中药自组装纳米体系: 无载体递送新策略

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摘要: 中药自组装纳米体系是指中药活性成分通过氢键、疏水作用、π-π堆积等非共价相互作用自发形成的无载体纳米结构, 因其在载药量、生物相容性及智能递送特性等方面展现出显著优势, 日益成为中药现代化研究的热点, 相关探索持续增多。本文从中药复方、药对、单味药及单体成分4个维度, 综述了中药自组装纳米体系的形成机制、优势特性及应用实例, 深入探讨了其研究价值, 并指出当前面临的关键挑战。本研究旨在整合现有认识, 为中药自组装策略的深入研究与实际应用转化提供理论依据。同时, 从自组装纳米技术的角度出发, 不仅为阐释中药药效物质基础及配伍机制提供了新思路, 也有助于推动中医药研究向精准化与现代化方向发展。

关键词: 天然产物; 自组装; 纳米体系; 中药复方; 无载体递送

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2026)06-2089-19

Self-assembled nano systems of traditional Chinese medicine: A new strategy for carrier-free delivery

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Abstract: The self-assembled nano systems of traditional Chinese medicine (TCM) refer to carrier-free nanostructures spontaneously formed by non-covalent interactions, such as hydrogen bonds, hydrophobic interactions, and π-π stacking, between the active components of TCM. Due to their significant advantages in drug loading, biocompatibility, and intelligent delivery characteristics, these systems have increasingly become a hotspot in the research of TCM modernization, and related research in this area has expanded rapidly. This article reviews the formation mechanisms, advantageous characteristics, and application examples of TCM self-assembled nanostructures from four dimensions: TCM compound formulas, pairs of herbs, single herbs, and individual active ingredients. It delves into the research value of these systems and highlights the key challenges currently faced. The study aims to integrate existing knowledge and provide a theoretical basis for the in-depth exploration and practical application of TCM self-assembly strategies. Furthermore, from the perspective of self-assembly nanotechnology, it not only offers new insights into the material basis of TCM efficacy and the mechanisms of herb combinations but also contributes to advancing TCM research toward precision and modernization.

Key words: natural product; self-assembly; nano system; Chinese medicine compound; carrier-free delivery

收稿日期: 2025-08-01; 修回日期: 2025-11-10.

基金项目: 陕西中医药大学科技创新人才体系建设计划项目 (2024-CXTD-03); 中药制药关键技术研究科技创新团队 (2025-CXTD-02); 陕西省中医药管理局中医药科研项目 (SZY-KJCYC-2025-JC-043); 陕西省重点研发计划项目−秦创原产业创新聚集区“四链”融合项目 (2024CY-JJQ-36, 2024CY-JJQ-78); 陕西省教育厅重点科学研究计划项目 (25JR059).

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DOI: 10.16438/j.0513-4870.2025-0902

中草药是我国传统医学的重要组成部分，在人类健康守护与疾病预防中发挥着重要作用[1-3]，从中提取的青蒿素、紫杉醇等天然产物因其独特结构能有效作用于药物靶点、调节生理过程，治疗疟疾、肿瘤等多种疾病[4,5]，然而，这些天然产物普遍存在水溶性差、生物利用度低、稳定性不足及体内代谢过快等固有缺陷，严重制约了其成药性优化与临床应用[6-8]。基于此，研究者开发了多种基于外源载体的纳米递送系统应用于中药领域，如聚合物纳米粒、脂质体和聚合物胶束等。尽管这些技术取得了一定进展，但基于载体的递送系统仍存在载药量低、载体降解及外源载体潜在毒性等缺点[9-12]。因此，开发更安全高效、易于临床转化的新型中药纳米递送平台仍面临挑战。

近年来，中药自组装纳米策略引起了广泛关注[13-15]。这些纳米结构由中药活性成分通过分子间弱相互作用 (如氢键、疏水作用、静电引力、π-π堆积) 自发形成，具有以下特点：① 无载体、高载药，即无需外源载体材料，活性成分自身即为结构单元，显著提升载药效率；② 生物相容性好、安全性高，组分多源于中药自身，减少外源载体的使用，从而降低部分载体材料带来的潜在风险；③ 制备简便、绿色高效，制备过程多在水相或温和条件下自发完成，操作简便；④ 兼具智能递送功能，可自发形成具有缓释、靶向、响应性释药特性的纳米结构 (图 1)。

鉴于上述显著优势，基于中药自组装的纳米体系被深入研究用于提升药效和阐明配伍机制。其中，中药复方、药对自组装 (如黄连解毒汤、四逆汤、逍遥丸、黄芪−当归共煎液等) 被发现能形成特征性纳米结构，通过富集活性成分、实现靶向、缓释递送、调控信号通路及修复组织屏障等机制，成为复方“配伍增效”的纳米物质基础[16-19]。与此同时，单一天然活性成分的自组装研究也取得显著进展，例如生物碱类成分，小檗碱 (berberine, BBR) 作为核心构建单元，可与肉桂酸、甘草酸、姜黄素等形成功能化纳米结构，用于增溶、结肠靶向、光活化抗菌甚至中和马兜铃酸肾毒性[20-22]。本综述将系统总结中药自组装纳米体系的最新研究进展，聚焦于中药复方、中药药对、单味药及天然活性成分自组装体系的构建、机制与应用，并深入分析该策略的核心优势、当前挑战及未来临床转化前景。

1 中药自组装的理论基础

自组装过程依赖于分子间的非共价相互作用，如氢键、静电引力、范德华力、π-π堆叠及疏水作用等，这些相互作用共同驱动分子有序排列，形成具有特定结构与功能的超分子体系。深入研究这些相互作用的类型、强度与方向性，有助于揭示自组装的内在机制，为设计新型自组装材料提供理论基础。同时，制备方法的选择与优化对自组装体系的成功构建至关重要。不同的制备方法会影响分子间的相互作用方式与程度，进而决定自组装体系的形态与性能。

1.1 自组装的驱动力

自组装作为自然界普遍存在的分子有序化过程，在中药活性成分的纳米化领域中展现出独特优势。该

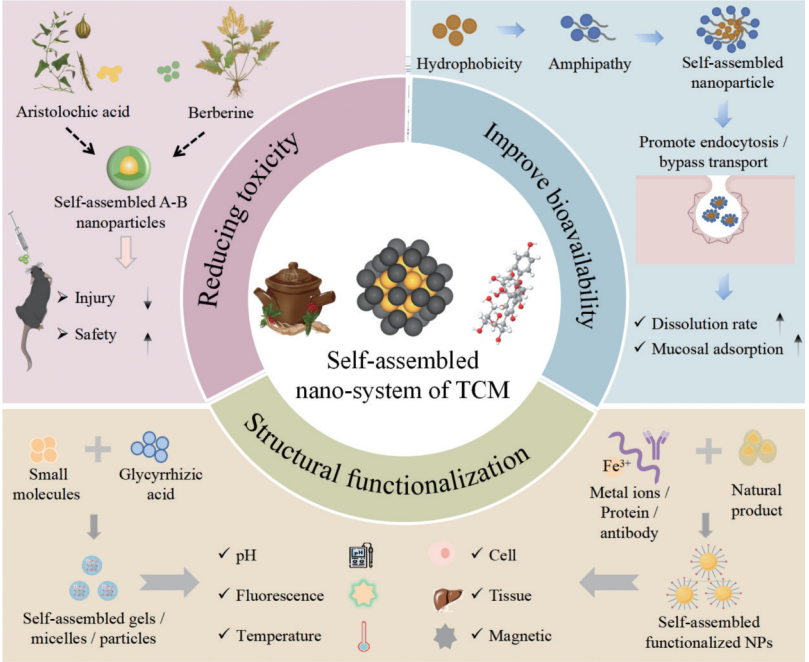


Figure 1 Functional application of self-assembled nano systems of natural products of TCM. TCM: Traditional Chinese medicine; NPs: Nanoparticles

过程依赖多种非共价键的协同驱动, 通过氢键、疏水作用、π-π堆积、静电引力及金属配位等弱相互作用力, 使分子在特定环境下自发形成稳定的有序结构 (如纳米粒、凝胶、纤维等)[23], 如图2所示。这些作用力因其可逆性与环境响应性, 不仅显著降低制备成本及溶剂残留风险, 更为改善药物溶解性、提升生物利用度及实现功能化递送提供了新路径[24]。

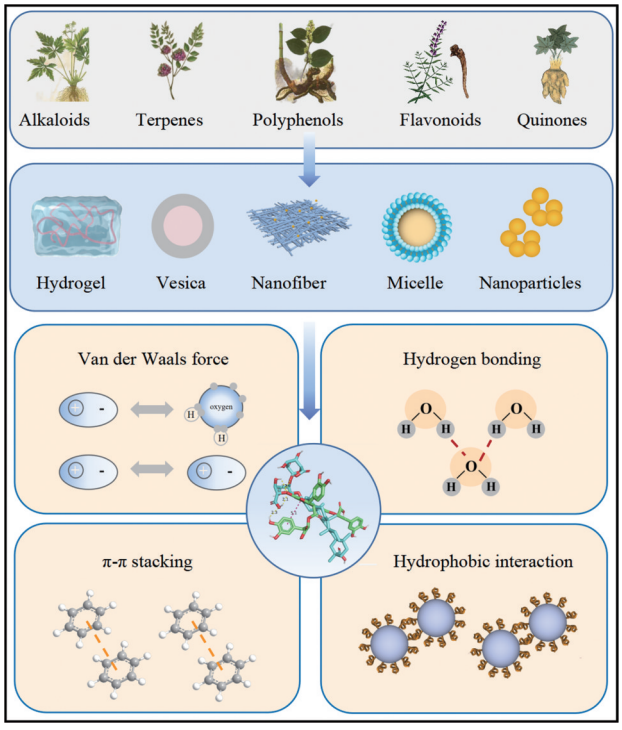


Figure 2 Natural product self-assembly system and interaction diagram

氢键是由电负性原子 (如O、N) 与氢原子形成的弱静电相互作用, 具有中等强度、明确的方向性及饱和度, 是天然小分子自组装的关键驱动力之一[25]。如BBR的季铵氮原子与肉桂酸羰基形成氢键, 构建X状一维单元, 进一步通过芳环π-π堆积拓展为三维层状晶体[26]; 在三萜类体系中, 分子亲水端的羟基通过氢键形成网络结构, 增强了组装体稳定性, 使难溶性成分溶解度显著提升[27]。

疏水相互作用是疏水性基团 (如芳香环、烷基链) 为减少与水分子接触而发生的聚集行为, 其本质是熵驱动的自发过程, 在水环境中对自组装的贡献尤为显著。许多中药成分 (如五环三萜类的熊果酸、雷公藤红素, 多酚类的白藜芦醇) 因含有疏水性结构, 在水溶液中倾向于通过疏水相互作用聚集, 形成纳米粒或胶束[28]。例如, 熊果酸、齐墩果酸与白藜芦醇以疏水相互作用为主要驱动力通过共沉淀法构建了三元自组装纳米体系, 提升了白藜芦醇的水溶性和稳定性[29]。疏水相互作用常与氢键协同作用, 通过动态平衡调控组装体的形态 (如球形、棒状) 及稳定性。

π-π堆叠是芳香族成分 (如黄酮类、蒽醌类) 通过芳香环之间的电子云重叠形成的相互作用。这种相互作用通常发生在富电子和贫电子的分子之间, 它通过空间有序排列推动自组装[30]。此外, π-π堆叠和配位键结合可实现结构强化与功能赋予[31,32]。例如, 木犀草素等儿茶酚类黄酮通过π-π堆叠形成层状结构, 进一步与Fe^{3+}配位通过配位键结合, 构建稳定的八面体配位结构, 赋予组装体光热响应特性, 实现化疗与光热协同治疗[33]。π-π堆叠不仅增强了分子间的结合力, 还赋予自组装体系特定的光学和电子性质, 为天然产物的功能化开发提供了新途径。

静电引力是带相反电荷的基团 (如生物碱的季铵阳离子与羧酸类的阴离子) 之间的库仑作用, 在pH敏感型自组装中起关键作用。例如, 四逆汤中甘草酸的羧基 ($-COO^-$) 与乌头类生物碱的氨基 ($-NH_3^+$) 通过静电引力形成复合物, 是汤剂自然沉淀的主要成因; 在pH驱动的自组装中, 通过调控溶液pH改变分子的电离状态, 可触发静电引力主导的组装, 形成粒径均一的纳米颗粒。

1.2 自组装体的制备方法

中药活性成分 (如生物碱、黄酮、三萜等) 在特定条件下可通过非共价键作用自发形成纳米颗粒、胶束及凝胶等有序结构, 其制备方法以绿色高效、结构可控为特点, 广泛适用于中药复方、药对及单体成分的纳米体系构建。图3从纳米颗粒、胶束和凝胶3个方面, 概括其主要制备策略。

1.2.1 纳米颗粒的制备方法 纳米颗粒的制备主要依赖分子在特定环境下的过饱和或电荷调控诱导自组装, 常用方法包括以下几种: ① 纳米沉淀法: 首先将药物溶解在有机溶剂中, 然后在剧烈搅拌下加入水相中, 形成过饱和环境, 诱导分子通过疏水作用或π-π堆积形成纳米颗粒。最后, 通过透析、超滤、冷冻干燥除去有机溶剂[34]; ② pH驱动法: 通过调控溶液pH值改变分子电离状态, 利用静电作用力与氢键重组触发药物自组装成核, 在过饱和条件下形成稳定纳米颗粒。将酸性成分溶于碱性缓冲液, 使其充分去质子化。在剧烈搅拌下, 向上述溶液中滴加反离子溶液, 维持终点pH继续搅拌, 使静电作用驱动的初级聚集体重组为均一颗粒[35], 此外, 基于溶剂缓慢挥发的组装策略及利用超声波能量促进组装的超声辅助法, 也因其在控制粒径与提升分散性方面的优势而被广泛应用。

1.2.2 胶束的制备方法 胶束由两亲性分子 (一端亲水、一端疏水) 通过疏水作用自组装形成, 具有中空结

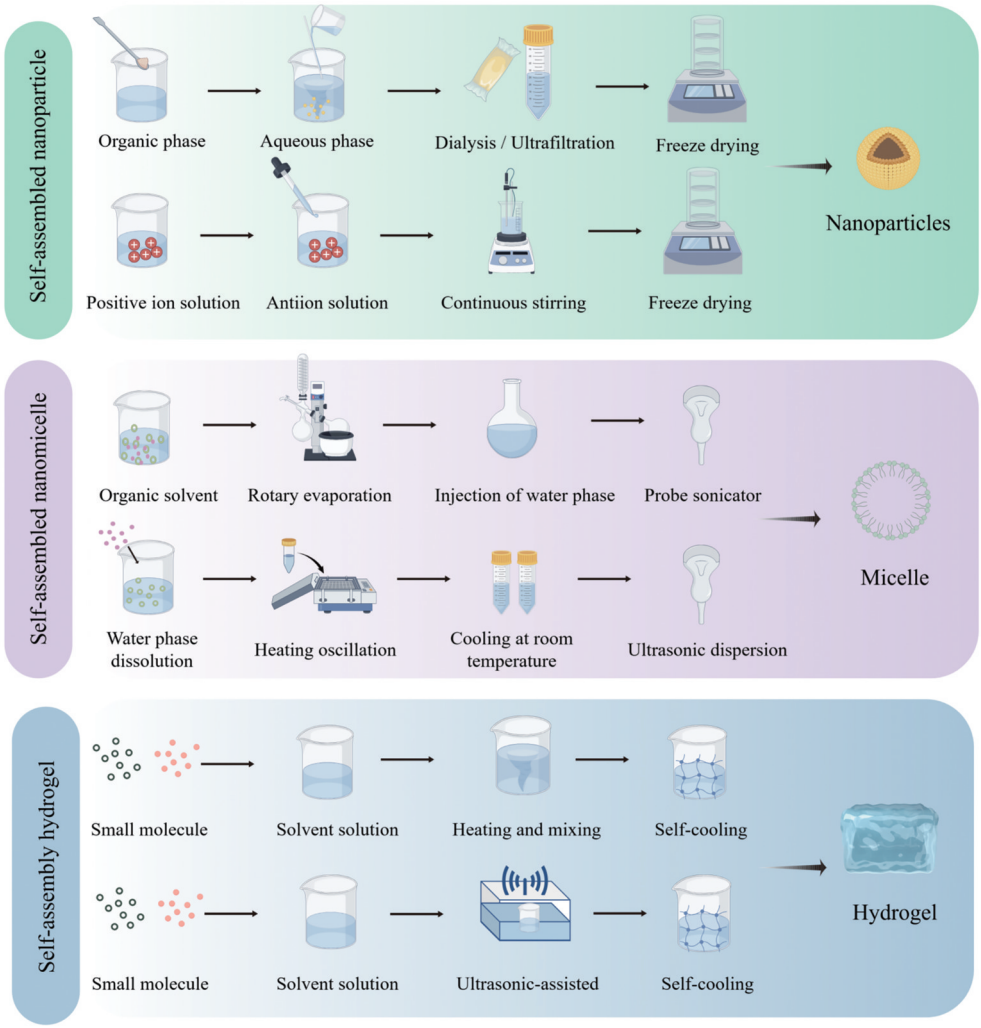


Figure 3 Preparation flow chart of self-assembled nanoparticles, micelles and hydrogels

构, 可包载疏水性药物。其常见的制备方法包括: ① 薄膜水化法: 将两亲性天然小分子及待包封的天然产物共溶于有机溶剂。随后, 通过旋转蒸发去除有机溶剂, 在容器底部形成均匀脂质薄膜。继而, 在高于表面活性剂相转变温度的条件下, 向薄膜中注入水相, 同时持续搅拌使薄膜充分水化。最后, 经探头超声处理分散聚集物, 获得粒径均一的胶束或囊泡溶液[36]; ② 超声分散法: 首先, 将两亲性天然分子溶于预热的蒸馏水。随后, 加入待包封药物, 并将混合体系置于水浴中恒温振荡孵育, 驱动分子自组装形成初级胶束。再将溶液冷却至室温以稳定胶束结构, 最后通过超声均化进一步分散聚集体, 形成均质胶束溶液[37]。除此之外, 直接溶解法、透析法和微乳液法也是构建功能性胶束的常用策略。

1.2.3 凝胶的制备方法 天然小分子凭借其多模式自组装能力, 可生成纳米凝胶、水凝胶、油凝胶及有机凝胶等四类超分子材料。其中, 水凝胶因兼具生物相容性、注射适应性和自修复特性, 在药物递送与组织工程中应用最广。其主要的制备方法有: ① 加热−冷却法: 将胶凝剂分散于溶剂中, 置于90 ℃水浴中恒温搅拌至完全溶解, 形成透明溶胶。将溶胶静置冷却至25 ℃室温, 分子经疏水作用与氢键重组, 形成三维网络凝胶[38]; ② 超声诱导法: 这是指通过超声诱导促进溶解、均质化和凝胶形成的过程, 适用于快速形成均质凝胶[39]。此外, 还有pH诱导法、溶剂交换法、离子诱导法和光诱导法等。

上述常见的制备方法通过调控分子间非共价相互作用, 实现了中药活性成分在纳米颗粒、胶束和凝胶等不同形态间的转化。方法的选择需根据成分的理化特性、目标结构与功能需求进行优化, 以确保自组装体系的稳定性与药效发挥。

2 中药自组装纳米体系概述

本部分将按照复方、药对、单味药及单体成分进行分类综述, 依据研究对象层次和配伍复杂度进行梳理。

复方、药对与单味药本质上均属于多成分自组装体系, 差异主要在成分来源与配伍方式。通过层次化的呈现方式, 一方面可反映现有研究的范围与现状, 另一方面也为比较不同体系的结构特征、功能表现及应用潜力提供逻辑框架。

2.1 中药复方

中药复方汤剂煎煮过程中常会产生沉淀物, 现有研究表明其中可包含蛋白质、多糖及若干小分子活性成分, 这些组分可能在疏水作用、静电引力等分子间相互作用下形成自组装纳米结构。已有研究表明, 沉淀中形成的自组装粒子在部分体系中可能富集活性成分并参与药效发挥, 关于中药复方自组装纳米体系的相关研究见表1[16-18,40-43]。

以黄连解毒汤为例, 作为经典中药方剂, 因其抗炎解毒功效而长期使用, 在临床上用于治疗多种疾病, 如肿瘤、关节炎、脓毒症、肝功能障碍、肾损伤等[44,45]。现代研究发现, 其水煎液中沉淀占总重2.63%, 主要由黄芩苷与小檗碱通过静电引力、氢键、疏水作用及π-π堆积等非共价键焓驱动组装而成。该沉淀中两种活性成分含量分别为上清液的21与18倍, 且对神经细胞的保护作用显著优于上清液, 其机制可能与自组装纳米结构促进细胞摄取有关, 这也印证了沉淀的药效价值[16]。类似地, 葛根芩连汤在煎煮过程中可自发形成以小檗碱、黄芩苷、葛根素等主要成分为主体的自沉淀, 该沉淀通过分子间非共价相互作用自组装形成。与上清液相比, 该自组装复合物在降糖及相关抗炎活性方面表现出更强的功效, 具体体现在可显著降低炎症因子TNF-α、IL-1β等的表达水平, 结合其纳米结构特征 (如粒径均一、包封率高等) 推测其可能通过改善成分溶解性和吸收效率从而增强整体药效[41]。芍药甘草汤 (Shaoyao-Gancao Decoction, SGD) 由白芍与甘草组成, 具有缓急止痛、敛阴养血、益气和中的药理作用。其配伍简单, 君臣相得 (方中白芍为君、甘草为臣, 相辅相成), 能酸甘化阴 (酸味与甘味药物配伍可滋生阴液)、化阳 (调和阴阳以助气化), 可快速缓解肌肉、肢体痉挛及疼痛, 且药性平和, 无毒副作用[46,47]。通过透析分离工艺, 从芍药甘草汤的自沉淀中成功分离出自组装纳米粒 (SGD-SAN)。该纳米粒呈球形, 粒径均一 (164.43 ± 1.34 nm), 多分散指数低, zeta电位为−12.35 mV, 表明体系稳定性良好。其含量测定显示SGD-SAN中芍药苷、甘草酸等7种活性成分占总汤剂的70%以上; 药效方面, 与模型组相比, SGD-SAN高剂量组可显著降低PASI评分、炎症因子TNF-α及脾脏指数, 其效果与SGD全汤组相当且呈剂量依赖性。其作用机制可能与自组装提高成分稳定性和生物利用度相关, 从而为“酸甘化阴”配伍提供了科学解释[42]。此外, 四逆汤是中医经典方剂之一, 载于中国古代医书《伤寒论》, 由附子、干姜、炙甘草按干重比为3∶2∶3混合而成[48]。研究通过UHPLC-Q-Orbitrap HRMS鉴定出上清液与沉淀中99种化合物, 并聚焦酸性成分 (甘草酸) 与碱性成分 (乌头碱、次乌头碱、新乌头碱) 的相互作用, 利用CSI-MS确证其以1∶1比例形成酸碱自组装复合物, 提示配伍减毒可能与分子间相互作用相关[17]。芪银三两三汤剂 (qiyin305, QY305) 的自组装研究进一步拓展了临床应用边界, 其水煎剂 (T-QY305) 中绿原酸 (chlorogenic acid, CHA)、异甘草苷、甘草酸 (glycyrrhizic acid, GA) 等活性成分自发组装形成稳定纳米颗粒 (N-QY305), 在模拟胃液中稳定性与汤剂相当, 并能靶向富集于炎症部位。该体系通过促进角质细胞和结肠上皮细胞增殖、抑制TNF-α表达及巨噬细胞浸润、修复表皮屏障与结肠杯状细胞功能, 显著缓解表皮生长因子受体 (epidermal growth factor receptor, EGFR) 抑制剂 (吉非替尼等) 的皮肤及肠道毒性, 在临床回顾性研究中, EGFR抑制剂相关皮肤不良反应患者口服QY305后皮疹、干燥及瘙痒均有改善 (如患者1皮疹评分由3级降至2级, 瘙痒由3级降至2级)。在BALB/c裸鼠肺癌模型中, 吉非替尼诱导的皮肤损伤和透皮失水 (trans epidermal water loss, TEWL) 升高, 经QY305干预显著缓解。结果提示QY305在临床与动物实验中均能改善EGFR抑制剂相关皮肤不良反应[43]。

综合现有研究结果来看, 中药复方煎煮过程中常可生成沉淀, 其中含有多种活性成分, 这些成分可能通过静电引力、氢键等非共价作用形成自组装结构, 从而在一定程度上促进活性物质的富集和稳定。一些研究提示, 在特定体系中沉淀所表现的药效可与上清液相当或更强, 提示沉淀并非杂质, 而是与不同相态共同参与药效作用, 但这一现象是否具有普遍性仍需进一步验证[49,50]。

2.2 中药药对

从补气养血的黄芪−当归, 到解毒缓急的甘草−附子, 中药药对作为中医“配伍增效减毒”理论的经典范式, 其共煎过程中活性成分通过自组装构建的纳米结构成为药效协同与毒性调控的关键物质载体, 具体研究内容如表2[19,51-53]所示。

黄芪与当归药对具有多种药理作用, 能补气养血, 黄芪善补中气、升阳固表, 当归可补血活血, 二者伍用, 对气血亏虚证效果更佳[54]。黄芪−当归 (Astragali radix-Angelicae sinensis radix, AA) 共煎液中自组装形成的超分子纳米颗粒 (AA-NPs) 有43种活性成分, 包括11种皂苷、13种黄酮及*Z*-藁本内酯等, 通过疏水作

Table 1 Self-assembled products from Chinese herbal decoctions and their applications. SEM: Scanning electron microscope; TEM: Transmission electron microscope; DLS: Dynamic light scattering; CSI-MS: Chemical spray ionization mass spectrometry; ESI-MS: Electrospray ionization mass spectrometry; FS: Fluorescence spectrophotometry; FTIR: Fourier transform infrared spectroscopy; HRMS: High-resolution mass spectrometry; SD: Sprague Dawley; MDO: Molecular docking; ^{1}H NMR: Proton nuclear magnetic resonance spectroscopy; UV: Ultraviolet-visible spectroscopy; UHPLC: Ultra-high performance liquid chromatography; BALB: Bagg albino

Source	Self-assembled component composition	Extraction/separation method	Self-assembled morphology	Morphology characterization method	Interaction force	Force characterization method	Experimental model	Dose /g·kg^{-1}	Pharmacological activity	Assembly effect	Ref.
Huanglian Jiedu Decoction	Baicalin, berberine	Water decoction, sedimentation, drying, ultrasonic dissolution, 0.20 μm filtration	Spherical nanoparticles	SEM; TEM; DLS	Electrostatic attraction, H-bonding, hydrophobic interactions, π-π stacking	FTIR; ESI-MS; ^{1}H-NMR; UV; FS	/	/	Anti-inflammatory, detoxification, neuroprotection	Enrichment and enhancement of active components	[16]
Xiebai Powder	Mulberroside A, digitidine B, digitidine A, liquiritin, liquiritin apioside, oxyresveratrol, ammonium glycyrrhizinate, mulberroside C	Centrifugal separation, dialysis, high-speed centrifugation	Spherical nanoparticles	TEM	Electrostatic interactions, H-bonding, hydrophobic interactions	FTIR; HRMS	SD rats	12.5	Anti-inflammatory, antipyretic, antitussive	Enhanced gastrointestinal stability, improved bioavailability of active components	[40]
Gegen Qinlian Decoction	Berberine, palmatine, wogonoside, baicalin, puerarin, glycyrrhizic acid	Solvent evaporation method	Spherical nanoparticles	TEM	π-π stacking; H-bonding, electrostatic interactions; van der Waals forces	UV; FTIR; MDO	Mice	/	Alleviate irinotecan-induced intestinal toxicity	Enhanced efficacy	[41]
Xiaoyao Pill	Senkyunolide I, ligustilide, paeoniflorin, liquiritin, gallic acid, chlorogenic acid, glycyrrhizic acid, *etc*.	Dissolved in deionized water, centrifugal dialysis	O/W nano emulsion	Microscopic staining; TEM	Hydrophobic interactions, electrostatic attraction	/	White rats	0.18	Anti-tumor	Enhanced solubility and sustained release, improved bioavailability of ferulic acid, targeted delivery	[18]
Shaoyao-Gancao Decoction	Paeoniflorin, glycyrrhizic acid	Water decoction, sedimentation, dialysis purification	Spherical nanoparticles	TEM	Hydrophobic interactions, H-bonding, electrostatic attraction	/	Mice	1, 2, 4	Anti-psoriasis, anti-inflammatory, immunomodulation	Synergistic effect of compatibility	[42]
Sini Decoction	Glycyrrhizic acid, aconitine-type alkaloids	Water decoction, sedimentation, drying, ultrasonic dissolution, 0.20 μm filtration	/	/	Electrostatic attraction	CSI-MS; UHPLC-Q-Orbitrap HRMS	/	/	Rescuing from collapse by restoring Yang	Retention of active components	[17]
QY305	Chlorogenic acid, isoliquiritin, glycyrrhizic acid	Water decoction, high-speed centrifugation, dialysis	Nanoparticles	/	/	/	BALB/c nude mice	0.1−0.3	Alleviate skin adverse reactions, improve intestinal injury, anti-inflammatory repair	Targeted enrichment, synergistic effect, enhanced stability	[43]

Table 2 Self-assembled products from Chinese herbal medicine pairs. ITC: Isothermal titration calorimetry; MDY: Molecular dynamics; FESEM: Field emission scanning electron microscope; XRD: X-ray diffraction; AD: Alzheimer's disease; ICR: Improved castle road

Source	Self-assembled component composition	Extraction/separation method	Self-assembled morphology	Morphology characterization method	Interaction force	Force characterization method	Experimental model	Dose	Pharmacological activity	Assembly effect	Ref.
Astragalus membranaceus-*Angelica sinensis*	*Z*-Ligustilide, astragaloside IV	Co-decoction in water, ultrafiltration centrifugation	Irregular spherical nanoparticles	TEM; SEM	Hydrophobic interactions	UV; FS; FTIR; UHPLC-HR-MS	C57BL/6 mice	20 and 80 mg·kg^{-1}	Treat myocardial fibrosis	Enhanced solubility and sustained release, improved stability, synergistic effect	[19]
Rhubarb-*Epimedium*	Rhein, icariin	Nanoprecipitation method	Spherical nanoparticles	TEM	H-bonding, π-π stacking	FTIR; ITC; MDY	C57BL/6	5 mg·kg^{-1}	Anti-inflammatory, anti-ferroptosis	Improved stability, synergistic sustained release, enhanced biocompatibility	[51]
Rhubarb-Coptis Chinensis	Berberine, rhein	Mixing with stirring, dialysis purification	Spherical nanoparticles	FESEM	Electrostatic interactions, π-π stacking	FTIR; ^{1}H NMR; XRD; FS	Caenorhabditis elegans	5 μmol·L^{-1}	Anti-AD	Sustained release, synergistic effect, improved bioavailability	[52]
Liquorice-*Aconiti Lateralis Radix*	Glycyrrhiza protein, aconitine	Protein purification, pH adjustment, ultrafiltration centrifugation	Spherical nanoparticles	SEM	Hydrophobic interactions	/	ICR mice	0.2 mL	/	Toxicity reduction	[53]

用自发组装成不规则球形结构, 纳米颗粒的粒径范围在133～280 nm, 表面羟基、羧基赋予优异水溶性与稳定性。其中*Z*-藁本内酯与黄芪甲苷IV以2∶1摩尔比通过疏水作用形成复合物, 驱动AA-NPs动态组装并实现缓释, 显著改善心肌纤维化, 疗效优于福辛普利[19]。甘草–附子配伍中, 甘草蛋白通过疏水包裹乌头碱形成近球形纳米粒 (GP-AC NPs), 平均粒径238.2 ± 1.2 nm, 包封率28.2%。毒性实验证实: 纯乌头碱溶液及未包封混合液致小鼠100%死亡, 而GP-AC NPs与共煎剂仅引起轻微中毒症状, 且所有实验小鼠均存活, 这为"甘草解附子毒"提供了有力的分子机制证据[53]。

大黄性寒味苦, 可清热泻火、凉血解毒; 淫羊藿辛温, 能补肾壮阳、祛风湿、强筋骨[55,56]。二者共煎, 能缓解便秘, 增强肠道通透性, 改善胃肠功能。其共煎剂大黄酸 (rhein) 与淫羊藿苷 (icariin) 通过非共价作用自组装成均一球形无载体纳米颗粒 (R-I NPs), 具高负电性及生理稳定性, 其pH响应缓释特性在pH 6.8时释放率较pH 7.4提升122%, 符合骨架腐蚀机制。该特性精准匹配脓毒症酸中毒微环境, 通过协同抗炎、抗铁死亡及肾脏靶向递送增强肾保护功能[51]。此外, 研究还发现了大黄–黄连这一常用药对中活性成分小檗碱与大黄酸以1∶1摩尔比经静电作用及π-π堆积形成具3D多孔框架晶体结构的无载体纳米组装体, 平均粒径约175 nm, 水溶液稳定性良好, 通过Fickian扩散实现缓释, 并展现多靶点协同抗阿尔茨海默病活性[52]。

综上, 这些研究共同表明中药药对自组装纳米颗粒均实现了药效增强或毒性调控, 体现了中药多成分、多靶点的作用特点; 另一方面, 这些天然纳米结构既是成分相互作用的产物, 也是药效协同、毒性调控的物质载体, 为阐释中药配伍机制、开发新型中药纳米药物提供了统一规律。

2.3 单味药

中药水煎液作为临床应用的主要形式, 其化学组成高度复杂, 不仅包含蛋白质、多糖、皂苷等生物大分子, 亦富含生物碱、萜类、醌类等结构多样的活性小分子。近年来研究发现, 在单味中药的水煎过程中, 部分成分可通过非共价相互作用自组装形成自组装体, 具体研究内容详见表3[57-59]。例如, 大黄中活性成分大黄酸在pH 8.0～9.4的PBS缓冲液中, 经超声与加热冷却处理, 通过π-π堆积、氢键及静电作用自组装形成水凝胶, 该结构具备良好稳定性、剪切变稀及温度响应等可逆刺激响应性, 可实现药物持续释放, 且能显著降低促炎因子释放, 抗神经炎症效果优于游离大黄酸, 毒性更低[57]。黄连水煎剂中存在的颗粒聚集体 (CCD-Ps) 主要由多糖及少量蛋白质构成, 呈纳米级尺寸且带负电

荷, 经超速离心结合阴离子交换树脂洗脱可分离, 其模拟体 (CCP-Ps) 通过类似自组装过程形成, 能以电荷依赖方式促进活性成分小檗碱的肠道吸收, 机制涉及调节肠上皮细胞紧密连接、增强主动运输及内吞作用, 证实此类聚集体是活性成分吸收的重要增强剂[58]。山茱萸中的没食子酸 (gallic acid, GAC) 则通过 π-π 堆积和氢键自组装形成水凝胶, 分子动力学模拟验证了非共价相互作用的驱动机制, 该水凝胶生物相容性良好, 在小鼠乙醇诱导急性胃损伤模型中, GAC 水凝胶处理显著缓解了胃黏膜损伤, 其胃损伤抑制率显著高于游离 GAC 组; 药代动力学研究表明, GAC 水凝胶的相对生物利用度较游离 GAC 提高了 1.55 倍, 半衰期延长了 2.53 倍, 且能显著上调抗氧化酶 (超氧化物歧化酶、过氧化氢酶、谷胱甘肽过氧化物酶) 活性、下调炎症因子 (TNF-α、IL-1β、IL-6) 表达及凋亡相关蛋白 (Bax、Caspase-3、Caspase-9) 水平, 综合药效优于游离 GAC[59]。综上, 单味中药的活性成分可通过自组装形成特定纳米结构, 借助增强药物递送、调控生理通路等机制提升药效, 为阐释中药药效物质基础提供了重要思路。

2.4 单体成分

2.4.1 基于生物碱的自组装体系 生物碱是天然植物中重要的活性成分, 大多数生物碱具有复杂的环状结构, 环中主要含有氮。根据其结构可分为有机胺类生物碱、异喹啉类生物碱、吡啶类生物碱、吲哚类生物碱、二萜类生物碱和东莨菪碱[60]。生物碱表现出多种药理活性, 包括抗炎、抗菌、血管扩张、降糖、抗癌等作用, 这可能归因于其结构的多样性[61,62]。

BBR 作为典型生物碱, 依托季铵盐阳离子特性与稠合芳香环结构, 成为自组装的核心单元。它可通过静电吸引、π-π 堆积及氢键等作用, 与多种活性成分形成功能化纳米结构。与肉桂酸或绿原酸经氢键、π-π 堆积作用形成 pH 响应性纳米颗粒, 显著提升对耐药菌 (如耐甲氧西林金黄色葡萄球菌) 的抑制活性[21,63]。通过亲脂性成盐策略与 GA 结合成盐后自组装的纳米颗粒, 提升了膜渗透性和靶向性, 还具有聚集诱导发光特性[64]。BBR-木兰通过静电及 π-π 作用形成结肠靶向纳米粒, 提升 BBR 口服生物利用度, 在溃疡性结肠炎模型中协同修复肠屏障并调节菌群[65], 这也揭示了天然产物自组装系统在靶向递送方面的重要作用。此外, BBR 与马兜铃酸自组装形成的异质线性超分子, 可屏蔽马兜铃酸毒性基团, 改善肾功能并维持菌群稳态[20]。而 BBR 与姜黄素自组装颗粒则通过光敏协同效应增强广谱抑菌活性[21]。此外, 喜树碱 (camptothecin, CPT) 与氨基甘露糖共轭物通过疏水作用及 π-π 堆积形成 100 nm 靶向纳米管[66], CPT-二氢青蒿素自组装前药

Table 3 Self-assembled products from single Chinese herbs. AFM: Atomic force microscope; CD: Circular dichroism spectroscopy

Source	Self-assembled component composition	Extraction/separation method	Self-assembled morphology	Morphology characterization method	Interaction force	Force characterization method	Experimental model	Dose	Pharmacological activity	Assembly effect	Ref.
Rhei Radix et Rhizoma	Rhein	Heating with ultrasonication	Hydrogel	TEM; SEM; AFM	π-π stacking, H-bonding	UV; FTIR; XRD; CD	BV2 microglial cells	15 μmol·L^{-1}	Anti-neuroinflammation	Sustained release, improved stability	[57]
Corni Fructus	Gallic acid	Ultrasonication, water bath heating, cooling	Hydrogel	TEM	π-π stacking, H-bonding	MDY	BALB/c mice	200 mg·kg^{-1}	Anti-oxidative stress, anti-apoptosis, anti-inflammatory	Synergistic effect, improved bioavailability	[59]
Coptidis Rhizoma	Coptis polysaccharide	Polysaccharide extraction, heating dissolution, cooling	Nanoparticles	TEM	H-bonding	/	SD rats, BALB/c mice	100, 200 mg·kg^{-1}	/	Promote absorption of active components	[58]

兼具pH响应释药与聚集诱导发光功能[67]; 葫芦巴碱则通过氢键/静电作用驱动姜黄素形成50 nm载药颗粒, 为糖尿病联合治疗提供新载体[68]。

2.4.2 基于萜类化合物的自组装体系 萜类化合物广泛来源于植物, 具有异戊二烯的基本结构单位, 其中以三萜最为普遍[69]。三萜类化合物具有亲水性和疏水性两种成分, 疏水主链的存在促进疏水相互作用, 亲水的羟基和羧基可以参与氢键的形成。GA作为典型三萜皂苷, 凭借亲水葡萄糖醛酸基与疏水三萜骨架的两亲性, 可自组装形成主体–客体复合物, 实现药物增溶与控制释放[70-72]。

通过加热冷却法, GA可直接自组装为胶束网络水凝胶, 无需添加剂即可高效包载姜黄素 (包封率80.17%)、槲皮素等, 氢键与疏水作用驱动其形成三维网络, 具有剪切稀化、自愈合及温敏响应特性[73]。与青藤碱 (sinomenine, SIN) 自组装的纳米水凝胶兼具热可逆性、自修复性及缓释功能, 在小鼠佐剂关节炎模型中, 口服S-G水凝胶 (以SIN计30 $mg·kg^{-1}·d^{-1}$) 较等剂量游离SIN能更显著地减轻关节肿胀和病理损伤, 有效保护软骨并抑制骨侵蚀, 降低血清TNF-α、IL-6水平, 并抑制关节局部中性粒细胞浸润及NETs形成[71]。Li等[74]首次以GA纳米纤维 (GA nanofibers, GN) 与BBR共组装, 构建全天然聚集诱导发光活性水凝胶 (GN-BBR), 其聚集纤维网络结构展现出强AIE荧光、优异机械强度、结构恢复能力及温度、pH双重刺激响应行为。此外, GA与黄芩素、芍药苷经超声构建的纳米胶束可提升药物溶解度与口服生物利用度, 并具pH响应缓释特性[70,75]。与木香烃内酯通过π-π堆积、氢键自组装的纳米颗粒, 在溃疡性结肠炎模型中呈现协同抗炎抗氧化作用, 显著改善结肠损伤[76]。此外, 甘草次酸也在多种有机溶剂中展现出自组装形成热可逆凝胶的能力[77,78]。熊果酸等三萜则能自组装为有机凝胶或纳米颗粒, 通过提升水溶性增强抗肿瘤活性并激活免疫[79-81]。

2.4.3 基于多酚类化合物的自组装体系 作为天然生物活性分子, 多酚不仅具有抗氧化和抗炎作用, 其丰富的酚羟基和儿茶酚结构还赋予其动态非共价自组装能力。通过氢键、疏水作用及金属–配体配位等分子间相互作用, 多酚可自组装形成能响应pH、酶或氧化还原刺激的智能纳米载体[82,83]。

通过两步酯化法将阿魏酸 (ferulic acid, FA) 接枝至低聚果糖 (fructooligosaccharides, FOS), 制得具有自组装特性的碟形微粒 (FA-FOS I), 其在水中形成均一悬浮液, 不溶于有机溶剂, 且在模拟胃肠液、肠酶及结肠菌群中高度稳定, 能抵抗上消化道降解实现结肠靶向, 为结肠癌防治提供新策略[84]。绿原酸是源自烟草、咖啡及多种草本植物的一种典型的酚酸化合物, 表现出卓越的抗癌、抗炎和抗菌特性[85,86]。然而, 其较差的溶解性和在血液循环过程中的低吸收效率限制了它的应用[87]。基于此, 研究人员用聚乙二醇 (polyethylene glycol, PEG) 修饰疏水性茄尼醇 (Sol) 形成自组装胶束, 包裹CHA和光敏剂IR780后连接靶向短肽K获得Cl@SPK, 解决了疏水性问题, 实现靶向递送与屏障穿透、活性氧清除、免疫微环境调控的三重协同功能[88]。针对呼吸道合胞病毒肺炎, 黄芩苷与白藜芦醇 (resveratrol, Res) 通过π-π堆叠和氢键自组装成约218 nm颗粒, 经雾化吸入实现肺靶向蓄积, 通过抑制病毒复制、清除活性氧 (reactive oxygen species, ROS) 及调节巨噬细胞平衡, 降低小鼠肺病毒载量并缓解炎症损伤[89]。此外, 少量白藜芦醇可触发没食子酸快速自组装成超分子水凝胶, 克服多酚类自组装产物多为颗粒形态的限制, 兼具抗菌、抗炎、促伤口愈合能力[90]。

2.4.4 基于黄酮类化合物的自组装体系 黄酮类化合物作为关键的植物次生代谢产物, 凭借其2-苯基色原酮母核结构, 通过羰基氢键作用、π-π堆积及糖苷化赋予的两亲性, 展现出独特的分子自组装能力。这类化合物具有广谱生物活性, 如抗氧化、抗炎、抗病毒和抗肿瘤作用, 在癌症与类风湿性关节炎治疗领域备受关注[91-94]。

针对传统纳米载体的生物相容性缺陷, 无载体自组装策略成为突破黄酮溶解性差、生物利用度低瓶颈的创新方向。在抗菌领域, 黄芩苷与巴马汀通过分子间作用构建的无载体递送系统, 实现了高效抗菌且规避了载体毒性[95]。而黄芩苷–血根碱自组装水凝胶体系, 更在无需化学修饰条件下同步整合抗菌、抗炎与组织再生功能, 为耐药菌感染创面提供了临床转化新方案[96]。在功能食品开发中, 槲皮素 (quercetin, Que) 因其水溶性与稳定性受限[97]。通过莲藕支链淀粉 (lotus root amylopectin, LRA)-藜麦蛋白 (quinoa protein, QP) 纳米胶束 (Que-QP-LRA) 的自组装包封, 显著提升包封率与胃肠缓释性能[98]。基于大麦醇溶蛋白–壳聚糖的QHCNPs纳米平台则进一步拓展了Que在耐药菌感染伤口协同治疗中的应用[99]。

2.4.5 基于醌类化合物的自组装体系 醌类化合物兼具抗菌、抗炎等活性, 以共轭环己二烯二酮结构为核心, 羰基作为氢键受体、芳香环驱动π-π堆积, 部分含羧酸基团 (如大黄酸) 更成为自组装关键位点, 近年来通过自组装策略在疾病治疗领域实现突破性进展[30,100]。

在伤口修复方面, 大黄酸与苦参碱 (matrine) 通过

分子间作用自组装形成75 nm球形纳米粒 (RM NPs), 负载于GelMA水凝胶后形成缓释多孔结构, 显著加速小鼠皮肤创伤愈合, 凸显天然产物协同增效潜力[101]。针对耐药菌感染, 创新性设计聚硫辛酸−聚乙二醇载体共价连接大黄酸与香叶醇 (geraniol), 构建H_2S响应型核壳纳米前药, 在降低细胞毒性、延长半衰期的同时实现靶向释放与协同抗菌[102]。在肿瘤治疗领域, 两亲性羧甲基壳聚糖−大黄酸共聚物胶束 (carboxymethyl chitosan-rhein copolymer micelles, CR PMs) 通过pH响应性缓释特性, 显著提升紫杉醇口服生物利用度[103]。同时, 研究人员以羧甲基壳聚糖为亲水骨架, 通过硫缩酮连接器偶联疏水性大黄酸, 并修饰甘草次酸, 制备出兼具肝癌靶向与ROS响应功能的壳聚糖基聚合物胶束, 用于高效递送抗肿瘤药物雷公藤红素 (celastrol)[104]。

表4[20,21,63-66,70,71,73-76,84,88-90,95,96,98,99,101-107]详细介绍了基于不同天然产物类型 (生物碱、萜类、多酚类、黄酮类和醌类化合物) 的自组装产物的应用实例和结构特征。总体来看, 各类单体因其化学结构和官能团差异, 展现出不同的自组装驱动力与功能特性: 生物碱多依赖氮杂环阳离子与芳香环结构, 通过静电作用、π-π堆积和氢键实现抗菌、抗炎及毒性屏蔽; 萜类化合物以两亲性骨架为核心, 易构建胶束或水凝胶, 常用于药物增溶、控释与抗炎治疗; 多酚类化合物凭借丰富的酚羟基和动态可逆相互作用, 常形成智能响应型纳米载体, 在抗氧化、抗病毒和组织修复中发挥作用; 黄酮类因其苯基色原酮母核和糖苷化特性, 既具协同抗菌抗炎能力, 也在功能食品开发中展现应用潜力; 醌类化合物则依托共轭羰基与芳香环结构, 常用于构建pH或ROS响应的纳米前药, 在肿瘤和感染治疗中具有优势。尽管驱动机制与结构特征各异, 这些体系均通过分子间非共价作用实现自发有序组装, 表现出提升溶解度、改善生物利用度、实现靶向递送及减毒增效等共同效应, 凸显了中药单体自组装在药效发挥和临床转化中的广阔潜力。

3 中药自组装纳米体系的研究意义

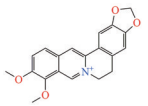
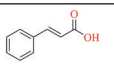
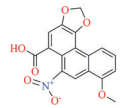
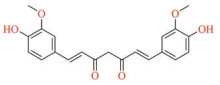
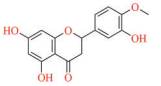
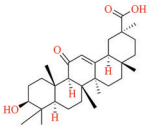
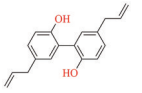
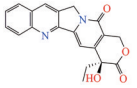
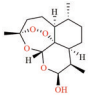
中药自组装纳米体系是由活性成分通过氢键、疏水作用、π-π堆积等非共价作用自发形成的无载体纳米结构, 可在一定程度上改善中药成分溶解性和生物利用度, 补充外源载体在载药量、降解性与生物安全性方面的不足, 并为临床转化提供潜在优势[30,105-107]。同时, 其动态组装特性赋予体系智能响应功能 (如pH、ROS、酶响应) 和靶向性, 如大黄酸−淫羊藿苷纳米颗粒在脓毒症酸中毒微环境中靶向释放, 实现病理微环境适配的精准递送[108]。在理论层面, 该体系为阐释中药“配伍增效减毒”机制提供了分子依据, 复方自组装沉淀中可能富集活性成分并参与药效作用; 药对自组装 (如甘草蛋白包裹乌头碱) 验证了“减毒”原理; 单组分自组装则通过递送优化增强疗效[109]。然而, 这些发现目前主要基于实验观察, 实际应用的普适性仍有待深入研究。近年来提出的“全活性纳米药物”(full-API nanodrug, FAND) 概念, 其核心特征在于依赖小分子间的非共价作用 (如氢键、疏水作用、π-π堆积) 或金属配位驱动形成纳米结构, 该结构几乎完全由活性成分 (API ≈ 100%) 构成, 这与中药自组装体系在“无载体、高载药量和非共价自组装”方面具有交集, 但FAND多基于结构明确的小分子药物或其衍生物, 强调载药比例和质量一致性, 旨在通过工程化设计促进临床转化[110-112]; 而中药自组装体系则主要源自复方、药对或单味药的复杂成分, 突出配伍间的协同互作及其与传统理论的联系。已有FAND在病理环境下实现靶向释放并展现良好体内安全性, 提示该理念为中药自组装的工程化与可监管化研究提供了有益借鉴。

4 总结与展望

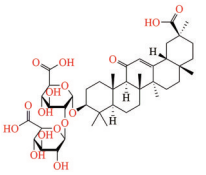
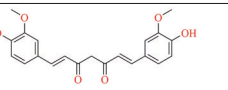
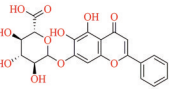
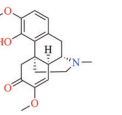
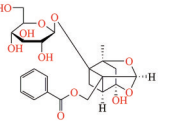
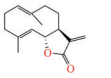
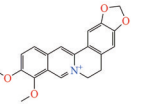
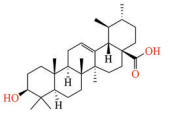
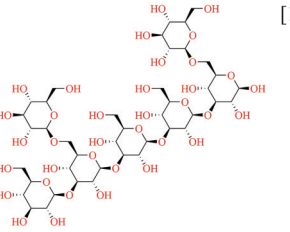
中草药煎剂成分复杂, 煎煮过程中的化学与物理变化使其生物活性的物质基础尚未完全阐明。随着纳米技术的发展, 研究者在中草药煎剂中发现了天然存在的纳米粒。本文首先综述了中药汤剂中纳米颗粒研究的主要进展, 强调和阐明了煎煮过程中自发形成的纳米颗粒, 可能是中草药复方发挥药效的重要物质基础之一。另外中医配伍理论认为, 某些药对可以产生协同作用, 如石膏和知母, 麻黄和桂枝等。这种“增效减毒”效应在自组装分子层面也得到了呼应, 例如, 含雷公藤红醇与含甘草酸的草药配伍时, 其毒性降低现象与二者相互作用形成的自组装纳米产物密切相关。因此, 中药自组装纳米体系的研究可为揭示中药配伍理论的增效减毒机制提供一种新的视角。利用中药成分固有的自组装特性, 可构建高载药量、良好生物相容性及智能响应功能的纳米递送系统, 改善药物的溶解度、生物利用度和靶向性。

在国际研究方面, 国外在天然产物自组装领域同样取得了显著进展, 但在研究思路、体系设计和应用方向上与国内研究存在明显差异。国外研究多集中于单一成分 (如多酚、黄酮、生物碱) 或简单复合体系的自组装, 侧重于利用脂质体、聚合物等合成载体进行功能化修饰, 致力于开发针对肿瘤、耐药菌感染和病毒性疾病的精准治疗策略[113,114]。例如, 采用葡萄籽多酚自组装纳米颗粒促进伤口愈合[115], 基于姜黄素与亚甲蓝共载的bilosomes实现光动力抗菌治疗[116], 以及利用单宁酸−多西他赛自组装纳米逆转前列腺癌化疗耐药

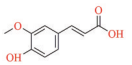
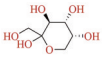
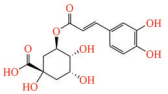
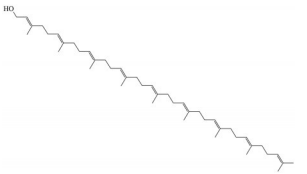
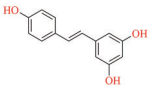
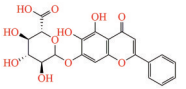
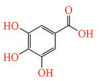
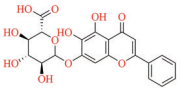
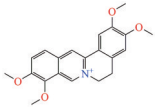
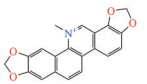
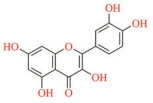
Table 4 Formation, classification, and structure of self-assembled products from natural products. MRSA: Methicillin-resistant *Staphylococcus aureus*; BBR: Berberine; MAG: Magnolol; CPT: Camptothecin; DHA: Dihydroartemisinin; APP/PS1: Amyloid precursor protein/presenilin 1; RAW: Mouse mononuclear macrophage leukemia cells; *E. coli*: *Escherichia coli*; *S. aureus*: *Staphylococcus aureus*; CMCS: Carboxymethyl chitosan; ROS: Reactive oxygen species

Natural product type	Structural type	Self-assembled component	Preparation method	Interaction force	Particle size/nm	Experimental model	Dose	Assembly effect	Molecular structure	Ref.
Alkaloids	Berberine 	Cinnamic acid	Nanoprecipitation-on, dialysis purification	Intermolecular H-bonding, π-π stacking	65.99	*Pseudomonas syringae* pv. *lachrymans*, *Clavibater michiganensis* subsp. Michiganensis	250 mg·L^{-1}	Enhanced efficacy, pH-responsive		[63]
		Aristolochic acid	pH adjustment, heating and stirring, centrifugation	Electrostatic attraction, π-π stacking, hydrophobic interactions	50−200	Citrus plants infected with *Xanthomonas axonopodis* pv. *citri*	33.3, 50, and 100 mg·L^{-1}	Toxicity reduction		[20]
		Curcumin	Nanoprecipitation-on, dialysis purification	Electrostatic attraction, π-π stacking, hydrophobic interactions	407	MRSA (ATCC43300) and *Candida albicans* (CA, SC5314)	50−100 μmol·L^{-1} for MRSA; 125 μmol·L^{-1} for CA	Enhanced efficacy		[21]
		Hesperidin	pH adjustment, room temp. stirring, centrifugation	Electrostatic attraction, π-π stacking, hydrophobic interactions	295.6	MRSA and CA mixed biofilms	75 μmol·L^{-1} for inhibition, 200 μmol·L^{-1} for eradication of MRSA biofilms, 125 μmol·L^{-1} for CA biofilms	Enhanced efficacy		[105]
		Glycyrrhetinic acid	Lipophilic salt formation, nanoprecipitation	π-π stacking, hydrophobic interactions, ionic interactions	307.8	Kunming mice, H22 tumor model	20 mg·kg^{-1}	Enhanced efficacy, targeting, low toxicity		[64]
		Magnolol	Nanoprecipitation-on, dialysis purification	Electrostatic attraction, π-π stacking	160	C57BL/6 mice	25 mg·kg^{-1} BBR; 16 mg·kg^{-1} MAG	Enhanced efficacy, targeting, pH-responsive, improved bioavailability		[65]
	Camptothecin 	Aminomannose	/	Hydrophobic interactions, π-π stacking	100	LM3 and A549 cell lines	40 μg·mL^{-1} CPT; 8 μg·mL^{-1} DHA	Enhanced efficacy, improved water solubility	/	[66]
		Dihydroartemisinic	Nanoprecipitation-on, dialysis purification	H-bonding, π-π stacking	149.65	LM3 and A549 tumor cells	40 μg·mL^{-1} CPT; 8 μg·mL^{-1} DHA	Enhanced efficacy, pH-responsive		[106]

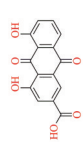
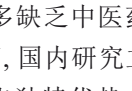
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Natural product type	Structural type	Self-assembled component	Preparation method	Interaction force	Particle size/nm	Experimental model	Dose	Assembly effect	Molecular structure	Ref.
Terpenoids	Glycyrrhizic acid 	Curcumin	Thin-film hydration method	H-bonding, hydrophobic interactions	/	/	/	Controlled release, enhanced bioactivity		[73]
		Baicalein	Thin-film hydration method	H-bonding, hydrophobic interactions	190	/	/	Enhanced solubility, sustained release		[70]
		Sinomenine	Pre-heat to 80 °C, mixing and stirring	Electrostatic attraction, H-bonding	50−100	C57BL/6 mic	70 mg·kg^{-1}	Enhanced solubility/ sustained release, efficacy enhancement		[71]
		Paeoniflorin	Ultrasonic dispersion	Hydrophobic interactions, H-bonding, electrostatic stabilization	58.89	SD rats	100 mg·kg^{-1}	Improved bioavailability		[75]
		Costunolide	Nanoprecipitation method	π-π stacking, H-bonding	200−300	ICR mice	10 mg·kg^{-1}	Synergistic effect		[76]
		Berberine	pH induction method	Electrostatic attraction, H-bonding, π-π stacking	110	Kunming mice	400 μL	Temperature/ pH dual-responsive fluorescence		[74]
	Ursolic acid 	Lentinan	Nanoprecipitation method	H-bonding, van der Waals forces	68.8	BALB/c mice	5 mg·kg^{-1}	Improved bioavailability		[107]

Continued

Natural product type	Structural type	Self-assembled component	Preparation method	Interaction force	Particle size/nm	Experimental model	Dose	Assembly effect	Molecular structure	Ref.
Polyphenols	Ferulic acid 	Fructooligosaccharides	Nanoprecipitation method	van der Waals forces, non-covalent interactions	1 840	APP / PS1 transgenic mice	2 mg·kg^{-1}	Colon targeting, high stability		[84]
	Chlorogenic acid 	Solanesol	Nanoprecipitation method	Hydrophobic interactions	198.4	BALB/c mice	1.5 mg·kg^{-1}	Targeted delivery, light-controlled release and synergistic therapy		[88]
	Resveratrol 	Baicalin	Nanoprecipitation method	π-π stacking, H-bonding	218.2	RAW 264.7 mouse macrophages; mice infected with *E. coli*	14 μg·mL^{-1}; 12 mg·mL^{-1}	High antiviral activity		[89]
		Gallic acid	Heat to 100 °C, cool to room temp	π-π stacking, H-bonding	/			Sustained release, efficacy enhancement		[90]
Flavonoids	Baicalin 	Palmatine	pH induction method	Electrostatic attraction, hydrophobic interactions	129	*S. aureus*; E. coli	0.05 μmol·mL^{-1}	Enhanced efficacy, improved water solubility		[95]
		Sanguinarine	pH induction, heating and stirring	Electrostatic attraction, π-π stacking, H-bonding	/	*S. aureus*; MRSA mice	7.5 μmol·L^{-1}; 3.75 μmol·L^{-1}; 512 mg·L^{-1}	Enhanced efficacy		[96]
	Quercetin 	Lotus root amylopectin-Quinoa protein	Nanoprecipitation method	H-bonding, hydrophobic interactions	157.3	/	/	Improved bioavailability	/	[98]
		Hordein-chitosan	Nanoprecipitation method	Electrostatic attraction, hydrophobic interactions	435.5	Kunming mice	512 mg·L^{-1}	Improved bioavailability	/	[99]

Continued

Natural product type	Structural type	Self-assembled component	Preparation method	Interaction force	Particle size/nm	Experimental model	Dose	Assembly effect	Molecular structure	Ref.
Quinones	Rhein 	Matrine	Co-solution stirring at 60 °C	π-π stacking, H-bonding	75	Skin wound-healing model in mice	50 and 100 μmol·L^{-1}	Enhanced efficacy and sustained release, improved water solubility		[101]
		Geraniol	Nanoprecipitation method	Electrostatic attraction, hydrophobic interactions	142−220	Salmonella infection model in mice	21 mg·kg^{-1}	Enhanced efficacy, improved bioavailability		[102]
		Carboxymethyl chitosan	Nanoprecipitation method	Electrostatic attraction, H-bonding, hydrophobic interactions	189.3	ICR mice	20 mg·kg^{-1}	Enhanced efficacy and sustained release, improved bioavailability	/	[103]
		CMCS-thioketal-glycyrrhetinic acid	Nanoprecipitation method	Hydrophobic interactions	165.67	ICR mice	2 mg·kg^{-1}	ROS-responsive, liver cancer targeting, improved bioavailability	/	[104]

等[117]。这些研究在材料精细化设计、机制深入剖析及临床前转化方面较为成熟, 部分体系已进入临床试验阶段。然而, 其依赖外源载体或化学修饰的策略可能引入生物相容性隐患, 且体系多缺乏中医药整体观与配伍理论的指导[118]。相比之下, 国内研究立足于中医药传统理论与丰富资源, 展现出独特优势: 其一, 强调复方与药对自组装的整体性与协同性, 如黄连解毒汤、黄芪−当归等体系, 不仅证实自组装沉淀在药效中的重要作用, 更从分子层面阐释了“配伍增效减毒”的科学内涵; 其二, 倡导无载体、绿色制备, 最大程度保留成分天然状态与活性, 避免外源材料潜在毒性; 其三, 应用场景更紧密契合中医临床需求, 如缓解化疗毒副作用、修复组织屏障、调节免疫微环境等。

尽管如此, 当前研究在机制解析、智能系统开发和临床转化方面仍面临诸多挑战: ① 中药成分复杂性使得自组装机制解析困难, 如果要精准设计特定纳米结构, 需深入研究分子间非共价作用、构象变化、药理活性及体内代谢过程; ② 不同天然产物结构与官能团对自组装构效关系的影响尚不明确; ③ 目前缺乏能够直接、完整观测中药纳米颗粒自组装全过程的技术手段, 当前研究主要依赖自组装产物的最终表征 (如形态、粒径)、光谱学分析及分子动力学模拟进行间接推断, 导致自组装发现主要依赖经验性重复实验; ④ 应用边界拓展存在局限, 保持中药自组装纳米体系天然状态虽能保留其药理活性与生物相容性优势, 却制约了智能控释与精准靶向功能的深度开发。未来突破需聚焦五大方向: ① 深化自组装体系结构−功能关系研究, 借鉴国外先进的表征技术 (如单粒子示踪、原位光谱、高分辨模拟) 解析复杂体系组装过程, 结合AI技术解析蛋白质、多糖与小分子在纳米结构形成中的作用机制, 建立官能团与组装模式的预测模型, 减少对偶然实验的依赖; ② 探索多靶向组分共组装策略 (如纳米粒−水凝胶协同体系), 针对特定病理过程设计多途径协同治疗方案; ③ 以临床转化为导向, 优化自组装产物的稳定性与理化性质, 明确其在口服递送过程中的胃肠道转运和代谢行为; ④ 开发刺激响应型智能系统 (光、pH、酶等), 拓展组织与细胞级靶向应用; ⑤ 探索中西医结合新模式, 利用自组装原理整合天然活性成分与合成材料优势, 设计兼具中药多靶点协同与西医精准治疗特征的新型纳米药物。

自组装纳米技术的应用为中医药现代化提供了重要契机, 将中医药理论与自组装纳米技术相结合, 可以为中医药的现代化提供创新策略和视角。总之, 将中药化学与分子自组装科学的原理和技术相结合, 代表了一个有价值的研究方向。这种方法对于阐明天然药

物小分子的相互作用机制及开发新的天然小分子纳米药物具有重要的研究意义。

作者贡献: 林笑霄负责查阅文献、整理并写作; 邹俊波、张小飞负责审阅及补充相关研究; 郭东艳、翟秉涛负责对文章进行指导完善; 栾飞、史亚军负责选题、监督和指导论文写作。

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