolution molecular microscopy techniques with spectroscopy techniques, electric field techniques, and molecular manipulation tools will enable real-time observation of molecular assembly behavior, thereby enhancing the controllability and comprehensive characterization of NHE self-assembly materials. In terms of improving the properties of NHE-based hydrogels, the construction of composite or multicomponent supramolecular networks, particularly those incorporating macromolecular scaffolds, offers a promising pathway to reinforce mechanical strength and expand functional performance. Furthermore, modifying molecular structures to adjust the final structure and function of NHE self-assembled materials represents another promising and yet under-explored strategy that warrants further investigation.

(2) Mechanism exploration: The translational potential of NHE-based assemblies will depend on elucidating their molecular mechanisms of action, including signaling pathways and therapeutic targets at disease sites. While current studies have primarily focused on self-assembly behaviors, the pharmacological mechanisms of NHEs and the pathways of multi-component interactions will be given greater attention in future studies. AI also offers significant potential for advancing pharmacological analysis and elucidating

self-assembly mechanisms. Its robust computational power enables large-scale screening of molecular structures, facilitating prediction of interaction patterns among NHEs and their therapeutic mechanisms at cellular and systemic levels. It is foreseeable that in the future, AI will promote the establishment of a comprehensive system for investigating the pharmacological mechanisms and self-assembly of NHEs, enabling precise prediction of the structure-activity relationship and molecular forces induced by different molecular structures, and rational design the entire molecular self-assembly process.

(3) Application design: For the clinical translation of NHE self-assembly materials, integration with other technologies is a key means of expanding applications. The field is expected to move toward the integration of NHE self-assembled materials with advanced biomedical technologies, such as microneedle delivery, PDT, PPT, and SDT, alongside other promising techniques, as highlighted in preceding sections. Such hybrid approaches are anticipated to enhance the permeability, antibacterial activity, and anti-inflammatory efficacy of NHE-derived assemblies. On the other hand, current NHE self-assembly research primarily targets model therapeutic applications, including skin wound repair, inflammatory organ damage, and tumors. Extending to intractable disorders and conducting in-depth treatments will therefore represent a critical direction in future translational exploration for NHE self-assembled materials.

In conclusion, NHE-derived supramolecular self-assembled materials offer a unique and versatile platform that bridges traditional herbal medicine with modern biomaterial science. Addressing the existing challenges through interdisciplinary strategies will be key to unlocking their full potential in biomedical applications.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data and code were created or analyzed in this review.