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Research progress on the *in vivo* fate of self-assembled traditional Chinese medicine ingredients: Absorption, transportation and distribution

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ABSTRACT

The active ingredients components of traditional Chinese medicine (TCM) can naturally create supramolecular structures like nanoparticles and micelles with well-defined functions through a dynamic assembly mechanism driven by noncovalent bonding interactions. In recent years, numerous studies have found that the supramolecular self-assemblies of TCM, which are also known as Chinese medicine supramolecules (CMS), exhibit better efficacy, higher bioavailability, and synergistic effects. *In vivo* fate analysis is a roadblock to revealing the active mechanisms of CMS. This review focuses on the *in vivo* dynamic biological fate of herbal self-assemblies and systematically elucidates their delivery characteristics in absorption barrier penetration, biofilm transport, and tissue-specific distribution. Meanwhile, this review summarizes the progress in applying cutting-edge detection techniques for tracking supramolecular behavior *in vivo*, including fluorescent labeling, isotope tracing, and multimodal imaging. By summarizing the existing research results, we aim to construct a systematic research framework for the *in vivo* behaviors of Chinese medicine self-assemblies and explore feasible analysis paths for Chinese medicine formulations.

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1. Introduction

Supramolecules are molecular assemblies with specific physicochemical properties that are self-assembled by molecules and intermolecular weak non-covalent interactions (*e.g.*, hydrogen bonding, hydrophobic interactions, π-π stacking) [1]. The self-assembly phenomenon in traditional Chinese medicine (TCM) was initially discovered in 1995 when Gröning *et al.* [2] observed the formation of nanoparticles (NPs) and precipitates in black tea extract, and then, more and more researchers have further verified that the phenomenon of self-assemblers is prevalent in TCM tonics or extracts [3,4]. Since TCMs are mostly compounded, their multiple active ingredients will form supramolecular self-assemblies with specific structures and functions, such as NPs, nanofibers, vesicles, and micelles, driven by weak bonds during the decoction process or after entering the human body [5,6]. This process can not only significantly enhance the efficacy [7] and effectively reduce drug toxicity [8], but also improve the poor solubility [9] and low bioavailability of TCMs [10–17]. Compared with conventional nanomedicines, TCM supramolecular self-assembled structures are derived from natural components, without external carrier materials and complex synthetic process, thereby exhibiting preferable endogenous biocompatibility. Additionally, the Chinese medicine supramolecules (CMS) assembled with multiple components not only preserves the "multi-target" characteristics of TCM but also achieves a "synergistic enhancement" effect. Therefore, the self-assembly strategy is considered a novel approach to enhancing clinical efficacy and modifying herbal toxicity [18].

It should be clear that in this review, the term "supramolecular self-assemblies of TCM" or "CMS" refers to the ordered aggregates of active ingredients of TCM (*e.g.*, flavonoids, alkaloids, saponins) that are dynamically formed through non-covalent interactions during the decoction process or in the physiological environment of compound compounding and that have clear biological activities. Such assemblies usually manifest as specific structural entities at the nanoscale, including but not limited to nanosphere, nano-gels, lipid micelles, fiber networks, polysaccharide copolymers (Fig. 1). Therefore, in this review, "NP" refers to the physical

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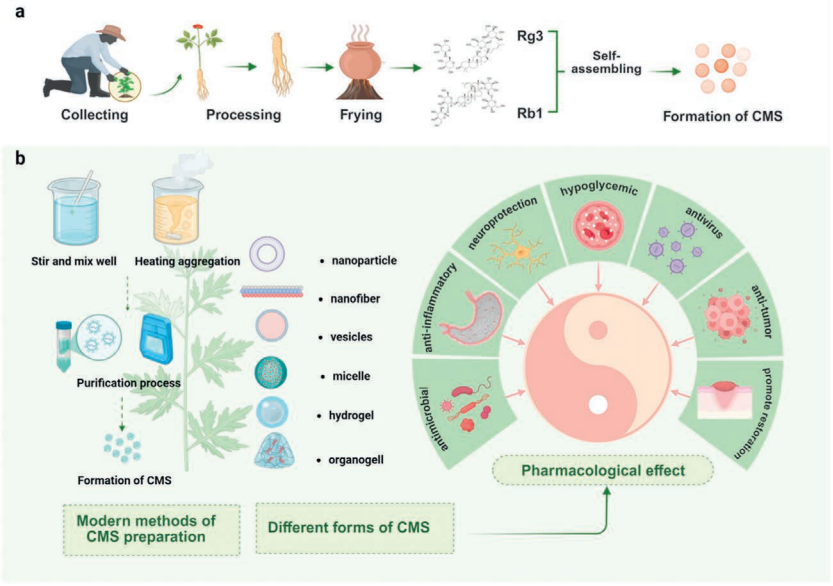


Fig. 1. Schematic diagram of the formation and pharmacological effects of CMS in TCM. (a) An example of CMS formation, ginsenoside Rg3 and Rb1 was abstracted from *Panax ginseng* C.A. Mey. (b) It presents the modern preparation method for CMS, which involves steps such as stirring, heating, and purification, and lists various forms of CMS, including NPs and nanofibers. It also highlights the broad pharmacological effects of CMS, which include anti-inflammatory, neuroprotective, hypoglycemic, antiviral, antitumor, and tissue repair properties.

manifestation of the self-assembled body, and CMS refers to native Chinese medicine NPs without a carrier. In the future, it should be emphasized that the self-assembled body of TCM is the functional carrier, the NPs are the material entities to realize the function, and the two together form a closed loop in which the structure and function interact with each other and are inseparable.

In recent years, research on CMS, especially the analysis of self-assembly mechanisms, optimization of drug efficacy, and development of novel structures, has attracted much attention, providing a breakthrough at the molecular level for revealing the synergistic effect of multiple components and compounding mechanisms of TCM. However, as a new research paradigm, the stability, transit efficiency and metabolic pathways of supramolecules in the body are the key to determining their efficacy. Existing papers have shown that lack of studies focus on the biological behaviors of CMS [19], a comprehensive and clear theoretical framework is essential to overcome the limitation. Therefore, this review aims to provide the first systematic and comprehensive overview of the dynamic fate of CMS in the body by reviewing their absorption, distribution, and metabolic pathways, including the mechanisms and challenges. This study seeks to establish a research foundation and provide reference guidelines for future investigations into TCM self-assembled molecules, thereby offering new directions for addressing the challenges of their clinical translation.

2. Absorption

The gastrointestinal tract of the human body is connected by four types of cells, predominantly intestinal epithelial cells, which absorb and digest nutrients *via* passive diffusion and active transport. Goblet cells secrete glycocalyx and mucin, which form a mucus barrier and are involved in immune defense. M-cells are found in specific areas of the Peyer's patches and are involved in lymphatic transport, and their presence facilitates the uptake of immunogens and large molecules such as proteins. Paneth cells have a limited absorption process in the gastrointestinal tract and mainly release lysozyme [20]. The pathways by which CMS crosses the gastrointestinal barrier encompass epithelial cellular transport, M cell transport, and paracellular transport (Fig. S1 in Supporting information); for the schematic diagram, please refer to the supporting information. The main pathway for CMS to cross the gastrointestinal barrier has the characteristic of "structure-oriented absorption". In addition, the absorption mechanism of CMS is significantly different from that of synthetic NPs, due to their spontaneous formation during decoction or in a physiological environment to promote multi-component synergy and endogenous response. The following section will focus on elucidating the absorption pathways of CMS, categorized by structural type. Representative self-assembled NPs based on different base structures were summarized in Table S1 (Supporting information).

2.1. Absorption mechanisms in the gastrointestinal tract

2.1.1. Small molecule co-assemblies

Small molecule co-assemblies are nanoscale supramolecular structures formed by two or more active small molecules (molecular weight <1000 Da) through noncovalent interactions. Small molecules of TCM, such as flavonoids, alkaloids, and saponins, have good self-assembly potential due to their unique chemical structures, including polyphenolic hydroxyl groups and conjugation systems, and realize efficient delivery and synergistic treatment through the self-assembly strategy of "drug-carrying drug". Such assemblies are currently the main research hotspots. The absorption mechanisms of such supramolecular co-assemblies primarily include self-defense and synergistic solubilization, micelle penetration, bio-barrier penetration enhancement, smart responsive release, and others. As a star small molecule in gel systems, glycyrrhizic acid (GA) leverages its unique structural characteristics (amphiphilic skeleton, rigid steroid nucleus conformation, and multi-functional group properties) to self-assemble with a variety of substances such as berberine [21], curcumin [22], and baicalein [9], demonstrating outstanding functional advantages such as spontaneous assembly, pH responsiveness, and excellent stability. Zhao and his team [23] showed that GA can improve the stability of readily degradable components in the gastrointestinal environment and enhance the pharmacological properties of

the compositions by utilizing the self-assembly properties, with a slow-release effect that promotes absorption by responsively controlling drug release.

2.1.2. Polysaccharide-based supramolecules

Polysaccharide-based supramolecules mainly refer to polysaccharide structures as the basic unit, utilizing their natural structural advantages and biocompatibility, and forming a dynamic structural network through non-covalent bonding interactions, which is both structurally diverse and dynamically responsive. Its absorption mechanism mainly relies on the following pathways: (1) Receptor- or non-receptor-mediated endocytosis: for example, Hu *et al.* [24] found that FS60-curcumin aggregates promote curcumin absorption from intestinal cells through lattice protein-mediated endocytosis and giant cell drinking. Meng and his team [25] obtained NHNPs from hawthorn after concoction induction, structural assembly, slow release of polyphenols, and promotion of absorption, and found that such assemblies enter cells through giant cell drinking and caveolin-mediated endocytosis and enhance the uptake of polyphenols by intestinal cells. (2) Improvement of intestinal mucosal permeability: Yang *et al.* [26] found that astragalus polysaccharides have typical self-assembly ability, and can self-assemble with flavonoids to form weak intermolecular bonds, which can not only enhance the permeation, owe to the complex formation after interaction between effective chemicals and lipid membranes, but also improve the intestinal mucosal permeability of the small intestine and the colon to improve the oral bioavailability of flavonoids.

2.1.3. Protein-based supramolecules

Protein-based supramolecular assemblers are protein-centered supramolecular self-assembling building blocks with core advantages such as biocompatibility, structural precision, and dynamic responsiveness. However, due to their physicochemical stability, such as low pH, gastrointestinal enzyme degradation, and other factors, compared with small-molecule drugs, they are more likely to be cleared in the body's circulatory process, therefore, their application is limited [27]. The uptake mechanisms involved in these macromolecules include endocytosis, receptor-mediated transport, and M cell transport [28]. To date, there are few reports on the *in vivo* fate of such herbal assemblies, and the main aspect of the study is to optimize the penetration of the intestinal mucus barrier to achieve controlled release and effective absorption through microenvironmental alteration-triggered structural rearrangement of the assemblies' structure or surface modification. For example, Xu *et al.* [29] prepared self-assembled materials for encapsulation and delivery of hydrophobic small molecules (HSMs) by attaching tannic acid (TA) to soybean globulin (SG), and further induced self-assembly with Fe^{3+}. It was found that the TA-Fe had a protective effect on the particles in the digestive phase of the stomach and intestines, which led to the retardation of the release of more HSMs in the intestinal tract, and with the protein micellar structure was formed, which improved the bioaccessibility. Ren *et al.* [30] prepared an assembly of soybean isolate protein (SPI) and curcumin using a pH-driven method, which overcame the problem of curcumin's low solubility and improved its bioavailability and stability.

2.1.4. Multi-component hybrid co-assemblies based on TCM decoctions

Hybrid co-assemblies refer to supramolecular complexes spontaneously formed by multiple noncovalent interactions between endogenous active ingredients (*e.g.*, alkaloids, flavonoid glycosides, saponins, and other small molecule compounds) and biomacromolecules (polysaccharides, proteins) of the herbal compound during the traditional water decoction process. This nanoscale complex is closely related to the onset of action of TCM. Studies have confirmed that it significantly enhances the bioavailability of tonics by maintaining the integrity of the active ingredient and improving the efficiency of intestinal absorption, as evidenced by a significantly higher blood concentration and area under the curve (AUC) of the active ingredient than that of the free monomer (*e.g.*, Nie *et al.* [31] on Xie-Bai-San). Specifically, self-assemblers in tonics improve absorption in the following ways. The first is to maintain the structural stability of the active substance. Nie *et al.* [31] found that polysaccharides in Xie-Bai-San acted as a self-assembling carrier skeleton, forming an anti-degradation barrier through synergistic assembly with NPs, effectively resisting the strong acidic environment of the gastrointestinal tract and hydrolysis by proteases, and maintaining the intact structure of the NPs. Secondly, the optimization of absorption efficiency. Lin *et al.* [32] demonstrated that Ge-Gen-Qin-Lian-Tang decoction nano-aggregates enhanced the uptake of baicalein by Caco-2 cells, highlighting the assembly's facilitation of transmembrane translocation. Finally, the exocytosis pump modulation effect: Based on the P-glycoprotein (P-gp) inhibition phenomenon in *Rhizoma Coptidis* extracts, Nie *et al.* [33] hypothesized that the components contained in diarrheal baixan NPs (N-XBSD) (sangpioside A, glycyrrhizin, and glycyrrhizinic acid ammonium salt) are P-gp substrates, and that their co-assembly may further promote intestinal absorption of the active ingredients by competitively inhibiting the exocytosis function of P-gp. However, the specific mechanisms of these absorption processes have not been clearly reported and still need to be explored in depth by researchers through more experimental validation.

2.2. Absorption efficiency at the gastrointestinal tract

2.2.1. The main factors affecting the efficiency of supramolecular absorption

The gastrointestinal tract is the main site of oral drug absorption, and its absorption efficiency directly determines the bioavailability and efficacy of drugs. During absorption in the gastrointestinal tract, changes in the shape, size, and surface properties of supramolecular assemblies significantly affect their absorption efficiency. By regulating their shape, size, and surface charge, they can affect endocytosis efficiency and cytokine secretion levels, activate specific signaling pathways, and further regulate the *in vivo* distribution and absorption efficiency of supramolecules, with the schematic diagram provided in the supporting information (Fig. S2 in Supporting information).

(1) Size

It has been shown that NPs with a size of <200 nm are more likely to penetrate the intestinal mucus layer and be absorbed by the intestine. NPs in the size range of 100–150 nm are readily endocytosed by the lattice protein-mediated pathway. NPs with a size range of 300 nm tend to be absorbed by fiducial protein-mediated endocytosis. NPs of 500 nm to 5 μm in size are difficult to pass through the mucus barrier and are more likely to be taken up by the less mucus-covered M-cells and released into the lymphatic system or accumulated in Peyer's patches. NPs that are transported through the lymphatic transport can avoid first-pass elimination by the liver and enter the body circulation directly [34]. Hillyer *et al.* [35] suggested as early as 2001 that the uptake of colloidal gold NPs is dependent on particle size, with smaller particles being more likely to cross the gastrointestinal tract to be ingested. In contrast, larger supramolecular aggregates may have difficulty crossing the intestinal barrier, resulting in less efficient absorption. Currently, assemblies based on small molecules such as flavonoids, alkaloids, and terpenoids typically have sizes ranging from 50 nm to 250 nm, thereby exhibiting excellent absorption properties. In

contrast, macromolecular assemblies such as polysaccharide-based structures often require size regulation to optimize their physicochemical properties. For example, Zhong *et al.* utilized a natural acid-desiccant (NADES) composed of lactic acid and glucose to induce self-assembly of SNP into different morphologies and sizes, resulting in NPs ranging from 406.7 nm to 104.6 nm in size, thereby enhancing their absorption performance [36,37]. In addition, NPs uptake is dependent on size effects, with larger NPs promoting the uptake of smaller NPs and smaller NPs inhibiting the internalization of larger NPs [38]. Therefore, controlling the size of supramolecules is crucial for optimizing their absorption properties.

(2) Shape

The shape of supramolecular assemblies also has an important effect on epithelial cell uptake. Currently, most supramolecular assemblies are spherical NPs, but some of them have other shapes, such as baicalein and berberine in a fibrous form [39]. Spherical NPs can rotate and jump in their interaction with the intestinal mucosa, penetrate the mucus layer, and are absorbed more easily than rod NPs. Banerjee *et al.* [40] found that rod-shaped NPs were more likely to be preferentially transported through the endoplasmic reticulum-Golgi pathway and more likely to be transported and absorbed across the intestinal epithelial layer than spherical particles. They compared rod, spherical, and disc-shaped NPs and found that the efficiency of cellular uptake of NPs: rod > disc > sphere.

(3) Surface properties

In addition, surface properties are important factors influencing the absorption of supramolecular assemblies. In general, hydrophilic and electrically neutral particles are more likely to penetrate the mucus barrier, whereas hydrophobic and positively charged particles are more likely to be taken up by intestinal epithelial cells. Wang and his team [41] enhanced intestinal epithelial cell uptake by adsorbing bovine serum albumin onto the surface of cationic liposomes to form a protein corona (PC), which was enzymatically cleaved during mucus permeation to expose the positive charge of the liposomal surface.

(4) Rigid

Rigidity is also an important physicochemical parameter of supramolecules and usually refers to the ability of NPs to resist deformation by external stresses, which essentially stems from the strength of intermolecular forces and intrinsic mechanical properties of materials. It has been shown that rigidity significantly affects the absorption efficiency of NPs in the gastrointestinal tract by modulating their deformability and mechanical interaction with the mucus matrix [42]. Yu *et al.* [43] found that different types of liposomes differ in their ability to penetrate the mucus layer with deformability and that the degree of rigidity directly leads to the morphology of the deformed form and thus influences the penetration efficiency. They found that liposomes maintained at medium stiffness had better diffusivity and oral absorption.

2.2.2. Effect of membrane adhesion on absorption

Membrane adhesion refers to the ability of a drug carrier to form a temporary bond with the mucosal layer by physical or chemical action, and its effect on absorption efficiency is characterized by a dynamic balance of "retention-penetration". Many polysaccharides exhibit adhesion ability, such as chitosan [44] and fucoidan [45], and the specific mechanisms include prolonging the local retention time and promoting the local enrichment of drugs to form a "reservoir effect". Zhao *et al.* [46] reported a hydrogen bond-driven assembly based on the effect of bioadhesive fluid aggregation, which can reduce systemic drug exposure, affecting absorption by controlling drug release. Chen *et al.* [45] found that fucoidan from the sea cucumber *Thelenota ananas* (Ta-FUC), a fucoidan from sea cucumber, had a much higher adhesion capacity in the intestines than in the gastric environment. This property was mainly attributed to the internal supramolecular interactions, including disulfide and hydrogen bonds, as well as hydrophobic interactions. The results showed that Ta-FUC significantly prolonged the retention time of cellulose derivatives in the intestinal mucosa and formed a stable three-dimensional network structure.

3. Transportation

3.1. Protein influences

A PC consists of one or more layers of proteins adsorbed on the surface of a nanomaterial after it enters a biological environment (*e.g.*, blood, serum, and cytoplasm) [47]. The formation of PC is a dynamic equilibrium process accompanied by the Vroman effect, in which multiple protein molecules compete for adsorption to a limited number of sites in the same environment, and those with high concentration and strong affinity are more likely to be adsorbed. According to the difference in affinity between protein and NPs, PCs are divided into "hard coronas" and "soft coronas", and with the change of time, the "soft coronas" that formed first will be gradually replaced by "hard coronas" with stronger affinity [48]. Similarly, after entering the body, supramolecules immediately contact biological fluids, leading to PC adsorption on the surface. The size, shape, surface modification, and environmental conditions influence PC formation, and the formation of PC also directly affects the physical properties of supramolecules, alters their interactions with biological systems, and participates in regulating supramolecular transport and reaction processes [49]. Therefore, accurate characterization of PC is crucial. Currently, the mainstream methods for PCs identification and characterization can be broadly categorized into two types: One is the bottom-up proteomics approach (BUP), which includes liquid chromatography-mass spectrometry (LC-MS), sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), fourier transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), atomic force microscopy (AFM), and other technologies; The other category is top-down proteomics methods (TDP), such as capillary electrophoresis (CE), capillary isoelectric focusing (clEF), CE-MS, and clEF-MS [50]. These technical methods have laid an important foundation for exploring the interaction mechanisms between supramolecular structures and PC. Previously, our team reported the influences of PC on nanocarriers [51]. Herein, the effects of PC on the transportation of supramolecules are briefly reviewed, with the schematic diagram available in the supporting information (Fig. S3 in Supporting information).

With the surface properties changing after PC formation, biological uptake and biodistribution also change. (1) The presence of PC may promote or inhibit the uptake of NPs which is determined by the varieties and properties of PC proteins, as well as the NPs characteristics. For example, Chen *et al.* [52] found that lipid NPs containing ApoE-PC enhanced uptake and absorption in the target cell line compared to lipid NPs containing hyaluronic acid (HA) and hyaluronan (Vtn), possibly because ApoE-containing PC altered the cellular uptake mechanism by converting the small-cell drinking effect into reticulocyte lattice protein-dependent endocytosis. In the study by Lesniak *et al.* [53] dispersed silica NPs in serum, the uptake level of PC–NP complexes was found to be much lower than the uptake efficiency of bare particles in serum-free medium, thus confirming that the higher uptake of bare particles in serum-free conditions is due to the absence of proteins on the NPs at the time

of exposure. Studies by Cheng and others [54] have also demonstrated that PCs can reduce cellular uptake in a size-dependent and cell-dependent manner. (2) Formation of PC alters the original biodistribution and clearance behaviors. On the one hand, PC may interfere with the specific binding of the target ligand to the receptor, or even lead to a complete loss of the targeting ability of NPs [55]. On the other hand, PC-induced changes in physicochemical properties may enhance targeting. For example, the formation of PCs may lead to an increase in NP size, making them less likely to reflux after crossing the vasculature, and thus more conducive to accumulation at the tumor site [56]. The accumulation of epidermal growth factor receptor (EGFR) nanobodies-modified NPs was significantly increased at the tumor site in a mouse tumor model with high EGFR expression [57]. Wu *et al.* [58] showed that pre-adsorbed human serum albumin (HSA) corona shielded serum proteins from non-specific interactions, thereby improving plasma stability and prolonging circulation time. Experiments have shown that naked NPs (*e.g.*, celastrol-loaded TPGS nanocomplex (CT)) are cleared faster *in vivo* and that natural HSA corona significantly improves the circulatory stability of the formulation compared to denatured HSA corona.

3.2. Macrophage phagocytic system (MPS) influences

Macrophages, as a component of the body's immune system, can present different functional states according to different stimulus signals in the immune microenvironment, and their main functions are phagocytosis and removal of foreign particles [59], thus playing an important role in supramolecular transport. Macrophages perform their functions in the following main steps: First, they recognize specific molecules on the surface of foreign substances using specific receptors. Subsequently, the target material is encapsulated and phagocytosed by expansion of the cell membrane. Finally, the phagocytosed material is broken down in the lysosome, and antigenic fragments are presented on the macrophage's major histocompatibility complex molecules, activating T cells [60]. More interestingly, the phagocytosis process itself enhances macrophage membrane fluidity, resulting in a "phagocytic memory effect", which enhances the secondary clearance efficiency of pathogens [61]. This suggests that supramolecular design should not only avoid non-specific clearance but also actively program macrophage function to build a "phagocytosis-delivery-activation" cascade therapeutic system.

Studies have demonstrated that the polarization state and phagocytic behavior of macrophages can be regulated directionally *via* supramolecular surface engineering. For instance, Li *et al.* [62] developed a mannose azocuproine (ManAC4A) inclusion complex that reprograms pro-inflammatory M1-type macrophages into anti-inflammatory M2 phenotypes through a dual mechanism involving mannose receptor targeting and reactive oxygen species (ROS) scavenging. This polarization modulation strategy can synergize with size effects to govern macrophage behavior. For example, Hu *et al.* [63] revealed that 400 nm-sized supramolecular particles, owing to their enhanced internalization by macrophages, enable efficient delivery of genes or drugs to the monocyte/macrophage lineage. Notably, the capture of circulating supramolecules by macrophages can be achieved using bionic membrane technology. For example, Liao *et al.* [64] designed macrophage membrane-encapsulated NPs that enabled synovial targeting through surface CD34 ligands while leveraging the "self-labeling" property of membrane proteins to evade immune clearance.

3.3. Blood flow influences

The dynamic behavior of supramolecular NPs in blood flow and their interaction with the vascular endothelium are central to determining their *in vivo* fate. In circulation, particles undergo key processes such as flow, marginalization, adhesion, and endothelial uptake [65]. Flow performance determines the homogeneity of their distribution in blood, marginalization drives particle migration, and adhesion efficiency, in conjunction with surface properties and blood flow shear, regulates endothelial uptake thresholds. These behaviors are influenced by multiple factors, including particle physicochemical properties (such as particle size, shape, elasticity, and surface charge) [66], blood constituents (*e.g.*, erythrocyte-induced two-phase flow [67], hematocrit [68], and plasma protein-corona formation [69]), and hemodynamic parameters (shear, flow velocity, and pulsation frequency) [70,71]. Advancements in microfluidics and biomimetic nanodesign have revealed that the shape, density, and surface properties of NPs can significantly influence their circulation time, organ targeting efficiency, and endothelial uptake capacity by modulating their hydrodynamic behavior.

For example, Zheng *et al.* [72] designed egg yolk shell-structured tBT@Au-RGD NPs, which triggered fibrin network degradation under high shear stress at the thrombus site through the synergistic action of piezoelectric-friction voltammetry effect, achieving nearly 100% revascularization rate. This precise thrombolytic strategy based on mechanical response provides a new paradigm for thrombus-targeted therapy. Zhao *et al.* [73] developed Fe_3O_4/mPDA Janus NPs with a featherball asymmetric mass distribution. Due to their significantly higher density in the "head" than in the "tail", the particles showed a stable linear trajectory in blood flow, a 50% reduction in collision frequency with the vessel wall, a prolongation of the blood half-life to twice that of conventional spherical particles, and a 15% reduction in hepatic and splenic uptake. This study reveals the potential of the asymmetric structure to optimize the particle trajectory by balancing the inertial force and fluid resistance, which provides a new idea for extend the circulation time. Notably, the heterogeneity of blood flow rate and vascular structure further complicates the *in vivo* fate of NPs. Using a microfluidic system with an adjustable flow rate, Chen *et al.* [74] demonstrated that changes in shear force dynamically remodeled the morphology and tight junctions of endothelial cells, which in turn affected the endocytosis efficiency of particles.

3.4. Diseases and lesion influences

The absorption, distribution, metabolism, and excretion (ADME) processes of drugs in the body are highly dependent on the homeostasis of the physiological environment. Pathological states can significantly affect the kinetic behavior of the supramolecular delivery system by altering key molecular mechanisms, such as transporter protein expression, metabolizing enzyme activities, and barrier permeability. In addition, different pathological states produce specific PC due to disease specificity, thus conferring different absorption of NPs. For example, Wu *et al.* [75] prepared polystyrene NPs adsorbed with healthy, diabetic, and colitis intestinal PCs (IPCs), and disease-specific IPCs conferred better *in vivo* intestinal absorption of NPs than healthy IPCs.

For example, patients with Alzheimer's disease (AD) may improve the absorption efficiency of oral medications due to dysbiosis and increased permeability of the intestinal flora, but at the same time exacerbate the risk of non-specific accumulation of NPs [76]. These differences imply that pathological states not only remodel the physicochemical properties of biological barriers but may also modulate molecular pathways, altering the safety and therapeutic potential of supramolecular systems. Lesions in the cardiovascular system cause changes in blood composition, vascular structure, and properties, affecting drug behavior [68]. For example, increased erythrocyte aggregation and hematocrit levels in patients with coronary artery disease lead to an increase in blood viscosity

[77], which in turn affects the circulatory transport of drugs in the blood.

4. Distribution

The *in vivo* biodistribution characteristics of supramolecular self-assemblies include organ-specific accumulation patterns, focal targeting efficiency, and off-target effects, which directly determine the effectiveness and safety of drug therapies. Existing studies have shown that physicochemical parameters such as particle size and surface charge of self-assemblies dominate their passive capture in reticuloendothelial systems such as the liver and spleen, while active targeting at tumor/inflammation sites can be enhanced by ligand modification or microenvironment response design. However, current research still faces two major challenges: (1) The complex mechanism of the dynamic assembly process *in vivo* based on the distributional characteristics has not been clarified. (2) the quantitative evaluation criteria of the targeting efficiency have not been standardized. In this section, we briefly elucidate the biodistribution laws of self-assemblers to provide a theoretical basis for the design of next-generation intelligent delivery systems.

4.1. Distribution properties

The *in vivo* distribution of supramolecular NPs is jointly regulated by their physicochemical properties and physiological microenvironment. Among the physicochemical properties, trait regulation is dominant, mainly including size effect, shape effect, and surface property effect. Studies have shown that the size of NPs is an important determinant of their organ distribution: Particles $<$5–8 nm are rapidly cleared by the glomeruli; particles of 20–150 nm are easily captured by the hepatic reticuloendothelial system, where the kupffer cells are predominant, and particles of $>$200 nm tend to accumulate in the spleen and lungs [78,79]. In addition, different shapes further modulated the distribution specificity. It has been shown that, compared to spherical NPs, elongated NPs are more readily distributed into the liver and spleen, and the accumulation rate is proportional to the length [80]. Compared to spherical micelles, worm-like micelles accumulate higher in the spleen, liver, and kidneys [81,82]. Finally, surface modifications coatings are also critical; for example, lipophilic NPs tend to accumulate in metabolically active tissues (*e.g.*, heart, brown fat), whereas hydrophilic NPs are more likely to be taken up by lymph nodes and testes because of their long-circulation properties [83].

Physiological and pathological modulations can also influence the distribution of supramolecules *in vivo*, including sex differences, microenvironmental factors associated with obesity, organ dysfunction, and routes of administration. A study by Poley *et al.* [84] found that gender differences affect NP distribution and clearance, that metabolisms are different between female and male animals, and that sex hormones can interact with NPs. Pathological states such as obesity can also alter organ distribution patterns. For example, in obesity models, the uptake of larger particles (280 nm) is enhanced in the liver. In comparison, smaller particles (58 nm) are more easily captured by the spleen [85]. Under conditions of experimental focal segmental glomerulosclerosis of the kidney, NP drug carriers transported the drug to the kidney more efficiently, with a 1.9-fold improvement compared to free drug [86]. The route of administration can also be an important factor affecting drug distribution. For example, intraperitoneal injection can achieve local enrichment of tumors [87], whereas intravenous injection is prone to triggering reticuloendothelial system (RES) clearance, leading to limited tumor accumulation [88].

Following the encapsulation or modification of NPs, the pharmacokinetic parameters of the drug, including the AUC, mean residence time (MRT), and plasma elimination half-life ($T_{1/2}$), are notably extended [37,89]. Prior investigations have demonstrated that the accumulation of orally administered exosome-loaded curcumin CMS in rat brains is approximately six fold greater than that of the free drug [90]. Similarly, Xu *et al.* [91] confirmed that after forming CMS assemblies, the bioavailability was significantly enhanced compared to that of the free drug, with increased accumulation in the colon, thereby enhancing therapeutic efficacy. Li *et al.* [92] constructed paclitaxel-16-MH prodrug nano-assemblies (PSSMH NPs) by combining 16-MH with redox-sensitive disulfide bonds and paclitaxel *via* ethylene glycol, and the area under the concentration-time curve ($AUC_{0-24\,h}$) was 14.95-fold compared with that of paclitaxel, which significantly improved the *in vivo* fate of paclitaxel and manifested a good antitumor efficacy. Currently, research on the *in vivo* biodistribution of NPs is increasing, and pharmacokinetic studies are critical components of this research. With the continuous development of bioinformatics technology, AI-driven pharmacokinetic prediction of NPs has emerged as a research hotspot. Therefore, constructing physiologically based pharmacokinetic models applicable to NPs is critical.

4.2. Targeting abilities

The lesion-targeting efficacy of these self-assembled NPs has been validated in three typical pathological scenarios: Tumors, brain diseases, and chronic inflammation, where the variability of the targeting mechanism mainly stems from the differentiation of lesion-specific biological barriers and molecular interaction patterns. The characteristic microenvironment of tumor tissues (*e.g.*, low pH, high ROS) provides a natural trigger "switch" for targeted release of CMS at the lesion site. In tumor therapy, passive targeting relies primarily on physical changes that enhance the effect of permeation and retention (EPR), such as tumor-targeted accumulation and retention of Aloe Emodin-copper NPs (AE-Cu NPs) [93]. Second, the enhancement of targeting at the chemical level, triggers drug release to enhance active targeting, mainly through pH and ROS of the internal environment [94]. In addition, targeting cancer cells at the biological level achieves specific binding to overexpressed receptors through surface modification of ligands (*e.g.*, folic acid), which increases the uptake efficiency of cancer cells by 3–5 times [88]. For brain delivery, synergistic strategies are required to overcome the blood-brain barrier (BBB) limitation. Zhao *et al.* [95] developed genistein NPs that leverage hydrogen bonding and π-π interactions to form a highly stable structure with enhanced BBB permeability, enabling precise targeting of brain lesions. For inflammation targeting, pathological microenvironmental features can trigger charge reversal or structural cleavage to enable targeted drug delivery to inflamed sites, highlighting the advantages of smart responsive design. For instance, Li *et al.* [96] developed chondroitin sulfate-modified silica particles (CA@MS-E) that released drugs in response to pH/ROS stimuli at colitis sites. Zhang *et al.* [97] obtained curcumin degree micelles with smart enzyme response based on self-assembly of hybrid polymers, which enhanced cellular uptake and colonic mucosal extension time, and achieved specific release of curcumin in the colonic microenvironment.

5. Analytical techniques for tracking *in vivo* fate

Studying the dynamic fate of supramolecular self-assemblies *in vivo* necessitates the systematic construction of a multidimensional analytical technique system. Traditional research methods primarily rely on physicochemical parameter detection, including liquid chromatography (HPLC), MS, and radioisotope labeling, or on characterizing the *in vivo* metabolic behaviors of NPs by quantifying parameters such as target concentration, fluorescence intensity, or radioactive signals. In recent years, the adoption of

high-throughput screening (HTS) techniques has significantly enhanced analytical efficiency while ensuring data accuracy. The profound integration of machine learning (ML) and artificial intelligence (AI) has driven further innovation in supramolecular tracking techniques for animal studies. This section serves as a concise overview of the current applications of analytical techniques in addressing key issues pertaining to CMS, including *in vivo* dynamic tracking, stability studies, and multi-component quantification. It places special emphasis on the value and challenges of these techniques in facilitating the translation of CMS formulations to clinical practice-such as predicting human pharmacokinetics, evaluating safety, and guiding quality control. Detailed introduction refers to the supporting information, with specific reference to Table S2 (Supporting information).

6. Conclusions and future perspectives

Due to the natural origin of its components, the *in vivo* fate of CMS differs fundamentally from that of synthetic NPs, primarily for the following reasons. In terms of safety, CMS rarely triggers immune rejection or severe toxicity because of its natural biocompatibility, whereas synthetic NPs, such as gold NPs [98], may cause metal ion toxicity. In terms of efficacy, CMS enhances efficacy through multi-component synergism, based on the combination of a "ruler, minister and enabler" (*e.g.*, self-assembly of berberine-glycyrrhetinic acid significantly enhances antimicrobial activity [14]). In terms of targeting, CMS does not require exogenous modifications, and its spontaneous assembly optimizes the physicochemical properties (size, morphology, and surface properties) to promote active retention and recognition at the lesion site (*e.g.*, lignocaine-GA self-assemblies increase the uptake rate of hepatocellular carcinoma cells by $>$1.6-fold and inhibit proliferation through changes in size and surface charge [99]). In terms of the response mechanism, CMS is dominated by endogenous response (*e.g.*, pH/enzyme-triggered dissociation of the natural structure [23]), whereas synthetic NPs require the artificial introduction of sensitive elements (*e.g.*, pH-sensitive bonds and enzymatic sites) [100] to achieve controlled release. These differences strongly suggest that CMS are not simply "natural NPs", but intelligent drug delivery systems with unique biological destinies.

As a bridge connecting TCM theory with modern nanotechnology, the CMS offers innovative Chinese medicine-inspired strategies to address pivotal delivery limitations such as synergistic multi-component delivery and bioavailability enhancement of low-solubility components. Existing investigations pay more attention to the discovery of new supramolecular structures, therapeutic efficacy assessment, and the underlying mechanisms of self-assembly. However, the dynamic analysis of the interactions between assemblies and biological interfaces in complex physiological microenvironments remains in its infancy. This is a critical scientific issue for understanding the theoretical foundations and mechanisms of TCM and its formulations. It is particularly important to note that precisely elucidating these interface processes not only concerns the safety and efficacy of CMS but also represents a key scientific breakthrough in elucidating classical TCM formula theories (such as the "sovereign, minister, assistant, and messenger" theory) and achieving a modern interpretation of TCM mechanisms of action.

To some extent, *in vivo* fate studies are constrained by insufficient targeting efficiency, unclear dynamic biological barrier penetration mechanisms, and the lack of systematic integration of cross-scale analytical technologies. To overcome these bottlenecks, future research must achieve substantial breakthroughs in the following areas. In terms of improving targeting efficiency, efforts should focus on developing novel surface engineering technologies, screening for target ligands that combine high affinity with biocompatibility, and designing surface-responsive switches (*e.g.*, enzyme, pH/ROS-responsive) to enable precise localization and release at the lesion site. Additionally, biomimetic engineering approaches and PC regulation strategies should be integrated to further enhance targeting efficacy. In terms of research methodologies, ML and AI technologies should be integrated to predict self-assembly behavior, assembly-biological interface interactions, and *in vivo* processes. A cross-scale research platform should be established, combining high-resolution imaging, single-cellomics, and organ-on-a-chip technologies to systematically elucidate the entire delivery process from molecular interactions to organ distribution. Ultimately, through deepening our understanding of the complexity of *in vivo* biological barriers and interactions, the preparation and characterization techniques of CMS will be optimized, which may further push systematic evaluations for its clinical translation, contributing unique value to the modernization of TCM and human health. Maybe our manuscript could provide useful references and ideas.

CRediT authorship contribution statement

Caihong Li: Writing – original draft. **Chen Li:** Writing – review & editing. **Jing Sun:** Writing – review & editing, Supervision. **Qingqing Xiao:** Writing – review & editing, Supervision, Funding acquisition. **Huaxu Zhu:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

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

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Supplementary materials

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