中药相态与药效: “一物多效”中药质量标志物研究策略

徐少华, 许晚霞, 刘月涛, 李爱平, 宫文霞*, 秦雪梅*

(山西大学中医药现代研究中心, 山西大学地产中药功效物质研究与利用山西省重点实验室, 山西 太原 030006)

摘要: 现行中药质控标准指标相对单一, 仅通过化学成分多寡难以深刻诠释一物多效中药的质量内涵, 而关注多成分物理存在形式的相态分析为中药药效物质基础研究提供新视角。本文聚焦多效中药质控困境, 系统剖析现行质控标准在反映中药多功效性方面的局限, 综述相态在中药药效物质基础的研究思路与现状, 阐述相态通过非共价键自组装形成的机制及结构−功能协同关系, 在此基础上, 提出“自上而下−自下而上相结合”的多效中药质控研究新策略, 旨在推动中药质控模式创新, 指导合理选药, 为构建符合中药特点的质量评价体系提供科学依据。

关键词: 一物多效中药; 中药相态; 活性超分子; 聚集体; 药效物质基础; 中药质量标志物

中图分类号: R917 **文献标识码**: A **文章编号**: 0513-4870(2026)04-1072-13

TCM phase states and pharmacodynamic effects: research strategy on quality markers of "one substance with multiple effects" in traditional Chinese medicine

XU Shao-hua, XU Wan-xia, LIU Yue-tao, LI Ai-ping, GONG Wen-xia*, QIN Xue-mei*

(*Modern Research Center for Traditional Chinese Medicine, Shanxi University, Key Laboratory of Effective Substances Research and Utilization in TCM of Shanxi Province, Shanxi University, Taiyuan 030006, China*)

Abstract: The current quality control standards for traditional Chinese medicine (TCM) are relatively simplistic, as relying solely on the quantification of chemical components fails to fully interpret the quality connotation of multi-effect medicinal substances. In contrast, phase-state analysis, which focuses on the physical forms of multiple components, is considered to provide a new perspective for researching the material basis of the efficacy of TCM. This article focuses on the challenges in quality control of multi-efficacy TCM, systematically analyzes the limitations of current standards in reflecting its multi-functional nature, and reviews research approaches and current progress on the role of physicochemical state in the material basis of TCM efficacy. It elaborates on the mechanism of self-assembly *via* non-covalent bonds and the structure-function synergy. Building on this, a new "top-down and bottom-up" integrated strategy for quality control research of multi-efficacy TCM is proposed. This aims to promote innovation in TCM quality control models, guide rational drug selection, and provide a scientific basis for constructing a quality evaluation system that aligns with the characteristics of TCM.

Key words: multi-efficacy traditional Chinese medicine; traditional Chinese medicine phase state; active supramolecule; aggregate; pharmacological substance basis; quality markers of traditional Chinese medicine

中药具有“一物多效”的重要特性, 即单味药材可呈现多种药理作用[1-4], 这一特性也给中药的质量控制带

收稿日期: 2025-10-17; 修回日期: 2025-12-30.
基金项目: 国家自然科学基金区域联合基金重点支持项目 (U23A20517).
*通讯作者 E-mail: gongwenxia@sxu.edu.cn;
Tel: 86-351-7011501, E-mail: qinxm@sxu.edu.cn
DOI: 10.16438/j.0513-4870.2025-1233

来了极大的挑战。传统质控方法多聚焦于特定化学成分含量, 忽视其相互作用构成的物理存在形式, 中药的多成分特性及分子间相互作用可能是其呈现多效性的基础, 同时其多元起效机制常导致经典量效关系偏移[5-8]。因此, 仅凭有限化学成分的含量难以阐明其起效机制, 导致对“一物多效”科学内涵的阐释缺乏可靠依据, 现有基于化学成分的质量标准难以充分体现中药的整体特性。多效中药药效物质基础研究的瓶颈与质量标志物发现策略局限性急需解决。因此完善现有质量控制体系, 使其兼具化学成分与物理结构双重属性, 并充分考量多功效中药生物学与物质基础的差异性, 是本文的核心目标。

1 中药“一物多效”质量控制困境: 现行质控标准与功效关联性的脱节

1.1 中药“一物多效”质量控制的核心矛盾

中药多效性 (亦称“一物多效”“一物多用”“一物多性”) 是中药中普遍存在的现象, 即同一中药在不同的配方和临床应用中, 能够发挥不同的药理作用, 这正是中药配伍“君臣佐使”理论的生动体现[9]。然而, 这一特性对中药质量控制构成了显著挑战。Liu 等[10]提出的中药质量标志物定义和研究策略推动了中药质控模式的发展[11]。但在应对多效中药的复杂性, 尤其是确证关联不同功效的 Q-marker 方面, 仍需探索新的解决方案。这一矛盾本质在于: 传统基于化学成分质控模式难以匹配中药多成分、多靶点、多功效的复杂体系。

1.2 现行质控指标与中药多元功效的关联性缺失

1.2.1 现行质控标准的“成分–功效”关联失衡 古代医家提出中药具有“在此方, 则取其此长, 在彼方, 则取其彼长”[3]的特点。然而现行标准以单一或少数成分作为质控指标, 未能体现多效中药“成分群–功效”的多元关联, 导致质控标准与临床疗效的脱节。以收载于中国药典 (2020 年版) 的典型多效中药为例, 三七具有活血、心血管保护、消肿定痛和止血等作用[12], 三七素是止血功效的关键成分及潜在质量标志物, 而人参皂苷 Rg1、Rb1 和三七皂苷 R1 为三七活血与镇痛的质量标志物[13], 然而, 中国药典仅以人参皂苷 Rg1、Rb1 和三七皂苷 R1 的含量作为统一质控标准, 导致活血与止血这两类相反功效共用同一评价指标, 这不仅难以全面反映三七散瘀止血、消肿定痛的综合药效, 更可能因质控导向偏差导致临床药效不达预期, 进而对治疗效果及患者生命安全构成潜在风险; 黄芪作为多效中药, 具有补气升阳、利水消肿、生津养血等功效, 研究发现黄芪的补气质量标志物为黄酮类和多糖类, 利水质量标志物为皂苷类[14-16], 而中国药典 (2020 年版) 黄芪项下规定了黄芪甲苷和毛蕊异黄酮葡萄糖苷的含量要求, 没有根据多效中药的不同功效精确不同质量标志物, 加剧了质控与临床的割裂; 当归作为补血要药, 具有补血活血、调经止痛、润肠通便的功效, 当归中发挥补血活血功效的主要以多糖与挥发油为主[17-19], 当归发挥镇痛消炎功效以阿魏酸、藁本内脂、酚酸、苯酞类成分为主[20], 然而, 中国药典 (2020 年版) 在当归项下规定了阿魏酸的含量要求, 该标准既无法全面反映其补血活血、调经止痛、润肠通便的综合药效, 也难以支撑其“一物多效”特性的充分发挥, 进而给临床精准用药带来实际困扰。

1.2.2 “成分–功效”线性思维的局限 中国药典 (2025 年版) 虽已对部分指标成分进行增列, 但破解上述困局并非通过简单增列与各功效相关的化学成分指标即可实现。Fan 等[21]团队研究指出, 中药量效关系在配伍背景下呈现出鲜明的非线性特征, 具体体现为基于整体观的用药逻辑、源于“七情和合”配伍思想的非线性量效特点, 以及因量效改变导致配伍关系调整所带来的多重疗效表达。大量研究证实, 中药多组分、多靶点的协同作用模式, 常使其整体药效响应偏离基于单一化合物的经典量效关系模型[5,7]。这种“多成分–多靶点–弱亲和”的作用特性, 决定了仅凭少数几个指标成分的含量高低, 既难以准确预测其整体药效强度, 也无法揭示其“一物多效”的内在科学规律与功效导向性。当前主要依赖化学成分定量的质控策略, 本质上沿用了化学药物的线性评价思维, 一方面未能充分考虑中药多成分间的协同或拮抗效应; 更为关键的是, 完全忽视了中药成分在制剂过程及体内环境中, 可通过氢键、疏水作用等分子间相互作用, 动态自组装形成纳米聚集体、胶体等活性相态, 这些相态具有独特的物理尺度 (如纳米级穿透性) 与动态结构[5,22], 可直接调控药物的生物利用度、靶向性及最终的功效表达。例如, 配伍或煎煮工艺可促使成分从游离态向聚集态转化, 进而改变其功效侧重 (如三七炮制后功效由止血偏向活血)[23,24]。这一现象证实, 化学成分的物理存在形式是调控中药多元功效的关键因素。因此, 这种脱离药物实际存在形式与多维作用机制的质控模式, 难以真实反映中药的整体性与复杂性, 已成为制约其质量精准评价与国际化发展的核心瓶颈。由此可见, 要突破当前质控瓶颈, 必须超越“成分–功效”的线性思维, 将中药成分的“物理存在形式”即活性相态纳入质量研究与评价的核心范畴。当前学界在中药相态研究领域已取得了哪些可为质控模式创新提供支撑的进展?

1.2.3 相态研究为质控创新提供新思路 目前, 中药超分子研究逐渐成为热点如图 1[25], 超分子最早由 Hirsch

等[26]受配位化学启发提出, 后续Zhu等[27]提出中药配位化学概念, He等[28]在此基础上正式引入中药超分子概念, Li等[29]将其用于阐释中药配伍内涵, Hui等[30]则提出中药超分子、生物大分子等存在是发挥药效的物质基础新形式; 但中药超分子研究存在脱离中医药整体性的局限。与之相对, Yang等[31]最早提出纳米中药概念, Zhuang等[32]发现中药汤剂中普遍存在聚集体, Zhang等[33]提出以汤液有效相态阐释中药复方的药性传递规律, Qiao等[5]提出了结构中药学的概念, 认为中药成分的互作关系、存在形式和物理状态是中药药效物质起效的物质基础。Liu等[34]提出中药软物质概念, 将中药汤剂中微纳聚集体概括为中药软物质。Qu等[35]提出“物相结构”特征是中药品质调控的新视角, 由中药多组分自发组装形成的物相结构是中药药效物质基础的显效形式。由此可见, 中药活性成分的起效依赖于其特定的存在形式和物理相态 (相态属性), 中药药效的本质是成分与相态结构的协同作用, 要解决目前的质控困局, 需要突破传统化学视角局限, 从物理存在形式角度构建“结构–功能”关联的研究新思路。

2 中药相态是中药功效物质基础研究新视角

2.1 中药相态的形成

中药复方汤剂是中医临床应用的主要剂型, 通过灵活配伍实现减毒增效, 集中体现了中医药的整体观念和辨证论治思想[36]。汤剂在煎煮过程中易出现浑浊、沉淀等现象已是共识, 药材饮片中的多种化学成分以不同的形式被有效溶出, 部分成分在特定环境下通过非共价键作用, 形成相对稳定的“聚集体”粒子, 具有相似理化性质的聚集体构成汤液的“相态”, 因此, 中药汤液是一个包含多种物理状态的“混相体系” (多重分散体系, 图2)。中药汤液内各类成分以多种存在形式实现均匀分布, 这一特性既赋予其吸收快、利用率高的优势, 又能适配中医药个性化治疗的理念, 进而彰显药效全面、作用高效的特点[33,37,38]。以聚集体粒径为指标, 通常可分为真溶液相 (粒径 < 1 nm)、胶体相 (粒径1～100 nm)、混悬相 (粒径0.5～10 μm) 和沉淀相 (粒径 > 10 μm)[36,38]。

中药汤液的相态形成过程与化学合成不同, 它是分子或部分分子通过氢键、范德华力、π-π堆积、阳离子-π吸附等非共价键作用且在无人为干预的情况下自发形成有序聚集体, 将难溶性或脂溶性成分药物包裹在凝胶、纤维、胶束、囊泡中, 从而起到增溶、助溶等作用[39-41]。通常, 具体的形成机制可能是小分子在煎煮过程中首先通过氢键形成二聚体, 进而沿轴向或螺旋方向叠加, 并通过π-π堆积或范德华力组装成高阶聚集体, 进而形成相态。

2.2 中药相态与功能的关系

2.2.1 中药配伍增效的相态基础 中药活性成分的溶解与药效实现高度依赖于特定相态 (如胶束相、纳米相) 的形成 (表1)[42-68], 其动态结构对增溶、靶向等功能的实现具有决定性作用[69,70]; 以葛根素、黄连素、黄芩素为例, 尽管作为分别从葛根、黄连、黄芩中分离出的活性成分, 却普遍存在口服生物利用度不高、溶解性差的问题[21]; 而在复方环境中, 这些成分的溶出与吸收行为可通过与其他组分的相态自组装得到显著改善。具体而言, 在经典方剂葛根芩连汤中, 葛根芩连汤通过与甘草配伍, 借助甘草酸的作用, 葛根素、黄连素、黄芩素的溶出度和生物利用度显著提高, 最终实现全方活性成分吸收增强、疗效提升的效果[71]。在白芍–甘草配伍

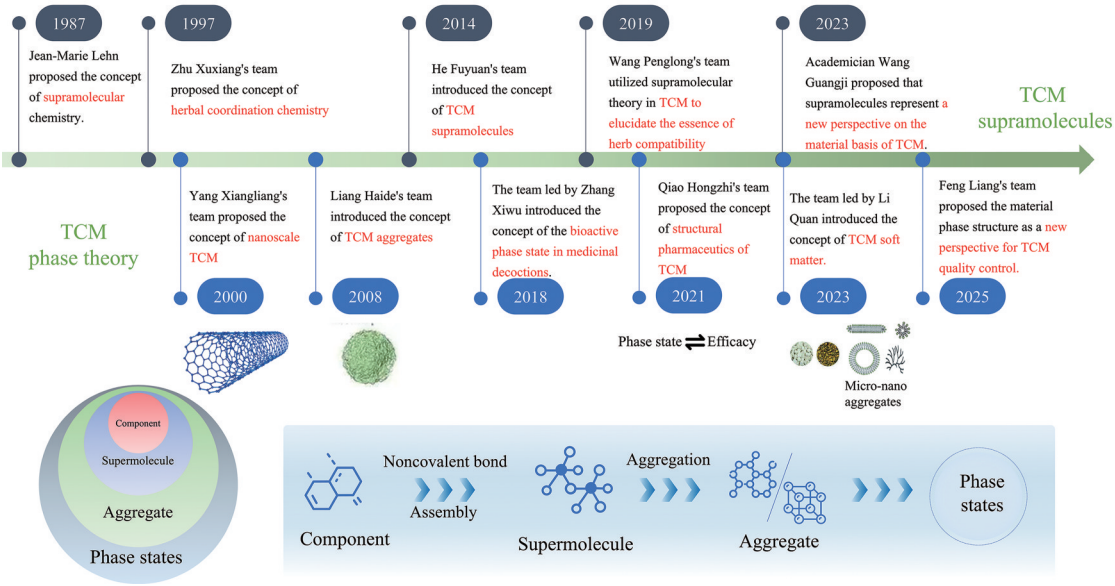


Figure 1 Research progress on phase states of Chinese herbal medicine

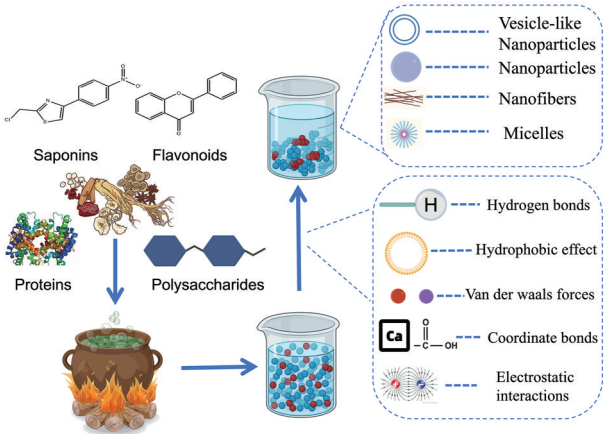


Figure 2 Phase state formation diagram of TCM decoction. Created with BioGDP.com

中, 甘草酸通过疏水作用包裹芍药苷, 抑制P-糖蛋白外排、增加药物渗透、延长释放时间, 进而有效提高芍药苷的口服生物利用度[72]。甘草次酸与姜黄素则通过π-π堆积和疏水作用形成聚集体, 借助甘草次酸与肝表面受体特异性结合, 提高了姜黄素的靶向性和渗透性[73]。黄连中的天然纳米粒通过吸附小檗碱促进其从晶体向非晶态的转变, 由此提高其溶解性和溶出度。小檗碱与大黄酸还可通过静电作用、氢键和π-π堆积自组装成层状骨架并嵌入其中, 形成类球状超分子结构, 不仅提高溶解度, 还增强其协同抗菌与靶向能力[74]。同样的, 黄芪多糖与黄酮类化合物可形成1∶1复合物, 将溶解度较低的黄酮类成分包裹于其中, 来实现增溶从而提高生物利用度[75]。白虎汤纳米相态中主要解热成分 (如芒果苷、新芒果苷、钙离子、甘草酸、甘草次酸) 含量显著高于其他相态, 表明纳米相态对其具有增溶作用, 是发挥解热功效的关键物理载体[46]。此外, 将白虎汤纳米相态进一步拆分成游离芒果苷和游离基团进行活体示踪分析, 发现纳米聚集体更能被细胞吸收, 且能靶向脑和肺发挥药效[76]。雷公藤红素与毛兰素通过水溶液自组装, 直接靶向Annexin A2蛋白, 不仅改善水溶性, 还增强其抗癌效果与靶向能力[77]。在当归补血汤中, 黄芪甲苷与*Z*-藁本内酯可能以2∶1的比例形成超分子达到缓释效果, 增强抗心肌纤维化的疗效[47]。由此可见中药活性成分的溶解与药效实现高度依赖于特定相态 (如胶束相、纳米相) 的形成, 其动态结构对增溶、靶向等功能的实现具有决定性作用。

2.2.2 中药配伍减毒的相态基础 中药相态的研究对中药复方的配伍增效解毒的阐释有重要意义, 多项研究表明, 毒性成分在与其他组分共组装为超分子或纳米结构后, 其释放、吸收或毒性位点可被有效屏蔽, 从而实现减毒目的 (表1)[42-68]。甘草–附子配伍研究中, Li等[78]通过小鼠毒性实验与结构表征, 推断其减毒机制与甘草成分和附子毒性生物碱自组装形成纳米粒有关。川乌经蜂蜜炮制后, 剧毒性二酯生物碱转化为单酯生物碱, 促进聚集体的形成, 从而减小川乌毒性[79]。黄连和马兜铃共煎后小檗碱与马兜铃酸通过静电作用、π-π堆积形成异质性线性超分子, 阻断了马兜铃酸的毒性位点, 从而降低其肾毒性[80]。甘草酸可与乌头碱类化合物发生酸碱络合形成复合物, 降低毒性成分体外释放, 并减缓吸收速率。此外, 甘草酸也能与士的宁自组装共沉淀从而缓释减毒。黄连解毒汤的混悬沉淀相是主要的活性相态[66], 其所含的小檗碱和黄酮类化合物形成了纳米粒和纳米纤维两种形式的自组装, 纳米粒的抗菌活性强于纳米纤维[29]。这些研究表明, 中药复方中成分的相态变化是其实现配伍增效、减毒的重要物质基础, 从微观层面揭示了中药“君臣佐使”配伍理论的本质, 为科学阐释中药复方配伍机制及指导中药炮制、制剂优化提供了关键的理论依据。

Table 1 Research progress on the relationship between phase states and function of traditional Chinese medicine (TCM)

Source		Phase disassembly	Phase	Mechanism	Principal active constituents	Supramolecular	Literature
Herbal pair	Glycyrrhizae Radix et Rhizoma, Strychni Semen	Sediment, 10 000 r·min^{-1} centrifuge for 30 min → Suspension (600 nm), dialysis → Colloidal solution (350 nm)	Sediment	Attenuation, sustained-release	Glycyrrhizic acid, glycyrrhetinic acid, brucine, strychnine, *etc*.	Glycyrrhizic acid-strychnine (1∶1)	[42,43]
	Carthami Flos, Persicae Semen	Safflower and Peach Kernel Decoction, 4 000 ×*g*, centrifuge for 10 min → Phase 1, *n*-butanol extraction → Phase 2, 100 000 ×*g*, centrifuge for 90 min → Phase 4; Phase 1, dialysis concentration → Phase 3, 200 000 ×*g* centrifuge for 120 min → Phase 5 and 6	–	–	–	–	[44]

Continued

Source		Phase disassembly	Phase	Mechanism	Principal active constituents	Supramolecular	Literature
	Ginseng Radix et Rhizoma, Schisandrae Chinensis Fructus	Co-decocted solution, centrifugation, filtration membrane and dialysis → Nanoscale aggregates (100 nm)	Nanoscale aggregates (100 nm)	Solubilization	Ginsenosides Ro, Rg1, Rb2, Re, Rg2, Rd and schisandrin	−	[45]
	Lonicerae Japonicae, Taraxaci Herba	Co-decocted solution, 10 000 r·min^{-1} centrifuge for 30 min → Precipitated phase (1 489 nm), dialysis and 13 000 r·min^{-1} centrifuge for 30 min → Nanophase (38.5) and true-solution phase	Nanophase	−	Chlorogenic acid, cichoric acid, isochlorogenic acid A, and isochlorogenic acid C	−	[46]
	Glycyrrhizae Radix et Rhizoma, Aconiti Radix	Co-decocted solution, 12 000 ×*g*, 25 °C centrifuge for 30 min → Nanoparticles	Nanophase	Toxicity reduction	Glycyrrhiza protein, aconitine	Glycyrrhiza-protein, Aconitie	[47]
	Glycyrrhizae Radix et Rhizoma, Coptidis Rhizoma	Co-decocted solution, 4 000 r·min^{-1} centrifuge for 30 min → Precipitated phase	Precipitated phase (185 nm)	−	Glycyrrhiza protein, berberine	Glycyrrhiza protein-Berberine	[48,49]
	Glycyrrhizae Radix et Rhizoma, Gypsum Fibrosum	Co-decocted solution (395.8 nm)	Co-decocted solution	Solubilization	Glycyrrhizic acid, liquiritin, Ca^{2+}	Glycyrrhizic acid -Ca^{2+}	[50]
Compound formula	Baihu Decoction	Baihu decoction, 4 000 r·min^{-1} centrifuge for 30 min → Precipitated phase, dialysis and 10 000 r·min^{-1} centrifuge for 30 min → Nanophase and true-solution phase	Nanophase (50 nm)	Solubilization	Mangiferin, neomangiferin, liquiritin, ammonium glycyrrhizinate	Neomangiferin-Glycyrrhizic acid (1∶1)	[51]
	Shengmai Yin	Shengmai Yin, 3 000 r·min^{-1} centrifuge for 10 min → Suspension phase, filtered through a 0.22 μm membrane and dialysis → True solution, 12 000 r·min^{-1} centrifuge for 30 min → Colloidal phase	Colloidal phase	−	−	−	[52]
	Liujunzi Decoction	Liujunzi Decoction, 6 000 r·min^{-1} centrifuge for 30 min → Precipitated phase, dialysis and 10 000 r·min^{-1} centrifuge for 30 min → Nanophase and true-solution phase	−	−	−	−	[53]
	Shaoyao Gancao Decoction	Shaoyao Gancao Decoction, 150 r·min^{-1} centrifuge for 60 min → Precipitated phase, filtered through a 50 nm membrane → True-solution phase, dispersed → Nanophase	Nanophase (250 nm)	Solubilization, potentiation	Albiflorin, paeoniflorin, liquiritin apioside, liquiritin, glycyrrhizic acid	Glycyrrhizic acid-flavone	[54,55]
	Huangqin Decoction	Huangqin Decoction, 13 000 r·min^{-1} centrifuge for 30 min → Precipitated phase (4 μm), 13 000 r·min^{-1} → Nanophase (129 nm) and true-solution phase	Nanophase	Solubilization	Paeoniflorin, liquiritin apioside, baicalin, and seven additional constituents	−	[56]

Continued

Source	Phase disassembly	Phase	Mechanism	Principal active constituents	Supramolecular	Literature
Qixue Shuangbu Prescription	Qixue Shuangbu Prescription, 6 000 r·min^{-1} centrifuge for 15 min → Suspension phase, filtered through a 0.45 μm membrane and membrane dialysis → True-solution phase, 12 000 r·min^{-1} centrifuge for 30 min → Nanophase	–	Potentiation	–	–	[57]
Maxing Shigan Decoction	Maxing Shigan Decoction, 12 000 r·min^{-1} centrifuge for 15 min → Colloidal phase, 10 kDa ultrafiltration tube at 6 000 r·min^{-1} and centrifuged for 15 min, repeated three times → large colloidal particles (1 108 nm), 3 kDa ultrafiltration tube, centrifuged → medium colloidal particles (473.9 nm) and small colloidal particles (371.9 nm)	Large colloidal particles	–	Ephedrine, amygdalin, glycyrrhizic acid	–	[58-60]
Dahuang Gancao Decoction	Dahuang Gancao Decoction, 8 000 r·min^{-1} centrifuge for 10 min → Precipitated phase, dialysis and 12 000 r·min^{-1} centrifuge for 30 min → Nanophase and true-solution phase	Nanophase	Enhancement of stability	SennosideA, sennosideB, aloe-emodin	–	[61]
Banxia Xiexin Decoction	Banxia Xiexin Decoction, 8 000 r·min^{-1} centrifuge for 30 min → Precipitated phase, dialysis and 12 000 r·min^{-1} centrifuge for 30 min → Nanophase and true-solution phase	Colloidal phase	The precipitated phase exhibits a sustained-release effect.	Baicalin, wogonoside, wogonin, berberine, palmatine, ammonium glycyrrhizinate, and isoliquiritin	Baicalin-Berberine	[62]
Linggui Zhugan Decoction	Linggui Zhugan Decoction, 600 ×*g* centrifuge for 10 min → Suspension phase, 3 kDa ultrafiltration membrane and ultrafiltered for 30 min → True-solution phase, 10 000 ×*g* centrifuge for 30 min → Colloidal phase	Colloidal phase	–	Cinnamaldehyde, liquiritin, cinnamic acid, glycyrrhizic acid	–	[63]
Huanglian Houpo Decoction	Huanglian Houpu Decoction, 4 000 ×*g* centrifuge for 10 min → Phase 1 (219.2 nm), dialysis → Phase 2 (164 nm), 100 000 ×*g* centrifuge for 60 min → Phase 3 (191.5 nm), 150 000 ×*g* centrifuge for 90 min → Phase 4 (173.6 nm) and Phase 5 (325.4 nm)	True solution and colloid	–	Epiberberine, coptisine, palmatine, berberine, magnolol and honokio	Berberine-Magnolol	[64]
Danggui Buxue Decoction	Danggui Buxue Decoction, 400 r·min^{-1} centrifuge for 10 min → Crude product, supernatant, 12 000 r·min^{-1} centrifuge for 40 min → *Astragalus membranaceus*-*Angelica sinensis* nanoparticles	Nanophase (150 nm)	Sustained-release	Baicalin, calycosin-7-glucoside, ferulic acid, formononetin, ononin, *Z*-ligustilide	Astragaloside IV-ligustilide (1:2)	[47]

Continued

Source	Phase disassembly	Phase	Mechanism	Principal active constituents	Supramolecular	Literature
Gegen Qinlian Decoction	Gegen Qinlian Decoction, 400 ×*g*, resuspended and centrifuge for 15 min → Micron-sized aggregates (2−3 μm) and the 400 g supernatant, 15 000 g·min^{-1} centrifuge for 15 min → Micro-nano aggregates (530 nm)	Micro-nano aggregates	Solubilization, enhancement of bioavailability	Puerarin, berberine, wogonoside, baicalin, glycyrrhizic acid, palmatine	Berberine-wogonoside, baicalin-palmatine, baicalin-glycyrrhizic acid	[65]
Huang-Lian-Jie-du-Tang	Huang-Lian-Jie-Du-Tang, 4 000 r·min^{-1} centrifuge for 15 min → Precipitated phase	Precipitated phase	Potentiation	Geniposide, coptisine, berberine, palmatine, baicalin, wogonoside	Baicalin-berberine (1∶1)	[66]
Siwu Decoction	Siwu Decotion, 4 000 ×*g* centrifuge for 30 min → Supernate, 8 000 ×*g* centrifuge for 30 min → Nanoparticles, 20 000 ×*g* centrifuged for 2 h → Nanoparticles 20000 (423 nm), 100 000 ×*g* centrifuged for 2 h → Nanoparticles 100000 (298 nm)	Nanoparticles 20000	−	Protein, polysaccharide, trace DNA	Protein, polysaccharide, DNA	[67]
Naoluo Xintong Decoction	Naoluo Xintong Decoction, 3 500 r·min^{-1} centrifuge for 10 min → Supernatant, dialysis, and 13 000 r·min^{-1} centrifuge for 30 min → Nano-solution	Nanophase	Potentiation	Astragaloside IV, *Panax notoginseng* saponins, citric acid, hydroxysafflor yellow A, *etc*	Polysaccharide, protein, saponins	[68]

2.3 相态研究: 重构多效中药质控体系的新维度

不同复方的配伍和煎煮形成不同的聚集体可能是多效中药发挥多种药效的物质基础。然而目前多成分对特定功效的贡献是简单的化学叠加, 还是通过分子互作形成功能性相态实现的协同增效尚不明确, 活性相态的动态演变如何影响中药非经典量效关系与功效特异性亦有待阐明, 基于活性成分的中药药效物质基础及其质量标志物研究, 对“一物多效”中药的功效质量评价模式尚不完善。因此, 如何利用相态研究, 突破传统质控局限, 本文提出以活性相态为核心的多效中药质控研究新策略。

2.4 中药相态的研究思路

目前中药相态的研究思路主要分为以下两种: 一是整体研究逐步拆分, 即“全方/药对−相态拆分−表征/分析−活性确证−机制推测”的路径, 通过药效实验找出活性相态, 将活性相态进一步拆分成聚集体和上清液, 通过化学和物理的方法破坏相态, 结合成分分析和药效验证找到相态的分子间作用力, 运用一些表征技术与结构分析技术研究其形成机制, 再对聚集体的体内过程进行分析, 得到药效物质成分组; 二是成分研究逆向组装, 即“成分−组装−表征−机制−活性”的路径, 通过方剂研究, 找到可能结合发生自组装的药效成分, 购买标准品制备纳米自组装体系, 通过药效实验验证自组装纳米粒的生物活性, 利用表征技术与结构分析技术研究形成机制, 最终得到药效物质成分组。

2.4.1 自下而上的成分研究 北京中医药大学Li等[29]发现黄连解毒汤液单煎澄清透明, 合煎浑浊, 对沉淀物进行分析发现主要成分为黄芩苷和小檗碱, 通过混合小檗碱与黄芩苷单体模拟获得自组装纳米复合物, 通过表征技术推出自组装机制, 然后通过斑马鱼与金葡菌对黄芩苷−小檗碱纳米粒的抗菌活性与安全性进行评价。同样的小檗碱和大黄酸单体模拟得到复合物, 将复合物进行表征和结构解析, 根据表征的结果推出纳米粒的组装机制, 发现纳米粒可以包裹小檗碱靶向给药增强药效, 溶血实验和毒理学评价显示小檗碱−大黄酸纳米粒具有良好的生物相容性与安全性。此外该团队通过相同的思路对黄连、肉桂配伍的黄连素−肉桂酸纳米粒以及甘草、黄连配伍的甘草苷−黄连素纳米粒进行了研究[7,41,42,81]。Luo等[82]对大黄酸−大黄酸钠纳米粒进行了表征。

2.4.2 自上而下的整体研究 黑龙江中医药大学Wu等[83,84]通过离心和透析将白虎汤分成四个相态, 对相

态进行了成分分析和形态表征, 药效实验发现纳米相态的药理活性与全方接近, 成分分析发现白虎汤中的纳米相态对其主要解热成分 (如芒果苷、新芒果苷等) 具有增溶作用。将纳米相态进一步拆分成游离芒果苷和游离基团进行活体示踪分析, 发现纳米聚集体更能被细胞吸收, 且能靶向脑和肺发挥药效[76]。南京中医药大学 Li 等[58,59]将麻杏石甘汤拆分成 3 个相态, 进行了成分分析和形态表征, 发现麻黄碱、苦杏仁苷、甘草酸在 3 个相态中的含量有差异, 药效实验发现加热过程中产生的自组装胶体是抗病毒的物质基础。浙江工商大学的 Liang 等[47]将甘草–附子配伍做了小鼠毒性实验, 发现甘草–附子配伍能降低附子的毒性, 并通过表征技术推断出纳米粒降低附子毒性的自组装机制。此外, 他们通过 Caco-2 单层细胞实验, 发现通过与甘草配伍, 葛根芩连汤中的难溶性成分的溶解度和生物利用度都明显提高。

3 多效中药质量控制新策略

3.1 中药相态在中药质量控制中的应用研究现状

中药相态研究, 作为连接中药宏观品质与微观物质的关键桥梁, 近年来, 日益广泛应用于中药质量精准评价与物质基础阐释研究。Qu 等[35]提出将“物相结构”特征应用于中药品质调控, 通过梳理中药中常见的六大物相结构 (胶束、囊泡、凝胶、纳米粒、纳米纤维、其他如共晶和碳点), 揭示结构与功能的紧密联系, 结合中药研发的四大环节 (炮制、煎煮、递送系统、质量控制), 例如, 在炮制中阐释“炭药止血”的科学内涵, 在煎煮中解析结构动态演变对药效的影响, 在递送系统中利用自组装结构实现“治疗–递送”一体化, 最终提出以“化学–结构–效应”三维质控新策略。该策略目前仍处于理论框架构建的初期阶段, 仅初步提出了相态结构在中药品质调控中的应用潜力, 尚未形成系统性的研究策略、清晰的技术路线或可操作的研究方法。质控思路存在明显局限性, 尤其未能充分考虑多效中药中不同活性组分通过组装形成多种特定结构、进而分别发挥不同药效作用的复杂机制。应致力于识别并表征与各临床功效相对应的特异性活性聚集体, 建立基于“功效–物相”关联的多维质控体系, 从而更全面、精准地反映中药的整体质量。

3.2 多效中药质控研究新策略

针对多效中药质控指标与药效脱节、相态稳定性系统性研究匮乏的核心瓶颈, 以及目前研究策略的局限性, 本研究首创“自上而下”与“自下而上”相融合的研究策略如图 3。本策略旨在自上而下地锁定体内药效导向的关键成分群, 并自下而上地于体外组装稳定、可控的黄芪功效活性聚集体。通过规范操作规程与阐明稳定

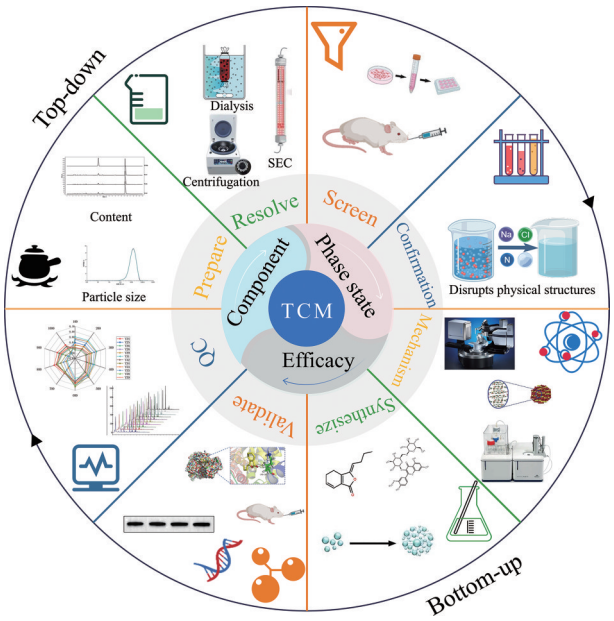


Figure 3 Research strategies for TCM phase states. Created with BioGDP.com

机制, 本策略旨在建立规范的相态分析操作规程, 攻克相态稳定性的技术难题, 最终为构建基于相态结构且关联药效的多效中药质量控制新范式奠定坚实基础。

3.2.1 自上而下的功效质量标志物发现策略 首先采用“自上而下”的整体研究策略, 旨在从药效确证的中药体系出发, 逐步拆分并锁定承载关键功效的质量标志物。该路径遵循“全方/药对→相态拆分→活性筛选→机制解析”的研究逻辑: 首先, 制备并拆分中药汤剂中的复杂相态系统; 继而通过药理模型筛选出主导药效的活性相态, 并利用化学干扰剂反向验证其功效必要性; 最后, 综合运用多种先进表征技术, 揭示活性聚集体的形成机制与结构特征, 从而将宏观功效与微观的化学成分群及其物理组装状态相关联, 最终发现涵盖化学与物理属性的多维功效质量标志物。

首先, 依据中国药典 (2025 年版) 及《中药饮片标准汤剂》制备中药汤剂, 煎煮时间与浓缩浓度对相态研究影响较大, 通过监测煎煮过程中粒径 (DLS)、分散系数 (PDI) 与化学成分的变化, 取长原则确定煎煮时间, 引入药物制剂中的芘荧光探针法测定临界聚集浓度确定最低浓度。

目前中药相态的拆分方法主要有 7 种 (表 2)[7,47,55,85-95], 差速离心与超滤法处理量大、效率高, 适用于初步分离与浓缩, 但分辨率有限; 密度梯度离心与尺寸排阻色谱分辨率优异、条件温和, 能有效分离纳米颗粒并保持活性, 却存在操作复杂、样本处理量小的局限; 膜透析法利于去除小分子, 但过程缓慢、损失显著; 有机试剂萃取虽可高效富集脂溶性成分, 但可能破坏

天然相态结构并引入污染。方法选择需结合研究目标 (规模化制备/精细分析/预处理)、相态特性 (疏水亲水成分/囊泡等精细结构) 及实验条件 (设备配置) 综合判定。为了后期实验的可重复性, 需建立“分辨率−回收率−活性保留率−污染程度”四维评价体系, 明确各方法核心操作参数, 规范操作步骤与结果判定标准, 形成标准化操作规范。

通过细胞和动物药效实验, 根据药效指标, 选出药效最佳的相态。通过正向分离与反向干预活性相态对相态的药效进行确证。一方面采用超滤透析技术分离全方活性相态 (如胶体相), 进一步拆分为聚集体与游离成分溶液, 通过体外药效模型 (如血虚小鼠模型、多柔比星肾病模型、慢性萎缩性胃炎等病症结合模型) 筛选主导功效的活性相态。另一方面利用吐温 20 (破坏疏水作用)、NaCl (干扰静电作用)、尿素 (解离氢键) 等化学干扰剂结合物理超声处理活性相态[96,97], 通过芘荧光探针技术考察相态是否被破坏, 结合体外动物实验药效保留率与X射线单晶衍射解析关键分子间作用力, 同时确证活性相态的起效方式。

利用冷冻电镜、分子动力学模拟、等温量热滴定、核磁及X射线单晶衍射技术, 表征活性聚集体, 揭示分子自组装路径与机制, 明确核壳结构对靶向递送的调控作用[29,47,98]。

3.2.2 “自下而上”的功效质量标志物确证策略 为确证由“自上而下”策略所发现的功效质量标志物, 这部分采用“自下而上”的还原验证策略。该路径遵循“成分→定向组装→表征验证→活性评价”的研究逻辑: 首先, 以已鉴定的功效成分群为标准, 在体外模拟其自组装过程, 定向构建目标活性聚集体; 随后, 对所合成聚集体的形态结构与理化性质进行全面表征, 以确认其成功组装; 最终, 通过体内外药效实验及分子生物学技术, 验证该人工组装体是否能够重现原生中药的特定功效, 从而反向确证此前所发现质量标志物的科学性与必要性, 为质量标准的建立提供坚实的实验依据。

购买活性聚集体标准品并模拟合成自组装聚集体, 进行形态表征与理化性质表征, 确定聚集体 (超分子) 的成功合成和结构。

进行药理实验与分子生物学技术对作用机制进行验证, 确证不同功效的质量标志物 (含化学成分与物理结构的活性超分子)[99,100]。

3.2.3 质量控制标准的建立 本研究旨在构建一个整合化学与物理属性的多维质量控制新标准。该体系的核心在于突破传统仅关注化学成分的局限, 将能显著影响药效的“活性相态”的物理特征纳入质控范畴。具体而言, 在化学层面, 针对已确证的活性成分, 建立含量测定方法与色谱指纹图谱, 可采用“一测多评”等策略进行整体质量控制。在物理层面, 参照化学指纹图谱的构建模式, 利用纳米颗粒示踪分析技术, 建立以粒径分布、PDI、zeta 电位等为核心指标的相态粒径分布指纹图谱与物化参数雷达图谱, 并规定其相似度判定标准。同时, 采用透射电镜或扫描电镜对活性聚集体的特征形态结构进行检查, 作为重要的鉴别项。

最终, 通过系统收集代表性样品进行分析测定与方法学考察, 制定包括活性成分含量限度、指纹图谱相似度及相态特征参数在内的综合判别标准, 从而构建一个能够切实反映中药多效性的功效质量标准草案。

4 总结

本研究系统阐述了中药“一物多效”特性与传统质控模式之间的核心矛盾, 指出仅凭有限成分的含量测定难以全面反映中药的整体疗效与多元功效特征。创

Table 2 Methods for phase separation of Chinese herbal decoction

Method	Advantage	Disadvantage	Application	Ref.
Differential centrifugation	Simple operation, high throughput	Resolution limited	3 000−5 000 r·min^{-1}: Precipitated phase; 13 000−20 000 r·min^{-1}: Nanophase or colloidal phase; 20 000−100 000 r·min^{-1}: Vesicles and other medium to small nanoparticles	[85,86]
Membrane dialysis	Favorable for removing small molecules	Significant loss and inability to produce in large quantities	200−3 500 Da: True solution; for the purification of supramolecules or vesicles, removing small molecules	[47]
Size-exclusion chromatography	High separation degree, maintaining particle activity	High loss, high cost, and complex operation	For further separation and analysis of colloidal and nanophase	[87-89]
Organic solvent extraction	Effectively separate the hydrophobic and hydrophilic phases	Chemical contamination and destruction of phase structure	Enrichment of lipophilic active ingredients	[90,91]
Density-gradient centrifugation	High resolution, mild conditions	Low sample capacity, requires gradient medium	Separation of vesicles, herbal carbon dots, *etc*.	[92-94]
Ultrafiltration	High efficiency with excellent retention of biological activity	Easy clogging, low resolution	Separation of colloidal phase, purification of macromolecules	[95]
Microporous membrane filtration	High efficiency, simple equipment	Easy fouling or clogging, low resolution	Routine pretreatment of colloidal and nanophases	[7,55]

新性地引入“中药相态”这一研究视角, 论证了其作为药效物质基础新形式的重要性, 具有增溶、靶向、减毒增效等“结构-功能”相关效应, 直接调控药效表达。进一步综合现有研究思路提出了一个融合“自上而下”(从汤剂到活性相态) 与“自下而上”(从成分到组装体)的双向研究策略, 旨在通过规范化的相态拆分、活性筛选、结构表征与机制解析, 锁定关联特定功效的活性超分子聚集体, 并将其确立为全新的质量标志物。该策略不仅能够解决多效中药功效质量标志物确证的难题, 还能为推动中药质量评价模式从“成分论”向“结构-功能一体化”创新转变提供科学依据。

未来研究需致力于相态分析方法的标准化、结构参数与药效指标的定量关联构建, 以及推动该策略在更广泛中药复方中的验证与应用, 最终实现从理论创新到实践应用的跨越。

作者贡献: 徐少华负责论文的撰写、图片与表格的绘制、文献的收集; 许晚霞负责图片表格的绘制优化; 宫文霞负责稿件的修改并指导论文的撰写; 李爱平、刘月涛负责稿件的修改; 秦雪梅负责论文的选题、构思并指导论文的撰写。

利益冲突: 本文作者声明无利益冲突。

References

[1] Liu XN, Che XQ, Li DF, et al. Research mode of quality marker research and quality evaluation of Chinese materia medica based on multi-source information fusion [J]. Chin Tradit Herb Drugs (中草药), 2019, 50: 4576-4581.

[2] Hou XT, Hao EW, Du ZC, et al. A hypothesis on the Q-markers based on characteristics of opposite-effect of herbs: an example of Sanqi [J]. Acta Pharm Sin (药学学报), 2019, 54: 211-221.

[3] Qin XM, Li AP, Liu YT, et al. Research strategies on orientated effective components of multi-effect Chinese materia medica [J]. Chin Tradit Herb Drugs (中草药), 2017, 48: 847-852.

[4] Liu YT, Jia L, Qin XM. Research advances of material basis of multi-effect Astragali Radix [J]. Chin Tradit Herb Drugs (中草药), 2018, 49: 1476-1480.

[5] Qiao HZ, Chen X, Chen J, et al. The perspective of the research on traditional Chinese medicine based on structural Chinese medicine: taking the external use of TCM as an example [J]. J Nanjing Univ Tradit Chin Med (南京中医药大学学报), 2022, 38: 970-975.

[6] Wang JB, Xiao XH. On indirect actions of Chinese medicines and innovation of indirect-acting Chinese medicines [J]. China J Chin Mater Med (中国中药杂志), 2021, 46: 5443-5449.

[7] Huang X, Wang P, Li T, et al. Self-assemblies based on traditional medicine berberine and cinnamic acid for adhesion-induced inhibition multidrug-resistant *Staphylococcus aureus* [J]. ACS Appl Mater Interfaces, 2020, 12: 227-237.

[8] Song C, Yang C, Meng S, et al. Deciphering the mechanism of Fang-Ji-Di-Huang-Decoction in ameliorating psoriasis-like skin inflammation *via* the inhibition of IL-23/Th17 cell axis [J]. J Ethnopharmacol, 2021, 281: 114571.

[9] Zhang TJ, Bai G, Liu CX. The concept, core theory and research methods of Chinese medicine quality markers [J]. Acta Pharm Sin (药学学报), 2019, 54: 187-196, 186.

[10] Liu CX. Five-year review on development of quality markers of traditional Chinese medicine [J]. Chin Tradit Herb Drugs (中草药), 2021, 52: 2511-2518.

[11] Ma SC, Wang Y, Wei F. Progress and exploration of quality control model of traditional Chinese medicine in the past decade [J]. Chin Pharm J (中国药学杂志), 2023, 58: 2-9.

[12] Zhang TJ, Guo HB, Xu J, et al. Study on quality marker of Panax notoginseng powder [J]. World Sci Technol-Mod Tradit Chin Med Mater Med (世界科学技术——中医药现代化), 2022, 24: 1-8.

[13] Shi LP, Zhang GZ, Liu CS, et al. Research summary of chemical constituents and pharmacological effects of Panax notoginseng and predictive analysis on its Q-markers [J]. China J Chin Mater Med (中国中药杂志), 2023, 48: 2059-2067.

[14] Hu J, Li K, Li AP, et al. Research progress on material basis of Danggui Buxue decoction [J]. Chin Tradit Herb Drugs (中草药), 2020, 51: 5658-5663.

[15] Xu WQ. Study on the Contribution and Directional Pharmacodynamic Components of Huangqi to Huangqi Jianzhong Tang for Intervention of Chronic Atrophic Gastritis (黄芪对黄芪建中汤干预慢性萎缩性胃炎的贡献及定向药效成分研究) [D]. Taiyuan: Shanxi University, 2020.

[16] Liu Y, Wang Z, Qin X. Metabolomics and molecular docking to compare of the efficacies of wild-simulated and transplanted Astragali Radix based on its compatibility with Angelicae Sinensis Radix against blood deficiency [J]. J Chromatogr B Analyt Technol Biomed Life Sci, 2021, 1173: 122682.

[17] Zhou LP, Zhang Y, Yin QN. Effect of angelica polysaccharide on peripheral blood cells and cytokines in mice with aplastic anemia [J]. Prog Anat Sci (解剖科学进展), 2023, 29: 529-532.

[18] Nie ZF. Analysis of research hotspots and development trends of *Angelica polysaccharides* based on CNKI (2000-2022) [J]. Doctor (大医生), 2024, 9: 103-106.

[19] Shi Y, Li MQ, Yang SY, et al. Advances on chemical constituents of volatile oil from Angelicae Sinensis Radix and their pharmacological effect [J]. Chin J Mod Appl Pharm (中国现代应用药学), 2024, 41: 1006-1014.

[20] Yao N, Wang ZW, Fu XY, et al. Advances in research on effects of the essential oil of Angelicae Sinensis Radix and its phthalide constituents on smooth muscle [J]. Chin J Mod Appl Pharm (中国现代应用药学), 2019, 36: 2738-2742.

[21] Fan XS, Duan JA, Wang ZY, et al. On characteristic properties of TCM dose-effect relationship [J]. China J Tradit Chin Med

Pharm (中华中医药杂志), 2009, 24: 270-274.

[22] Qiao HZ, Di LQ, Ping QN, et al. Structural Chinese medicine: new research field on pharmacodynamic substance basis of traditional Chinese medicine [J]. China J Chin Mater Med (中国中药杂志), 2021, 46: 2443-2448.

[23] Wei G, Zhang G, Li M, et al. Panax notoginseng: panoramagram of phytochemical and pharmacological properties, biosynthesis, and regulation and production of ginsenosides [J]. Hortic Res, 2024, 11: uhae170.

[24] Fan W, Liao Q, Fan L, et al. An innovative processing driven efficient transformation of rare ginsenosides enhances anti-platelet aggregation potency of notoginseng by integrated analyses of processing-(chemical) profiling-pharmacodynamics [J]. J Ethnopharmacol, 2024, 319: 117126.

[25] Liu RY, Wang ZC, Li X. Research progress on self-assembly supramolecules of traditional Chinese medicine [J]. Acta Pharm Sin (药学学报): 2025, 60:2752-2767.

[26] Hirsch AK. Supramolecular chemistry … and beyond [J]. Angew Chem Int Ed Engl, 2015, 54: 11013-11014.

[27] Zhu XX, Mao HB. Frontier of TCM research-TCM coordination chemistry [J]. Chin Tradit Herb Drugs (中草药), 1997, 28: 373-375.

[28] He FY, Zhou YQ, Deng KW, et al. Special impact of supramolecular chemistry on Chinese medicine theories [J]. China J Chin Mater Med (中国中药杂志), 2014, 39: 1534-1543.

[29] Li T, Wang P, Guo W, et al. Natural berberine-based Chinese herb medicine assembled nanostructures with modified antibacterial application [J]. ACS Nano, 2019, 13: 6770-6781.

[30] Hui X, Zhang JY, Kang A, et al. Study on new forms of TCM material basis and its pharmacokinetics/pharmacodynamics (PK/PD) [J]. J Nanjing Univ Tradit Chin Med (南京中医药大学学报), 2024, 40: 1013-1023.

[31] Yang XL, Xu HB, Wu JZ, et al. Application of nano-technology in the research of traditional Chinese medicine [J]. J Huazhong Univ Sci Technol (华中科技大学学报), 2000, 12: 104-105.

[32] Zhuang Y, Yan J, Zhu W, et al. Can the aggregation be a new approach for understanding the mechanism of traditional Chinese medicine? [J]. J Ethnopharmacol, 2008, 117: 378-384.

[33] Zhang XW, Liu MX, Li QH, et al. Laws of the delivery of drug property in compound TCM formulas from the perspective of effective phase [J]. Acta Chin Med Pharmacol (中医药学报), 2018, 46: 1-4.

[34] Liu Y, Li Q, Ma SC. Soft matter science of traditional Chinese medicine: a new frontier at the intersection of traditional Chinese medicine and modern material science [J]. Chin J Pharm Anal (药物分析杂志), 2023, 43: 45-50.

[35] Qu ZH, Yang YJ, Yang B, et al. A new perspective on quality control of traditional Chinese medicine based on characteristics of "physical phase structure" [J]. China J Chin Mater Med (中国中药杂志), 2025, 50: 3579-3588.

[36] Guan QX, Zhou XY, Lü SW, et al. Analysis on the formation principle and present situation of nano phase state of multi-component self-assembly of traditional Chinese compound medicine decoction [J]. J Hainan Med Univ (海南医学院学报), 2023, 29: 872-880.

[37] He Y, Zhang JM, Gao F, et al. Advances and prospects on the combination mechanism for toxicity reduction and pharmacological effect improving between Aconiti Lateralis Radix Praeparata and Glycyrrhizae Radix et Rhizoma (a classic TCM herb-pair) [J]. Pharmacol Clin Chin Mater Med (中药与临床), 2013, 4: 62-65.

[38] He Z, Pu YQ. Phase difference of traditional Chinese medicine compound decoction: a review [J]. Chin J Exp Tradit Med Formulae (中国实验方剂学杂志), 2022, 28: 259-266.

[39] Whitesides GM, Grzybowski B. Self-assembly at all scales [J]. Science, 2002, 295: 2418-2421.

[40] Rybtchinski B. Adaptive supramolecular nanomaterials based on strong noncovalent interactions [J]. ACS Nano, 2011, 5: 6791-6818.

[41] Zhi K, Wang J, Zhao H, et al. Self-assembled small molecule natural product gel for drug delivery: a breakthrough in new application of small molecule natural products [J]. Acta Pharm Sin B, 2020, 10: 913-927.

[42] Ma WB. Study on Correlation between Phase Difference with the Growth and Decline of Toxicity-Efficacy in "Glycyrrhizae Radix-Strychni Semen" Decoction (I) ("甘草-马钱子"药对汤液相态差异与毒效消长相关性的研究(I)) [D]. Harbin: Heilongjiang University of Chinese Medicine, 2019.

[43] Li CC. Study on Correlation between Phase Difference with the Growth and Decline of Toxicity-Efficacy in "Glycyrrhizae Radix-Strychni Semen" Decoction (II) ("甘草-马钱子"药对汤液相态差异与毒效消长相关性的研究(II)) [D]. Harbin: Heilongjiang University of Chinese Medicine, 2021.

[44] Tao CX, Ye TW, Li M, et al. Exploration of delivering effects of decocting process on pharmacodynamic substances of Carthami Flos-Persicae Semen herb pair based on variation of phase states [J]. Chin Tradit Herb Drugs (中草药), 2023, 54: 5550-5559.

[45] Zhang S. Study on Separation, Characterization and Activity of Phase States of Ginseng Radix et Rhizoma-Schisandrae Chinensis Fructus Herbal Pair Decoction (人参-五味子药对汤液相态的拆分、表征及活性研究) [D]. Changchun: Changchun University of Chinese Medicine, 2024.

[46] Zhao SC, Tao Y, Lu Y, et al. Determination of contents of major components in different phases of Lonicerae Japonicae Flos-Taraxaci Herba extract and screening of effective phases for its inhibitory effect on *Propionibacterium acnes* [J]. Chin Tradit Herb Drugs (中草药), 2024, 55: 6167-6173.

[47] Liang P, Bi T, Zhou Y, et al. Insights into the mechanism of supramolecular self-assembly in the *Astragalus membranaceus*-*Angelica sinensis* codecoction [J]. ACS Appl Mater Interfaces,

2023, 15: 47939-47954.

[48] Li W, Wang ZJ, Lin XY, et al. Study on the substance basis of "property-taste-efficacy" of liquorice and Rhizoma Chinensis based on supramolecular system induced by weak bond [J]. Acta Pharm Sin (药学学报), 2022, 57: 1901-1908.

[49] Li W, Wang ZJ, Liu XJ, et al. Based on weak bond chemistry, the interaction mechanism between glycyrrhiza protein and berberine in water decocting process of Rhizoma Coptidis and liquorice was investigated [J]. Acta Pharm Sin (药学学报), 2021, 56: 2119-2126.

[50] Zhang YZ, Pi WM, Wu LY, et al. Based on supramolecular chemistry to explore the scientific connotation of the compatibility between licorice and the insoluble mineral medicine gypsum [J]. Acta Pharm Sin (药学学报), 2024, 59: 1048-1056.

[51] Lü SW, Wu YQ, Li YP, et al. Determination of main components in Baihutang with separation of different phase states and different phase states [J]. Chin J Exp Tradit Med Formulae (中国实验方剂学杂志), 2020, 26: 154-160.

[52] Dou JJ, Zhang XW, Wang LX, et al. Research of effective iterative phase state and pharmacodynamic verification of Shengmai Yin from perspective of effective phase [J]. Chin Tradit Herb Drugs (中草药), 2021, 52: 993-999.

[53] Shang EY, Ma XQ, Yu X, et al. Study on phase separation and characterization of Liujunzi decoction [J]. J Pharm Res (药学研究), 2021, 40: 216-220.

[54] Shen CY, Zhu JJ, Qin ZJ, et al. Phase separation and analgesic and anti-inflammatory activities of Shaoyao Gancao decoction [J]. Pharm J Chin People's Liberation Army (解放军药学学报), 2022, 35: 209-213, 218.

[55] Shen CY, Zhu JJ, Dai B, et al. Effect of self-assembled nanoparticles from Shaoyao Gancao decoction on release and absorption of main components of Baishao [J]. China J Chin Mater Med (中国中药杂志), 2021, 46: 2190-2196.

[56] Shen CY, Wu WM, Hou XJ, et al. Fingerprint establishment of Huangqin decoction and study on spectrum-effect relationship of its antidermatophytic activity in different phase states [J]. China Pharm (中国药房), 2023, 34: 687-692.

[57] Wang Q, Yuan CY, Jiang Y, et al. Traditional Chinese medicine processing synergistic mechanism of Qixue Shuangbu Prescription against chronic heart failure based on "decoction phase state-nano assembly" [J]. Chin J Hosp Pharm (中国医院药学杂志), 2023, 43: 1185-1190.

[58] Li HZ, Song DD, Chang CQ, et al. Separation, characterization, and antiviral activity of colloidal phase state of Maxing Shigan decoction [J]. China J Chin Mater Med (中国中药杂志), 2023, 48: 4394-4401.

[59] Zhu YX, Chen W, Wang ZZ, et al. Spatial heterogeneity and physical structure basis of antibacterial activity of Ma-Xing-Shi-Gan decoction [J]. Acta Pharm Sin (药学学报), 2021, 56: 2112-2118.

[60] Wang JF. Study on Compatibility Mechanism of Ma Xing Shi Gan Tang based on Biopharmaceutics and Liquid Phase of Decoction (基于生物药剂学与汤液相态的麻杏石甘汤配伍机制研究) [D]. Tianjin: Tianjin University of Traditional Chinese Medicine, 2023.

[61] Hao BY. Study on the Compatibility Mechanism of Dahuang Gancao Decoction based on Decoction Phase and Biopharmaceutics (基于汤剂相态和生物药剂学的大黄甘草汤配伍机制研究) [D]. Tianjin: Tianjin University of Traditional Chinese Medicine, 2024.

[62] You G, Feng T, Zhang G, et al. Preparation, optimization, characterization and in vitro release of baicalein-solubilizing glycyrrhizic acid nano-micelles [J]. Int J Pharm, 2021, 601: 120546.

[63] Wu X, Mao YP, Wang D, et al. Investigation of substance analysis and protective effect on obstructive kidney of the active phase of Ling-Gui-Zhu-Gan decoction [J]. Acta Pharm Sin (药学学报), 2025, 60: 2342-2351.

[64] Xie MH, Zhang JY, Jiang TQ, et al. Exploration of material basis in Huanglian Houpu decoction based on comprehensive characterization of "composition-content-phase" in chemistry [J]. Chin Tradit Herb Drugs (中草药), 2025, 56: 3879-3892.

[65] Wu SY, Yang XQ, Cheng WJ, et al. Improvement of irinotecan-induced enterotoxicity by self-assembled nanoparticles between components of Gegen Qinlian decoction [J]. Chin Tradit Herb Drugs (中草药), 2024, 55: 3987-3997.

[66] Zhang C, Zhao R, Yan W, et al. Compositions, formation mechanism, and neuroprotective effect of compound precipitation from the traditional Chinese prescription Huang-Lian-Jie-Du-Tang [J]. Molecules, 2016, 21: 1094.

[67] Zhang X. Study on the Protective Effect of Siwu Decoction and its Nanoparticles against Hematological System Injury in Zebrafish (四物汤及其纳米粒子对斑马鱼血液系统损伤的保护作用研究) [D]. Beijing: Minzu University of China, 2020.

[68] Zhao G, Hong L, Liu M, et al. Isolation and characterization of natural nanoparticles in Naoluo Xintong decoction and their brain protection research [J]. Molecules, 2022, 27: 1511.

[69] Chen FW, Wang FX, Zhang SC, et al. Research progress on the compatibility mechanisms and innovative formulation design and application of Glycyrrhizae Radix et Rhizoma based on molecular self-assembly [J]. Acta Pharm Sin (药学学报), 2025, 60: 2158-2166.

[70] Zheng HX, Li T, Yin HY, et al. Progress in pharmacological effects of glycyrrhizic acid and its application as drug carrier [J]. Acta Neuropharmacol (神经药理学报), 2025, 15: 43-48.

[71] Lin D, Du Q, Wang H, et al. Antidiabetic micro-/nanoaggregates from Ge-Gen-Qin-Lian-Tang decoction increase absorption of baicalin and cellular antioxidant activity *in vitro* [J]. Biomed Res Int, 2017, 2017: 9217912.

[72] Shen C, Shen B, Zhu J, et al. Glycyrrhizic acid-based self-assembled micelles for improving oral bioavailability of paeoniflorin [J]. Drug Dev Ind Pharm, 2021, 47: 207-214.

[73] Wang J, Gu XM, Zhang SY, et al. Preparation and evaluation of

dual-targeting pH-sensitive baicalin/curcumin co-loaded liposomes [J]. Drug Eval Res (药物评价研究), 2024, 47: 2816-2829.

[74] Tian X, Wang P, Li T, et al. Self-assembled natural phytochemicals for synergistically antibacterial application from the enlightenment of traditional Chinese medicine combination [J]. Acta Pharm Sin B, 2020, 10: 1784-1795.

[75] Liu F, Sun L, You G, et al. Effects of *Astragalus* polysaccharide on the solubility and stability of 15 flavonoids [J]. Int J Biol Macromol, 2020, 143: 873-880.

[76] Lü S, Su H, Sun S, et al. Isolation and characterization of nanometre aggregates from a Bai-Hu-Tang decoction and their antipyretic effect [J]. Sci Rep, 2018, 8: 12209.

[77] Zheng Y, Wei N, Lü C, et al. Mechanistic insights into honey-boiled detoxification of Chuan Wu: a study on alkaloid transformation and supramolecular aggregation [J]. J Pharm Anal, 2025, 15: 101205.

[78] Li BJ, Shen Y, Liao RT, et al. Investigating mechanism of toxicity reduction by combination of Glycyrrhizae Radix et Rhizoma and Aconiti Lateralis Radix Preparata on terms of proteins self-assembly [J]. China J Chin Mater Med (中国中药杂志), 2015, 40: 661-666.

[79] Tian J, Chen K, Zhang Q, et al. Mechanism of self-assembled celastrol-erianin nanomedicine for treatment of breast cancer [J]. Chem Eng J, 2024, 499: 155709.

[80] Wang P, Guo W, Huang G, et al. Berberine-based heterogeneous linear supramolecules neutralized the acute nephrotoxicity of aristolochic acid by the self-assembly strategy [J]. ACS Appl Mater Interfaces, 2021, 13: 32729-32742.

[81] Wang Z, Li W, Lü J, et al. Revealing the active ingredients of the traditional Chinese medicine decoction by the supramolecular strategies and multitechnologies [J]. J Ethnopharmacol, 2023, 300: 115704.

[82] Luo W, Yang Z, Zheng J, et al. Small Molecule hydrogels loading small molecule drugs from Chinese medicine for the enhanced treatment of traumatic brain injury [J]. ACS Nano, 2024, 18: 28894-28909.

[83] Wu YQ, Lü SW, Li YP, et al. Separation and characterization of nano phase in Baihu decoction (白虎汤) [J]. Chin Arch Tradit Chin Med (中华中医药学刊), 2021, 39: 121-124+286-289.

[84] Lü SW, Wu YQ, Li YP, et al. Effects of different phase Baihu decoction on the serum TNF-α, IL-1β and IL-6 level in fever model rabbits [J]. J Int Pharm Res (国际药学研究杂志), 2020, 47: 870-875.

[85] Ping Y, Li Y, Lü S, et al. A study of nanometre aggregates formation mechanism and antipyretic effect in Bai-Hu-Tang, an ancient Chinese herbal decoction [J]. Biomed Pharmacother, 2020, 124: 109826.

[86] Su H. Study on the Separation and Formation Mechanism of Nanophase States in Baihu Decoction (白虎汤中纳米相态的分离与表征及其解热作用研究) [D]. Harbin: Heilongjiang University of Chinese Medicine, 2017.

[87] Gurriaran-Rodriguez U, De Repentigny Y, Kothary R, et al. Isolation of small extracellular vesicles from regenerating muscle tissue using tangential flow filtration and size exclusion chromatography [J]. Skeletal Muscle, 2024, 14: 22.

[88] You JY, Kang SJ, Rhee WJ. Isolation of cabbage exosome-like nanovesicles and investigation of their biological activities in human cells [J]. Bioact Mater, 2021, 6: 4321-4332.

[89] Zhang J, Tian S, Guo L, et al. Chinese herbal medicine-derived extracellular vesicles as novel biotherapeutic tools: present and future [J]. J Transl Med, 2024, 22: 1059.

[90] Kalarikkal SP, Prasad D, Kasiappan R, et al. Author correction: a cost-effective polyethylene glycol-based method for the isolation of functional edible nanoparticles from ginger rhizomes [J]. Sci Rep, 2024, 14: 16145.

[91] Jang J, Jeong H, Jang E, et al. Isolation of high-purity and high-stability exosomes from ginseng [J]. Front Plant Sci, 2022, 13: 1064412.

[92] Tan S, Liu Z, Cong M, et al. Dandelion-derived vesicles-laden hydrogel dressings capable of neutralizing *Staphylococcus aureus* exotoxins for the care of invasive wounds [J]. J Control Release, 2024, 368: 355-371.

[93] Kim J, Zhu Y, Chen S, et al. Anti-glioma effect of ginseng-derived exosomes-like nanoparticles by active blood-brain-barrier penetration and tumor microenvironment modulation [J]. J Nanobiotechnol, 2023, 21: 253.

[94] Xie Q, Gu J, Sun Y, et al. Therapeutic potential of ginger exosome-like nanoparticles for alleviating periodontitis-induced tissue damage [J]. Int J Nanomedicine, 2024, 19: 11941-11956.

[95] Zhang LR, Wang WP, Yang YR, et al. Influence of preparation process on basic properties of different phases from Gegen Qinlian decoction [J]. Lishizhen Med Mater Res (时珍国医国药), 2023, 34: 1117-1121.

[96] Biswas S, Karishma S, Ramesh B, et al. Light-induced destabilisation of oil-in-water emulsions using light-active bolaform surfactants [J]. Soft Matter, 2023, 19: 199-207.

[97] Kuevi DNO, Kuntworbe N, Ayertey E. Effects of pH and electrolytes on castor oil emulsions with various stabilisers using Khaya senegalensis gum as an emulsifier [J]. Adv Pharmacol Pharm Sci, 2021, 2021: 7049332.

[98] Fu S, Yi X, Li Y, et al. Berberine and chlorogenic acid-assembled nanoparticles for highly efficient inhibition of multidrug-resistant *Staphylococcus aureus* [J]. J Hazard Mater, 2024, 473: 134680.

[99] Liu H, Jin X, Liu S, et al. Recent advances in self-targeting natural product-based nanomedicines [J]. J Nanobiotechnol, 2025, 23: 31.

[100] Li J, Zhang YL, Jin T, et al. Advanced pharmaceutical nanotechnologies applied for Chinese herbal medicines [J]. Adv Sci (Weinh), 2025, 12: e00167.