肠道菌群β-葡萄糖醛酸苷酶与中草药的互作关系研究进展

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摘要: 口服中药在吸收入血前与肠道菌群的互作是中药发挥整体作用的重要机制, 也使得对中药的研究有别于以系统暴露 (入血水平) 为起点和核心的西药的研发。肠道菌群与宿主代谢互补, 共同参与众多内源性生物活性分子的代谢平衡及外源成分的体内处置。其中, 肠道菌群中广泛分布的β-葡萄糖醛酸苷酶 (gut bacterial β-glucuronidases, BGUSs) 与宿主尿苷二磷酸葡萄糖醛酸转移酶 (UDP-glucuronosyltransferases, UGTs) 协调互作, 调节内外源化合物肝肠循环, 通过影响葡萄糖醛酸化稳态, 改变其肠道局部和/或系统暴露, 对疾病的发生及干预发挥作用。一方面, 许多中草药 (Chinese herbal medicines, CHMs) 成分发生肝肠循环; 另一方面, CHMs可直接作用于BGUSs或通过对肠道菌群结构的广泛影响间接改变其分布和功能。BGUSs和CHMs之间的多重互作可能在CHMs的整体治疗益处中发挥重要作用。本综述首先概括了BGUSs的最新研究进展; 进而根据BGUSs的底物谱从营养利用、代谢稳态、治疗响应等多层面解读BGUSs介导内外源化合物代谢的生理、病理及药理意义; 最后, 整合文献, 总结BGUSs与CHMs的多重互作关系。

关键词: β-葡萄糖醛酸苷酶; 肠道菌群; 中草药; 葡萄糖醛酸化稳态; 肠黏膜屏障; 代谢稳态; 系统暴露

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Research progress on the interactions between gut bacterial β-glucuronidases and Chinese herbal medicines

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Abstract: In traditional oral practice, the presystemic interactions with gut microbiota is an important mechanism underlying the holistic health benefits of Chinese herbal medicines (CHMs), making the study of CHMs distinct from the research of Western medicines of which the systemic exposure (level in blood) is the starting point and the core. Gut microbial metabolism complements host metabolism in maintaining metabolic homeostasis of many biologically important endogenous molecules and the disposition of numerous exogenous compounds. Among them, the widely distributed gut bacterial β-glucuronidases (BGUSs) coordinate with host UDP-glucuronosyltransferases (UGTs) to play a role in the occurrence and intervention of diseases by affecting the glucuronidation homeostasis and altering the intestinal local and/or systemic exposure of endogenous compounds and xenobiotics. On one hand, many ingredients of CHMs undergo enterohepatic circulation; On the other hand, CHMs can act on BGUSs directly or indirectly change the distribution and function of BGUSs through reprogramming gut microbiome. The multiple interactions between BGUSs and CHMs may play an important role in the overall therapeutic benefits

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of CHMs. This work firstly summarizes the latest research progress on BGUSs; then the physiological, pathological and pharmacological significance of BGUSs are exemplified with representative endogenous and exogenous compounds from the aspects of nutrient utilization, metabolic homeostasis, and therapeutic response based on the varied substrate spectra of BGUSs; finally, the scattered data in literature were integrated to summarize the multiple interactions between BGUSs and CHMs, highlighting the important role of BGUSs in the holistic actions of CHMs.

Key words: *β*-glucuronidase; gut microbiota; Chinese herbal medicine; glucuronidation homeostasis; gut mucosal barrier; metabolic homeostasis; systemic exposure

肠道菌群通过神经、内分泌、免疫、体液和代谢等多种途径在器官间建立双向或多向联系, 在宿主健康与疾病中扮演重要角色[1]。其中, 肠道菌群与宿主间的代谢性互作通过调节机体代谢稳态、参与塑造宿主代谢表型, 最终影响其营养利用、健康状态、疾病进展、药物治疗响应等[2]。

肠道菌群数目巨大、种类丰富, 具有强大的代谢能力, 主要通过催化水解及还原反应, 与宿主代谢系统介导的结合与氧化反应形成功能互补, 协调大量内源性物质的代谢稳态和外源性成分 (食物、药物、环境化学物等) 的体内处置[3,4]。此外, 肠道菌群通过其外膜囊泡或代谢物等参与调控宿主的代谢和转运系统[5-7]。胆红素、甾体激素类、神经递质、胆汁酸、炎性介质等多种重要的内源性生物活性分子、大量食源性成分、许多药物 (40%～75%)[8]及环境化学物进入体内后, 在宿主肠道或肝脏尿苷二磷酸葡萄糖醛酸转移酶 (UDP-glucuronosyltransferases, UGTs) 作用下, 通过结合内源性葡萄糖醛酸分子, 生成极性更强、水溶性更高的代谢物, 促进其从尿液或胆汁中排泄。*β*-葡萄糖醛酸苷酶 (*β*-glucuronidase, GUS) 是一类重要的水解酶, 催化*β*-葡萄糖醛酸苷键的断裂, 在人和多种肠道菌中均有表达 [人 GUS: human GUS (hGUS); 肠道菌 GUS: gut bacterial GUSs (BGUSs)]。宿主UGTs催化产生的葡萄糖醛酸结合物经过胆汁排泄进入肠腔, 在BGUSs作用下发生去结合, 提高原型 (苷元) 分子的局部暴露, 促进其在肠道的再激活及重吸收[9], 增加系统暴露, 使药效增强或产生毒性[3]。目前, 已知多种疾病、药物治疗、饮食等因素能引起肠道菌群结构和/或功能的改变, 影响宿主−肠道菌代谢轴, 包括UGTs-BGUSs轴介导的葡萄糖醛酸化稳态, 后者进一步对疾病进展、治疗响应等产生影响[10,11]。

1 BGUSs的分布及结构

BGUSs在肠道菌群中分布广泛, 主要存在于厚壁菌门、变形菌门、疣微菌门和拟杆菌门中。已从人肠道菌中鉴定出大约300种不同的BGUSs蛋白[12]。2010年, Redinbo团队[13]首次报道了大肠杆菌 (*Escherichia coli*, *E. coli*) 来源的GUS蛋白 (*Eco*GUS) 的晶体结构, 通过与hGUS蛋白的序列进行比对, 发现两者结构中预测*α*/*β*水解酶折叠的活性位点和核心区域序列高度保守, 而临近活性位点的loop结构序列为*Eco*GUS蛋白独有, 存在高度可变性; 其后, 该团队根据loop区域序列的长度将人肠道BGUSs蛋白大致分为6类, 发现其中超过1/2的BGUSs并不具有loop结构 (no loop, NL)[14]。目前已有约20种BGUSs蛋白的晶体结构被报道, 显示作为四聚体的BGUSs蛋白其组成单元间通过多种不同方式交联[12]。研究数据显示, loop结构的差异不仅与BGUSs底物选择性存在一定联系, 也影响其被抑制的倾向性; 通常具有loop 1结构的BGUSs对小分子葡萄糖醛酸苷类底物的催化能力更强, 对BGUSs选择性抑制剂UNC10201652的敏感程度也更高[15]; 而loop结构更开放的BGUSs (如mini loop 1、loop 2、mini loop 2及NL类BGUSs) 可代谢大分子葡萄糖醛酸苷如乙酰肝素[14]; 此外, NL类BGUSs能特异性水解*N*-葡萄糖醛酸苷底物瑞格非尼葡萄糖醛酸苷 (regorafenib glucuronide)[16]。

2 BGUSs的功能

BGUSs在肠道菌中的广泛分布及结构的多样性使其功能具有复杂性。尽管现有数据显示BGUSs具有一定的底物偏好, 但其底物谱较宽且存在不同程度的交叉。通过催化不同底物的去葡萄糖醛酸反应, 可释放不同结构的苷元, 同时产生葡萄糖醛酸, 影响菌群结构及肠道微环境。

2.1 维持内源性成分的代谢稳态 UGTs-BGUSs轴参与诸多具有重要生理意义的内源性物质的代谢循环, 包括类固醇激素 (如雌激素、雄激素)、神经递质 (如多巴胺、去甲肾上腺素、血清素)、胆红素和胆汁酸等[17]。

雌激素受体在生殖系统及脑、肠、骨骼和脂肪等多种组织广泛表达, 雌激素的代谢水平会影响神经和骨骼发育、心血管系统健康等[18]。雌激素暴露增加与乳腺癌风险直接相关[19], 其在人胆汁和粪便中的回收率分别为20%～50%和1%～11%[20]。具备雌激素葡萄糖醛酸苷水解能力的BGUSs在肠道菌群中广泛分布, 在35种不同种属来源的BGUSs中, 17种可分别将雌酮-3-葡萄糖醛酸苷和/或雌二醇-17-葡萄糖醛酸苷代

谢为雌酮和雌二醇[21]。Plottel等[22]于2011年提出雌激素组 (estrobolome) 的概念以囊括与雌激素代谢相关的所有肠道微生物, 并推测能通过改变相关BGUSs的活性变化来影响雌激素循环水平。雌激素的代谢水平随年龄变化, 雌性小鼠随着年龄增长, GUS活性及血清雌二醇和雌酮水平急剧下降[23,24]。雌激素也会影响BGUSs水平, 游离型雌二醇对*Eco*GUS活性有抑制作用[25], 采用雌激素替代疗法 (结合型雌激素/巴多昔芬) 的患者的BGUSs活性显著降低, 这与厚壁菌门中乳酸杆菌科 (Lactobacillaceae) 和链球菌科 (Streptococcaceae) 的丰度减少及瘤胃球菌科 (Ruminococcaceae) 的丰度增加显著相关[14,26]。雄激素 (如睾酮和二氢睾酮) 在男性发育和前列腺生理中起关键作用。在正常两性小鼠的小肠中检测到高浓度葡萄糖醛酸结合型睾酮和二氢睾酮, 而远端肠道游离睾酮和二氢睾酮水平超过血清水平20倍, 无菌小鼠的远端肠道葡萄糖醛酸化的睾酮和二氢睾酮水平高, 而游离二氢睾酮的水平非常低; 类似地, 年轻健康的成年男性粪便中的游离二氢睾酮比血清中高70倍以上[27]。以上结果提示, 肠道BGUSs可能在维持雄激素代谢稳态中具有关键作用。肠道菌群可通过调节雄激素水平影响前列腺癌的发生及发展[28]。Pernigoni等[29]对两种不同的前列腺癌模型小鼠手术去势后再进行广谱抗生素处理, 发现与单一手术去势处理的小鼠相比, 联合抗生素处理的小鼠肿瘤体积显著变小且肿瘤生长迟缓, 表明肠道菌群会促进前列腺癌小鼠产生去势抗性; 机制研究发现, 某些肠道菌能直接合成雄激素, 部分肠道菌则通过BGUSs介导机制导致雄激素的重新释放。

胆红素是血红素代谢终产物, 也是葡萄糖醛酸化程度最高的内源性分子之一, 约16%、80%分别以单、双葡萄糖醛酸结合物形式存在于健康人胆汁中[17], 游离胆红素在总胆红素循环水平中占比小于0.01%[30]。游离胆红素水平增加可形成不溶性钙盐, 促进色素性胆结石的形成[31], 在新生儿高胆红素血症、黄疸和一些肠病中, 胆红素的循环水平也会显著增加[32]。GUS抑制剂能减少胆红素的肠肝循环[33], 向人胆汁中添加GUS抑制剂*D*-葡萄糖二酸-1,4-内酯 (*D*-glucaro-1,4-lactone) 可抑制BGUSs活性, 从而显著减少胆红素在人胆汁中培养的蛔虫卵表面的沉淀[34]。游离胆红素具有肠道蛋白水解酶抑制活性[35]。肠易激综合征患者感染后, 肠道菌群组成发生变化, 特别是*Alistipes*分类群减少, BGUSs介导的胆红素葡萄糖醛酸苷去结合反应降低, 使对肠道蛋白水解活性的抑制减弱, 导致肠屏障破坏, 产生内脏过敏。将过表达GUS的*E. coli*移植给小鼠可上调肠道局部游离胆红素的暴露, 抑制肠道蛋白水解活性, 维护肠屏障[10]。

BGUSs参与了多巴胺、去甲肾上腺素和血清素等内源性神经递质的代谢调控, 对保持胃肠道健康和节律性运动具有重要调节作用[33]。研究表明[36], 正常小鼠盲肠中的多巴胺、去甲肾上腺素和血清素水平是无菌小鼠的数倍。无菌小鼠定植GUS蛋白编码基因被敲除的*E. coli*菌株后, 其盲肠内容物中游离多巴胺和去甲肾上腺素水平显著低于定植野生型*E. coli*菌株的无菌小鼠[37]。在血清素与哺乳动物肝微粒体共孵体系中检测出血清素葡萄糖醛酸苷, 在该反应体系中加入GUS蛋白则使血清素葡萄糖醛酸苷消失[38]。

葡萄糖醛酸结合型胆汁酸占人尿液排泄胆汁酸的12%～36%[17]。结直肠癌 (colorectal cancer, CRC) 患者粪便中的BGUSs活性升高 (1.7倍)[39], 次级胆汁酸也增加[40]。与雌激素类似, 胆汁酸水平也会影响BGUSs活性。胆汁酸盐能抑制从大肠杆菌和产气荚膜梭菌提取的GUS蛋白的活性[41], 阻断大鼠的胆汁排泄则能显著降低其盲肠和直肠的BGUSs活性[42]。

2.2 介导外源性成分体内处置 宿主UGTs介导的葡萄糖醛酸化过程被认为是机体对异源性化合物的重要“解毒”机制[43]。食源性致癌物杂环胺类如PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine)、氨基-3-甲基咪唑[4,5-f]喹啉 (2-amino-3-methylimidazo[4,5-f]quinoline)、甲基偶氮甲醇 (methylazoxymethanol, MAM)等, 经I相代谢产生*N*-羟基衍生物与宿主DNA形成加合物, 导致DNA损伤, 与CRC和乳腺癌风险密切相关[44,45], 肝脏UGT1A催化*N*-羟基衍生物的葡萄糖醛酸化促进排泄, 而肠道BGUSs的水解则导致原型在肠道重新释放, 使致癌风险增加。多种GUS表达菌如*E. coli*、肺炎克雷伯菌 (*Klebsiella pneumoniae*)、产气肠杆菌 (*Enterobacter aerogenes*) 和粪杆菌 (*Faecalibacterium prausnitzii*) 能将PhIP葡萄糖醛酸苷水解为PhIP, 其中粪杆菌的转化活性高达93%[46]。MAM经UGTs-BGUSs轴作用被重新释放, 其在肠道进一步分解产生甲基重氮离子, 与宿主DNA形成具有高致突变性的加合物, 成为CRC重要的诱发因素[47]。三氯生是存在于多种消费品和工业产品中的一种抗菌化合物, 也是普遍存在的环境污染物。最近研究证明[11], loop 1型BGUSs介导了三氯生葡萄糖醛酸结合物的水解, 增加三氯生在结肠的暴露, 引发肠道炎症, 促进结肠炎相关CRC的发展。

对DrugBank数据库中的药物进行预测, 发现包括多种抗癌药物、非甾体类抗炎药 (non-steroidal anti-inflammatory drugs, NSAIDs) 及阿片类药物等至少100种药物经UGTs-BGUSs轴进行肠肝循环[48]; 已知

155种抗癌药物中有24种可发生葡萄糖醛酸化，其中21种引起胃肠道毒性[17]。CRC一线用药伊立替康(irinotecan, IRT)的体内活性形式7-ethyl-10-hydroxycamptothecin (SN-38)为拓扑异构酶I抑制剂，经由肝脏UGT1A-肠道BGUSs轴再激活，直接损伤肠黏膜，引起广泛的迟发性腹泻，成为其临床应用及疗效的限制因素[49]。IRT治疗本身也会改变菌群结构，影响BGUSs活性。大鼠经IRT处理后，GUS表达菌*E. coli*、葡萄球菌属(*Staphylococcus* spp.)和梭菌属(*Clostridium* spp.)的丰度增加[50]。BGUS抑制剂TCH-3562 (pyrazolo[4,3-c]quinoline derivative)可特异性抑制小鼠BGUSs活性，改善IRT的肠毒性而不影响疗效[49]。酪氨酸激酶抑制剂瑞格非尼(regorafenib)用于治疗肝细胞癌、胃肠道间质瘤和转移性CRC。由于瑞格非尼*N*-葡萄糖醛酸化发生在分子结构中间位置，空间位阻使其葡萄糖醛酸苷不易被具有loop结构的BGUSs代谢，但可被NL类BGUSs水解[13]。肠炎是NSAIDs临床常见的不良反应，30%～40%的服用者出现胃肠道黏膜损伤，50%～70%和60%～70%的长期服用者则分别出现小肠通透性升高和炎症[51]，BGUSs介导的去葡萄糖醛酸化被认为是NSAIDs导致胃肠道损伤的重要原因之一[52,53]。

2.3 影响肠道菌能量利用和菌群结构 BGUSs催化去葡糖醛酸化在肠道重新释放苷元，同时产生葡萄糖醛酸(glucuronic acid, GlcA)，后者可被多种肠道细菌利用为碳源。Martin等[54]从健康婴儿的粪便中分离出16种贪婪疮疱表皮杆状菌(*Cutibacterium avidum*)，其中5株被证实可代谢GlcA生成等比例的乙酸和丙酸。此外，沙门氏菌(*Salmonella Typhimurium*)[55]、*E. coli*[56]、产气肠杆菌(*E. aerogenes*)[57]、短乳酸杆菌(*Lactobacillus brevis*)[58]、多型拟杆菌(*Bacteroides thetaiotaomicron*)[59]、副溶血性弧菌(*Vibrio parahaemolyticus*)[60]也被证实具有代谢利用GlcA的能力。

在沙门氏菌和大肠杆菌内[61]，GlcA首先被己糖醛酸异构酶UxaC转化生成果糖酮酸，后者进一步被氧化还原酶UxuB和*D*-甘露糖酸水解酶UxuA催化生成2-羰基-3-脱氧-*D*-葡萄糖酸(2-keto-3-deoxy-*D*-gluconate, 2K3DG)，2K3DG再被激酶KdgK催化生成2-羰基-3-脱氧-6-磷酸-*D*-葡萄糖酸(2-keto-3-deoxy-gluconate-6P, 2K3DG-6P)，2K3DG-6P进入Entner-Doudoroff代谢途径，被醛缩酶KdgA催化生成丙酮酸和3-磷酸甘油醛。比较基因组学研究发现，大肠杆菌的GlcA代谢途径在其他γ变形菌如一些肠杆菌目、弧菌目和巴斯德氏菌目的菌株中是保守的[61]。此外，在枯草芽孢杆菌(*Bacillus subtilis*)[62]、解糖热解纤维素菌(*Caldicellulosiruptor saccharolyticus*)[63]和嗜热脂肪芽孢杆菌(*Bacillus stearothermophilus*)[64]中也鉴定出GlcA代谢基因*UxaC*、*UxuA*和*UxuB*，但这些菌代谢GlcA的能力有待验证。

不同肠道菌利用GlcA作为碳源的能力有差别，提示不同疾病中肠道GlcA水平可能影响菌群结构及肠道微环境。CRC患者粪便BGUS水平较健康个体显著增加[39]，GlcA水平也显著高于健康人[65]，健康个体粪便GUS活性则比炎症性肠病患儿高2.5倍[66]。运动障碍型帕金森患者的粪便GlcA及GUS表达菌埃希氏菌属水平显著高于以震颤为主和少动−强直表型的帕金森患者，推测GlcA和埃希氏菌属增加可能促进肠道内炎症环境并上调游离多巴胺和血清素水平，使运动障碍型患者表现出更频繁的多动症状和胃肠道功能障碍[67]。

2.4 维护肠屏障 GlcA是构成肝素的两种单糖之一。肝素是哺乳动物肠黏膜的重要组成成分，分布于肠道基底膜外侧，参与肠屏障的发育和维护及维持基底膜完整性[68]；肠道蛋白聚糖参与肠道的胚胎发育、促进上皮细胞生长和再生，并对细胞的成型和分化具有调节作用[69]，肝素也参与组成这些肠道蛋白聚糖的糖链。*B. thetaiotaomicron*、类鼻疽伯克氏菌(*Burkholderia pseudomallei*)和单形拟杆菌(*Bacteroides uniformis*)的GUS酶能水解肝素结构中的GlcA成分，破坏肠屏障[70-72]。GlcA也存在于包括细菌细胞壁、胞外多糖和荚膜等多种结构中。致病菌荚膜中的透明质酸成分能与宿主上皮细胞表面的透明质酸结合糖蛋白CD44结合，促进致病菌对上皮细胞的侵袭[73]，BGUSs能降解这些结构中的GlcA侧链[74]，抑制细菌对肠屏障的侵袭。此外，将*Eco*GUS经直肠给予葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导的结肠炎小鼠[75]，能显著缓解模型小鼠的症状，并增加肠道紧密连接蛋白的表达，增强肠道屏障。

2.5 影响肠道免疫反应 经BGUSs代谢转化的多个内源性代谢物如血清素、胆红素和20-羟基二十碳四烯酸(20-hydroxyeicosatetraenoic acid, 20-HETE)等，参与机体免疫调控。血清素是结肠炎发生的重要信号分子，其一方面通过激活树突状细胞促进炎症因子分泌；另一方面直接促进致病菌生长，抑制结肠上皮细胞产生β-防御素，导致肠道炎症长期存在[76]。游离胆红素能通过激活芳烃受体(aryl hydrocarbon receptor, AhR)和Mas-相关G蛋白偶联受体参与免疫调控[77]。BGUSs介导花生四烯酸代谢产物20-HETE的肠肝循环[78]。20-HETE在癌症中激活多种细胞内蛋白激酶、促炎介质和趋化因子。在侵袭性乳腺癌模型中，通过抑制20-HETE的体内合成能抑制癌细胞肺转移[79]。

肠道组织内胞外基质 (extracellular matrix, ECM) 的重塑同时涉及ECM成分的降解增加和肠道纤维化过度, 是炎症性肠病进展的决定性特征。透明质酸和硫酸软骨素蛋白聚糖 (chondroitin sulfate proteoglycans, CSPGs) 为ECM的重要组成部分。CSPGs具有增强白细胞迁移、激活白细胞、结合趋化因子/细胞因子等促炎特性[80]。透明质酸与CD44受体结合, 刺激动脉粥样硬化斑块中的炎症细胞向病灶募集[81]。BGUSs能降解硫酸软骨素和透明质酸结构中的GlcA成分[82]。

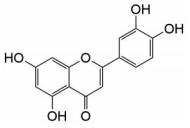
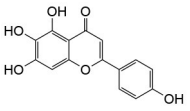
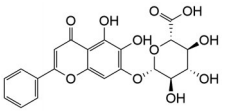
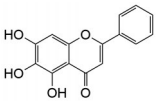
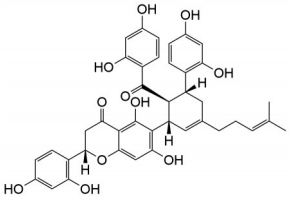
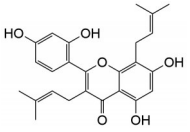
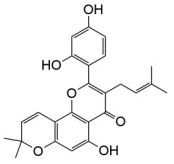
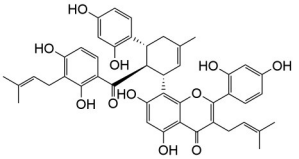
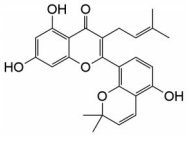
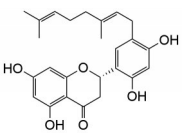
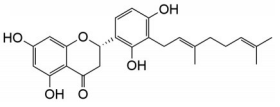
3 BGUSs与中草药的多重互作

3.1 BGUSs通过肠肝循环影响中草药成分的系统暴露 宿主UGTs-BGUSs或肠道菌糖苷酶类-宿主UGTs-BGUSs间的二元或三元代谢性互作在口服中草药的体内处置中扮演重要角色。中草药中广泛存在的糖苷类成分由于极性较强, 不易被吸收, 经肠道菌β-葡萄糖苷酶或BGUSs水解生成疏水性较强的苷元, 促进吸收或产生活性代谢物。大黄中蒽醌类化合物主要天然存在形式是葡萄糖苷, 口服后经肠道菌葡萄糖苷酶水解、肠/肝UGTs催化葡萄糖醛酸结合, 在体内主要以葡萄糖醛酸苷形式存在, 后者在肠道BGUSs作用下进行肝肠循环[83]。黄芩中的主要成分黄芩苷、汉黄芩苷、千层纸素A苷均为天然葡萄糖醛酸苷, 口服后在肠道中主要由BGUSs水解, 以苷元形式吸收, 后者经肠/肝UGTs再次生成原型, 入血或经肝肠循环, 使药−时曲线呈现典型多峰现象[84]。疾病或药物干预等造成的菌群扰动影响BGUSs分布及功能。DSS引起的慢性结肠炎大鼠其肠道BGUSs活性降低, 肠肝循环被抑制, 导致大黄蒽醌成分结合物的系统暴露降低[85]。胃肠动力障碍小鼠的肠道菌群紊乱, 小鼠口服枳实总黄酮糖苷 (主要含柚皮苷和新橙皮苷) 后的含药血清 (含有柚皮素及新橙皮素的葡萄糖醛酸结合物) 与*Eco*GUS共孵, 发现胃肠动力障碍小鼠血中柚皮素和新橙皮素的水平升高[86]。

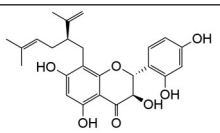
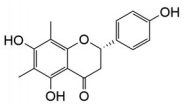
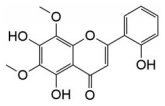
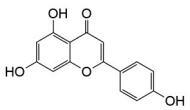
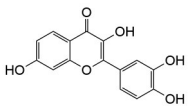
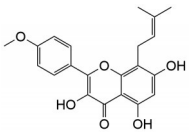
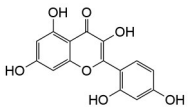
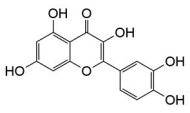
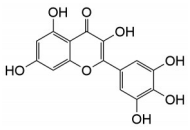
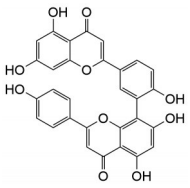
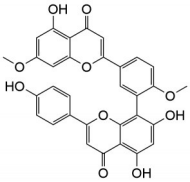
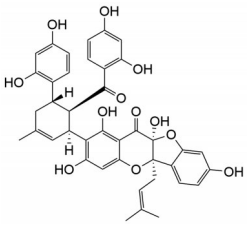
3.2 BGUSs代谢中草药成分引起增效或解毒 尽管葡萄糖醛酸化被普遍认为是“解毒”过程, 多种中药成分代谢产生的葡萄糖醛酸结合物具有重要的生物活性, 并是主要入血成分, 如中药黄芪主要黄酮成分毛蕊异黄酮7-氧-β-*D*-葡萄糖苷经肠道菌β-葡萄糖苷酶、肠肝UGTs共代谢, 生成的3′-葡萄糖醛酸苷是血中主要药物相关成分, 具有更强的促血管新生作用, 进行肠肝循环[87]; 白藜芦醇-3-*O*-葡萄糖醛酸苷能抑制*E. coli* O157: H7、*S. Typhimurium* 和 *Listeria monocytogenes* Scott A对结肠上皮细胞系Caco-2和HT-29的黏附, 表明其具有肠屏障保护作用[88]。将黄芩根提取物灌胃甲型流感病毒诱导的急性肺损伤小鼠, 可使其粪菌中拟杆菌和变形菌比例升高, 厚壁菌下降, BGUSs活性升高; 相应地, 粪便中检测到的葡萄糖醛酸苷类减少, 而具有抗补体系统活性的黄酮类苷元成分在肺肠局部及系统暴露增加[89]。黄芩汤 (黄芩、白芍、甘草、大枣) 在中医临床用于多种肠道疾病。黄芩汤制剂PHY906能通过增强Wnt信号通路介导的多重机制缓解CRC治疗药物IRT导致的肿瘤移植模型小鼠的肠道损伤, 经GUS酶处理后的黄芩水提物是PHY906 Wnt信号增强的最主要贡献者, UGT的过表达则抑制Wnt信号, 表明水提物经GUS水解产生的黄酮类苷元的Wnt信号增强作用更强[90]。七叶皂苷 (escin) 是三萜皂苷的天然混合物, 具有抗水肿特性, 临床应用产生肾毒性。七叶皂苷经与*Eco*GUS共孵后对肾近端肾小管细胞HK-2的毒性降低[91], 这与七叶皂苷经口服的肾脏不良反应低于静脉注射的临床观察结果一致。

3.3 中草药直接抑制BGUSs活性 一些中草药复方、提取物及多种化学成分具有BGUS抑制作用, 表1汇总了中草药抑制GUS活性的主要研究数据[92-102]。六味地黄丸能抑制BGUSs和肝溶酶体中的GUSs, 同时显著降低正常大鼠尿液中的两种代谢物染料木黄酮葡萄糖醛酸苷 (genistein glucuronide) 和大豆苷元葡萄糖醛酸苷 (daidzein glucuronide), 通过活性导向的分离, 鉴定出六味地黄丸中GUS抑制成分*D*-glucaro-1,4-lactone[103]。丁香水提物 (100 μg·mL^{-1}) 能完全抑制*Eco*GUS介导的PNPG (*p*-nitrophenyl-β-*D*-glucuronide) 水解, 从中分离出的尿石素M_5 (3,4,8,9,10-pentahydroxy urolithin), 通过结合在*Eco*GUS的非活性催化残基部位, 非竞争性抑制该酶对PNPG的水解[92]。卷柏乙醇提取物对*Eco*GUS水解SN-38G有良好的抑制作用, 从中分离得到的穗花杉双黄酮 (amentoflavone) 对*Eco*GUS介导的SN-38G和DDAOG (6,8-dichloro-7-hydroxy-9,9-dimethylacridin-2-one-β-*D*-glucuronide) 水解呈现强效抑制 (IC_{50}: 0.49和0.62 μmol·L^{-1}), 并在细胞水平上剂量依赖性抑制*E. coli* DH5α BRL和*Enterococcus faecalis* 20247_4 CHB对DDAOG的水解[97]。红茶乙醇提取物剂量依赖性抑制*Eco*GUS介导的PNPG和DDAOG水解 (IC_{50}: 4.60 μg·mL^{-1}), 其中7种儿茶素和茶黄素类多酚成分能强效抑制*Eco*GUS[95]。从虎刺梅全草中分离出7种新的二萜类化合物, 其中euphominoid C对*Eco*GUS水解PNPG活性有中等抑制作用 (IC_{50}: 45.87 μmol·L^{-1}), 是首个被报道的具有*Eco*GUS抑制活性的玫瑰烷型二萜类化合物[101]。从仙草中分离的亚麻酸 (linolenic acid) 能选择性抑制*Eco*GUS, 对宿主GUS没有作用[94]。

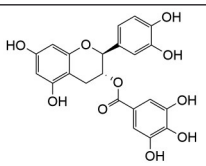
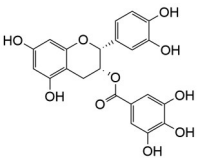
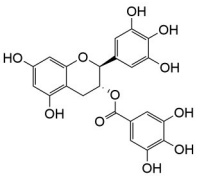
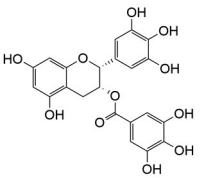
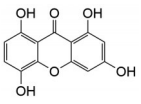
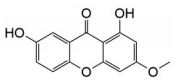
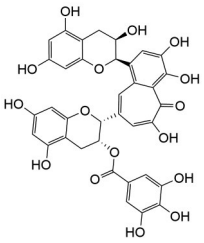
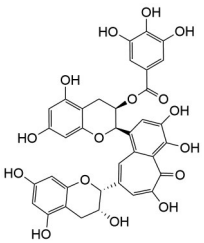
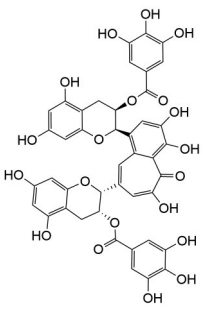
Table 1 *In vitro* inhibitory effects of Chinese herbal medicines and their components on gut bacterial *β*-glucuronidases (BGUSs). IC_{50}: Half-maximal inhibitory concentration; GUSs: *β*-Glucuronidases; PNPG: *p*-Nitrophenyl-*β*-*D*-glucuronide; DDAOG: 6,8-Dichloro-7-hydroxy-9,9-dimethylacridin-2-one-*β*-*D*-glucuronide; SN-38G: SN-38 glucuronide; 4-MUG: 4-Methylumbelliferyl-*β*-*D*-glucuronide; *Eco*GUS: *Escherichia coli* GUS; *Cp*GUS: *Clostridium perfringens* GUS; *Saga*GUS: *Streptococcus agalactiae* GUS; *Spas*GUS: *Staphylococcus pasteuri* GUS; −: Not detected; *: Inhibition rate

Chemical type	Chinese medicine compound	Structure	Substrate	Inhibition potency (IC_{50}/μmol·L^{-1})		Ref.
				*Eco*GUS	Other GUSs	
Flavonoid	Luteolin		PNPG	8.68 ± 2.02	−	[100]
				5.70	*Spas*GUS, 5.50; *Saga*GUS, 12.5	[98]
	Scutellarein		PNPG	5.76 ± 1.53	−	[100]
	Baicalin		PNPG	45.24	*Spas*GUS, 48.80; *Saga*GUS, 44.05	[98]
	Baicalein		PNPG	54.44	*Spas*GUS, 39.12; *Saga*GUS, 52.70	[98]
				5.76 ± 1.53	−	[100]
	Kuwanone G		PNPG	7.4 ± 1.6	*Spas*GUS, 0.98 ± 0.25	[99]
			PNPG	2.37 ± 0.11	−	[92]
	Kuwanone C		PNPG	4.27 ± 0.32	−	[92]
	Morusin		PNPG	5.59 ± 0.67	−	[92]
	Kuwanone H		PNPG	6.97 ± 0.97	−	[92]
	Kuwanone A		PNPG	7.92 ± 0.24	−	[92]
	Kuwanone E		PNPG	10.63 ± 0.32		[92]
	Sanggenol A		PNPG	3.27 ± 0.17	−	[92]

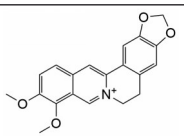
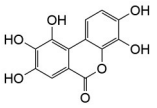
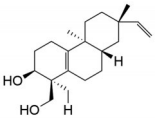
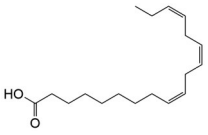
Continued

Chemical type	Chinese medicine compound	Structure	Substrate	Inhibition potency (IC_{50}/μmol·L^{-1})		Ref.
				*Eco*GUS	Other GUSs	
	Kushenol X		PNPG	2.07 ± 0.26	–	[96]
	(2*S*)-Farrerol		PNPG	8.95 ± 0.74	–	[96]
	5,7,2′-Trihydroxy-8,6′-dimethoxy flavone		PNPG	4.97 ± 0.61	–	[96]
	Apigenin		PNPG	156.42	*Spas*GUS, 48.03; *Saga*GUS, 30.14	[98]
	Fisetin		PNPG	2.02	*Spas*GUS, 10.83; *Saga*GUS, 76.58	[98]
	Icaritin		PNPG	29.43	*Spas*GUS, 76.57; *Saga*GUS, 7.59	[98]
	Morin		PNPG	11.89	*Spas*GUS, 8.36; *Saga*GUS, 76.81	[98]
			PNPG	1.12 ± 0.09	–	[92]
	Quercetin		PNPG	4.91	*Spas*GUS, 4.06; *Saga*GUS, 110.25	[92]
	Myricetin		PNPG	1.58	*Spas*GUS, 9.25; *Saga*GUS, 86.94	[92]
	Amentoflavone		PNPG	3.43	*Spas*GUS, 2.88; *Cp*GUS, 2.36	[93]
					*Saga*GUS, 2.88 ± 0.38	[92]
			SN-38G	0.49	–	[97]
			DDAOG	0.62	–	[97]
	Bilobetin		PNPG	> 100	*Cp*GUS, 1.32 ± 0.17; *Saga*GUS, 9.83 ± 2.62	[92]
	Sanggenon C		PNPG	12.5 ± 5.0	*Spas*GUS, 0.33 ± 0.05	[99]
			PNPG	2.07 ± 0.06	–	[92]

Continued

Chemical type	Chinese medicine compound	Structure	Substrate	Inhibition potency (IC_{50}/μmol·L^{-1})		Ref.
				*Eco*GUS	Other GUSs	
Catechin	(−)-Catechin gallate		SN-38G	1.48	−	[95]
			DDAOG	1.64	−	[95]
	(−)-Epicatechin gallate		SN-38G	6.94	−	[95]
			DDAOG	6.52	−	[95]
	(−)-Gallocatechin gallate		SN-38G	6.84	−	[95]
			DDAOG	4.02	−	[95]
	(−)-Epigallocatechin gallate		SN-38G	14.86	−	[95]
			DDAOG	16.52	−	[95]
Anthracene ketone	Demethylbellidifolin		PNPG	0.91 ± 0.11	−	[96]
	Gentisin		PNPG	0.68 ± 0.10	−	[96]
Theaflavin	Theaflavin-3-monogallate		SN-38G	1.92	−	[95]
			DDAOG	2.35	−	[95]
	Theaflavin-3′-monogallate		SN-38G	1.03	−	[95]
			DDAOG	0.77	−	[95]
	Theaflavin-3,3′-digallate		SN-38G	1.41	−	[95]
			DDAOG	0.48	−	[95]

Continued

Chemical type	Chinese medicine compound	Structure	Substrate	Inhibition potency (IC_{50}/μmol·L^{-1})		Ref.
				*Eco*GUS	Other GUSs	
Alkaloid	Berberine		4-MUG	54.04 ± 5.104	–	[102]
Tannic acid	3,4,8,9,10-Pentahydroxy urolithin		PNPG	2.70 ± 0.19	–	[92]
Diterpene	Euphominoid C		PNPG	12.5 ± 5.0	–	[101]
Fatty acid	Linoleic acid		PNPG	*68.27% ± 0.96%	–	[94]

一些研究以*Eco*GUS代谢为体外模型同时比较多个黄酮类成分的抑制作用, 尝试建立结构-活性(抑制)关系。Weng等[100]比较了30多种天然黄酮类化合物, 其中野黄芩素(scutellarein)、木犀草素(luteolin)、黄芩素(baicalein)、槲皮素(quercetin)和灯盏花乙素(scutellarin)对*Eco*GUS表现出强至中度抑制作用(IC_{50}: 5.76～29.64 μmol·L^{-1}), 而异黄酮类和二氢黄酮类对*Eco*GUS抑制较弱; A环上的连苯三酚结构有助于抑制*Eco*GUS, 甲氧基或糖基取代任一羟基则显著降低抑制作用; C-3羟基的存在也减弱抑制。另一研究以DDAOG水解反应为探针测定了36种黄酮类化合物对*Eco*GUS的作用, 发现苦参醇X (kushenol X)、(2*S*)-farrerol、5,7,2′-trihydroxy-8,6′-dimethoxy flavone、去甲基雏菊叶龙胆酮(demethylbellidifolin)和龙胆素(gentisin)抑制作用较强(IC_{50}: 0.68～8.95 μmol·L^{-1}), 去甲基雏菊叶龙胆酮和龙胆素的抑制作用表现为混合型(K_i: 4.05和2.02 μmol·L^{-1})[96]。

采用多个BGUSs组合, 发现中草药多种成分能特异或广谱抑制BGUSs。Bai等[92]系统评价了桑白皮、银杏中天然成分对BGUS的抑制作用, 发现银杏中的双黄酮成分白果素(bilobetin)和穗花杉双黄酮对3种菌源的loop 1型BGUSs都表现出较强的抑制性, 穗花杉双黄酮对*Cp*GUS (*Clostridium perfringens* GUS)、*Spas*GUS (*Staphylococcus pasteuri* GUS)和*Eco*GUS的IC_{50}为2.36～3.43 μmol·L^{-1}, 主要通过氢键作用与3个GUSs的变构位点紧密结合, 采用非竞争性机制剂量依赖性地抑制PNPG水解(K_i < 2 μmol·L^{-1})[93]。最近的一项研究[98]用3种不同分类来源的菌的loop 1型BGUSs水解PNPG的活性系统评估了21种黄酮的GUS抑制偏好, 发现多个化合物如黄芩素、黄芩苷(baicalin)、芹菜素(apigenin)、漆黄素(fisetin)、木犀草素、桑黄素(morin)、槲皮素、杨梅素(myricetin)具有作为广谱或特异性GUS抑制剂的应用潜力; *Eco*GUS和*Spas*GUS表现出非常相似的抑制倾向, 其效力与黄酮分子总羟基数、B环上的羟基数均呈正相关, 而分子对接分析则提示这些黄酮分子通过环A和/或C与GUS蛋白产生较强的互作; 但大多数受试化合物对*Saga*GUS (*Streptococcus agalactiae* GUS)表现为迟发性抑制及陡峭的剂量反应曲线, 该蛋白的loop 1区域形成α-螺旋, 导致空间位阻, 但提供了与黄酮C环上的羰基接触的疏水表面, 被认为是*Saga*GUS的变构抑制所必需。

狄尔斯-阿尔得(Diels-Alder, DA)加合物是桑属植物中的特征性成分, 结构新颖、复杂多样。Wei等[99]首次以人肠道细菌总蛋白和多个GUS表达菌为筛选工具, 发现桑根酮C (sangenon C)和桑黄酮G (kuwanon G)剂量依赖性抑制肠道菌混合总蛋白对PNPG的水解(IC_{50}: 12.5和7.4 μmol·L^{-1}), 均能强效抑制*Eco*GUS和*Spas*GUS (IC_{50}: 0.33～1.60 μmol·L^{-1})。

3.4 中草药调节BGUSs介导的内源性成分的代谢平衡 对宿主的代谢重建是中草药发挥整体治疗作用的重要机制。口服中草药可能通过直接作用于BGUSs和/或影响肠道菌群中GUS表达菌的丰度和多样性, 影响多种内源性生物活性分子的代谢平衡及葡萄糖醛酸化稳态。代谢组学分析显示, 一些内源性葡萄糖醛酸苷可作为中药发挥药理作用的生物标记物。例如, 在链脲佐菌素(streptozotocin, STZ)诱导的糖尿病模型

大鼠上证实胡芦巴类黄酮有抗糖尿病活性, 而五味子对糖尿病大鼠肾病并发症有一定改善作用, 这两种中药均能显著降低糖尿病模型大鼠血清中被上调的对甲酚葡萄糖醛酸苷 (*p*-cresol glucuronide)[104,105]; 类似地, 通心络对甲硫氨酸诱导的内皮功能障碍模型大鼠有内皮功能修复作用, 而广藿香油对2,4,6-三硝基苯磺酸诱导的结肠炎模型大鼠有明显的治疗效果, 尿液代谢组学表明它们同样显著降低两种模型大鼠中上调的对甲酚葡萄糖醛酸苷[106,107]。鸡血藤在抑郁模型大鼠上显示出抗抑郁作用, 同时鸡血藤能显著降低模型大鼠尿液中被上调的2-苯乙醇葡萄糖醛酸苷 (2-phenylethanol glucuronide) 水平[108]; 白藜芦醇能降低正常大鼠尿液中的甲苯基葡萄糖醛酸苷 (cresyl glucuronide)[109]; 而临床血浆代谢组学分析则证实, 与正常人相比, 滋肾育胎丸能显著上调不孕症患者的褪黑素葡萄糖醛酸苷 (melatonin glucuronide)[110]。在一些肠道疾病如溃疡性结肠炎、肠易激综合征的患者或动物模型体内均检测到内源性甾体激素的葡萄糖醛酸化水平的变化[111,112]。将黄芩水煎液灌胃给予DSS诱导的结肠炎大鼠, 发现黄芩改善模型动物疾病指数, 显著升高尿液中内源性甾体激素脱氢孕烯醇酮葡萄糖醛酸苷 (dehydropregnenolone glucuronide) 和雌三醇葡萄糖醛酸苷 (estriol glucuronide) 水平, 两者均与黄芩对肠道菌 *Acetatifactor* 属的上调呈强正相关[113]。

此外, 作为许多内源性/外源性化合物的常见“解毒”途径, 葡萄糖醛酸化过程可增加化合物的水溶性而促进排泄。某些中药的毒性可能与抑制相关成分的葡萄糖醛酸苷生成有关。例如, 草乌显著降低尿液中5-羟基-6-甲氧基吲哚葡萄糖醛酸苷 (5-hydroxy-6-methoxyindole glucuronide) 和3-吲哚羧酸葡萄糖醛酸苷 (3-indole carboxylic acid glucuronide, ICAG) 水平, 因此, 草乌的毒性可能部分源于其对宿主葡萄糖醛酸化解毒功能的抑制[114]。大黄提取物显著降低DSS诱导的结肠炎大鼠尿液中的ICAG, 可能是导致其升高模型大鼠疾病治疗指数的因素之一[113]。

BGUSs对多种食源性致癌物或环境化学物的再激活在结直肠癌发生中起重要作用。用复方肠胃清干预由偶氮甲烷和DSS联合诱导的肠炎相关癌症小鼠模型, 可改变肠道菌群组成, 下调模型小鼠中 *F. prausnitzii* 的相对丰度, 降低粪便菌BGUSs活性, 改善肠黏膜的完整性 (抑制 *D*-乳糖和内毒素的渗漏)[115]。

3.5 BGUSs介导中草药−西药互作 中草药对BGUSs的直接作用和/或对菌群结构的影响提示中草药可能直接或间接通过BGUSs介导的机制与一些具有肠肝循环的临床药物产生草药互作 (herb-drug interactions, HDIs), 影响药效或用药安全。黄芩汤制剂PHY906通过BGUSs代谢提升具有Wnt信号增强功能的黄酮类苷元水平, 而非阻断对BGUSs介导的IRT活性代谢物SN-38的再激活, 达到对联用的抗癌药IRT治疗荷瘤BDF1小鼠的增效减毒作用[90]。

加味香连汤 (白芍、黄芩、黄连、陈皮、茯苓、木香、黄柏、乳香、没药) 能部分逆转IRT对UGT1A1的抑制及对BGUSs活性的增强, 通过同时抑制SN-38G的产生及其去葡萄糖醛酸化, 降低SN-38在肠道的暴露, 缓解IRT引起的小鼠腹泻和黏膜损伤, 抑制相关炎症因子的表达[116]。给小鼠灌胃生姜泻心汤 (生姜、干姜、黄芩、黄连、半夏、党参、大枣、甘草) 能抑制肠道细胞凋亡和降低肠道BGUSs活性, 显著改善IRT在大鼠诱发的迟发性腹泻[117]。灌胃小檗碱 (berberine) 能有效抑制IRT处理小鼠的粪便样本中BGUS活性, 减少GUS产生菌, 减缓IRT诱导的肠黏膜炎小鼠模型中SN-38的产生[102]。

4 总结与展望

中草药与肠道菌群的互作是中草药传统口服应用发挥整体作用的关键环节。一方面, 肠道菌群的代谢转化是中药起效的枢纽, 决定了哪些成分入血、起效依赖于系统暴露水平, 哪些成分作用于肠道微环境 (肠道的菌群、黏膜、上皮等)、作用依赖于局部药物暴露, 从而使中草药整体作用有别于靶点明确但依赖于系统暴露的西药, 体现为“双轨制” (double-track mode), 即吸收前主要与肠道菌群间的互作产生的局部作用和入血成分的系统性作用的加和[87]; 另一方面, 人们已对肠道菌群结构失调与多种人类疾病发生发展的密切关联获得共识, 中草药成分的复杂性决定了其对菌群结构的改变是普遍的, 但对其引起的相应代谢功能的改变尚认识不足。因此, 从肠道菌群代谢的角度理解中草药整体作用的本质是用现代科学语言诠释中医药传统理论的关键切入点。

宿主与肠道菌群通过代谢性互补, 在宿主健康、疾病进展、营养利用与治疗响应中协调互作, 是疾病机制研究和药物靶标发现的新领域。作为宿主−肠道菌群代谢性互作的典型, UGTs-BGUSs轴通过调节葡萄糖醛酸化稳态, 影响许多内源性分子的循环水平和外源性成分的体内处置。BGUSs是促成多种中草药成分发生肝肠循环的主要代谢酶, 这在中草药体内处置研究中已获得共识; 目前, 多组学、生物信息学、成像等多学科手段的整合, 加快了对BGUSs结构多样性、分布广泛性、功能复杂性的深入认识[12], 但对其代谢中草药的研究仍较为宏观、粗放, 绝大多数研究采用总菌或总菌粗蛋白进行, 对中草药代谢的关键菌/关键酶的组群

特征的表征研究尚待开展, 相关发现将有助于在中草药的体内处置、治疗响应与个体的菌群结构、BGUSs分布之间建立关联, 丰富中草药临床个体化用药的科学内涵。

此外, BGUSs通过催化多种不同的内/外源性成分, 实现对不同结构的原型成分的再激活, 导致不同的代谢后果 (增加局部或系统暴露, 产生活性或毒性成分, 增效或引起不良反应等); 同时, 所有内外源成分的去葡萄糖醛酸化殊途同归, 产生GlcA。GlcA可为多种肠道菌群提供碳源, 也拥有广泛的生理、病理作用。近期对中草药中多种成分作为广谱或特异BGUSs抑制剂的报道提示, 可从中草药影响内外源物质葡萄糖醛酸化稳态的角度理解中草药的整体作用。但目前对中草药作为BGUSs抑制剂的关注, 多从药物代谢角度集中于与抗癌药联用的减毒增效, 仅少数研究探讨了其用于肿瘤预防和治疗的可行性[118]。

综上, 从影响葡萄糖醛酸化平衡的角度理解中草药的整体作用 (药效和毒性), 无疑将有助于加深对疾病机制的认识, 推动中草药的合理科学应用、创新应用。对BGUSs与中草药之间的多维互作的深入研究, 对推动复方配伍科学、中西药合用增效解毒也具有重要的指导意义。

作者贡献: 陈智强、汤帅、张畅煊、李婷、陈宏绮负责文章不同部分的文献搜集梳理、正文撰写、表格内容整理、格式检查及起草图文摘要; 燕茹负责统筹文章结构及内容, 撰写摘要及总结和展望, 指导写作, 审阅修改文稿并完善图文摘要。

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