基于组分结构理论的中药炮制现代研究进展

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摘要 炮制是中药区别于天然药物的最主要特征,也是中医临床用药的特点,蕴含着丰富的科学内涵。由于中药化学成分的复杂性和多样性,多数中药的炮制机理尚不明确,亟待进行全面深入的研究。近年来,组分结构理论被提出并应用于指导中药研究,取得了一定的研究进展。本文系统探讨了在中药炮制机理研究中,借鉴组分结构理论的思路和方法,可以进行炮制过程的组分含量变化研究、组分体内过程研究、组分药效毒性研究、组分代谢组学研究等,并展望了组分结构理论在中药炮制机理研究中的应用前景。通过组分结构理论结合各种新方法和新技术,有望更好地研究揭示中药炮制机理,加快中药现代化的进程。

关键词 组分结构, 中药炮制, 机理

中医药是中华民族的宝贵财富,数千年来为中华民族的健康做出了不可磨灭的贡献,是人类文明的重要结晶。我国科学家屠呦呦从古籍中发现青蒿素,并因此而获得诺贝尔生理学或医学奖,让人们看到了创新中药研究的重要性^[1]。中药炮制和方剂配伍是中医药理论体系中最具特色的研究领域,其中揭示中药药效物质基础和作用机理是核心问题。中药的物质基础是由多种化学成分共同构成的,这些成分通过共同作用产生整体的功效,揭示这些化学成分之间的组合应用规律,对于揭示中药药效物质基础具有重要意义。

1 组分结构理论在中药研究中的应用

中药中的单体成分是最基本的单位,相似的单体成分按照一定的比例构成了组分,不同的组分又按照一定的比例构成了中药的整体。这些组分并不是简单的堆积,而是一个有序的整体,中药发挥药效强调的是其整体的协同作用。张伯礼课题组^[2]在长期开展组分中药研究的基础上,提出了组分中药配伍理论。该理论认为,中药组分来源于有效部位或部位群,是具有较高同质性的成分群或具有一定比例的组合物,其

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化学成分可识别,且各成分比例相对固定.组分中药配伍研究是在中医药理论指导下,按照配伍的原则,针对具体适应病证,将若干中药组分按照强化主效应、兼顾弱效应、减少副效应的配伍原则,进行配伍配比优化设计过程.中国药科大学贾晓斌课题组^[3]认为,“组分”是指成分间存在一定的量比关系,理化性质和药理活性相似的一类成分,不同的组分又按照一定的比例构成了中药的物质基础.这种构成中药整体的成分间、组分间的量比关系,称之为“组分结构”(图1),组分结构不同,功效也会有差异,合理的组分结构特征可以产生协同增效作用.

基于上述研究思路和方法,近年来,国内外专家开展了很多关于组分中药配伍的研究工作,从饮片、组分和成分等不同层面,揭示了基于组分结构理论可以实现中药的协同增效作用^[4].

1.1 不同饮片配伍

中医临床用药最常见的形式就是饮片配伍,将不同种类的中药饮片通过辨证论治,按照“君臣佐使”的原则配伍应用,最终起到协同增效的作用.这种饮片配伍应用的内在规律是饮片所含有的多类成分配伍组合,也属于组分配伍的存在形式.Wang等人^[5]研究了川芎和葛根不同配伍比例治疗偏头疼的作用,通过测定5-羟色胺等神经递质含量,结果显示,川芎、葛根两味药按照4:3配伍时,效果最好.黄芪和莪术配伍后,可以显著提高莪术中莪术醇、莪术烯醇和莪术二酮等6个脂溶性成分的溶出,组分结构发生变化,从而产生协同抗肿瘤作用^[6].

1.2 不同组分配伍

组分配伍既包括不同药物间组分配伍,也包括同一药物中不同组分的配伍,组分结构不同,药效作用就会有差异.因此,通过研究可以选择更优的中药组分结构,如研究显示,黄芪总苷组分和马鞭草总苷组分按照1:1配伍组合时,对缺血再灌注损伤大鼠模型的相关生化指标,具有更好的改善作用^[7].本课题组^[8]前期针对黄芪(A)、山茱萸(B)药对进行了组分配伍研究,建立了一种新的与生物活性相关联的UHPLC-Q-TOF-MS技术,可以快速筛选有效的组分(图2),结果发现黄芪中多糖组分、皂苷组分和黄酮组分,与山茱萸中环

图1 中药物质基础的结构层次^[3] (网络版彩图)

Figure 1 Structural levels of the substance base of traditional Chinese medicine (color online)

烯醚萜组分按照一定比例配伍效果最优,并且这一组分结构与药物本身固有的含量不同.单味药胡芦巴中的多糖组分、皂苷组分和黄酮组分按照3:6:1配伍时,能更好地调节I型糖尿病大鼠的血糖,保护大鼠的胰腺与肾脏组织,具有协同增效的作用^[9].

1.3 不同成分配伍

在组分配伍研究的基础上,进一步从各组分中筛选出活性单体成分,按照一定的比例组合,也会产生协同增效的作用.如复方黄黛片由青黛、雄黄和丹参等配伍组成,陈竺课题组^[10]分别选择其中的靛玉红、四硫化四砷和丹参酮II A三个成分进行配伍研究,结果发现,复方黄黛片中3个成分配伍后对急性早幼粒细胞白血病具有更好的效果,与传统中医药理论强调的君臣佐使有较好的对应关系(图3),受到了国内外同行的广泛关注.

近年来,有研究发现,牛蒡苷元、没食子儿茶素没食子酸酯(Epigallocatechin gallate, EGCG)与姜黄素配伍后应用,对于卵巢癌和乳腺癌细胞有更好的抑制作用^[11].丹参和黄芪中的丹参酮II A和黄芪甲苷IV按照1:5配伍时,对缺氧导致的心肌细胞损伤具有更好的保护作用,效果优于两成分单一应用的效果^[12].白藜芦醇和槲皮素按照1:2配伍联合使用,对高脂饮食肥胖大鼠模型肠道菌群有更好的调节作用,进而降低血脂,改善肥胖症状^[13].由此可见,药物组分结构变化,可以导致药效作用改变,而炮制过程可以改变药物的组分结构,因此,开展中药炮制过程组分结构变化规律研究,对于揭示炮制机理具有重要指导意义.

图 2 黄芪山茱萸组分配伍研究思路^[8] (网络版彩图)

Figure 2 Research ideas on component compatibility of *Radix Astragali* and *Cornus officinalis* (color online)

图 3 复方黄黛片成分配伍对急性早幼粒细胞白血病的作^[10] (网络版彩图)

Figure 3 Effects of compound Huangdai tablets on acute promyelocytic leukemia (color online)

表 1 炮制过程引起组分含量变化

Table 1 Component content changes caused by processing

序号	中药名称	炮制方法	分析方法	组分含量变化	参考文献
1	槟榔	炒焦	FTIR	挥发油类组分减少; 生物碱类组分中槟榔碱等含量降低	[20]
2	川芎	酒制	HPLC-DAD-MS	内酯类组分中洋川芎内酯A, H, I含量升高, 藁本内酯含量下降	[21]
3	地黄	酒蒸	UHPLC-TOFMS	环烯醚萜苷类组分中益母草苷等成分含量降低	[22]
4	何首乌	蒸制	RRLC/DAD/ESI-MS ⁿ	蒽醌类组分中大黄素等3个成分含量升高	[23]
5	黄芪	蜜制	UPLC/ESI-Q-TOF-MS	异黄酮类组分含量降低, 皂苷类组分含量升高	[24]
6	苦杏仁	炒制、燻制	HPLC-ESI-MS/MS	苷类组分中苦杏仁苷、苦杏仁酰胺和新苦杏仁苷含量比例变化	[25]
7	人参	蒸制	HPLC-ESI-MS/MS ⁿ	皂苷类组分发生脱水、脱羧、异构化等反应, 新产生11个成分	[26]
8	三七	蒸制	HPLC	皂苷类组分中人参皂苷Rg1等8个成分含量下降, 人参皂苷Rh1等5个成分含量升高	[27]
9	山茱萸	酒蒸	HPLC-MS/MS	环烯醚萜苷类组分中莫诺苷和山茱萸新苷含量下降	[28]
10	生姜	炒制	UPLC/QTOF-MS	挥发油组分中6-姜酚、8-姜酚和10-姜酚含量下降, 姜烯酚和姜酮含量升高	[29]
11	乌头	蒸煮	HPLC-Q-TOF-MS	脂肪型和双酯型生物碱类组分含量下降, 单酯型含量升高	[30]
12	延胡索	醋制	HPLC-DAD	生物碱类组分中原阿片碱和 α -别隐品碱含量下降, 四氢小檗碱等5个成分含量升高	[31]
13	芫花	醋制	UPLC-MS	二萜内酯类组分和黄酮类组分中16个含量降低, 18个含量升高	[32]
14	栀子	炒制	UPLC-ESI-QTOF	环烯醚萜苷类组分中京尼平苷等6个成分含量下降, 京尼平酸含量升高	[33]
15	自然铜	煅制	X射线衍射	元素类组分中Fe和Zn元素溶出增加, As元素溶出减少	[34]

表 2 炮制引起组分体内过程变化

Table 2 Processing induces changes of components *in vivo*

序号	中药名称	炮制方法	目标组分	分析方法	组分体内过程变化	参考文献
1	大黄	酒制	蒽醌类组分	LC-MS/MS	大黄酸吸收减少, 大黄素等5个成分吸收增加	[38]
2	黄芩	酒制	黄酮类组分	LC-MS/MS	在肺和心分布增加, 在肝、脾和肾的分布降低	[39]
3	五味子	酒制	木脂素类组分	UPLC-QTOF-MRM	吸收速度加快, 消除过程变慢, 体内过程延长	[40]
4	续断	酒制	酚酸类、皂苷类和环烯醚萜类组分	UPLC-MS/MS	隐绿原酸、马钱苷酸、马钱苷和续断皂苷VI的吸收显著增加	[41]
5	黄连	酒制	生物碱类组分	HPLC	组分中3个成分的达峰时间显著变化	[42]
6	芫花	醋制	二萜内酯类组分	UHPLC-MS/MS	芫花素等4个成分吸收增加, 芫花酯甲等2个成分吸收降低	[43]

步研究, 从而全面揭示中药的炮制机理. 乌头是一种有毒中药, 临床常采用蒸煮法炮制后使用. 研究发现, 在炮制过程中, 乌头中生物碱类组分发生显著变化, 双酯型生物碱水解生成单酯型生物碱, 毒性显著降低, 但镇痛和抗炎作用得以很好的保留, 甚至略有增强^[44]. 在炮制过程对组分结构与药效和毒性改变相关性研究方

面, 近年来代表性的研究成果见表3.

2.4 炮制过程引起组分代谢组学改变

近年来, 组学技术由于适用于研究复杂体系的整体性规律^[51], 逐渐引入到的中药现代研究中, 对于揭示中药作用机理起到了很好的作用. 在中药炮制机理

图 5 中药多组分药动学研究策略^[36] (网络版彩图)
Figure 5 Strategies for multicomponent pharmacokinetics of traditional Chinese medicine (color online)

表 3 炮制过程引起组分药效与毒性改变
Table 3 Changes in efficacy and toxicity of components during processing

序号	中药名称	炮制方法	主要组分变化	药效与毒性变化	参考文献
1	附子	蒸煮	生物碱类组分结构改变, 发生水解反应	对大鼠肝脏线粒体代谢活性作用减弱	[45]
2	甘草	蜜制	多糖类组分结构改变	促进肠道上皮细胞分泌粒细胞击落刺激因子	[46]
3	何首乌	蒸制	蒽醌类组分结构改变, 发生分解反应	改善脂肪变性干细胞的脂肪代谢	[47]
4	黄芪	蜜制	多糖类组分结构改变, 单糖组成变化	促进干扰素- γ 、白介素- 1β 等分泌, 抗炎作用增强	[48]
5	黄芩	酒制	黄酮类组分结构改变, 含量升高	酒制后对模型大鼠缓解偏头痛作用增强	[49]
6	甘遂	醋制	萜类组分结构改变, 发生分解反应	醋制后对斑马鱼胚胎模型毒性降低	[50]

研究中, 采用代谢组学方法, 有助于揭示炮制过程对组分药效及毒性作用影响的机理^[52]。钟凌云等人^[53]采用 UPLC-TOF-MS 高分辨质谱联用技术, 研究黄连炮制前后组分变化对大鼠尿液代谢组学的影响, 结果显示, 黄连经姜汁炮制后, 生物碱类组分含量变化, 进而对其能量代谢产生显著影响, 确定了肌氨酸、马尿酸、L-色

表 4 炮制过程引起组分代谢组学变化

Table 4 Metabolomic changes of components caused by processing

序号	中药名称	炮制方法	主要组分变化	分析方法	代谢组学变化	参考文献
1	甘遂	醋制	萜类组分结构改变	¹ H-NMR	炮制品与糖代谢和氨基酸代谢有关	[54]
2	何首乌	蒸制	蒽醌类组分变化	HPLC-MS	16个生物标志物有变化, 涉及色氨酸代谢等3个通路	[55]
3	川乌	蒸煮	生物碱类组分变化	UPLC-Q-TOF-HDMS	甘油磷脂等4条代谢通路发生变化	[56]
4	乌头	蒸煮	生物碱类组分改变	UPLC-Q-TOF-HDMS	15个生物标志物变化, 涉及脂肪酸等4条代谢通路	[57]
5	附子	蒸煮	生物碱类组分变化	LC-Q-TOF-MS	代谢标志物甜菜碱含量升高, 磷脂酰胆碱含量下降	[58]
6	芫花	醋制	二萜内酯类组分变化	UPLC-MS	8个生物标志物发生变化, 涉及色氨酸等代谢通路	[59]

氨酸等9个生物标记物, 这些变化是黄连炮制前后抗炎作用差异的机理. 近年来, 国内多个课题组开展了甘遂、何首乌等炮制机理的代谢组学研究, 取得了一定的成果(表4).

3 总结与展望

中药炮制过程可以改变药物的组分结构, 这种改变既包括组分内部成分含量的变化和结构的改变, 还包括不同组分间配伍比例的变化. 因此, 基于组分结构理论以及多种研究思路和方法, 对于揭示中药炮制过程中组分结构的变化以及与药效作用的相关性规律, 进而揭示中药炮制机理具有重要的意义. 近年来, 国内外专家基于组分结构理论对地黄、人参等中药炮制机理已经开展了较为深入的研究^[60,61].

中药是由多成分组成的复杂体系, 其炮制机理研究要基于整体性研究的思路, 在进行炮制对组分结构影响及与药效作用相关性研究中, 可以采用谱效关系的研究思路和方法. 目前, 已经有研究采用谱效关系的研究方法揭示半夏炮制后止咳作用的药效物质基础^[62]. 此外, 也有研究采用网络药理学结合代谢组学方法, 从整体上研究揭示款冬花醋制前后药效物质基础及炮制机理^[63].

通过将组分结构理论应用于中药炮制研究, 有利于全面揭示中药炮制机理, 进而指导中药炮制工艺研究和饮片质量标准研究, 为临床提供优质的中药饮片. 同时, 在具体研究过程中, 采用谱效关系和代谢组学等整体性研究思路和方法, 有助于揭示中药的药效物质基础和作用机理, 为中药炮制研究提供更为理想的思路和方法, 加快中药的现代研究进程.

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Research progress of traditional Chinese medicine processing based on component structure theory

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Processing is the main characteristic of the products used in traditional Chinese medicine (TCM), and this is how they differ from natural medicines. The characteristics of the medicines used in TCM have rich scientific connotations. Because of the complexity and diversity of TCM, the processing mechanism has not been fully elucidated. In recent years, the theory of component structure has been put forward and applied to guide TCM research, resulting in substantial progress. This paper presents a systematic review of mechanism research in TCM processing. It can be used as a reference of the ideas and methods of component structure theory for studying component content changes caused by processing, for studying *in vivo* changes in components caused by processing, for studying the effects and toxicity changes in components caused by processing, for studying metabolic changes of components caused by processing, and for developing component structure theory in the study of the mechanism of TCM processing. Combining component structure theory with various new methods and technologies will enable better understanding of the processing mechanisms of TCM and speed up the modernization of TCM.

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