中药自组装超分子研究进展

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摘要: 中药汤剂在煎煮过程中其成分不仅发生化学键的相互结合还产生非共价键间的相互作用。近年来, 研究发现在中药汤剂中存在由非共价键连接的聚集体, 统称为中药超分子 (supramolecules of traditional Chinese medicine, STCM)。本文对STCM相关文献进行梳理, 从单体成分、单味药、药对、复方4个维度, 围绕STCM的研究方法、形成机制和研究价值3个方面进行综述, 以期为后续STCM的研究提供参考和借鉴。由于中药成分复杂多样, 复方、药对和单味药煎煮液中的STCM形成机制研究尚不完善, 这也是未来STCM研究的一个重点和难点。自组装超分子化学的视角为研究中药药效物质基础提供了新的思路, 将中药领域研究推向了一个新的高度。

关键词: 中药; 自组装; 超分子; 形成机制; 研究价值; 研究方法

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Research progress on self-assembly supramolecules of traditional Chinese medicine

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Abstract: During the decoction process of traditional Chinese medicine (TCM), not only do chemical bonds interact, but non-covalent interactions also occur. In recent years, studies have discovered the presence of aggregates connected by non-covalent bonds in TCM decoctions, collectively referred to as supramolecules of traditional Chinese medicine (STCM). This review summarizes the literature on STCM, discussing research methods, formation mechanisms, and research significance from four perspectives: individual components, single herbs, medicinal pairs and compound prescriptions. The aim is to provide a reference for future research on STCM. Due to the complexity and diversity of TCM components, the research on the formation mechanism of STCM in compound formulas, drug pairs and single herb decoction liquids is not perfect, which is also a key and difficult point in future STCM research. The perspective of self-assembled supramolecular chemistry provides a new idea for the study of the pharmacodynamic material basis of TCM, and pushes the research in the field of TCM to a new height.

Key words: traditional Chinese medicine; self-assembly; supramolecular; formation mechanism; research value; research method

早在晋朝就有汤液 (汤剂) 始于伊尹 (商朝) 的说法, 汤剂是中药传统八大剂型之一 (汤剂、丸剂、散剂、膏剂、丹剂、露剂、酒剂和锭剂), 也是我国乃至世界上较早的药物剂型之一[1-3]。《汤液本草》中记载: “汤者, 荡也, 其行速。”这体现了汤剂对百病疗效之迅速[4,5]。汤剂的煎煮并不是简单的提取过程, 不仅存在中药成

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分的单纯溶出, 同时也存在各成分之间的相互作用, 这种相互作用不仅包含化学相互作用也包含物理相互作用[6]。近年来, 越来越多的研究发现中药汤剂中存在着成分自组装形成超分子的现象[7]。中药超分子 (supramolecules of traditional Chinese medicine, STCM) 是指中药成分在一定条件下通过非共价键, 如氢键、π-π堆积、静电作用和疏水作用等自发形成结构有序且具有一定稳定性的聚集体[8]。

Alfred Werner 教授因对配位化学的贡献获得了1913年的诺贝尔化学奖[9]。Jean-Marie Lehn 教授受到配位化学的启发, 提出了超分子化学的概念, 并于1987年获得诺贝尔化学奖[10]。2014年贺福元教授将超分子化学应用于中药研究, 首次提出并阐明了中药作用的超分子“印迹模板”作用机制[11]。2021年乔宏志教授提出“结构中药学”理论, 在中药学研究领域构建起自组装聚集体层次的新兴方向[12]。结构中药学认为, 成分是药效的基础, 结构是起效的形式, 中药的特点是成分多样, 这必然引起成分间的相互作用, 继而会形成不同的结构, 而成分和结构共同影响了药效的发挥[12]。随着超分子化学的提出与发展, 中药药效物质基础的认识维度被极大地拓宽 (图1)。由于单纯地从成分视角并不能很好地解释中药药效物质基础, 所以结构中药学成为了中药药效物质基础研究的一个新方向。有学者提出中药成分通过非共价键自组装成二维分子, 然后这些二维分子彼此之间再进行自组装成为三维STCM, 如球形、纤维等物质[13]。这些物质具有凝胶、沉淀等不同的宏观形态, 不仅可以发挥抗炎、镇痛、抗菌和抗癌等生物活性, 也可作为载体用于药物递送, 提高药物的生物利用度, 具有广泛的应用前景[14-16]。因此, STCM 的提出为中药药效物质基础研究提供了超分子化学这个新的视角。

尽管目前研究者对中药成分相互作用关系的研究提出了先进的方法和技术, 比如红外光谱 (infrared spectrophotometry, IR)、核磁共振 (nuclear magnetic resonance spectroscopy, NMR)、X 射线衍射 (X-ray diffraction, XRD)、分子动力学模拟 (molecular dynamics, MD) 等, 但仍不能准确分析中药复杂成分之间的相互作用关系[17]。因此, STCM 的形成机制将会是未来研究的重点和难点。本文对 STCM 相关文献进行梳理, 从单体成分、单味药、药对、复方4个维度, 围绕STCM 的研究方法、形成机制和研究价值3个方面进行综述, 以期为后续STCM 的研究提供参考和借鉴。

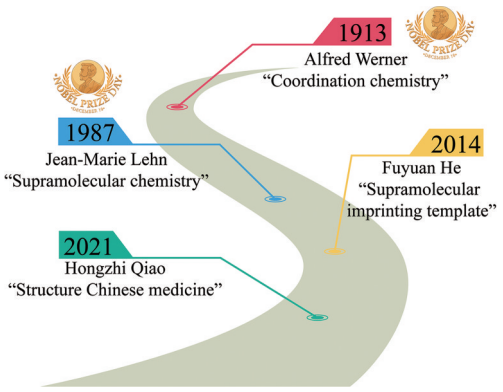


Figure 1 The timeline of the supramolecules of traditional Chinese medicine (STCM)

1 中药超分子研究进展

我国学者于2000年左右发现中药汤剂中存在STCM[18-20]。中药汤剂是一个复杂体系, 可以拆分为真溶液相、胶体相和混悬相等不同的相态, 而相态的多样性又决定了其存在粒子的多样性, 其微观形态有球形、纤维、簇状等, 其形成可能是由于汤剂中成分自组装成STCM 所致[13,21,22]。中药在煎煮过程中形成的 STCM 及其形成机制和药理活性逐渐引起了人们的关注。在对 STCM 的研究中, 复方研究多集中在 STCM 的性能分析; 药对中主要通过探究合煎液与单煎液 STCM 的各种区别, 从而阐明其配伍的药效物质基础; 单味药的主要关注点是 STCM 的主要组成成分分析; 以上三者对 STCM 的形成机制研究并不深入, 而单体成分自组装形成的 STCM 研究则主要集中在对其形成机制和药效方面的研究, 并以此来反向验证汤剂中确实存在超分子自组装现象 (图2)。

1.1 单体成分

中药中的一些小分子成分常被用来验证中药中可能存在的自组装现象。小檗碱作为黄连的主要有效成

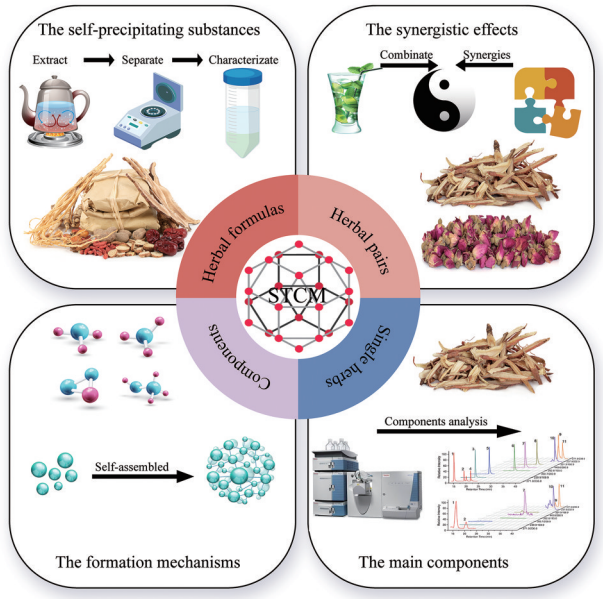


Figure 2 The research dimensions of STCM

分, 常被用来验证黄连与其他中药之间可能存在的自组装, 如黄连–黄芩药对中的成分小檗碱–黄芩苷通过热力学驱动可形成球形自组装超分子[23]。蛋白质、多糖和皂苷是自然界中广泛存在的天然大分子, 由于其结构的特殊性常会发生本身自组装或者与中药中其他成分自组装。如反式-2,3,5,4′-四羟基二苯乙烯-2-*O*-*β*-*D*-葡萄糖苷和花青素-3-*O*-*β*-葡萄糖苷作为黑豆和何首乌的代表性成分, 用来验证黑豆炮制何首乌过程中发生自组装形成STCM[24]。通过对单体成分超分子形成机制及药效研究, 佐证汤剂复杂体系中的超分子自组装现象。关于中药单体成分STCM研究的详细内容见表1[13,14,16,23-49]。

Table 1 STCM in TCM components. UV: Ultraviolet-visible spectrophotometry; IR: Infrared spectrophotometry; NMR: Nuclear magnetic resonance spectroscopy; FS: Fluorescence spectrophotometry; MS: Mass spectrometry; ITC: Isothermal titration calorimetry; XRD: X-ray diffraction; MD: Molecular dynamics; CD: Circular dichroism; DSC: Differential scanning calorimetry; TGA: Thermogravimetric analysis; EDX: Energy dispersive X-ray spectroscopy; DLS: Dynamic light scattering; SEM: Scanning electron microscope; TEM: Transmission electron microscope; AFM: Atomic force microscope; NTA: Nanoparticle tracking analysis

Component	Extraction and separation	Microscopic morphology	Non-covalent bond	Method to determine non-covalent bond	Morphological characterization	Pharmacological effect	Value	Ref.
Curcumin, arecoline	Membrane filtration, high-speed centrifugation	Spherical		UV, IR, XRD, NMR, ITC	SEM	Antitumor	Reduced toxicity and enhanced efficacy	[25]
Ursodeoxycholic acid, berberine	Heating, stirring, vacuum filtration, centrifugation (8 000 r·min^{-1} for 10 min)	Tetrahedral	Electrostatic, hydrophobic interactions	UV, IR, NMR, FS, MS	DLS, SEM	Ulcerative colitis	Sustained release, pH sensitivity, intestinal retention	[26]
Berberine, baicalin	Heating, stirring, centrifugation (9 000 r·min^{-1} for 10 min)	Spherical	Electrostatic, hydrophobic interactions, *π*-*π* stacking	UV, IR, FS, MS, NMR, XRD, CD	SEM, TEM, DLS	Antibacterial	Selective antibacterial activity	[13, 23, 27, 28]
Ursolic acid, paclitaxel	Emulsion solvent evaporation	Spherical	Hydrogen bonds, *π*-*π* stacking, hydrophobic interactions	UV, MD, IR	SEM, DLS, TEM	Antitumor	Drug delivery, reduced toxicity, and enhanced efficacy	[29, 30]
Ursolic acid	Solvent exchange	Spherical	Hydrophobic interactions, hydrogen bonds	UV, FS, MD, inhibitors	XRD, TEM, AFM	Antitumor	Sustained release	[31]
Tanshinone IIA, glycyrrhizin	Membrane filtration (0.8 μm)	Spherical			DLS, TEM	Anti-glioma	Sustained release	[32]
Astragalus polysaccharides, ononin, calycosin, calycosin-7-*O*-*β*-*D*-glucoside, formononetin	High-speed centrifugation (12 000 r·min^{-1} for 5 min)	Hollow, layered	Hydrogen bonds	MD, XRD, IR, DSC	DLS, SEM, TEM		Improved solubility and absorption	[33]
Glycyrrhetic acid	Freeze-drying	Fibrous	Hydrogen bonds, electrostatic interactions, *π*-*π* stacking	IR, NMR	SEM, AFM, TEM, CD	Antibacterial, anti-inflammatory		[14]
Trans-2,3,5,4′-tetrahydroxystilbene-2-*O*-*β*-*D*-glucoside, anthocyanin-3-*O*-*β*-glucoside	Mixing (stored in the dark for 30 min)	Smooth glassy lamellar	*π*-*π* stacking	UV, FS, MD, XRD, NMR	SEM, AFM		Improved stability	[24]

Continued

Component	Extraction and separation	Microscopic morphology	Non-covalent bond	Method to determine non-covalent bond	Morphological characterization	Pharmacological effect	Value	Ref.
Berberine, curcumin	Dialysis (500 Da)	Spherical	Electrostatic interactions, π-π stacking, hydrophobic interactions	UV, IR, NMR	TEM, LPSA	Antibacterial		[34]
Ursolic acid, lentinan	Nanoprecipitation	Spherical	Hydrogen bonds, van der Waals forces	IR	TEM, SEM, DLS	Colorectal cancer	Improved solubility and efficacy	[35]
Gallic acid	Heating (70 ℃)	Rod-like fibers	Hydrogen bonds, π-π stacking	FS, IR, CD, XRD, NMR	AFM, SEM	Antibacterial, wound healing	Sustained release, non-cytotoxic, good biocompatibility	[36]
Berberine, tannic acid	Heating, stirring, dialysis (2 000 Da)	Spherical	Hydrophobic interactions	UV, IR, XRD, ITC	DLS, TEM	Colitis		[37]
Berberine, aristolochic acid	Heating, stirring, centrifugation (4 500 ×g for 20 min)	Cross-linked network structure	Electrostatic interactions, π-π stacking	UV, IR, ITC, NMR, XRD, MS	SEM, TEM	Detoxification	Neutralizes acute nephrotoxicity of aristolochic acid	[38]
Glycyrrhizic acid, paeoniflorin	Ultrasonic dispersion	Near-spherical			DLS, TEM		Solubilization, absorption enhancement	[39]
Berberine, 3,4,5-trimethoxycinnamic acid	Dialysis (3 500 Da)	Spherical	Hydrogen bonds, π-π stacking	UV, IR, FS, NMR, XRD,	DLS, TEM, SEM	Antibacterial		[40]
Berberine, rhein	Dialysis (2 500 Da)	Spherical	Electrostatic interactions, π-π stacking, hydrogen bonds	UV, IR, FS, NMR, ITC, XRD	DLS, TEM, SEM	Antibacterial	Good biocompatibility	[41]
Walnut polyphenols, yellow mushroom polysaccharides	Stirring (1 000 r·min^{-1} for 2 h), centrifugation (10 000 ×g for 15 min)	Spherical	Hydrogen bonds, hydrophobic interactions	IR, XRD	SEM, TEM		Sustained release	[42]
Paclitaxel, betulinic acid	High-speed centrifugation (11 000 r·min^{-1} for 40 min)	Spherical	Hydrogen bonds, hydrophobic interactions	UV, IR, MD	DLS, SEM	Antitumor	Reduced toxicity, enhanced efficacy, extended half-life	[43]
Glycyrrhizin protein		Spherical			DLS, SEM		Drug delivery	[44]
Bitter almond protein		Spherical	Electrostatic interactions, hydrophobic interactions, hydrogen bonds		DLS, TEM		Drug delivery	[16]
Berberine, paclitaxel	Nanoprecipitation	Spherical	π-π stacking, hydrophobic interactions	MD	DLS, TEM	Antitumor, antibacterial	Synergistic enhancement	[45]
Oleanolic acid, glycyrrhetic acid, paclitaxel	Emulsion solvent evaporation	Spherical	Hydrogen bonds, hydrophobic interactions	UV, IR, MD	DLS, SEM, TEM	Antitumor	Drug delivery, reduced toxicity, enhanced efficacy	[46]

Continued

Component	Extraction and separation	Microscopic morphology	Non-covalent bond	Method to determine non-covalent bond	Morphological characterization	Pharmacological effect	Value	Ref.
Rhein		Fibrous,	Hydrogen bonds, π-π stacking, electrostatic interactions	UV, IR, FS, MS, CD, XRD	SEM, TEM, AFM	Alleviates neuroinflammation	Sustained release	[47]
Pseudostellaria heterophylla protein, curcumin	Centrifugation (7 000 ×*g* for 20 min)	Spherical	Hydrophobic interactions	FS, XRD	DLS, TEM		Drug delivery	[48]
Berberine, cinnamic acid	Stirring, dialysis (3 500 Da)	Spherical	Hydrogen bonds, π-π stacking	UV, IR, XRD, NMR	TEM, DLS, SEM	Antibacterial	Controlled release	[49]

1.2 单味药

中药有效成分复杂多样, 在水煎液中存在蛋白质、多糖、皂苷等大分子, 也存在生物碱、萜类、醌类等小分子。近年来已有研究报道单味药水煎液中也存在STCM, 已有研究显示在板蓝根水煎液中存在STCM, 且具有抗病毒的作用[50]。在没食子水煎液中发现了球形STCM, 其主要由没食子酸和蛋白质等物质组成[51]。在黄连水煎液中发现的STCM具有促进小檗碱溶解度和溶解速率, 改善肠道吸收的作用[52]。当前单味药汤剂中STCM研究主要聚焦于解析其成分组成。关于中药单味药STCM研究的详细内容见表2[51-57]。

1.3 药对

药对又称“对药”、“姊妹药”、“对子药”等, 药对之名最早见于《雷公药对》, 基于《神农本草经》“当用相须

Table 2 STCM in TCM single herbs

Source	Component	Extraction and separation	Microscopic morphology	Non-covalent bond	Method to determine non-covalent bond	Morphological characterization	Pharmacological effect	Value	Ref.
Isatis tinctoria L.	Proteins, polysaccharides	Dynamic light scattering and gel chromatography	Spherical	Hydrophobic interaction, electrostatic interaction		DLS, TEM, SEM	Antiviral		[53]
Chrysanthemum × *morifolium* (Ramat.) Hemsl.	Polyphenols, polysaccharides	dialysis (3 500 Da)	Spherical	Hydrophobic interactions, hydrogen bonding	UV, IR	DLS, TEM			[54]
Herpetospermum pedunculosum (Ser.) C. B. Clarke	Dehydrobruceol, bruceine A, bruceantin	Water extract, alcohol extract	Spherical		UV, IR, XRD, DSC, TGA	DLS, TEM		Drug delivery	[55]
Turkish gall	Gallic acid, digallic acid, mono-*O*-galloyl-*β*-*D*-glucose, proteins	Differential centrifugation (1 000 ×*g* for 10 min; 6 577 ×*g* for 10 min; 9 500 ×*g* for 10 min)	Spherical	Hydrogen bonding, hydrophobic interaction, ionic interaction	UV, IR, EDX	SEM, TEM, DLS	Antibacterial, antioxidant		[51]
Coptis chinensis Franch.	Berberine, coptisine, proteins	Centrifugation (3 000 r·min^{-1} for 10 min), dialysis (3 500 Da)	Spherical			DLS, SEM, DSC, XRD		Increased solubility and absorption	[52]
Isodon rubescens (Hemsl.) H. Hara	Rosmarinic acid	Centrifugation (2 000 ×*g* for 10 min)	Spherical			TEM, AFM	Antithrombotic		[56]
Pueraria lobata (Willd.) Ohwi		Solution	Clustered			SEM	Treatment of blood stasis		[57]

相使者良, 勿用相恶相反者”中“良”的关系而提出[58,59]。药对是指两味药成对配伍相辅相成, 多有减毒增效的作用[60]。有学者发现药对中各成分单煎液物理混合与合煎液之间存在药效和成分的差异[61,62]。例如, 有研究发现大黄–黄连合煎液呈黄褐色, 与单煎液相比更浑浊, 这可能与STCM有关, 并且合煎液较单煎液物理混合对肠道菌群的影响更小, 表明其具有配伍减毒的作用[63]。附子–甘草配伍可以通过甘草蛋白与附子中主要毒性成分乌头碱自组装成STCM达到减毒增效的作用[64,65]。药对STCM研究通过揭示传统中药配伍的科学内涵, 为中药现代化研究提供了新范式。关于药对STCM研究的详细内容见表3[8,63,66-71]。

1.4 复方

中药复方在应用中常倾向于将煎煮产生的沉淀弃去, 黄连解毒汤和葛根芩连汤等许多复方在煎煮过程中都会产生沉淀, 在对黄连解毒汤的研究中发现其自沉淀主要是由焓驱动的非共价键结合的STCM组成[72]。有学者通过将黄连解毒汤的自沉淀和上清液拆分, 分别验证两者对神经细胞的保护作用, 发现自沉淀较上清液表现出更佳的神经保护作用[73]。此外, 有研究发现葛根芩连汤中自沉淀的降糖作用较上清液药效更优[74]。有学者发现芍药甘草汤中存在的STCM为不规则球形; 后续研究表明, STCM组和全汤组的药效并无显著性差异[75,76]。也有研究发现在芍药甘草汤中, 甘草中成分比如甘草酸, 可以通过形成STCM, 包裹芍药的成分, 从而达到缓释的作用[77]。当前复方STCM研究主要聚焦于共沉淀现象及其药效特性, 通过自组装的视角揭示传统煎煮过程中出现沉淀及是否该弃去的科学内涵。关于中药复方STCM研究的详细内容见表4[7,15,72-87]。

2 中药超分子形成机制

2.1 中药超分子中的非共价键

中药成分复杂, 在煎煮的过程中存在分子剧烈运动, 基团之间相互吸引、排斥和碰撞, 促使彼此间发生物理相互作用, 并通过静电作用、氢键、π-π堆积和疏水作用等非共价键自组装连接起来, 形成超分子聚集体, 其中氢键是存在最广泛的一种非共价键[88]。由于结构多样, 不同种类的成分在形成STCM中所依赖的非共价键也不尽相同, 各类天然产物分子基于其独特的化学结构特征, 表现出不同的超分子自组装机制。比如蛋白质、多糖、皂苷和萜类物质主要通过氢键和疏水作用协同驱动自组装; 生物碱类物质因其分子结构中含有的碱性基团, 其自组装过程涉及静电作用, 同时伴随氢键作用和π-π堆积作用; 甾体类物质则凭借其刚性甾核结

Table 3 STCM in TCM herbal pairs

Source	Component	Extraction and separation	Microscopic morphology	Non-covalent bond	Method to determine non-covalent bond	Morphological characterization	Pharmacological effect	Value	Ref.
Glycyrrhiza uralensis Fisch.-*Gypsum fibrosum*		Solution	Spherical		IR, ETC	SEM, DLS			[66]
Rheum palmatum L.-*Coptis chinensis* Franch.	Epicatechin, rhein, emodin, berberine, *etc.*	Dialysis (3 500 Da)	Spherical	Electrostatic interaction, hydrogen bonding, π-π stacking	ITC, UV, IR, NMR	TEM, DLS, SEM	Alleviates intestinal microbiota damage	Sustained release, taste masking, neutralization of bitterness, and cold nature	[63, 67, 68]
Glycyrrhiza uralensis Fisch.-*Coptis chinensis* Franch.	Licochalcone A, liquiritin, berberine, glycyrrhetinic acid, *etc.*	Centrifugation (3 000 r·min^{-1} for min), dialysis (3 000 Da)	Spherical	Electrostatic interaction, hydrophobic interaction	UV, IR, FS, ITC	SEM, DLS	Antimicrobial	Taste masking, toxicity reduction, efficacy enhancement	[8, 69, 70]
Astragalus membranaceus (Fisch.) Bunge-*Angelica sinensis* (Oliv.) Diels	Formononetin, *Z*-ligustilide, astragaloside IV, *etc.*	Centrifugation (4 000 r·min^{-1} for 10 min), Dialysis (3 500 Da), high-speed centrifugation (12 000 r·min^{-1} for 40 min)	Spherical		UV, IR, NMR	SEM, TEM, DLS		Sustained release	[71]

Table 4 STCM in TCM herbal formulas

Source	Component	Extraction and separation	Microscopic morphology	Non-covalent bond	Method to determine non-covalent bond	Morphological characterization	Pharmacological effect	Value	Ref.
Huanglian Jiedu Decoction	Baicalin, berberine, coptisine, *etc.*	Centrifugation (3 000 r·min^{-1} for 30 min)	Spherical	Hydrogen bonds, hydrophobic interactions	MS, UV, NMR, IR, FS, ITC	SEM, DLS, TEM	Neuroprotection		[72, 73, 78, 79]
Shaoyao Gancao Decoction	Paeoniflorin, glycyrrhizin, glycyrrhizic acid, *etc.*	Ultrafiltration (30 000 Da), centrifugation (4 000 r·min^{-1} for 40 min)	Spherical			DLS, TEM	Analgesic		[15]
Shaoyao Gancao Decoction		High speed centrifugation (15 000 r·min^{-1} for 60 min)	Spherical			DLS, TEM		Sustained release and enhanced absorption	[75, 77]
Shaoyao Gancao Decoction		Centrifugation (5 000 r·min^{-1} for 30 min), dialysis (100 Da), high speed centrifugation (13 000 r·min^{-1} for 30 min)	Spherical			DLS, TEM	Psoriasis		[76]
Maxing Shigan Decoction	Ephedrine, pseudoephedrine, *etc.*	Gel filtration chromatography	Spherical			DLS, SEM, AFM	Antiviral		[7, 80]
Maxing Shigan Decoction	Ephedrine, amygdalin, glycyrrhizic acid, *etc.*	Centrifugation (5 000 ×*g* for 10 min; 13 500 ×*g* for 10 min)	Spherical	Hydrophobic interactions, hydrogen bonds	Interferometers	TEM, NTA	Antibacterial		[81]
Maxing Shigan Decoction		Centrifugation (9 500 r·min^{-1} for 30 min)	Spherical		ETC	SEM, DLS	Allay a fever		[82]
Bai-hu Decoction	Neomangiferin, mangiferin, glycyrrhizin, ammonium glycyrrhizinate, *etc.*	Centrifugation (4 000 r·min^{-1} for 30 min), filter membrane (0.45 μm), dialysis, high-speed centrifugation (10 000 r·min^{-1} for 30 min)	Spherical			TEM, DLS	Allay a fever		[83-85]
Gegen Qinlian Decoction		High-speed centrifugation (15 600 r·min^{-1} for 15 min)				DLS	Hypoglycemic	Promotes absorption of baicalin	[74, 86]
Nao-luo-xin-tong Decoction	Ginsenoside Rg1, ginsenoside Rb1, astragaloside IV, *etc.*	Centrifugation (3 500 r·min^{-1} for 10 min), high-speed centrifugation (13 000 r·min^{-1} for 30 min), dialysis (3 500 Da)	Clustered			TEM, DLS, SEM	Brain protection		[87]

构特征, 主要依赖疏水作用驱动自组装; 黄酮类物质的自组装行为主要源于氢键作用和疏水作用。此外, 醌类物质主要依赖于氢键作用和π-π堆积作用 (图3)。

蛋白质分子具有氨基和羧基, 彼此间形成的氢键可以使蛋白质有序排列形成聚集体; R基的不同使蛋白质具有亲水性和疏水性, 当某些蛋白质同时具有亲水基团和疏水基团时, 表现出两亲性, 可以通过疏水作用自组装形成蛋白质胶囊[89]。基于上述特性可以推测蛋白质成分主要通过氢键和疏水作用与其他成分进行自组装。

多糖是一类在自然界中广泛存在的大分子化合物, 具有调节免疫、抗癌等药理活性[90,91]。多糖是由10个以上的单糖分子通过糖苷键聚合而成, 分子质量较大, 属于多羟基亲水化合物, 可以通过羟基形成氢键进行自组装。黄芪多糖能够通过氢键结合黄酮类成分, 形成层状排列的结构, 从而提升黄酮类成分在体内的稳定性、溶解度、渗透性和吸收[33]。丹皮多糖本身可以通过链间氢键作用组装成球形结构[92]。大葱多糖在水中可以自组装成球形, 随着浓度的升高可以继续组装成圆柱形胶束[93]。基于以上研究结果, 可以推测多糖类大分子不仅能够通过氢键实现自身的自组装, 还能够通过氢键或疏水作用与其他成分进行自组装, 形成功能性的超分子聚集体。

皂苷类物质是由亲水糖基和一个甾体或三萜的疏水母核组成的, 结构中存在疏水主链, 所以皂苷类多通过疏水作用进行自组装。甘草酸与芍药苷可通过疏水作用自组装形成STCM来提高芍药苷的生物利用度[39]。甘草酸和丹参酮IIA通过氢键和疏水作用形成水凝胶, 发挥协同抗肿瘤的作用[94]。人参皂苷由于其两亲性的特性可以作为载体包载疏水性的药物[95]。根据以上研究可推测皂苷类物质更倾向于通过氢键和疏水作用与其他成分组装成超分子。

萜类物质具有疏水母核, 容易通过疏水作用与其他物质发生自组装。熊果酸可以通过氢键和疏水作用组装成球形结构[34]。甘草次酸和齐墩果酸可以通过氢键和疏水作用自组装成球形结构[46]。基于以上研究结果, 可以推测萜类物质不仅能够通过疏水作用和氢键实现自身的自组装, 还可能与其他小分子成分通过类似的非共价键作用形成功能性超分子聚集体。

自然界中广泛存在喹啉类、吲哚类等生物碱。其中属于异喹啉类的小檗碱由于其独特的结构而备受关注, 小檗碱具有多芳环结构和季铵离子而具有自组装的倾向, 由于季铵离子的存在, 小檗碱容易和酸性成分通过静电作用进行自组装, 小檗碱和大黄酸通过静电作用、氢键、π-π堆积形成类球形结构; 小檗碱和马兜铃酸可以通过静电作用、π-π堆积形成纤维结构[38,41]。小檗碱还能和酸性苷自组装, 黄芩苷属于黄酮类苷且为葡萄糖醛酸苷, 可以与小檗碱中的N离子通过静电作用和疏水作用进行自组装[13]。此外, 由于多芳环结构, 小檗碱可以与其他多芳环结构通过π-π堆积自组装, 比如小檗碱还能通过氢键和π-π堆积与肉桂酸及其衍生物进行自组装[39,48]。由于其碱性特性, 目前研究主要聚焦于生物碱与酸性物质通过静电作用进行自组装。此外, 生物碱分子通常富含共轭结构, 因此在自组

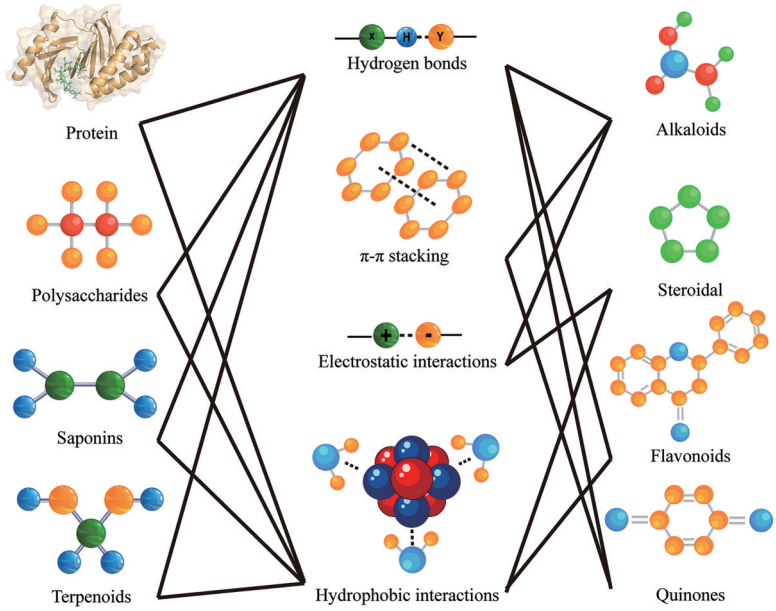


Figure 3 The non-covalent bonds in STCM

装过程中还可能存在π-π堆积作用, 这两种非共价键作用共同促进了超分子体系的形成与稳定。

甾体类成分有疏水骨架和疏水烷基侧链, 可以通过疏水作用实现自组装。熊去氧胆酸和小檗碱可以通过静电作用和疏水作用形成纳米颗粒[26]。由于结构的特殊性, 甾体类成分多通过疏水作用与其他类成分发生自组装。

黄酮类化合物是广泛存在于自然界、种类繁多且具有广泛生物活性的一类化合物。黄酮类化合物具有2-苯基色原酮的基本母核, 现在泛指具有C_6-C_3-C_6结构的化合物[96]。芹菜素可以通过氢键和疏水作用与生物碱类的氧化苦参碱进行自组装, 从而增强其抗炎活性[97]。因此, 黄酮类化合物可以通过氢键和疏水作用与生物碱类等其他成分形成超分子聚集体。

中药中的醌类化合物可以分为苯醌、萘醌、菲醌和蒽醌4类, 其中以蒽醌类最为常见。醌类化合物具有抗菌、抗病毒、止血等生物活性[98,99]。大黄酸可以通过氢键和π-π堆积自组装成纳米纤维, 大黄酸和小檗碱可以通过氢键、π-π堆积和静电作用自组装成类球形结构[41,47]。所以推测由于蒽醌类化合物存在苯环, 可以提供π-π作用, 所以与其他存在芳环结构的物质可以通过π-π堆积进行自组装。

2.2 中药超分子表征技术

在探究STCM形成机制过程中多使用紫外光谱 (ultraviolet-visible spectrophotometry, UV)、IR、荧光光谱 (fluorescence spectrophotometry, FS)、NMR、质谱 (mass spectrometry, MS)、XRD、等温量热滴定技术 (isothermal titration calorimetry, ITC) 和MD等进行分析。

UV是鉴定共轭结构的有效手段, 其在超分子组装体的表征中具有重要作用。研究表明, 小檗碱参与构建的超分子体系可呈现其特有的紫外吸收特征。例如, 在小檗碱自组装体系中可观察到227、262和342 nm处的特征吸收峰[26]。在小檗碱–马兜铃酸超分子体系中, 同时存在228 nm处的马兜铃酸特征吸收峰及238和349 nm处的小檗碱特征吸收峰[38]。类似地, 在小檗碱–肉桂酸衍生物超分子体系中, 可同时检测到小檗碱 (230、266、350、428 nm) 和肉桂酸衍生物 (228、297 nm) 的特征吸收峰, 证实了该超分子的成功构建[40]。进一步研究发现, 小檗碱–大黄酸超分子体系同时呈现428 nm处的小檗碱特征吸收峰和230 nm处的大黄酸特征吸收峰, 证实了超分子的形成[41]。在小檗碱–肉桂酸超分子体系中, 最大吸收峰出现在267 nm处, 介于小檗碱 (264 nm) 和肉桂酸 (273 nm) 的最大吸收波长之间, 表明该超分子同时包含这两种组分[49]。在甘草–黄连共煎液形成的超分子体系中, 可同时观察到黄连的特征吸收峰 (424、342 nm) 和甘草的特征吸收峰 (262 nm)[70]。此外, 波棱瓜子超分子体系的吸收光谱研究显示, 与水提液和醇提液相比, 其吸收峰分别发生约20和80 nm的红移, 且吸光度显著增加, 这表明水提液和醇提液中发生了分子间相互作用并形成了超分子结构[55]。在没食子水煎液的研究中, 270 nm处检测到没食子儿茶酚的特征吸收峰, 而超分子去除后的液相中该吸收峰强度显著减弱, 证实了没食子儿茶酚参与了超分子的组装[51]。基于上述研究结果可以得出结论: 当多种组分形成的超分子体系在UV中同时呈现各组成物质的特征吸收峰时, 可作为超分子成功组装的重要证据。

IR通过分析官能团特征吸收峰的变化, 为研究超分子组装过程中的作用力和结合位点提供了重要依据。研究表明, 在小檗碱–熊去氧胆酸超分子体系中, IR同时呈现两组分的特征吸收峰, 其中熊去氧胆酸的羟基和羰基吸收峰发生149 cm^{-1}的移动, 表明羰基是该超分子组装的关键结合位点[26]。类似地, 在小檗碱–肉桂酸超分子体系中, 与游离肉桂酸相比, 超分子中羧基的伸缩振动带向低波数移动135 cm^{-1}, 进一步证实羧基参与了分子间相互作用[49]。在藕粉–小檗碱水凝胶体系中, 红外光谱显示小檗碱的多数特征吸收峰消失, 且2 926 cm^{-1}处的吸收峰向高波数移动至2 930 cm^{-1}, 表明小檗碱不仅被包载在水凝胶中, 还与基质发生了分子间相互作用[99]。波棱瓜子超分子的红外光谱分析显示, 体系中同时存在水提液和醇提液的特征吸收峰, 并出现新的吸收峰和部分峰的消失, 其中1 544 cm^{-1}处酰胺基团的弯曲振动吸收峰消失, 证实酰胺基团是自组装的重要作用位点[55]。在没食子超分子体系中, 1 720 cm^{-1}处的芳香酯伸缩振动吸收峰证实了没食子儿茶酚的存在, 而1 658 cm^{-1}处的特征吸收峰则表明酰胺基团参与了分子间相互作用[51]。此外, 大黄酸自组装水凝胶的红外光谱显示, 氢键特征峰从3 436 cm^{-1}移动至3 429 cm^{-1}, 证实氢键在该体系的凝胶化过程中发挥了重要作用[47]。综上所述, 红外光谱分析可通过官能团特征吸收峰的位置移动、强度变化或消失等现象, 揭示超分子组装过程中的分子间作用力和关键结合位点, 为超分子体系的形成机制研究提供了重要的实验依据。

FS可以通过荧光强度和峰偏移来分析超分子之间的相互作用。研究表明, 黄芩苷–小檗碱超分子体系的荧光吸收峰相较于小檗碱单体发生了30 nm的蓝移, 这可能是分子间相互作用导致激发态与基态之间的能级差异所致[79]。类似的, 小檗碱–熊去氧胆酸超分

子体系的荧光吸收峰较单体蓝移了 13 nm, 这一现象证实了超分子的成功组装[26]。在小檗碱–大黄酸超分子体系的研究中, FS 综合特征与 UV 的分析结果一致, 均证实了自组装的成功组装[41]。此外, 通过比较小檗碱与黄芩苷、汉黄芩苷自组装形成的超分子的最大激发波长, 发现两者分别较小檗碱单体发生了 13 和 5 nm 的微弱蓝移, 表明小檗碱与这两种组分的自组装作用模式存在差异[13]。综上所述, FS 与 UV 通过分析吸收峰的偏移, 能够有效验证超分子体系的成功组装, 并为研究分子间相互作用机制提供了重要的光谱学依据。

NMR 通过化学位移的变化, 能够有效验证红外光谱推测的分子间作用力和结合位点, 为超分子组装机制的研究提供了重要的实验依据。研究表明, 在姜黄素–槟榔碱超分子体系中, 通过分析-CH_3信号 (姜黄素和氢溴酸槟榔碱各含有 2 个-CH_3) 可知, 两者以 1∶1 的比例聚集。此外, 羟基的化学位移增大了 0.06, 而叔胺基信号 (δ = 10.02) 的峰形消失, 这些结果与红外光谱推测的羟基为结合位点的结论一致[25]。在甘草次酸超分子体系的研究中, 随着浓度的增加, 氢信号逐渐向低场方向移动, 这一现象证实了 π-π 堆积作用在自组装过程中发挥了重要作用[14]。类似地, 小檗碱–肉桂酸衍生物超分子体系的 NMR 谱图显示, 化学位移从 δ = 7.52、7.02 和 6.53 分别变化至 δ = 6.98、6.75 和 6.34, 表明羧基、芳香烃环和烯烃键可能参与了分子间相互作用, 进一步支持了红外光谱的分析结果[40]。

MS 通过分析谱图中的分子离子峰和碎片离子峰, 为超分子体系的相对分子质量、组成比例及单一自组装体的成分分析提供了重要信息, 为超分子组装机制的研究提供了重要的实验依据。研究表明, 在熊去氧胆酸–小檗碱超分子体系的质谱图中, 最主要的碎片离子峰为 728.408 7 和 336.119 8, 且两者的峰强度相近, 表明该超分子是由熊去氧胆酸和小檗碱以 1∶1 的比例组装而成[26]。此外, 在大黄酸自组装形成的水凝胶体系中, 质谱分析检测到大黄酸单体 (*m*/*z* 283.024 9) 和大黄酸钠盐 (*m*/*z* 305.006 1) 的碎片离子峰, 推测这两种组分是大黄酸纳米纤维的基本结构单元[47]。

XRD 技术不仅可用于确定超分子体系的晶型, 还能通过分析晶面间距 (*d* 值) 揭示分子间作用力, 为超分子组装机制的研究提供了重要的结构信息。研究表明, 在姜黄素–槟榔碱超分子体系中, XRD 谱图中的尖锐衍射峰消失并转变为宽化的包峰, 表明该超分子呈现较差的结晶性或非晶态特征[25]。结合 XRD 研究小檗碱–肉桂酸衍生物超分子体系, 谱图显示比较尖锐的峰形, 表明纳米颗粒具有良好的结晶性能, 此外通过分析 *d* 值的分布, 发现在 *d* = 3.9、3.2 Å 处显示出尖锐而强烈的峰, 证实存在 π-π 堆积作用; 在 *d* = 2.2、2.0 和 1.9 Å 处的峰则对应氢键的典型距离, 这表明氢键也参与了自组装过程[40]。

ITC 通过测定热力学参数, 比如吉布斯自由能 ΔG, 可以确定成分间反应是否具有自发性, 并且某些情况可以揭示分子间作用力, 为超分子组装机制的研究提供了重要的热力学依据。研究表明, 在甘草–黄连超分子体系的研究中, ITC 测定结果显示 $\Delta G < 0$, 表明该反应为放热反应, 且反应过程自发进行; 由于甘草和黄连的有效成分分别为酸性和碱性物质, 而酸碱反应通常为放热过程, 因此推测两者之间可能存在静电相互作用[69]。此外, 有学者利用 ITC 法分析了大黄–黄连超分子体系的作用力, 发现 $\Delta G < 0$, 表明该反应为焓驱动的自发过程; 结合热力学参数分析, 推测大黄和黄连的活性成分通过氢键和静电作用等非共价键相互作用结合[68]。

MD 通过计算能够直接揭示分子间作用力的类型及其动态行为。在模拟过程中, 通过分析溶剂可及表面积、溶剂化自由能等与距离相关的参数, 可以推断分子间相互作用的具体机制。当供体与受体之间的距离小于 4.0 Å (常见范围为 2.5～3.5 Å) 且相应角度大于 120°时, 可判定存在氢键作用。此外, 溶剂可及表面积的减小通常表明分子结构变得更加紧凑, 这可能是由于氢键等作用力促进了分子自组装, 从而使体系结构趋于稳定。例如, 有学者通过分子动力学模拟技术证实, 黄芪多糖与黄酮类苷之间的自组装主要依赖于氢键作用[33]。

由于中药成分复杂, 虽然目前技术手段先进, 但仍对分子间存在的作用力及其形成机制分析不够透彻。

3 中药超分子研究价值

已有研究表明, STCM 的形成能够增加中药成分的溶出并促进中药成分的肠道吸收; 同时可通过阻断毒性位点、形成三维空间结构的形式发挥减毒增效的作用; 也有研究发现 STCM 是一种潜在的自组装药物递送系统, 可改变原型成分的药代动力学行为 (图 4), 因此 STCM 具有较大的研究价值。

3.1 增溶促吸收

甘草–石膏配伍合煎会形成均匀的球形颗粒, 合煎后的出膏量高于两者两单煎液的物理叠加值, 所以推测两者合煎形成超分子会促进彼此成分的溶出[66]。与单独使用小檗碱相比, 由藕粉与小檗碱自组装形成的水凝胶显著加快了平衡速率, 其达到平衡所需时间仅为单纯小檗碱的 1/8; 此外, 水凝胶体系中小檗碱的最小析出浓度约为单纯小檗碱的 2 倍, 表明其在增溶和缓释方面具有更优性能, 有助于提高小檗碱的稳定

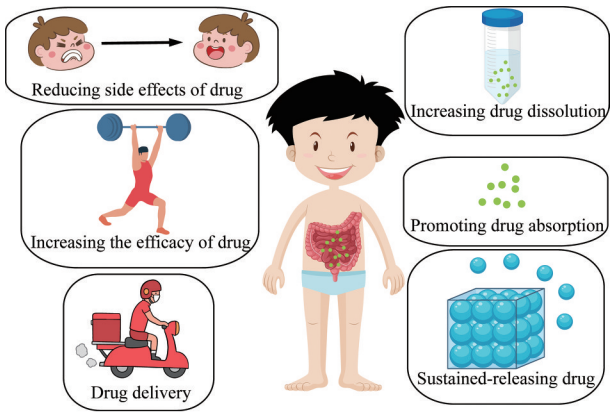


Figure 4 The research value of STCM

性和生物利用度[100]。芍药甘草汤中存在的超分子能够显著促进甘草和芍药中有效成分的溶出, 并增强其在回肠中的吸收, 具体表现为: 在体外释放实验中, 甘草素在单煎液中的 24 h 累积释放量仅为合煎液的 25.85%; 同时, 合煎液的回肠吸收参数 K_s 约为单煎液组的 2 倍, 这些结果表明, 芍药甘草汤中的超分子结构不仅显著提高了难溶性成分的溶出效率, 还通过优化吸收机制, 进一步增强了成分在肠道中的吸收效果[75,77]。黄芪多糖在水溶液中通过自组装形成具有多孔结构和大比表面积的纳米聚集体, 能够有效负载黄酮类化合物, 并显著改善其在体内和胃肠道的溶解与吸收性能; 具体表现为: 毛蕊异黄酮和芒柄花素的单体平衡溶解度分别提升了近 2 倍, 此外, 黄芪多糖还显著提高了黄酮类化合物的肠道吸收效率, 毛蕊异黄酮的吸收速率常数 K_a 从 0.12 提升至 0.28 h^{-1}, 增幅达 2 倍以上[33]。黄连汤剂中, 超分子结构的存在显著提升了小檗碱的溶解度和肠道吸收效率; 研究表明, 小檗碱在超分子中的溶解度达到小檗碱单体的 2 倍, 此外微囊泡介导的内吞作用促进了人结肠腺癌细胞对小檗碱的摄取[52]。通过自组装形成的超分子, 不仅可以提高难溶性化合物的溶解度和稳定性, 还可以通过优化其脂溶性与亲水性平衡, 增强肠道渗透和吸收效率。这一机制为超分子作为药物载体的应用提供了科学依据, 尤其适用于低溶解度成分的递送系统设计。

3.2 减毒增效

姜黄素−槟榔碱自组装形成的球形超分子在相同槟榔碱剂量下表现出显著的安全性提升; 与槟榔碱单独给药组相比, 超分子给药组小鼠未观察到明显的毒性反应, 而槟榔碱单独给药组则表现出典型的急性中毒症状[25]。小檗碱和马兜铃酸自组装形成的网状超分子能通过阻断马兜铃酸的毒性位点从而显著减轻其诱导的急性肾损伤, 组织病理学分析显示马兜铃酸单独用药组和混合组均出现典型肾损伤特征, 而超分子用药组与正常对照组无显著性差异[38]。紫杉醇和桦木酸通过氢键和疏水作用形成的球形超分子, 能够减轻紫杉醇的不良反应, 并具有协同增效的结果[43]。经过蜂蜜炮制过的川乌可以通过形成 STCM 减少剧毒性二酯生物碱成分在体内的暴露, 比如经炮制后新乌头碱的血药浓度仅为未处理样品的 50% 左右[101]。自组装策略为天然药物的减毒增效提供了新的思路和方法。通过合理设计自组装结构, 可以通过阻断毒性位点和改变药代动力学性质等方式有效降低药物的毒性, 同时增强其治疗效果, 具有广阔的应用前景。

3.3 药物递送

熊果酸通过疏水作用和氢键装载紫杉醇形成高载药量的超分子, 超分子的半衰期为游离紫杉醇的 6 倍, 而且具有协同增效的作用[30]。苦杏仁蛋白加热形成的球形超分子可以包载紫杉醇, 包封率最高为 92.6%, 最高释放率为 54.7%[16]。雷公藤红素与毛兰素制备成稳定均匀的纳米药物, 能够直接靶向 annexin A2, 活体成像结果表明, 该超分子不仅能够实现精准的肿瘤靶向递送, 更在停药后表现出持续的抑瘤效应, 其肿瘤生长抑制率显著优于其他组[101,102]。甘草酸与小檗碱制备成水凝胶, 能够使小檗碱在酸性条件下释放仅有 30%, 有效地达到了缓释的效果[103]。通过自组装技术, 天然成分能够高效装载药物, 优化药物递送, 实现减毒增效。这种策略在提高药物稳定性、靶向性和治疗效果方面展现出显著优势, 为天然药物的开发和临床应用提供了重要参考。

3.4 其他

通过对甘草黄连合煎液中分离出来的超分子研究发现, 共煎组抑菌率约为黄连组的 1.5 倍, 并且具有矫味、缓释和中和黄连苦寒之性的作用[67,70]。在黄芪当归共煎液中分离出来的不规则球形超分子, 通过包封和释放测试, 发现其中的有效成分被有效包封进超分子并在 48 h 内表现出缓慢释放特性, 累积释放率仅为 40%[71]。

4 中药超分子研究方法

目前关于 STCM 研究方法大概分为 3 个主要方面, 首先是理化性质研究, 涉及制备与分离、形貌表征、定性与定量分析、形成机制研究; 其次是药理学研究, 主要包括药效及作用机制研究; 最后是稳定性、流变性、生物安全性和缓释性等其他研究。

4.1 理化性质研究

4.1.1 制备与分离 中药汤剂成分复杂, 组成多样, 在加热过程中, 不同成分彼此之间会发生聚集。可以通过粒子大小不同, 用凝胶色谱法对超分子进行分离[50]。

其中, 中药汤剂最常用的方法是离心透析法, 通过3 000 r·min^{-1}的低速离心首先将沉淀去除, 再通过截留量为3 000或3 500 Da透析膜将未参与组装的小分子滤除, 所得的STCM通常经冷冻干燥保存。而对于单体分子的自组装, 多采用乳液溶剂蒸发法、超声沉淀法、溶剂交换法等进行制备。

4.1.2 形貌表征 STCM的形貌通常需要结合多种分析技术。DLS常用于测定超分子的粒径、电位和多分散指数。SEM和TEM对表面形貌和内部结构提供可视化证据, 其中TEM成像可以验证DLS的粒径数据。AFM可实现纳米级三维形貌解析, 其表面粗糙度分析结果可与电子显微成像形成数据互证[24]。

4.1.3 定性与定量分析 针对STCM复杂的成分组成, 所以需要其建立组分分析体系。采用液质联用技术进行多组分定性定量分析。对于蛋白质、多糖、鞣质等大分子通过特异性显色反应结合分光光度法进行鉴别与定量, 比如多糖含量测定采用硫酸–蒽酮法或苯酚–浓硫酸显色法, 鞣质定量基于磷钼钨酸–干酪素比色法, 蛋白质检测则综合运用Folin-酚法、BCA法及考马斯亮蓝法等比色技术[15,52,64,67,87]。

4.1.4 形成机制分析 在分析STCM形成机制过程中, 需要结合多谱学技术, 比如NMR、UV、IR、FS、XRD、ITC、MD等手段, 具体原理详见2.2。

UV确定成分之间成功自组装; IR依据官能团特征峰位移解析结合位点和作用力; NMR通过化学位移变化揭示存在的结合位点和分子间作用模式; MS依据分子离子峰强度比得出组装体的比例; FS通过发射峰强度和位移分析超分子间存在的作用力; XRD从晶体结构参数解析晶型和作用力模式; ITC通过热力学系数定量确定自组装作用力; MD从分子层面动态解析结合能贡献, 为多维度表征提供理论计算验证。根据以上内容对STCM通用分析表征方法进行了分类总结, 具体内容见表5。

4.2 药理学研究

黄连的有效成分小檗碱, 是研究抗菌超分子较常见的一个成分, 所以在对小檗碱或者含黄连的药对或复方的药效研究过程中, 常采用抑菌实验[23,34,40,41]。验证中药超分子抗肿瘤药效常采用细胞实验和动物实验, 有时还会加上分子对接进行验证[43]。在解热、降糖等其他功效中常采用细胞实验和动物实验[27,84]。然而由于汤剂中STCM是由多种成分通过非共价键自组装形成的复杂结构, 其组成和构象具有高度动态性和多样性, 难以在体内环境中准确表征; 同时体内复杂的环境及吸收代谢过程中还可能破坏STCM结构或引发其重构甚至与体内分子进行自组装的现象, 导致其原始形态和功能发生改变, 从而难以实时追踪其变化, 这进一步增加了分析的难度。将来可采用分子印迹技术或特异性探针, 实现对STCM的选择性识别和检测; 开发适用于体内环境的原位检测技术, 如荧光标记、同位素标记等, 实时追踪超分子在体内的动态变化; 结合代谢组学、蛋白质组学等多组学技术, 全面分析STCM在体内的代谢途径及其对生物系统的影响。

4.3 其他研究

STCM体系研究中, 稳定性研究是其应用评估的重要方面, 鉴于时间、温度、pH值及光照等环境因素均可能影响超分子体系的稳定性, 所以在实验过程中会考察在不同环境因素下超分子的稳定性, 比如在各条件下, 超分子的形貌特征、平均粒径及zeta电位均未发生显著改变 ($P > 0.05$), 表明该超分子体系具有良好的物理化学稳定性[34,71,87]。对于水凝胶态STCM, 动态流变学分析可解析其黏弹响应机制[14,36,47,100,104]。同时, 生物安全性也是STCM研究中一个重要的模块, 其评估体系的建立对生物医学应用具有重要的意义, 在生物安全性研究中通常有体内体外实验评估, 比如在体外有细胞毒测试和溶血实验等, 体外实验比如毒性测试等[36,41,51]。此外, 药物释放特性可通过透析扩散模型、外翻肠囊模型及在体肠灌流技术进行系统评价[39]。

5 展望

中药汤剂在煎煮过程中产生的STCM在药效发挥方面具有重要作用, 虽然目前研究手段较为先进, 但是由于汤剂中成分复杂, 使不同成分彼此之间进行相互作用的作用力和形成的结构各不相同, 所以目前仍没有有效的手段可以准确分析中药汤剂中STCM的具体形成机制。结构中药学认为, 结构决定药效, STCM的

Table 5 STCM general analytical characterization method

Classification	Objective	General methodology	Specific application
Preparation and separation	Separation and preparation of supramolecular components	Centrifugal dialysis	Separation and preparation of supramolecular components in TCM decoction
Topography characterization	Observe the morphology, particle size, and surface properties	DLS, SEM, TEM, AFM	Measure particle size and verify morphology
Qualitative and quantitative analysis	Determine the chemical composition and content	LC-MS	Qualitative quantification of supramolecular composition
Formation mechanism analysis	The assembly forces and thermodynamic behavior are studied	UV, IR, FS, NMR, XRD, ITC, MD	The binding sites, force types and assembly mechanisms were analyzed

研究为中药药效物质基础提供了一个新的研究视角，并有望将中药领域的研究推向一个新的高度。

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