基于分子自组装的甘草配伍机制及其创新制剂设计与应用研究进展

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摘要: 甘草在古今方剂配伍中应用广泛, 可调和诸药, 增效减毒。探究甘草配伍理论的科学内涵, 对于指导甘草配伍的临床应用及方药开发具有重要意义。本文在概述甘草配伍应用与研究概况的基础上, 着重从分子自组装的角度综述甘草配伍增效、缓性、减毒及配伍禁忌机制的研究进展, 同时阐述基于分子自组装的甘草组分创新制剂设计与应用研究进展, 以期为进一步阐释和丰富甘草配伍理论的科学内涵提供借鉴和参考, 为基于甘草组分自组装的创新制剂设计与开发提供一定的理论和实践依据。

关键词: 甘草; 自组装; 配伍机制; 增效减毒; 配伍禁忌; 制剂设计

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Research progress on the compatibility mechanisms and innovative formulation design and application of *Glycyrrhizae Radix* et Rhizoma based on molecular self-assembly

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Abstract: *Glycyrrhizae Radix* et Rhizoma (GRR) is widely used in ancient and modern Chinese herbal compounds, which can moderate property of herbs with the effect of improving efficacy and reducing toxicity. Exploring the scientific connotation of GRR compatibility theory is of great significance for guiding the clinical application of GRR compatibility and related drug development. Based on summarizing the application and research status of GRR compatibility, this paper mainly reviews the research progress on the mechanisms of GRR compatibility in terms of enhancing efficiency, alleviating property, reducing toxicity, and incompatibility from the perspective of molecular self-assembly, and simultaneously expounds on the research progress of innovative formulation design and application of GRR components based on molecular self-assembly, so as to provide reference and guidance for further explaining and enriching the scientific connotation of GRR compatibility theory,

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and to provide certain theoretical and practical basis for the design and development of innovative formulations based on GRR component self-assembly.

Key words: *Glycyrrhizae Radix* et Rhizoma; self-assembly; compatibility mechanism; synergy and attenuation; drug incompatibility; pharmaceutical design

伴随超分子化学及纳米技术的发展, 中药的多种物相形式和特征被发现和揭示, 中药功效发挥的物质成分存在形式与物理结构受到广泛关注[1-4]。中药化学成分来源广泛、结构独特、修饰位点众多, 因而易发生化学成分的分子识别与自组装现象[3-5]。大量研究表明, 中药复杂体系普遍存在自组装聚集体, 是中药及复方功效发挥的关键物理结构形式[3-5]。中药自组装聚集体的发现为揭示中药复方药效物质基础与方剂配伍理论的科学内涵提供了新视角, 也为中药创新药物、新型辅料及纳米递药系统的设计与开发等提供了新思路和借鉴[6,7]。

甘草为豆科植物甘草 (*Glycyrrhiza uralensis* Fisch.)、胀果甘草 (G. inflata Bat.) 或光果甘草 (G. glabra L.) 的干燥根和根茎, 具有补脾益气、清热解毒、祛痰止咳、缓急止痛、调和诸药的功效[8,9]。甘草在古今方剂配伍中应用广泛, 素有“十方九草”之说。《伤寒论》113首方剂有70首方剂含有甘草, 南京中医药大学中医方剂文献数据库中9万余首古今方剂, 其中有26 185首包含甘草[10]。因此, 探究甘草配伍的机制, 对于进一步揭示中药复方配伍的原理及科学内涵具有重要意义。现代研究表明, 甘草配伍增效减毒、调和诸药的功效主要体现在其影响配伍药味效应成分的生物药剂学行为及药理的协同或拮抗等方面[11-13]。

近年来, 受中药自组装现象的启发, 许多学者从分子自组装的角度探究甘草配伍增效减毒及配伍禁忌的机制; 也有一些学者, 基于甘草成分的自组装开展了创新制剂的设计与应用研究。本文在概述甘草配伍应用与研究概况的基础上, 着重从分子自组装的角度综述甘草配伍增效、缓性、减毒及配伍禁忌机制的研究进展, 同时阐述基于分子自组装的甘草组分创新制剂设计与应用进展, 以期为进一步阐明和丰富甘草配伍理论的科学内涵提供借鉴和参考, 为基于甘草组分自组装的创新制剂设计与开发提供一定的理论和实践依据。

1 甘草的配伍应用与研究概况

中医药理论认为, 甘草调和诸药的作用与其性味、功效密切相关[11]。甘草味甘性平, 可协调寒热, 平调升降, 缓和药物烈性, 减轻不良反应, 并改善组方的疗效[12]。甘草与附子、干姜配伍可缓其热; 与黄连、石膏配伍可缓其寒; 与大黄、芒硝配伍可缓泻下作用, 使泻而不速; 而与黄芩、黄连、干姜、半夏等寒热药同时配伍用可调和寒热。此外, 甘草具有补脾益气、清热解毒、祛痰止咳、缓急止痛等功效, 与人参、白术、茯苓同用, 能够增加补益功效, 用于治疗脾虚气陷、脾胃气虚诸证; 与桔梗、干姜、麻黄、苦杏仁等配伍等用于祛痰止咳; 与黄芩、黄连配伍同用既可增清热解毒之功, 又可缓清泄之力; 与白芍配伍则可调和肝脾, 有柔筋止痛之效[11]。除中医方剂配伍外, 现代研究及临床上也有将甘草及其活性成分与化学药物联合使用, 以实现减毒增效的目的[14], 如甘草与顺铂联用, 可以减轻顺铂产生的肾毒性[15], 复方甘草酸苷注射液与甲泼尼龙联用能够增强其治疗紫癜的效果[16]。

甘草配伍减毒增效、调和诸药的机制与其所含化学成分及具有的药理作用密切相关, Li等[11]和Luo等[12]分别综述了甘草“调和诸药”的生物药剂学机制和配伍应用的药理作用机制。一方面, 甘草及其活性成分可通过影响配伍药味效应成分的溶解溶出、吸收代谢等生物药剂学行为, 发挥配伍增效减毒作用[12,13]; 另一方面, 甘草及其活性成分具有抗炎、抗肿瘤、抗病毒、神经保护等药理作用, 在临床方剂配伍中用于多种炎症、心脑血管系统疾病、神经系统疾病、病毒感染和肿瘤方面的治疗, 通过药理作用的协同或拮抗实现增效减毒[11,17]。现代研究还发现, 甘草各组分及其与配伍药味效应成分的分子组装可显著影响配伍药味效应成分的溶解溶出、吸收分布及药理毒理活性, 是揭示甘草配伍理论内涵的关键物理结构形式 (图1)[18-20], 甘草不同成分的自组装及其配伍作用与机制如表1[20-36]所示。

2 基于分子自组装的甘草配伍增效减毒机制研究

目前, 文献[31,36,37]报道甘草化学成分甘草酸、甘草蛋白、甘草多糖等均可自组装或与其他成分组装形成聚集体, 影响配伍药味效应成分的溶解、吸收或生理活性, 发挥配伍增效减毒作用。

2.1 基于分子自组装的甘草配伍增效机制研究

甘草各组分及其与配伍药味效应成分的分子自组装是甘草配伍增效的关键物理结构基础, 其配伍增效的机制与自组装聚集体的增溶促稳及促吸收作用密切相关。研究表明, 甘草有效成分甘草酸、甘草蛋白等自组装形成纳米胶束或纳米粒, 能够改善配伍药味效应成分的溶解和吸收, 从而增加生物利用度, 提高疗效,

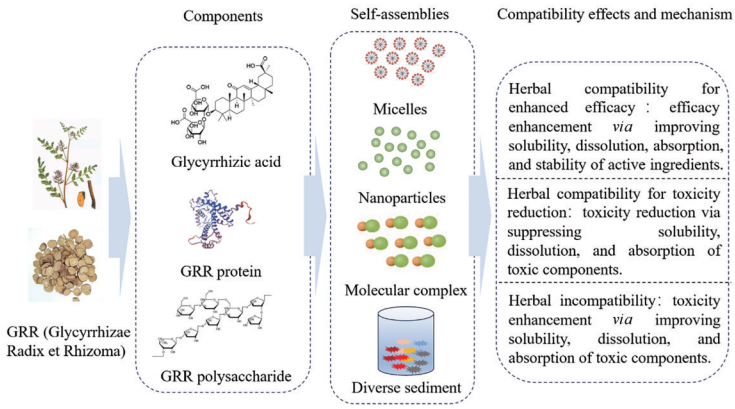


Figure 1 Schematic diagram of the compatibility mechanisms of GRR based on molecular self-assembly. Self-assemblies are formed by either a single component from GRR or by two or more components derived from GRR and compatible herbs. GRR: *Glycyrrhizae Radix* et Rhizoma

Table 1 Summary of self-assembly and compatibility effects of different components from GRR. *Self-assemblies are formed by either a single component from GRR or by two or more components derived from GRR and compatible herbs

GRR component	Self-assembly*	Compatibility effect and mechanism	Compatible example (active/toxic ingredient)	Ref.
Glycyrrhizic acid	Micelles	Enhancing effect by promoting absorption of active ingredients	*Paeoniae* Radix Alba (paeoniflorin)	[21]
			Scutellariae (baicalin, baicalein)	[22]
	Nanoparticles	Enhancing effect by enhancing dissolution and/or promoting absorption of active ingredients	*Scutellariae* (baicalin)	[22]
			Paeoniae Radix Alba (paeoniflorin)	[23]
			Gypsum ($CaSO_4·2H_2O$)	[24]
		Enhance antibacterial activity and mitigate diarrhea-related adverse effects	*Coptis chinensis* (berberine)	[25]
		Toxicity enhancement by compatibility *via* increasing solubility of toxic ingredients	*Daphne genkwa* (yuanhuacine)	[20,26]
	Precipitant	Toxicity reduction *via* suppressing dissolution of toxic ingredients	*Strychni Semen* (brucine; strychnine)	[27]
			Aconite (Aconitine)	[28-30]
GRR protein	Nanoparticles	Enhancing effect by promoting absorption of active ingredients	*Paeoniae* Radix Alba (paeoniflorin)	[31]
			Scutellariae (baicalin)	[32]
		Enhance antibacterial activity and mitigate diarrhea-related adverse effects	*Coptis chinensis* (berberine)	[33]
		Toxicity reduction *via* encapsulation of toxic ingredients	*Aconite* (aconitine)	[34,35]
GRR polysaccharide	Complex	Increasing solubility and stability of active ingredients	*Paeoniae* Radix Alba (paeoniflorin)	[36]
			Radix Puerariae (puerarin)	[36]

发挥配伍增效作用[18-23,31,32,36-39]。课题组前期研究发现，甘草酸自组装纳米胶束能够显著改善芍药苷的口服生物利用度[21]，芍药甘草汤中由蛋白、多糖等自组装形成的纳米粒能够显著促进芍药苷、甘草酸等的肠吸收，且具有较好的抗炎活性[19,23,39]。研究人员研究发现，甘草蛋白由氢键作用和疏水作用驱动形成自组装纳米粒可以通过小窝蛋白介导的内吞作用途径促进芍药苷的吸收[27,38]。Feng[36]研究发现，甘草多糖对葛根素、芍药苷等14种中药单体成分具有增溶促稳作用，Fe^{3+}的加入会对甘草多糖的增溶促稳作用产生不利影响，推测可能是甘草多糖的分子组装或与各成分的相互组装产生增溶促稳作用，而Fe^{3+}的加入影响了甘草多糖的分子组装，进而影响其增溶促稳作用。Wang等[20]研究发现，芍药甘草汤在煎煮过程中芍药苷和甘草蛋白自组装形成的胶体微粒是芍药甘草汤镇痛作用的关键。此外，甘草酸自组装体系对黄芩素、木犀草素、芦荟大黄素等多种难溶性均具有增溶及促吸收作用，还能改善小檗碱、芦荟大黄素、绿原酸等成分的稳定性[22,32,37]。

2.2 基于分子自组装的甘草配伍缓性机制研究

甘草各组分及其与配伍药味效应成分的分子组装也是甘草配伍缓和药性的关键物理结构基础，其配伍缓和药性的机制与自组装聚集体改变化学成分物理结构、存在形式进而影响其在体内的溶解、释放、吸收的过程及药理毒理作用有关[24,25,33,40,41]。黄连性味苦寒，可清热燥湿、泻火解毒，但易引起“苦寒败胃”，导致腹泻等不良反应。Li等[25]研究发现甘草缓和黄连苦寒之

性的作用机制不是简单的甘草生物拮抗, 而是共煎形成超分子体系进而“和合”黄连的药性、药效、药味。甘草配伍黄连共煎过程由甘草酸和小檗碱自组装形成的超分子纳米球不仅可以增强黄连的抑菌活性, 还明显改善黄连苦寒引起小鼠腹泻的不良反应, 表现出配伍缓性增效作用[25]; 还发现甘草蛋白可以和小檗碱通过静电引力和疏水作用等弱键诱导自组装形成纳米粒能够增强小檗碱的抗菌活性[33]。另有研究表明, 甘草酸可以与小檗碱发生分子络合组装形成沉淀, 降低小檗碱的溶解, 从而抑制其提取转移以缓和黄连的苦寒之性[40]。此外, 甘草缓大黄峻烈之性与两者共煎发生分子组装产生沉淀使有效成分发生相关变化或降低毒性成分含量有关[41], 甘草石膏配伍缓性增效也与两者合煎形成的超分子纳米粒有关[24]。

2.3 基于分子自组装的甘草配伍减毒机制研究

甘草各组分及其与配伍药味毒性成分的分子组装还是甘草配伍减毒的关键物理结构基础, 其配伍减毒的机制与自组装聚集体抑制毒性成分溶解、溶出, 减少毒性成分的吸收及降低毒性作用等有关。马钱子、附子是常见有毒中药, 临床常配伍甘草以解其毒, 研究人员分别从化学成分变化、体内吸收代谢、毒理效应等方面剖析了甘草的配伍减毒机制[28,29,42]。大量研究表明, 甘草各组分还可通过与马钱子、附子的毒性成分的超分子组装沉淀毒性成分以达缓释作用, 实现配伍减毒增效[27,30,34,35,43-46]。Guo 等[27,43]分析了马钱子–甘草药对配伍汤液不同相态中毒效物质的变化规律, 结果发现马钱子单煎液不同相态中马钱子碱和士的宁量的分布呈现相同变化规律, 即胶体组 > 溶液组 > 沉积物组 > 混悬组, 而与甘草配伍汤液不同相态马钱子碱和士的宁的分布为沉积物组 > 胶体组 > 混悬组 > 溶液组; 进一步的体外释放研究发现, 马钱子配伍甘草后的沉积相态主要毒效成分士的宁呈现明显的缓释特性, 这表明马钱子与甘草配伍合煎形成的具有缓释作用的沉积相态是两者配伍减毒增效的关键形式。此外, 附子–甘草也存在相似的配伍减毒机制[30,34,35,44-46], 一方面, 甘草酸可以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[27,30]; 另一方面, 甘草蛋白–乌头碱自组装形成的纳米粒可以显著降低乌头碱的毒性[34,35]。

3 基于分子自组装的甘草配伍禁忌机制研究

中药十八反有言“藻戟遂芫俱战草”, 指的是海藻、大戟、甘遂、芫花和甘草不宜配伍合用[47]。甘草各组分自组装增溶促吸收作用也可能增加毒性成分的溶解溶出及吸收, 从而产生配伍增毒作用。因此, 甘草各组分及其与反药毒效成分的分子组装也是甘草配伍禁忌的物理结构基础[47]。甘草中的皂苷、多糖、蛋白等成分可与“藻戟遂芫”中的诸多成分自组装形成超分子复合物, 从而促进毒性成分溶出、抑制毒性成分代谢或抑制有效成分溶出等产生增毒减效的的配伍禁忌[47,48]。Yang 等[18]研究发现芫花乙酸乙酯部位与甘草酸共煎煮后可以形成分布均匀的纳米颗粒, 增加毒性成分芫花酯甲的溶出, 并增强其对 L-02 细胞的细胞毒作用; 进一步研究表明, 芫花与甘草酸自组装形成的超分子复合物含有 58 种化学成分 (8 种二萜类、35 种黄酮类、5 种苯丙烷类、4 种核苷、2 种氨基酸和 4 种其他化合物), 其中甘草酸与芫花碱可通过疏水作用自组装形成纳米复合物, 从而增强细胞毒作用[26]。

4 基于分子自组装的甘草组分创新制剂设计与药物递送应用研究

甘草各组分的自组装特性, 不仅可以揭示甘草配伍的机制, 还可以用于药物递送的创新制剂设计。当前主要的文献报道集中在甘草酸、甘草蛋白及甘草多糖等成分的自组装创新制剂设计及药物递送研究[49,50], 如表 2[38,49,51-71]所示。

4.1 基于甘草酸自组装的创新制剂设计与应用

甘草酸是由一分子甘草次酸和两分子葡萄糖醛酸构成的皂苷类成分, 具有两亲性, 在一定条件下能够在水溶液中自组装形成具有疏水性内腔的胶束或凝胶, 也可作为纳米晶药物的稳定剂, 递药应用广泛[50]。

4.1.1 胶束 甘草酸胶束不仅可以增加难溶性药物的溶解度, 还可通过 P-gp 抑制及调节细胞膜流动性等促进药物的跨膜吸收[12]。Yang 等[52]研究发现甘草酸胶束可使紫杉醇的口服生物利用度增加 6 倍, Cai 等[53,72]开发的可注射载羟基喜树碱甘草酸胶束可改善其溶解性, 并显著增强抗肿瘤效果。除上述药物外, 甘草酸胶束还用于丹参酮 IIA[51]、黄芩素[54]、多柔比星[55]、穿心莲内酯[56]、吴茱萸碱[57]、甘草查尔酮 A[58]和姜黄素[59]等多种难溶性或难吸收药物的递送, 以改善这些药物的溶解或吸收, 增强疗效。

4.1.2 水凝胶 甘草酸在溶液中可以自组装形成水凝胶, 也可以分别与小分子化合物、聚合物分子、金属离子等共同组装形成水凝胶[59,73]。研究表明, 甘草酸在质量浓度 5～60 mg·mL^{-1} 均可自组装形成凝胶, 可显著增加黄芩素、橙皮苷等难溶性药物的溶解度, 并具有缓释作用[60,61]。此外, 甘草酸具有抗病毒、抗炎、抗菌等药理作用, 其自组装水凝胶在抗病毒、抗菌及促进伤口愈合的药物递送应用中具有协同增效作用[62,63,74-78]。Song 等[62]开发了一种甘草酸和麻黄碱共组装纳米凝胶, 可增加麻黄碱的口服生物利用度并维持相对稳定的血药浓度, 且能够阻止呼吸道合胞病毒 (respiratory

Table 2 Advanced drug delivery systems based on molecular self-assembly of *Glycyrrhiza* components

Glycyrrhiza component	Innovative preparation	Loaded drug/cargo	Function and application	Ref.
Glycyrrhizic acid	Micelle	Paeoniflorin	Enhancing permeability of drug in duodenum, jejunum, ileum and colon intestine and promoting oral absorption	[38]
		Tanshinone IIA; paclitaxel	Enhancing drug dissolution, oral bioavailability and anti-tumor effect	[51,52]
		Camptothecin	Enhancing drug dissolution, stability and anti-tumor effect	[53]
		Baicalein	Increasing solubility and controlling release	[54]
		Doxorubicin; andrographolide	Enhancing drug dissolution, and anti-tumor effect	[55,56]
		Evodiamine	Enhancing drug solubility, anti-hepatic fibrosis activity and can be sustained-release	[57]
		Licochalcone A	Enhancing penetration of drug to the epidermis and synergistic whitening effect	[58]
		Curcumin	Enhancing drug stability, and antioxidant properties	[59]
	Hydrogel, nanogel	Baicalein	Enhancing solubility and can be sustained-release	[60]
		Hesperidin	Enhancing solubility, *in vitro* release rate and can be sustained-release	[61]
		Ephedrine	Enhancing cellular uptake of drug, bioavailability and the effect of inhibiting respiratory syncytial virus	[62]
		Berberine	Enhancing drug anti-ulcerative colitis effect	[63]
	Nanocrystal	Andrographolide	Enhancing solubility	[64]
		Baicalin	Enhancing solubility and absorption	[65]
		Herpetrione	Enhancing drug dissolution and oral bioavailability, and synergistic hepatoprotective effect	[66]
GRR protein	Nanoparticle	Astragaloside	Enhancing solubility	[49]
		Curcumin	Enhancing solubility and stability, with improved cellular antioxidant activity in RAW 264.7 cells and anti-tumor efficacy against HepG2 cells	[67]
		Dexamethasone	Ameliorate the immune microenvironment and mitigate tissue damage	[68]
		Baicalin; paeoniflorin; liquiritin	Ameliorate psoriasiform manifestations and decrease pro-inflammatory cytokine concentrations in the serum of murine psoriasis models	[69]
GRR polysaccharide	Nanoparticle	Licoricchalcone A	Enhancing permeability and therapeutic of drug on atopic dermatitis-like skin	[70]
	Hydrogel	Rhein	Enhancing antioxidant, anti-inflammatory properties and can be pH-controlled drug release	[71]

syncytial virus, RSV) 吸附到宿主细胞上, 从而显著抑制RSV的增殖, 减轻病毒感染引起的肺部损伤。Lei等[63]设计构建了一种小檗碱和甘草酸自组装无载体水凝胶, 在治疗溃疡性结肠炎方面具有显著的抗炎活性; 与阳性药美沙拉嗪、甘草酸或小檗碱单药相比, 该自组装水凝胶能更有效的改善溃疡性结肠炎的各项指标。

4.1.3 纳米晶 纳米晶是由少量表面活性剂或聚合物稳定的纯药物结晶纳米粒, 主要用于难溶性药物的递送[79]。甘草酸作为一种天然表面活性剂, 可以与难溶性药物相互作用共组装形成纳米晶粒子。目前, 甘草酸已用于波棱甲素[2]、穿心莲内酯[64]、黄芩苷[65]和槲皮素[80]等多种难溶性药物纳米晶的制备, 可以显著改善药物的溶出和吸收。此外, 甘草酸的抗炎保肝作用, 可以协同增强波棱甲素的保肝活性[68], 而肝细胞表面存在的甘草酸及其代谢产物甘草次酸的特异性受体, 使其可以实现槲皮素纳米晶的肝靶向递送[80]。

4.2 基于甘草蛋白自组装的创新制剂设计与应用

甘草蛋白组分可以自组装形成纳米粒, 用于药物递送, 是一种很有前景的天然生物活性纳米材料[49,67-69]。甘草蛋白纳米粒可以增加难溶性药物的溶解度, 改善生物利用度, 增强疗效。Zhou等[49]从甘草水煎液中分离得到分子质量为28 kDa甘草蛋白, 并基于热诱导优化组装形成纳米粒, 该纳米粒可以包封黄芪甲苷, 并显著增加其溶解性。Wang等[67]构建了在姜黄素甘草蛋白自组装纳米粒, 该纳米粒主要通过疏水作用驱动形成, 能够显著增加姜黄素的溶解度、光化学稳定性及在不同pH值、储存和生理条件下的稳定性, 并增强姜黄素在RAW 264.7细胞上的细胞抗氧化活性及对HepG2细胞的抗肿瘤活性。Li等[69]在分离和分析清血除湿合剂抗银屑病纳米粒的物质组成基础上, 以甘草蛋白为载体构建了共载黄芩苷、芍药苷和甘草苷的甘草蛋白自组装纳米粒, 该纳米粒可以显著缓解银屑病样症状, 并降低银屑病小鼠模型血清中促炎因子的水平。甘草蛋白纳米粒还可以通过介导中性粒细胞原位凋亡和巨噬细胞外泌作用, 实现炎症免疫调节, 递送抗炎药物用于急性炎症治疗。Liu等[68]开发了一种负载地塞米松的甘草蛋白纳米粒, 可通过结合原位中性粒细胞凋亡和巨噬细胞外泌作用, 在急性呼吸窘迫综合征和败血症的小鼠模型中, 显著改善紊乱的免疫微环境, 并减轻组织损伤。

4.3 基于甘草多糖自组装的创新制剂设计与应用

甘草多糖水溶性较好, 不易单独自组装形成纳米粒, 但其可以和其他成分相互作用组装形成纳米粒, 用于药物递送。Chen等[70]采用微沉淀法构建了甘草查尔酮A-甘草多糖自组装纳米粒 (GPA-SANs), 并探讨了其在健康及二硝基氯苯诱导的特应性皮炎Balb/c小鼠的皮肤渗透性差异, 结果表明, GPA-SANs对特应性皮炎小鼠的皮肤的渗透性更强。Yang等[71]从甘草中分离得到一种中性均质多糖GP1-2, 并探讨了Ca^{2+}与GP1-2交联凝胶化的能力, 进一步制备了GP1-2的Ca^{2+}交联物理水凝胶, 结果发现GP1-2-Ca^{2+}水凝胶具有非凡的粘弹性、细胞相容性、抗氧化性、抗炎活性和促进伤口愈合能力, 能够包封大黄酸, 并显示pH依赖的释放特性; GP1-2-Ca^{2+}水凝胶具有载体材料和生物活性成分的双重作用, 显示了良好的药物递送潜力。

5 结语与展望

运用现代科学技术科学诠释中医药原理一直是传承创新发展中医药、推进中医药现代化的关键。甘草临床上不仅与中药配伍, 也可与化学药物联用, 应用十分广泛, 具有很高的临床价值。近年来, 甘草调和诸药的作用机制及创新应用研究受到广泛关注, 尤其是甘草各组分的自组装特性及其在揭示甘草配伍机制及药递送中的应用。现代研究表明, 甘草化学成分甘草酸、甘草蛋白、甘草多糖等均可参与自组装, 从而促进有效成分或抑制毒性成分的溶解、吸收, 发挥配伍增效减毒作用; 而其具有的载体材料和生物活性成分的双重作用, 在递送药物时不仅能改善药物的溶解或吸收, 还能发挥协同增效作用, 显示了良好的药物递送潜力。

目前, 大多数研究都是针对甘草某一 (类) 成分的自组装特性及作用展开, 一定程度上可以揭示甘草的配伍机制, 但甘草不同成分的相互组装对配伍药味效应成分溶解、吸收和生物活性有何影响、体内转运过程中甘草成分自组装聚集体的结构变化规律及与成分迁移是否相关、甘草成分自组装聚集体的配伍增效减毒作用是不同成分的药效协同还是特定自组装聚集体结构的贡献等诸多问题尚未明确, 仍无法完全诠释甘草配伍理论的科学内涵。因此, 针对以上问题, 未来研究应重点围绕以下方面开展: ①系统开展甘草不同配伍复方汤液超分子组装结构的分离和解析, 研究甘草不同配伍超分子组装结构的物质组成与形成机制, 评价超分子组装结构的增溶、促吸收作用及生物活性, 明确甘草不同成分的超分子组装结构、功能及对配伍药味效应成分溶解、吸收和生物活性的影响; ②借鉴荧光探针标记、放射性同位素标记等技术, 结合HPLC-MS^n等定量分析技术, 同步追踪体内转运过程中甘草成分自组装聚集体的结构变化及相关指标成分吸收分布行为, 阐明体内转运过程中甘草成分自组装聚集体的结构变化规律及与成分迁移的相关性; ③通过“化学成分–超分子结构–生物活性”的关联研究与分析, 明确甘草成分自组装聚集体的配伍增效减毒作用, 运用药效协同与结构贡献的拆解实验, 评估超分子组装结构、物理混合物及单体成分的生物活性差异, 结合分子动力学模拟和数据整合建模, 量化超分子组装结构、物质组成等因素对甘草配伍增效减毒的贡献。此外, 源于数千年应用历史的中药虽然具有较好的安全性, 但由于物理结构和应用剂量的改变, 基于分子自组装的甘草组分创新制剂的安全性仍然不容忽视。系统评估甘草化学成分自组装创新制剂的安全性, 明确自组装体系的毒性风险, 有助于推动甘草相关成分的创新制剂系统设计, 为开发高效低毒的新型中药制剂奠定基础。

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