Food & Medicine Homology

ISSN 3006-6867 (print); 3006-4252 (online)
https://doi.org/10.26599/FMH.2025.9420022

Review Article

Co-assembly strategies of natural plant compounds for improving their bioavailability

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Received: 4 May 2024 / **Revised:** 10 June 2024 / **Accepted:** 13 June 2024

Abstract: Natural plant compounds have long served as crucial sources of medicinal therapies, spanning millennia and underpinning the field of drug discovery and development. Their profound impact is rooted in their extensive diversity and broad spectrum of pharmacological activities. Inspired by the decoction methods of traditional Chinese medicine, we have delved into the co-assembly strategy of natural plant compounds. This strategy involves the coalescence of active components from various drugs into nanocomplexes via non-covalent interactions during the decoction process. Consequently, this approach enhances the biocompatibility, biodegradability, and pharmacological efficacy of natural plant small molecules while mitigating their toxicity. The co-assembly strategy capitalizes on the inherent advantages of natural plant compounds, thereby expediting drug discovery by repurposing existing drugs. This review outlines the evolution of co-assembly strategies involving natural plant compounds, provides illustrative examples of co-assembly, elucidates the mechanisms underlying assembly, and highlights the resultant advantages. By shedding light on the transition from single molecule to multi-component interactions, this review advances our understanding, facilitating further research and the practical application of co-assembly strategies for natural plant compounds.

Keywords: food and medicine; natural plant compounds; co-assembly strategies; nanomedicine

Citation: Miao Y. H., Wang X., Zhao X. M., et al. Co-assembly strategies of natural plant compounds for improving their bioavailability. *Food & Medicine Homology*, 2025, 2: 9420022. https://doi.org/10.26599/FMH.2025.9420022

1 Introduction

Throughout human life, the consumption of nutritious food is essential for maintaining overall health[1]. Human hunting and gathering activities have been linked to the discovery of pharmaceutical substances, demonstrating the evolving understanding of food's potential. Initially, food primarily served as a non-toxic source of sustenance to meet basic dietary needs, but its additional therapeutic and health-promoting properties were later recognized[2]. The concept of medical nutrition equivalence has been interpreted internationally in various ways, including the equivalence between certain foods and herbal remedies, the correlation between medicine and dietary items, and the classification of food-medicine components[3,4]. In the current era, with a growing emphasis on personal wellness, the consumption of functional foods that enhance immune strength and prevent diseases has gained increased attention and importance[5]. This trend reflects a shift in public health awareness from merely treating illness to a comprehensive approach that includes both preventive measures and curative interventions[6]. This evolving health consciousness has led to the emergence of novel alternative healing practices and the advancement of the nutrition and wellness sector[7].

Natural plant compounds, constituting the largest class of drugs, have played a crucial role in drug discovery and form the basis for most early-stage drugs[8-11]. Strategies for drug discovery and development from natural products (NPs) vary across stages, with herbal preparations and compositions being the predominant drug modalities in the clinical application of natural products[12]. Active ingredients in NPs are often encapsulated in cell walls or membranes, making them challenging for direct absorption by the body. However, these ingredients can be effectively dissolved through decoction[13]. Importantly, the physicochemical reaction between the active ingredients and water during decoction enhances their release, improving the safety and efficacy of NPs compounds[14,15]. This reaction also alters the composition and morphological structure of pharmacodynamic molecules, leading to synergistic or toxicity-reducing therapeutic effects (Fig. 1)[16-18]. Inspired by the decoction process in traditional Chinese medicine, which is closely related to the co-assembly of NPs, we explore the microscopic manifestation of decoction in the co-assembly of NPs molecules. Both processes are utilized similarly in the use of NPs as drugs or functional foods to enhance bioavailability and oral targeting of NPs.

Co-assembly methods of natural plant active molecules (NPAMs) are widely employed in constructing nanomedicine platforms due to their simplicity, environmental friendliness, and efficiency[19,20]. Throughout the co-assembly process, the NPs,

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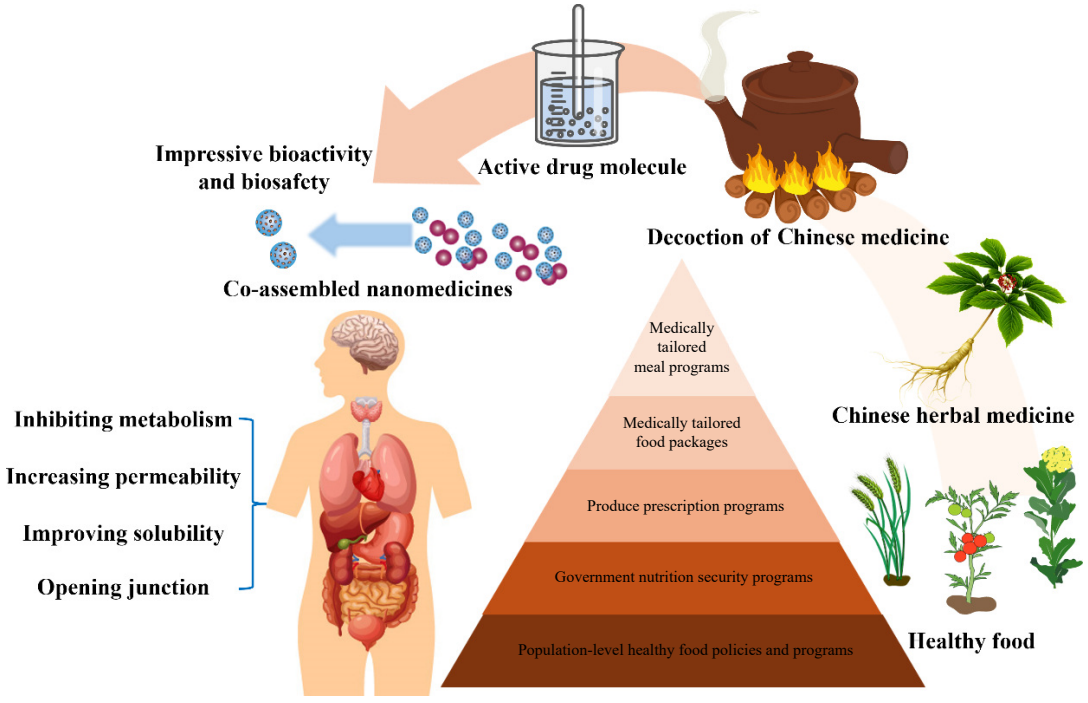


Figure 1 Schematic illustrating the developmental process from herbal decoction to natural product co-assembly[1].

serving as structural units, can preserve their individual bioactivity while enhancing the overall structural stability of the nanomedicine[21]. Such co-assembled nanomedicines can leverage the advantages of each NP component, demonstrating a synergistic effect where the combined effect exceeds the sum of individual effects in terms of bioavailability and pharmacological activity. Particularly noteworthy is the NPs' co-assembly strategy for its synergistic therapeutic effects[22,23]. By utilizing rich molecular scaffolds and functional groups during assembly to create nanomedicines with multi-target interactions, this approach can mitigate off-target effects, enhancing the systematic therapeutic role. Co-assembled nanomedicines underscore the unique advantages of NPs over monomer molecules in terms of bioactivity, safety, and efficacy[24,25]. As co-assembled monomer molecules are mainly derived from NPs, the significance of herbal decoction extends to the NPs' co-assembly strategy. Simultaneously, this strategy aids in understanding the mode of action of traditional Chinese medicines through novel perspectives and technological approaches. Reflecting the adage "unity is strength", exploring the co-assembly strategy of NPs deepens our understanding of assembly mechanisms and the actions of various active molecules, providing a theoretical foundation for developing novel NPs co-assembled nanomedicines.

2 Diversity of natural plant compound co-assemblies

Secondary metabolites of medicinal food congeners, such as alkaloids, terpenoids, polysaccharides, phenolic compounds, and saponins, exhibit a wide range of pharmacological actions and are essential for drug development[26-30]. The utilization of drug delivery systems (DDS) to distribute natural small molecules is a prominent area of research in drug delivery. DDS possess unique features, including slow and controlled release, as well as targeting capabilities, which can enhance drug bioavailability, improve pharmacokinetics and drug biodistribution, and reduce harmful side effects[18,31]. Small molecule compounds with self-assembling and co-assembling properties have been consistently identified and utilized as exceptional drug carriers for developing DDS[32]. Given the vast assortment of natural plant compounds and the diverse nature of secondary natural small molecules, continuous investigation is required to identify suitable natural small molecules for co-assembly and to understand their assembly mechanisms[33,34]. This article emphasizes the co-assembly of flavonoids, triterpenoids, polyphenols, phenylpropanoids, and alkaloids within natural plant compounds. In this article, we mainly focus on the co-assembly strategies of five types of natural plant compounds widely used in the fields of medicinal chemistry and nanomedicine, including flavonoids, triterpenoids, polyphenols, phenylpropanoids, and alkaloids (Fig. 2).

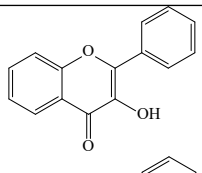
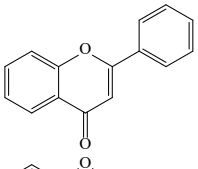
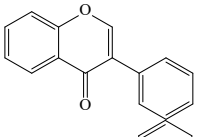
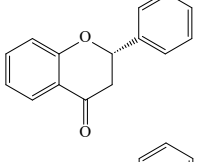
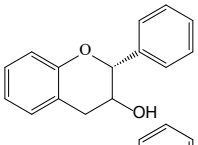
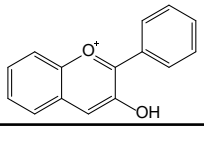
2.1 Flavonoid-based co-assembly systems

Flavonoid compounds, naturally occurring in various traditional Chinese herbal remedies like honeysuckle and turmeric, exhibit diverse pharmacological effects, including tumor growth inhibition, inflammation reduction, and immune system modulation[35]. Despite their abundance in nature and favorable compatibility with the human body, their limited solubility and stability have hindered their medicinal use[36]. Thus, employing co-assembly techniques to enhance their properties holds significant promise for practical applications.

Flavonoids are structurally diverse and exhibit a wide range of pharmacological activities and high nutritional value (Table 1). However, they still have limitations in practical applications. Studies have shown that the oral bioavailability of these compounds is typically below 10% and even lower than 5%. Additionally, they are easily affected by environmental factors and prone to oxidation and decomposition. In recent years, co-assembly strategies have been considered a promising approach to address the issues of low bioavailability and poor stability of flavonoids. Through co-assembly modification, flavonoids can enhance their water solubility and broaden their administration routes. By imparting targeting properties, the bioavailability of

Figure 2 Types of natural plant compounds, including flavonoids, triterpenoids, polyphenols, phenylpropanoids, and alkaloids.

Table 1 Categories, chemical compositions, and principal dietary origins of flavonoid compounds

Subclass	Structure	Type	Food
Flavonol		Quercetin (Que), kaempferol, galandin, myricetin	Apples, cherries, berries, onions, tomatoes, broccoli, tea, read win
Flavone		Luteolin, apigenin, chysin	Fruits, vegetables, cereals
Isoflavone		Genistein, daidzein, glycitein	Legumes such as soybean
Flavanone		Naringenin, hesperetin, eriodictyol	Citrus fruits
Flavanol		Catechin, epicatechin, gallocatechin	Apples, red grapes, tea
Anthocyanidin		Cyanidin	Fruits

flavonoids *in vivo* can be effectively increased. Co-assembly strategies offer a promising method to overcome these drawbacks.

Natural flavonoid small molecules are structurally diverse, and leveraging their molecular interactions to construct composite structures can unveil novel drug delivery platforms[37,38]. He *et al.*[39] co-assembled two hydrophobic natural small molecules into water-soluble drug nanospheres at pH 7 using a simple pH cycling method. The nano composite material was designed and synthesized by the inspired co-folding of two hydrophobic biomolecules, wheat gluten proteins (WPs) and chitosan. The conformational conversion of the protein and chitosan drove the encapsulation of silybin within the hydrophobic core of the nanostructure to form the nanocomposite (Fig. 3). Structural characterization revealed that the protein secondary structure and wormwood formed a relatively unfolded three-dimensional conformation during the acid-induced co-assembly process,

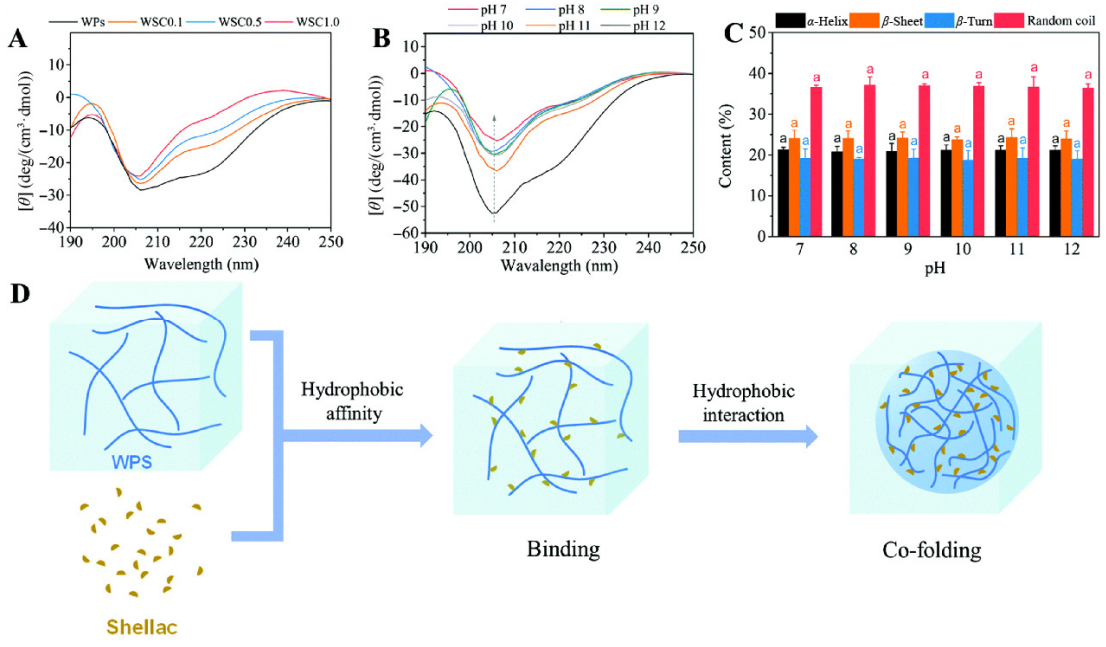


Figure 3 Schematic diagram demonstrating the control of WP–shellac composites (WSC) formation through pH modulation and wormwood. (A) Far-UV CD spectra of WPs and WSCs at pH 7, (B) Far-UV CD spectra of WSC0.5 during neutralization, (C) The secondary structure content of WSC0.5 at pH 7–12, (D) Schematic illustration of the formation of WSCs[39]. Different letters close to bars indicate significant differences ($P < 0.05$).

resulting in enhanced nanosphere stability. Cell proliferation experiments demonstrated improved bioavailability of silymarin loaded in the cordyceps-wheat gluten protein co-assemblies due to enhanced dispersion and cellular internalization of the co-assemblies. This co-assembly strategy based on simple pH modulation can encapsulate a wide range of hydrophobic drugs with broad applicability.

Curcumin (Cur), a typical flavonoid, exhibits rich pharmacological activity but low bioavailability, being poorly absorbed and utilized[40-43]. To address this issue, Zou *et al.*[44] constructed nanocomplexes using low-cost wheat by-products, wheat bran cellulose (WBC), and WPs, co-assembled through pH cycling and addition of sodium tripolyphosphate (STP). The encapsulation of Cur in the composites through co-assembly effectively enhances its absorption and enables its slow and controlled release in the gastrointestinal tract. *In vitro* simulated gastrointestinal digestion experiments demonstrated that the release of Cur could reach (77.8 ± 2.3)%. This co-delivery strategy effectively expands the application of Cur (Fig. 4)[44].

Several studies have demonstrated that co-assembling natural

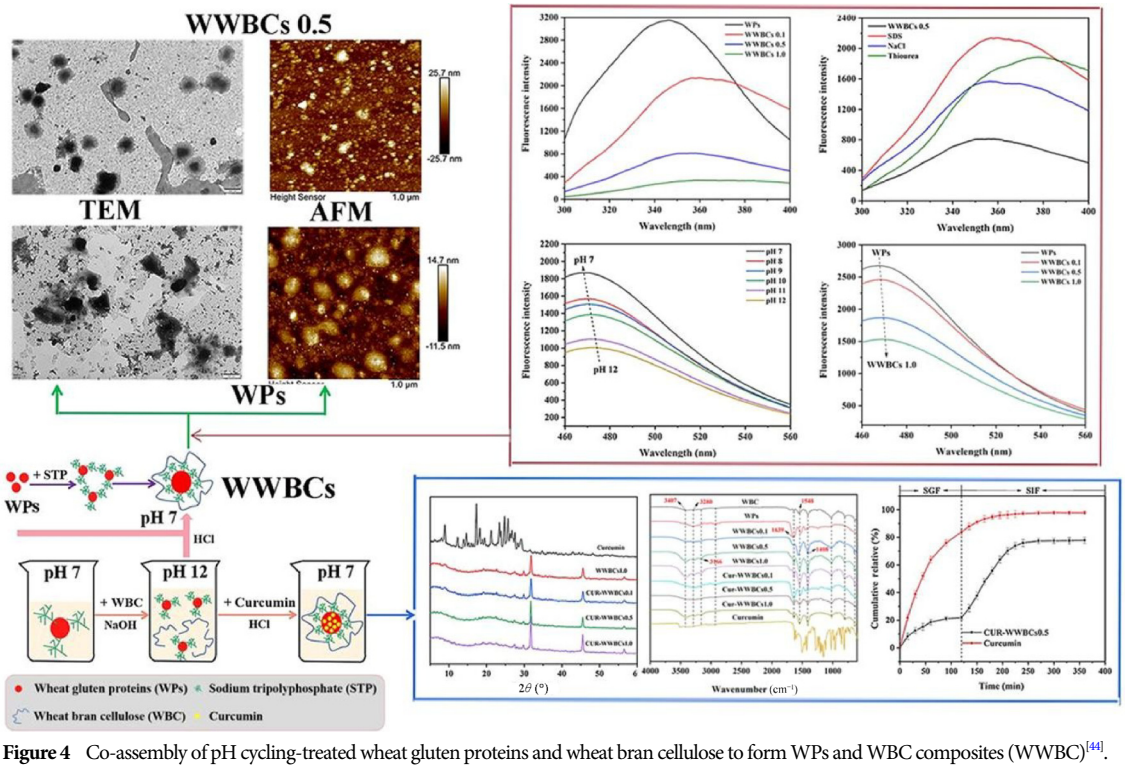


Figure 4 Co-assembly of pH cycling-treated wheat gluten proteins and wheat bran cellulose to form WPs and WBC composites (WWBC)[44].

small molecules with similar solubility into a single carrier is not difficult, but there remain technical challenges in co-assembling natural small molecules with different solubilities[45]. The cohesive effect can integrate different functional components, achieve controlled release, and enhance the stability of each component to improve the bioavailability of small molecules[46, 47]. Yang *et al.* successfully prepared zeaxanthin-chitosan complexes (ZCSCs) with a co-encapsulated bilayer structure using zeaxanthin (Z) and chitosan (CS) as raw materials for the co-encapsulation of Cur and Que. Cur in the co-delivery system was mainly encapsulated in the hydrophobic core of the zeinolysin particles, while Que mainly aggregated in the CS shell. The complexes and aggregates remained physically stable during storage, and this novel co-delivery system may improve the application of natural small molecules with different solubilities in the food and medical industries (Fig. 5)[48].

Enhancing the specific activity of flavonoid-based natural small molecules through local co-assembly strategies significantly increases drug availability, an important aspect of applying co-assembly strategies[49, 50]. Huo *et al.*[51] tailored multifunctional nanomedicines using co-assembly strategies that provide insights into enhancing multifaceted penetration of mult mechanism-based modulators for enhanced metastasis inhibition of tumors. The scheme combines both modulation of the physicochemical properties of the nanomedicine and remodeling of the TME to construct an integrated penetration strategy. Experimental results demonstrated that nanomedicines enhanced the permeation of free Que within the TME. Actively internalized methotrexate (MTX) nanodrug (MTX-GC-DEAP), together with Que, effectively resisted tumor cell proliferation and induced apoptosis. More importantly, cancer-associated fibroblast (CAF) inactivation-mediated reversal of the metastasis-promoting microenvironment and Que-mediated direct regulation of the entire process of pre-metastatic initiation of tumor cells collectively resulted in significant anti-metastasis effects. The combined penetrance was demonstrated in a 4T1 breast cancer model (Fig. 6)[51].

2.2 Triterpenoid-based co-assembly systems

Two pharmacologically active triterpenoid natural small molecules can be combined to construct a drug delivery platform through a co-assembly strategy, leveraging synergistic effects and mitigating drug toxicities and side effects[52, 53]. Terpenoids are hydrocarbons or their oxygen derivatives with a molecular formula that is a multiple of the isoprene unit. These oxygen derivatives can be alcohols, aldehydes, ketones, carboxylic acids, esters, etc. In recent years, assembly-capable terpenoid compounds have been continuously developed, which can form nanoparticles of different shapes and sizes and may become potential platforms for efficient drug delivery. Cheng *et al.*[53] developed a green and simple supramolecular co-assembly of photosensitizing drugs. After screening 17 terpenoid compounds, it was determined that 11 of them could form suitable-sized co-assembly small molecules. The representative betulinic acid (BC) formed nano co-assemblies (BC-Ce6 NPs) through strong intermolecular π-π stacking and hydrophobic interactions. BC-Ce6 NPs synergistically enhanced the *in vitro* and *in vivo* anti-tumor effects, triggering an excellent

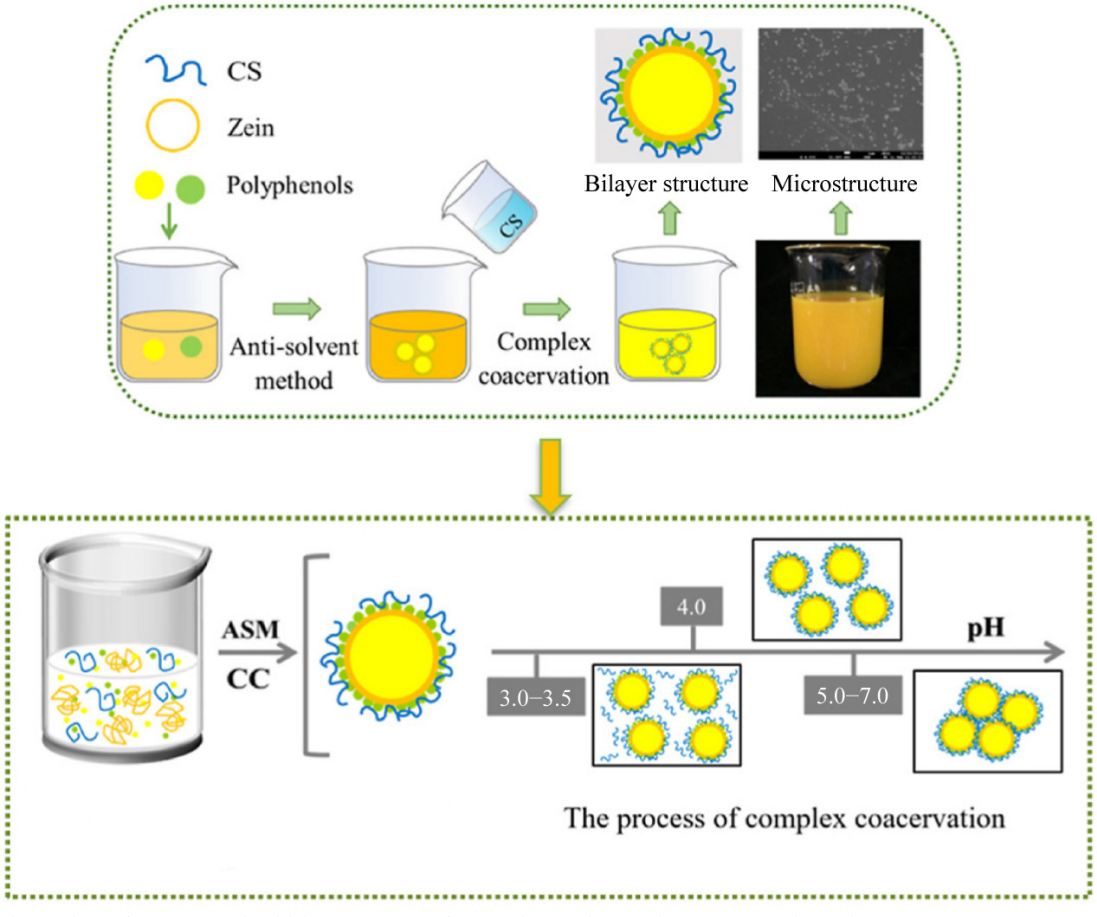


Figure 5 Synthesis scheme for co-encapsulated bilayer structures of nanoscale complexes and micrometer-scale condensates ZCSC-Cur-Que. ASM: Anti-solvent method, CC: Complex coacervation[48].

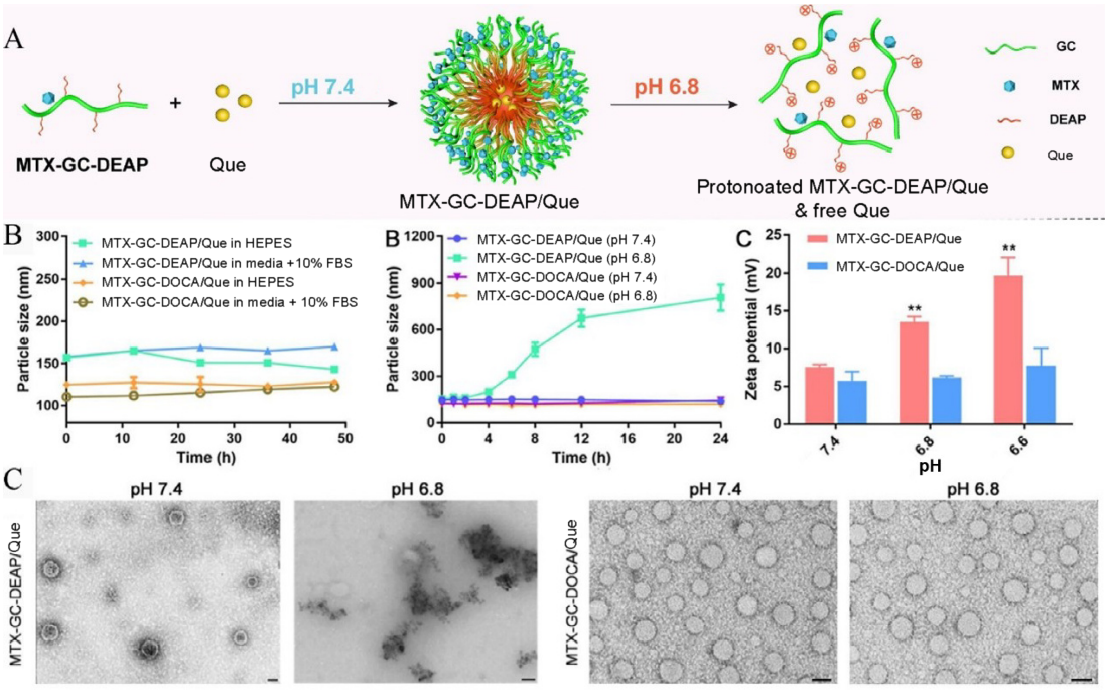


Figure 6 Structure of MTX-GC-DEAP and assembly and characterization of MTX-GC-DEAP/Que. (A) Size-time profiles in pH 7.4 HEPES buffer solution and DMEM media with 10% FBS as determined by DLS (n = 3). (B) Size and Zeta potential changes against different pH values. $^{**}P < 0.01$ *vs* MTX-GC-DEAP/Que at pH 7.4, n = 3. (C) TEM images in PBS with different pH values. Scale bar was 100 nm[51].

and safe chemophotodynamic combination therapy with highly efficient tumor ablation. The research results provide insights into the tunable co-assembly of terpenoid compounds and offer a new perspective for constructing natural product-mediated nano co-assemblies (Fig. 7)[53].

Wang *et al.*[54] used representative pentacyclic triterpenoids, oleanolic acid (OA), and glycyrrhetinic acid (GA), to prepare composite NPs as drug carriers. The OA-GA NPs exhibited 15% paclitaxel (PTX) loading, along with good stability and slow release. In antitumor therapy, this drug carrier not only demonstrated a synergistic antitumor effect but also addressed the issue of applying bioactive compounds directly (Fig. 8).

Although triterpenoids have a wide range of pharmacological effects, the mode of action of their therapeutic effects requires further elucidation[55]. Chen *et al.*[56] revealed the co-assembly properties of cucurbit triterpenoids and steroids derived from the Chinese herb *Hemsleya penxianensis* and constructed a series of β-sitosterol-Sito-mediated co-assembled drugs (Sito-hemslecin A (HA) co-assembly). These co-assembled drugs exhibited enhanced synergistic anti-tumor efficacy. It is hypothesized that this may be attributed to the improved hydrophilicity and morphology of the drugs after interaction, making them easier to adhere to cells. This study not only expands the potential applications of triterpenoid natural small molecules but also offers new perspectives on the therapeutic co-assembly of multiple natural small molecules (Fig. 9)[56].

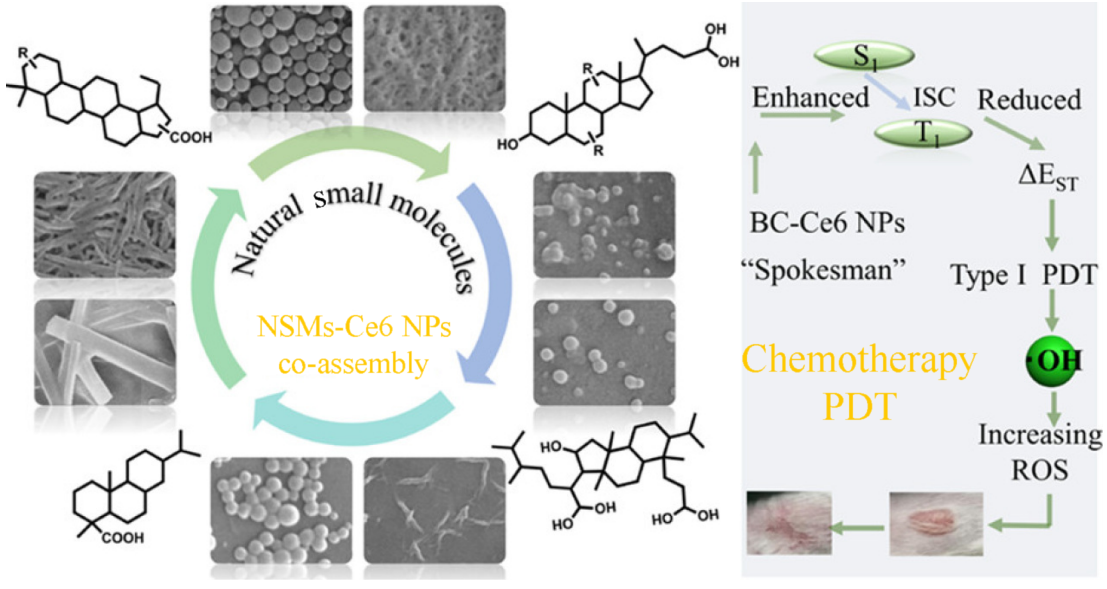


Figure 7 A range of nano-sized terpenoid NSM-tuned co-assembled photosensitizers was developed via a direct co-assembly strategy. These nanostructures are tunable in morphology and size, making them suitable for combination chemophotodynamic therapy. PDT: Photodynamic therapy, ROS: Reactive oxygen species[53].

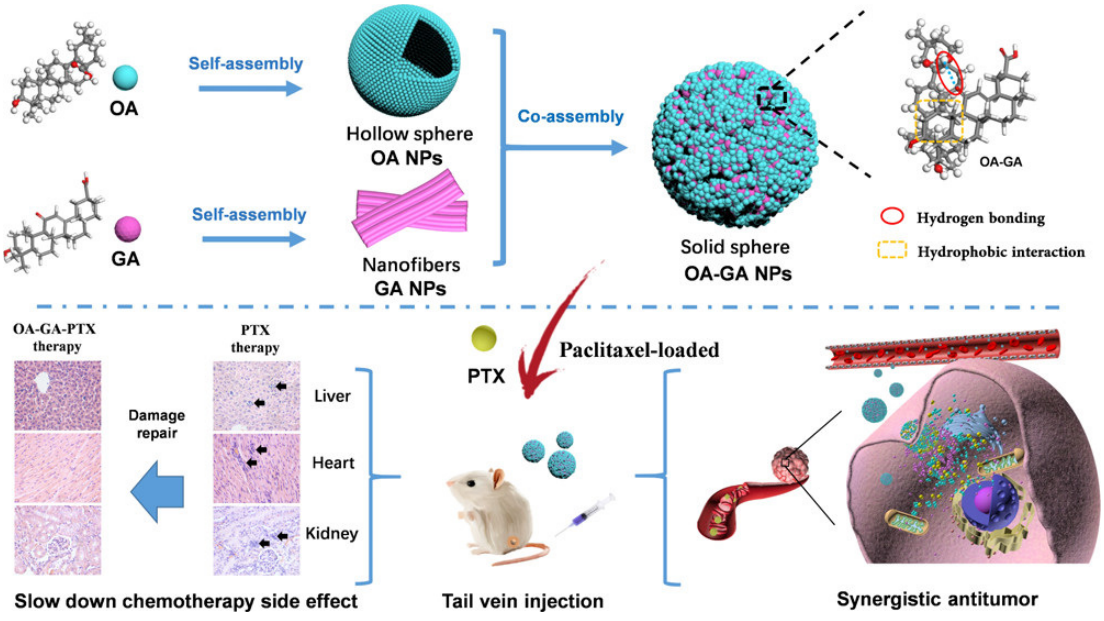


Figure 8 OA-GA co-assembled NPs for synergistic anti-tumor effects while mitigating the side effects of chemotherapeutic drugs[54].

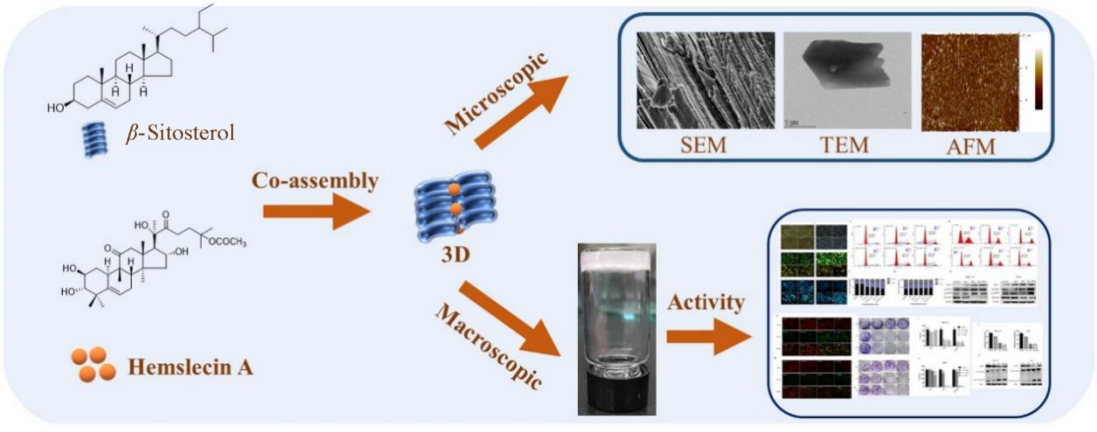


Figure 9 Co-assembled nanodrugs derived from Sito and HA with biosafety and bioactivity[56].

2.3 Polyphenol-based co-assembly systems

Polyphenols are natural small molecules abundant in plants, characterized by phenolic hydroxyl groups, and known for their beneficial effects on human health. Recent discoveries have unveiled a variety of polyphenolic small molecules with outstanding antioxidant, antitumor, anti-inflammatory, antibacterial, and antiviral activities[57-60]. Additionally, polyphenolic small molecules offer advantages in stability and modification, making them highly promising for bioimaging and nano delivery applications[61-64]. Polyphenols exhibit a wide range of co-assemblies, not only with multi-component small molecules but also with metal ions, inorganic materials, polymers, proteins, and nucleic acids. This paper discusses a few cases of co-assemblies involving typical polyphenolic small molecules (Fig. 10)[65].

The co-assembly of small molecules inspired by nature finds wide application in various biomedical fields. While the co-assembly of hydrophobic and hydrophilic drug- and food-derived active small molecules has been less explored, there is growing interest in developing such nanomedicines for applications in medicine, biology, materials, drug delivery, and more[66-72]. Sun *et al.*[22] drew inspiration from the unique self-assembly properties of the natural bioactive small molecules, cinnamaldehyde (CA), and tannic acid (TA), to create a novel multifunctional nanomedicine using an ultrasound-triggered irreversible equilibrium self-assembly and ionic crosslinking co-driven approach. CA, extracted from cinnamon, offers antimicrobial, anti-inflammatory, anti-cancer, nutritional, and health benefits. However, its practical applications are limited due to hydrophobicity and susceptibility to degradation in the external environment. TA, known for its hydrophilicity and excellent bioactivities, is commonly used as an antiseptic agent and in the modification of biomedical nanomaterials. The antimicrobial properties of CA and the antioxidant properties of TA were harnessed in the creation of nanomedicines. The CA-TA-ZA nanospheres (CA-TA-ZA NSs) system was synthesized by strong ionic cross-linking between zinc acetate (ZA) and TA molecules. This green and simple synthesis process, utilizing natural raw materials, ensures that the CA-TA-ZA NSs hydrogels are safe, degradable, and biocompatible. This hydrogel synthesized by the co-assembly of bioactive small molecules from natural medicinal and food sources provides a theoretical basis for the application of antimicrobial wound dressing, making it a competitive antimicrobial wound dressing (Fig. 11)[22].

Natural polyphenols can combine chemotherapy and gene therapy due to their polyhydroxyl groups, which synergistically

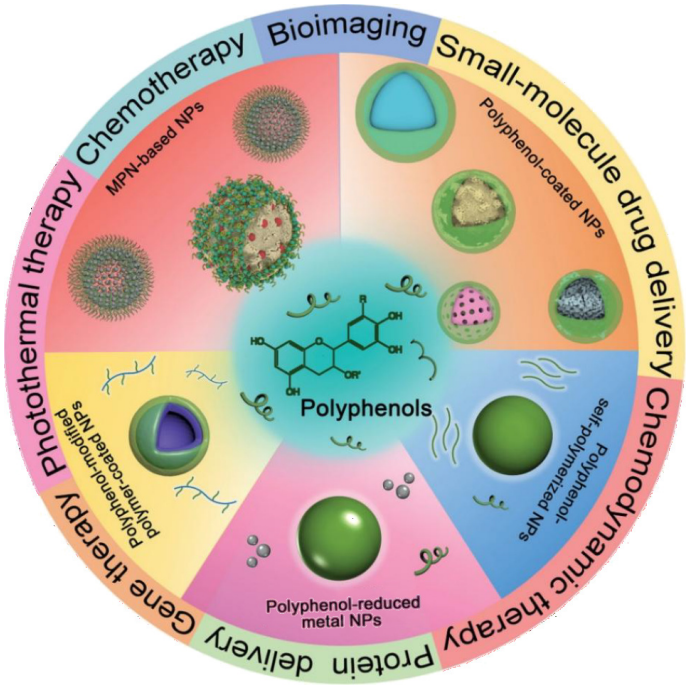


Figure 10 Polyphenolic small molecules as building blocks for the preparation of polyphenol-containing nanomedicines and delivery modes, and other biomedical applications[65].

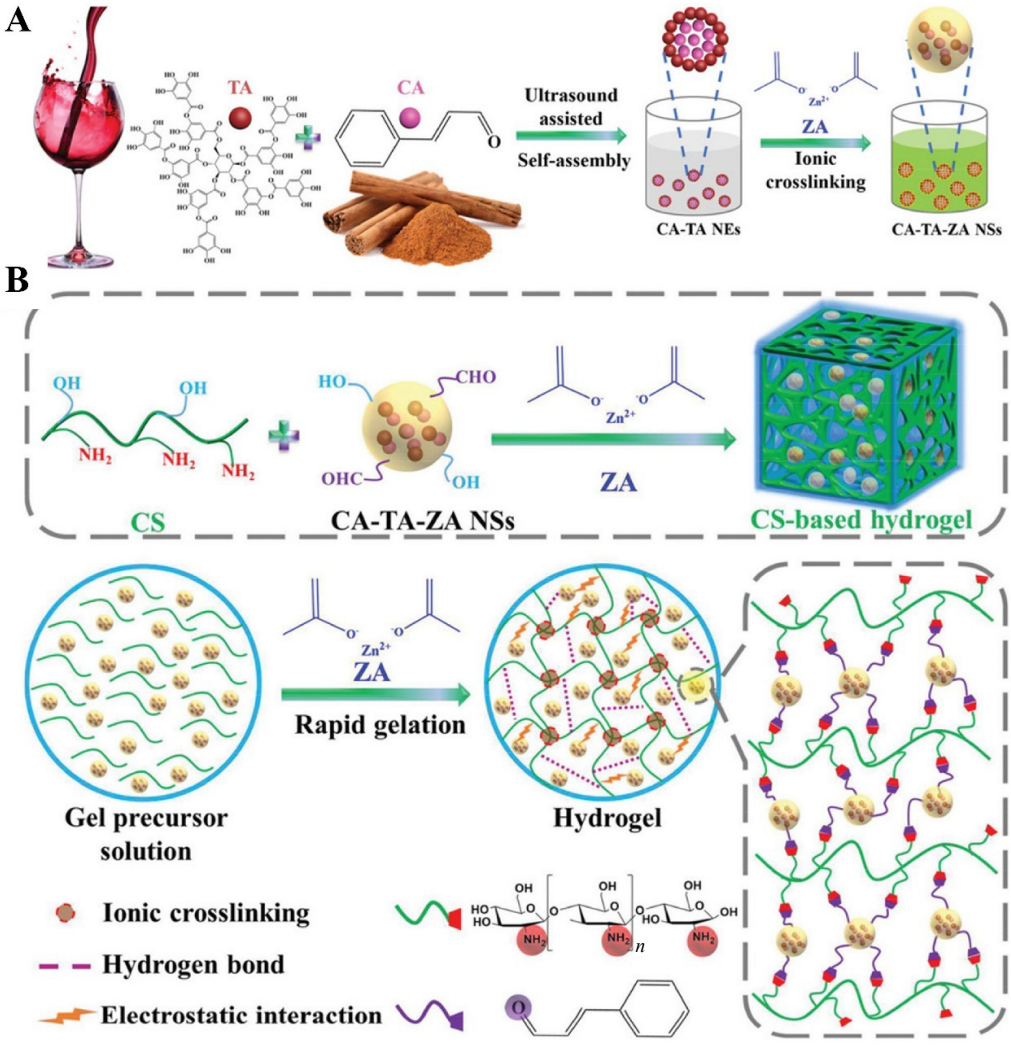


Figure 11 (A) Flowchart of the preparation of CA-TA-ZA NSs; (B) Synthesis process and potential gelation mechanism of CS-based hydrogels[22].

enhance the efficacy of chemotherapeutic drugs by silencing tumor-related genes[73]. TA, a typical natural polyphenol compound, is commonly used in co-assembly strategies and can regulate the assembly of nucleic acid nucleating nanocomplexes in cells for smart drug delivery and gene therapy. Studies have demonstrated that polyphenolic compounds have a high affinity for nucleic acids and proteins, forming the theoretical basis for nucleic acid-polyphenol co-assembly. Han *et al.*[74] designed a nucleating nanocomplex with controlled degradation in cells using an assembly strategy, suitable for smart drug delivery and gene therapy. TA played a dual role in structural stabilization and therapeutics by mediating the assembly of nanocomplexes and cell membrane camouflage. In terms of bioactive function, TA regulated the acidic response of nanocomplexes and induced apoptosis in tumor cells. This work integrates the multifunctionality of polyphenols and the programmable design of nucleic acid sequences to create engineered nanoplatforms for precision medicine, further expanding the application of polyphenols in biomedicine (Fig. 12)[74].

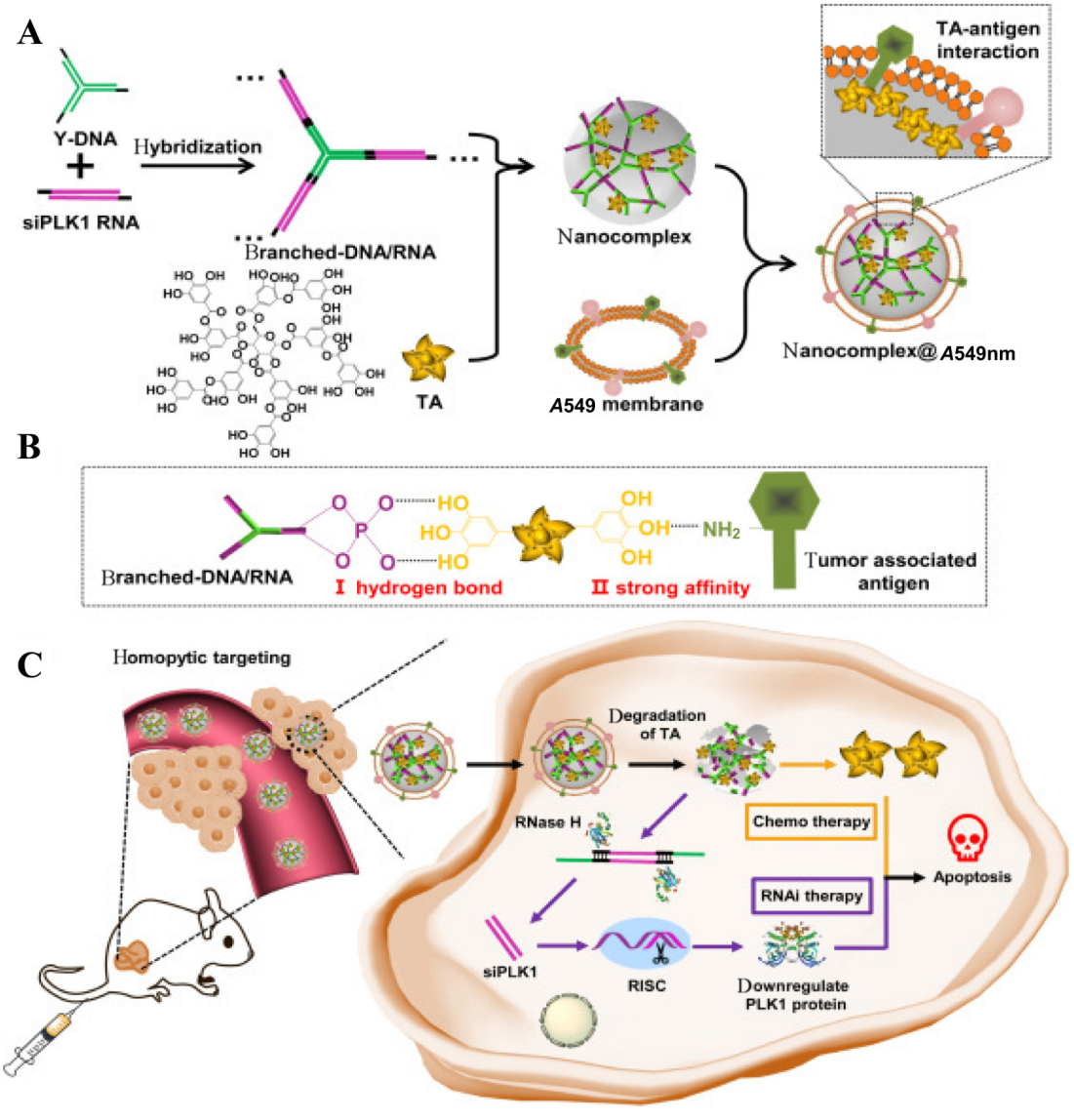


Figure 12 (A) Construction of nucleic acid nanocomplexes through nucleic acid self-assembly mediated by TA and cell membrane camouflage. (B) Development of a "dual interaction" force scheme for constructing nanocomplexes. (C) Controlled disassembly of nanocomplexes in target cells for intelligent drug delivery and gene therapy[74].

2.4 Phenylpropanoid-based co-assembly systems

Phenylpropanoid compounds, characterized by three linear carbon chains linked to a benzene ring, form the basic structural unit. They are classified into simple phenylpropanoid compounds, coumarins, and lignans based on their structure[75]. These compounds play a crucial role in the metabolism of natural plant compounds, exhibiting rich pharmacological activities, particularly in inhibiting tumor cell proliferation in cancer therapy. The hydroxyl and carboxyl groups present in their structure make phenylpropanoid compounds amenable to structural modification, allowing them to act as coupling active molecules in co-assembly, imparting special activity to the co-assembled monomer molecules. Phenylpropanoid compounds possess notable antioxidant, antitumor, and anti-inflammatory activities, making them a class of active natural small molecules worthy of further development (Fig. 13)[76].

Jia *et al.*[77] synthesised a bimodular antioxidant prodrug, ethyl 4-(hydroxymethyl)phenylborate caffeate (HPEC), by conjugating ethyl caffeate (EC) with 4-(hydroxymethyl)phenylboronic acid.

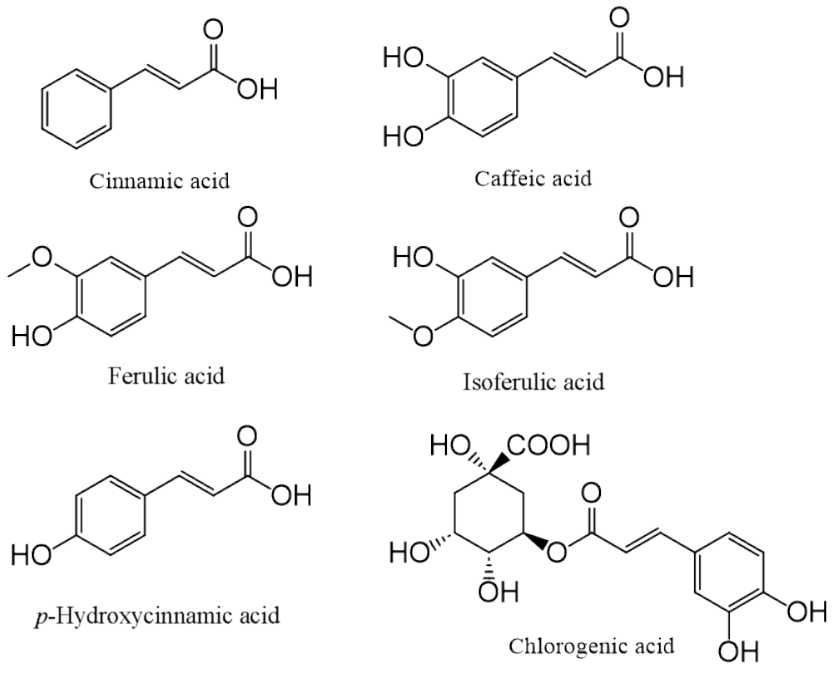


Figure 13 Structures of common phenylpropanoids cinnamic acid, *p*-hydroxycinnamic acid, caffeic acid, ferulic acid, isoferulic acid, and chlorogenic acid[76].

Then, HPEC-conjugated supramolecular nano-assemblies containing *L*-serine crowns (Ser-HPEC) were prepared based on the concept of subject-object chemistry for the targeted treatment of acute kidney injury (AKI). The selective accumulation of Ser-HPEC nanoparticles in AKI kidneys is achieved through specific interactions between l-serine and Kim-1, maximizing the efficacy of the nanoparticles. Two antioxidants, ethyl caffeate and 4-hydroxybenzyl alcohol (HBA), can be released from individual modules to enhance ROS scavenging efficacy. HPEC can scavenge high levels of ROS at the AKI site, and then rapidly decompose into the potent antioxidants EC and HBA, which can further eliminate harmful ROS and reduce detrimental acute inflammation. After intravenous injection, circulating nanocomponents can selectively accumulate in injured kidneys due to recognition between *L*-serine and overexpressed Kim-1 on the damaged renal tubular epithelial cell membrane. By consuming pathological ROS in damaged renal tissues and cells, the antioxidant fractions EC and HBA can be further released from Ser-HPEC nanocomponents, alleviating AKI. This strategy combines a multi-step ROS scavenging approach with precise targeting capabilities, holding great potential for treating ROS-related diseases (Fig. 14)[77].

Zheng *et al.*[78] proposed a method for the synthesis of a homopolymer with repeating units of ferulic acid. The nanoparticles exhibit a reasonable drug-loading capacity of approximately 8.3% PTX and possess excellent biocompatibility and degradability. *In vitro* and *in vivo* studies demonstrated a significant inhibitory effect of the nanoparticles poly ferulic acid (PFA) @PTX NP on colon cancer, confirming the inherent anticancer properties of PFA *in vivo*. These novel nanoparticles based on polyferulic acid not only effectively deliver chemotherapeutic drugs but also provide additional anticancer therapeutic effects, offering a promising platform for the clinical treatment of colon cancer (Fig. 15).

2.5 Alkaloid-based co-assembly systems

Alkaloids are nitrogenous alkaline organic compounds found in nature, primarily in plants but also in some animals, exhibiting alkaloid-like properties. Most alkaloids have a complex ring structure with nitrogen predominantly contained in the ring. They are categorized into organic amine alkaloids, isoquinoline alkaloids, pyridine alkaloids, indole alkaloids, diterpene alkaloids and scopolamine alkaloids based on their structure[79]. Alkaloids exhibit a variety of pharmacological activities, including anti-inflammatory, antibacterial, vasodilator, hypoglycemic, and anticancer effects, which may be attributed to their diverse structures. Quinoline alkaloids represent the most numerous and structurally complex class of alkaloids. The well-known natural anticancer drug camptothecin (CPT) belongs to the quinoline alkaloid group. Quinine, derived from quinoline alkaloids, was first extracted from the bark of the cinchona tree and its relatives in the Rubiaceae family and has been an effective antimalarial drug that has saved countless lives[80-82].

Alkaloids have unique and complex nitrogen-containing ring structures, which can be assembled through various non-covalent interactions, mainly including hydrogen bonding, π-π conjugation, and hydrophobic interactions. Additionally, alkaloid structures can form basic stacking units through non-covalent interactions, which can further assemble to construct the basic framework of materials. Most alkaloid structures contain asymmetric carbon atoms, hence exhibit optical activity. Due to the complexity of molecular conformation and intermolecular forces, serendipity exists in the exploration of co-assembly. Further enrichment of compound co-assembly cases is needed. Currently, self-assembly can effectively enhance the stability and drug loading capacity of alkaloid compounds, making co-assembly of alkaloids an economical and efficient preparation strategy.

Berberine (BBR) is the main alkaloid in goldenseal with potent antibacterial properties. Its low bioavailability limits its clinical applications. Dong *et al.* utilized a co-assembly strategy to prepare nanoparticles of BBR and (−)-epigallocatechin-3-gallate (EGCG) through solvent evaporation. BBR-EGCG NPs exhibited enhanced pharmacological activity, low toxicity, and economic feasibility. The antibacterial effect against Staphylococcus aureus and Methicillin resistant staphylococcus aureus (MRSA) was superior

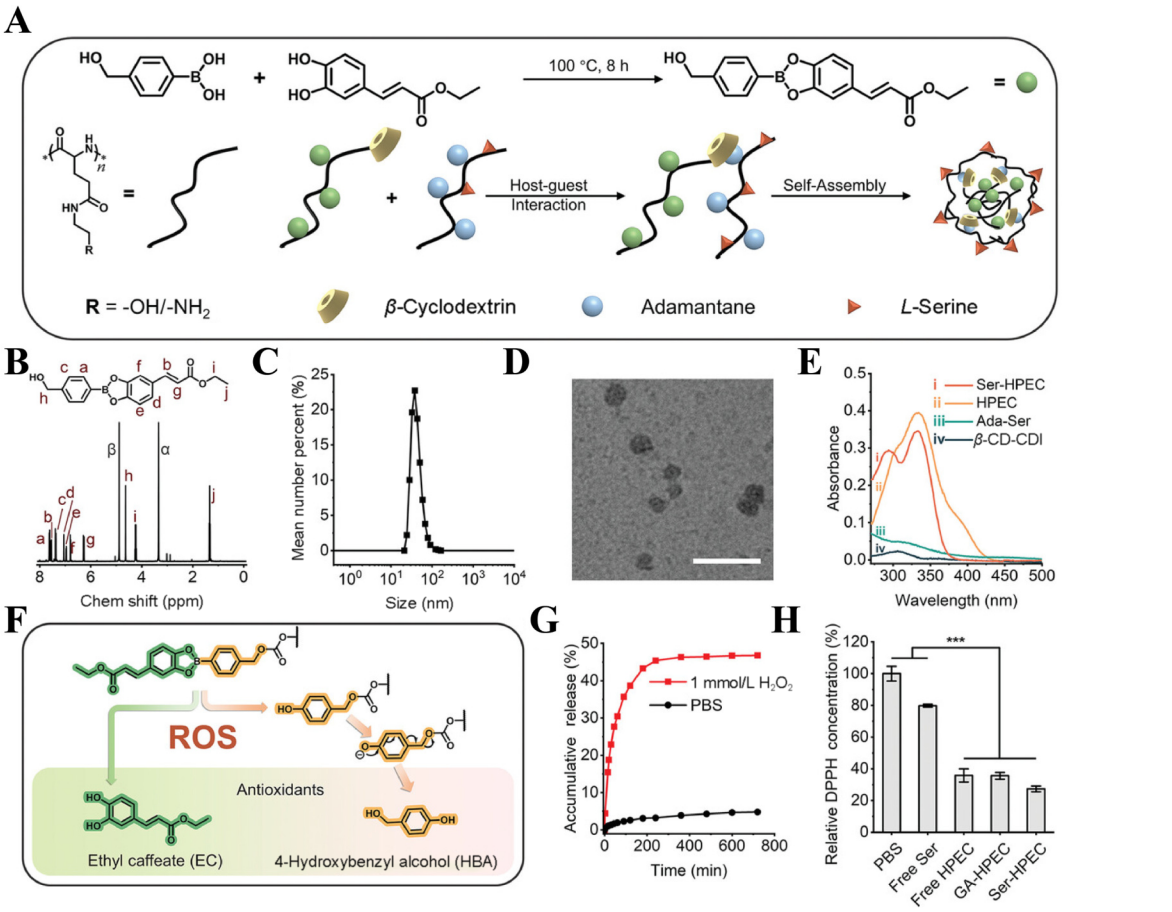


Figure 14 Schematic and characterization results of Ser-HPEC synthesized by supramolecular nano-assembly[77]. (A) Schematic of the synthesis of HPEC and Ser-HPEC nano-assemblies. (B) ^{1}H NMR spectra of HPEC (500 MHz, MeOH-d4). (C) Size distribution. (D) TEM images of Ser-HPEC nano-assemblies. Scale bar: 100 nm. (E) UV-Vis spectra of Ser-HPEC and its precursors. (F) UV-Vis spectra of Ser-HPEC and its precursors. (G) UV-Vis spectra of Ser-HPEC and its precursors. (H) UV-Vis spectra of Ser-HPEC and its precursors. Data are expressed as means ± s.d., n=3, ***P<0.01 (one-way ANOVA).

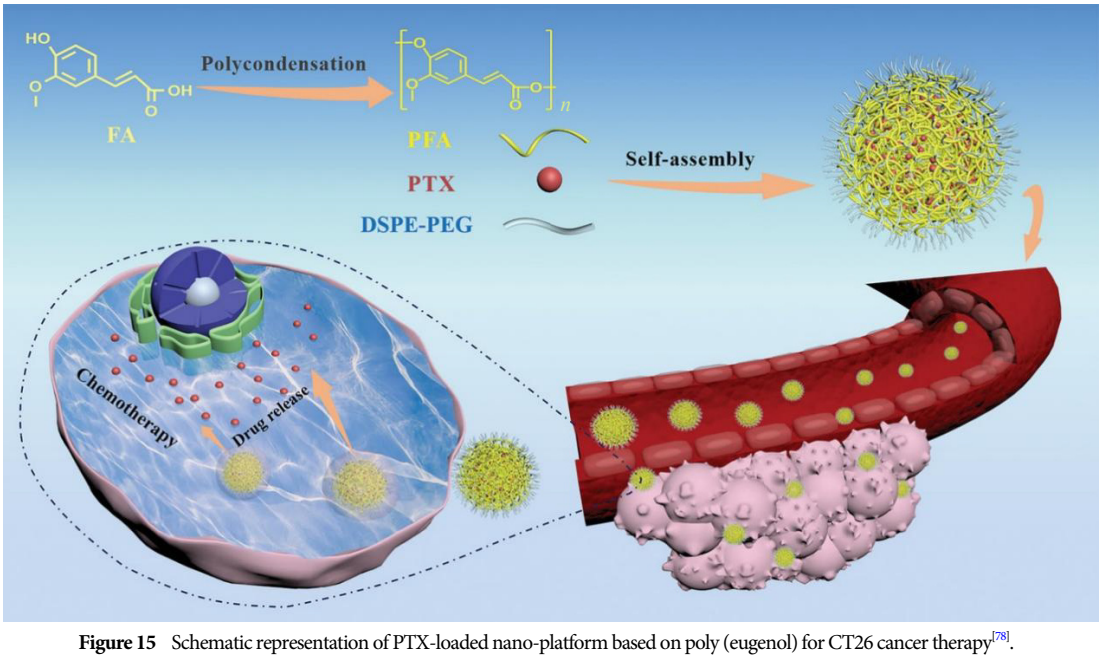


Figure 15 Schematic representation of PTX-loaded nano-platform based on poly (eugenol) for CT26 cancer therapy[78].

to monotherapy. Importantly, BBR-EGCG NPs showed better inhibition against MRSA compared to first-line antibiotics such as potassium benzylpenicillin (BP) and ciprofloxacin (Cip). Furthermore, BBR-EGCG NPs effectively promoted wound healing in mice by removing bacteria (Fig. 16)[83].

PTX is one of the most widely used anticancer drugs and can mediate co-assembly with other amphiphilic drugs to synthesize nanomedicines with enhanced activity. The potent activity of PTX

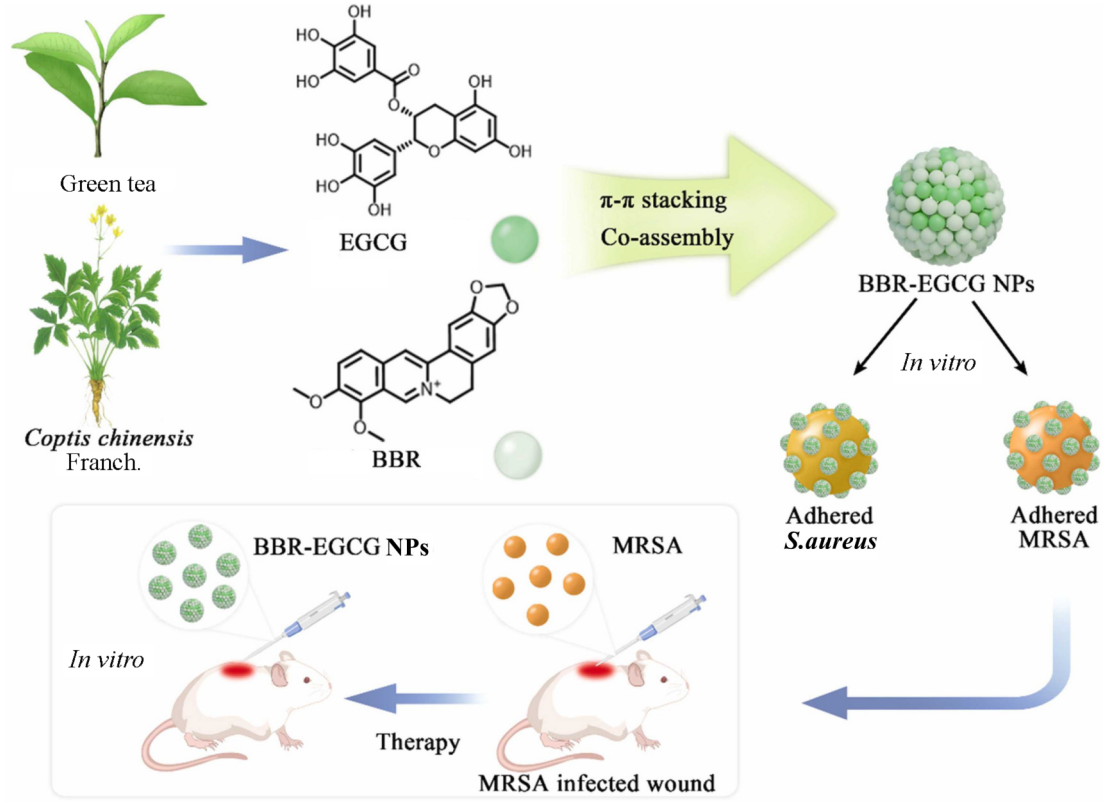


Figure 16 Schematic representation of the co-assembly of BBR-EGCG NPs and the antibacterial mechanism[83].

can also contribute to synergistic effects in combination therapies, offering valuable insights into translational nanomedicine. Zou *et al.*[84] proposed a strategy for PTX-mediated co-assembly with the amphiphilic prodrug Evans Blue Conjugated CPT molecule (EB-CPT). Since EB-CPT can spontaneously self-assemble into micelle-like particles, effective anticancer activity can be achieved *in vivo*. By optimizing the synthetic route of EB-CPT and adjusting the weight ratio between EB-CPT and PTX to mediate the amphiphilic self-assembly of another anticancer prodrug, EB-CPT, the researchers observed a shape transition from spherical particles to spherical vesicles and vesicular tubular structures. Importantly, the co-assembled nanomedicine exhibited uniform size and morphology, with close to 100% drug loading efficiency and high PTX content. This work, utilizing a co-assembly strategy to combine two anticancer drugs/precursors, exemplifies the potential of nanomedicine (Fig. 17)[84].

Wang *et al.*[85] devised an innovative drug delivery system utilizing photothermal energy for tumor cell eradication and surgical guidance via the second near-infrared (NIR-II) imaging. This system effectively integrates the advantages of chemotherapy and immunotherapy. They employed the quinoline alkaloid CPT for its cytotoxic effects on tumor cells, esterifying CPT's conjugated double bond with polyethyleneglycol (PEG) to form an amphiphilic compound. Using the nanoprecipitation technique, they co-assembled CPT-S-PEG, a new NIR-II molecule named TST, and the novel immune checkpoint inhibitor AZD4635 into nanoparticles. Upon release, TST improved non-radiative attenuation and accelerated photothermal conversion, enhancing the drug's efficacy in the high H_2O_2 environment at the tumor site. Photothermal therapy induced cancer cell immunogenic cell death (ICD), releasing ATP into the tumor microenvironment, recruiting immune cells for cancer cell destruction. Excess ATP was converted to adenosine via the CD39-CD73-A2-AR pathway, suppressing immune cell activity. Subsequently, the photothermal breakdown of nanoparticles released AZD4635, effectively blocking this inhibitory pathway and achieving successful coordination of photothermal therapy, chemotherapy, and immunotherapy (Fig. 18).

3 Co-assembly mechanism of natural plant compounds

The concept of co-assembly entails the formation of functional systems with unique properties through intermolecular interactions between two or more small molecules. Non-covalent interactions, including hydrogen bonding, charge transfer interactions, van der Waals forces, π-π stacking interactions, and hydrophobic interactions, are crucial in constructing co-assembled systems[86-88].

The strategy of supramolecular co-assembly based on metal coordination is common in the research process of nanomedicine. Metal coordination breaks the clear boundary between traditional inorganic and organic materials. Metal coordination bonds are stronger than hydrogen bonds and van der Waals forces but weaker than covalent bonds. Most importantly, the strength of metal coordination bonds can be adjusted according to changes in the environment. In addition, metal coordination bonds can specifically respond in the acidic microenvironment of tumors according to the theory of coordination equilibrium, destroying the tumor microenvironment and exerting excellent therapeutic effects (Table 2)[89].

4 Advantages of co-assembly of natural plant compounds

Nanomedicine technology has significantly advanced drug

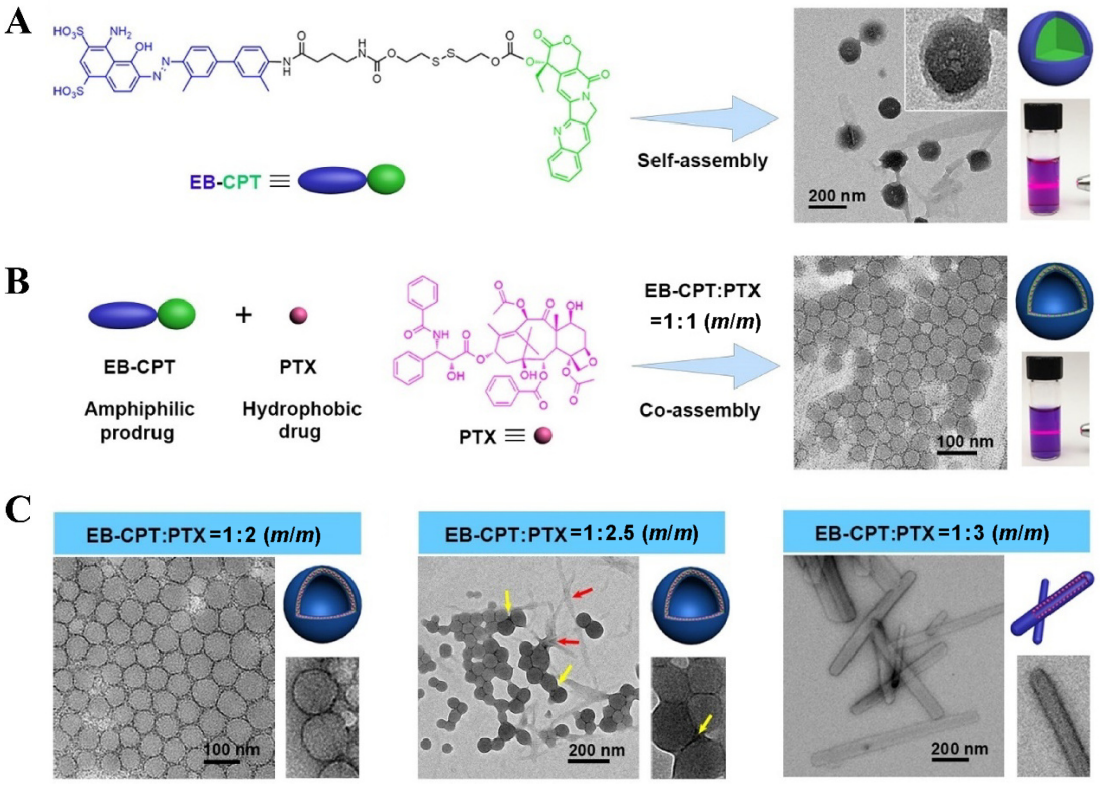


Figure 17 Schematic synthesis of PTX ultra-high drug loading vesicular nanomedicine via a co-assembly strategy with another amphiphilic pre-drug[84]. (A) Schematic diagram of EB-CPT self-assembly alone and TEM images of the obtained EB-CPT particles. (B) Schematic diagram of EB-CPT and PTX co-assembled at a weight ratio (*m*/*m*) of 1:1 and TEM images of ECX NV obtained. (C) TEM images of ECX NV with different weight ratios (1:2, 1:2.5 and 1:3). Red arrows indicate fibrillar structures and yellow arrows indicate vesicle fusion structures. Corresponding cartoons and magnified TEM images are shown on the right.

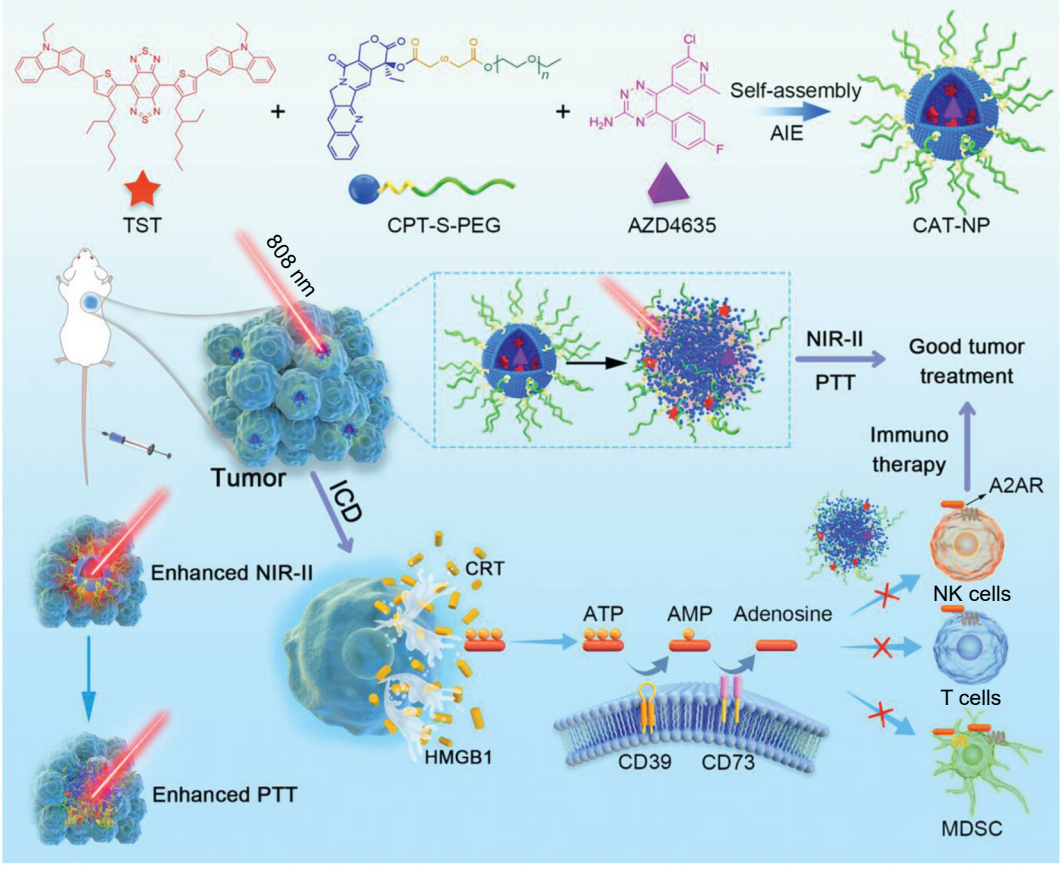
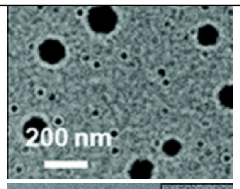
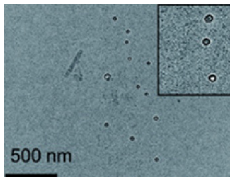
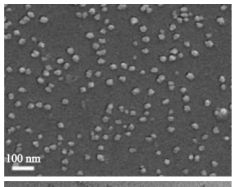
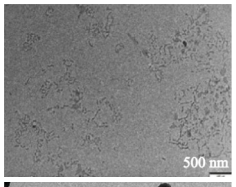
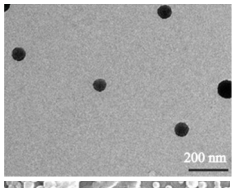
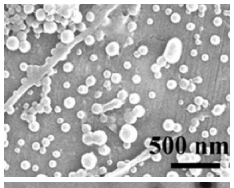
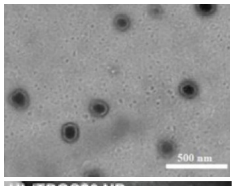
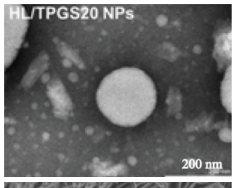
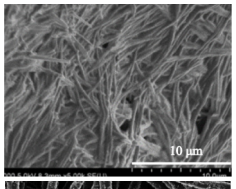
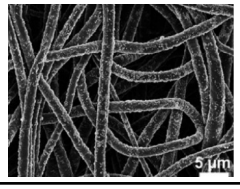


Figure 18 Co-assembly of TST, CPT-S-PEG, and AZD4635 into nanoparticles (CAT-NP) by nanoprecipitation, achieving excellent synergy of photothermal therapy, chemotherapy, and immunotherapy[85].

Table 2 Mechanism and morphology of co-assembly of typical natural plant compounds

Natural plant compounds	Morphology	Electron microscope pictures	Assembly mechanism	Reference
Cur	Spherical		Hydrophilicity	[41]
Cur/Cyanine	Spherical		Electrical charge interaction	[90]
EGCG/lanthanide metal ions (Sm^{3+})	Spherical		Coordination	[91]
Resveratrol	Hydrogel		Hydrophobic interactions/Hydrogen bonding	[92]
Gallic acid/Epigallocatechin gallate EGCG/TA	Spherical		Metal coordination/Hydrogen bond	[93]
Pentacyclic triterpene BC	Spherical		Hydrophilicity	[52]
Camptothecin	Spherical		Hydrophilicity	[94]
Camptothecin	Spherical		Hydrophilicity	[81]
Chlorogenic acid	Hydrogel		π-π stacking/hydrogen bonding	[95]
TA	Fibroid		Electrostatic interaction	[96]

delivery and bioimaging, contributing to improved healthcare in clinical medicine. Nanotechnology enhances drug efficacy by improving solubility, bioactivity, and targeting effects, thereby minimizing side effects on non-targeted organs and efficiently delivering drugs to the target site. The rapid evolution of nanomedicines is exemplified by the U.S. Food and Drug Administration (FDA) approval of Abraxane, a formulation of human albumin particles containing PTX, for treating metastatic breast cancer.

Natural plant compounds, such as flavonoids, alkaloids, terpenoids, phenylpropanoids, and polyphenols, are extensively used in disease prevention and treatment due to their nutritional richness, structural diversity, and remarkable biological activity. However, these compounds face challenges in clinical applications, including poor solubility and bioavailability. Their multi-target properties can be advantageous as multi-target drugs to enhance efficacy, but they can also lead to toxic side effects due to their complex activity. Therefore, the benefits of natural plant compounds can be maximized through better utilization with adjuvants. Natural phytochemicals can self-assemble into carrier-free structures with higher drug loading capacity, exhibiting excellent pharmacological activity, biocompatibility, and relatively low immunogenicity.

The co-assembly strategy of natural plant compounds harmonizes the relationship between natural phytochemicals and nanotechnology, achieving a win-win situation. Co-assembled nanomedicine structures based on natural phytochemicals offer high safety, improved biodegradability and biocompatibility, and better structural modification for enhanced targeting. These structures not only deliver drugs but also act as active ingredients at the target site. By applying the concept of synergistic therapy to multi-component compounds, ideal co-assembled nanostructures can be constructed. These features make natural plant compounds more widely applicable and adaptable to the rapidly developing field of nanomedicine, promising to enrich the clinical treatment of diseases.

5 Conclusions and prospects

In the evolution of the universe, materials have progressed from simplicity to complexity, from lower to higher levels of organization. Assembly is the fundamental principle governing the formation of each entity, where molecules, with their unique chemical properties, orderly arrange and interact with each other. Whether in chemical or biological transformations, these processes ultimately boil down to changes in forces. Natural plant compounds harness abundant non-covalent forces to undergo myriad changes, transitioning from monomers to supramolecular structures, deepening our understanding of nature. The co-assembly of natural plant compounds represents a promising area of chemistry. Current drug screening strategies based on these compounds face increasing challenges, making the exploration of existing natural plant compounds' therapeutic potential through co-assembly strategies a compelling research interest. Co-assembly provides a dual benefit, endowing certain natural plant compounds with unique microstructures, functions, and advantages, freeing them from the limitations of other excipients, and expanding the application scope of natural plant compounds through the design of novel prodrugs and the repurposing of existing drugs.

While the co-assembly strategy of natural plant compounds has garnered significant research attention, the design of specific nanostructures requires a clear understanding of the potential intermolecular interactions, conformational relationships, pharmacological activities, and *in vivo* degradation and metabolism processes of these compounds. This necessitates considerable time and technological advancements before clinical translation can be realized. Additionally, the complex structures and functional groups of natural plant compounds, and their effects on co-assembly during the assembly process, require further elucidation. The transition from traditional Chinese medicine decoction to the co-assembly of nanoparticles provides inspiration. Combining the chemistry of traditional Chinese medicine with the principles and techniques of molecular co-assembly science represents a valuable research direction. This approach holds significant research significance in elucidating the interactions of natural medicinal small molecules and in developing new natural small-molecule nanomedicines.

Conflicts of interest

The authors declare no competing financial interest

Acknowledgments

This work was financially supported by the National Key R&D Program of China (No. 2022YFF1100303), the National Natural Science Foundation of China (No. 82172085), the Double First-Rate construction plan of China Pharmaceutical University (No. CPU2022QZ14), and the Jiangsu Provincial Natural Science Fund for Distinguished Young Scholars (No. BK20190028).

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