“有毒”中药生物碱类成分的毒性及代谢研究进展

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摘要: 中药的“毒性”、安全性问题已成为舆论关注的焦点。生物碱 (alkaloids) 是许多种常用中药的主要药效成分, 很多生物碱类成分在较低的浓度表现出很强的生物活性; 但如使用不当, 也会引发毒副作用。这些生物碱类既是中药的“活性”成分又是“毒性”成分, 相关中药的安全性尤其值得注意。生物碱作用于有机体所产生的药效或毒副作用, 可能是原型成分及代谢产物共同作用的结果, 既与化合物的结构类型有关, 还具有明显的生物种属差异。本文以《中华人民共和国药典》中“有毒”中药所含生物碱类成分为研究对象, 查阅近20年来中外文献, 归纳、评述不同结构类型的代表性生物碱的代谢途径及代谢机制, 以期为含有此类成分中药的临床用药的安全性和有效性提供参考。

关键词: 中药安全性; 生物碱; 药物代谢; 减毒; 代谢酶

中图分类号: R917 **文献标识码**: A **文章编号**: 0513-4870(2023)11-3285-11

Advances on toxicity and metabolism of alkaloids from the "toxic" traditional Chinese medicines

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Abstract: The "toxicity" and safety of traditional Chinese medicines have been seriously concerned. Alkaloids are the main pharmacodynamic components of many kinds of traditional Chinese medicines, which show strong biological activity at low concentration. It will also cause toxic side effects but if used improperly. Some alkaloids are both active and toxic, and the safety of related traditional Chinese medicines is particularly noteworthy. The efficacy or toxicity of alkaloids may be the result of the combined action of parent compounds and metabolites, which is not only related to the structural types of compounds, but also has obvious species differences between humans and animals. This review focused on the alkaloids contained in the "toxic" traditional Chinese medicines that are officially recorded in Chinese Pharmacopoeia and the metabolism patterns of alkaloids with different structures as well as the enzymes involved were summarized and discussed by referencing the publications in recent two decades. The present study will be beneficial to the rational use of these traditional Chinese medicines in clinic.

Key words: safety of traditional Chinese medicine; alkaloid; drug metabolism; detoxification; metabolic enzyme

收稿日期: 2023-03-01; 修回日期: 2023-07-12.

基金项目: 上海市自然科学基金 (20ZR1473300, 23ZR1463200); 上海市人才发展资金 (2020099); 上海市卫计委三年行动计划 [ZY(2021-2023)-0215]; 上海中医药大学“杏林学者”计划 (B1-GY21-409-04-06).

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DOI: 10.16438/j.0513-4870.2023-0241

中药的“毒性”、安全性问题一直是人们关注的热点和焦点。既有因对“中药安全无毒”的盲目认知而导致中药滥用、误用, 也有部分不了解情况者甚至别有用心者对中药“毒性”的过度解读。其实中医对中药的“毒性”早有认识, 如《周礼·天官冢宰》言“医师掌医之政令, 聚毒药以供医事”;《神农本草经》收载中药365种, 分为上、中、下三品, 其中“下药一百二十五种为佐使, 主治病以应地, 多毒, 不可久服。欲除寒热邪气, 破积聚、愈疾者, 本〈下经〉”; 明代张景岳《类经》云“药以治病, 因毒为能, 所谓毒者, 因气味之有偏也……气味之偏者, 药饵之属是也, 所以去人之邪气, 其为故也, 正以人之为病, 病在阴阳偏胜耳 ..... 大凡可辟邪安正者, 均可称为毒药”。以上均论述了毒药的广义含义, 阐明“毒性”就是药物的偏性。历代本草及现行《中华人民共和国药典》将部分中草药标识为“大毒”、“有毒”、“小毒”, 则大都用于描述药性的毒副作用的大小, 一方面提示其中毒剂量与治疗剂量比较接近 (或某些治疗量已达到中毒剂量范围), 这些中草药临床应用的安全窗口较窄; 另一方面提示这些中草药可能对机体组织器官造成严重损伤, 引发严重或不可逆的后果。因此, 此类中草药的用法、用量有别于普通中草药, 在使用中应加以注意。中医中更有“以毒攻毒”、“配伍解毒”的理论与实践。

生物碱 (alkaloids) 多具有较复杂的环状结构, 可分为吲哚类、吡啶类、莨菪烷类、异喹啉类、有机胺类等。多数生物碱在较低的浓度就有很强的生物活性, 是“有毒”中药的重要活性/毒性成分, 也是中药创新药物研发的重要源泉, 如异喹啉类生物碱吗啡及其衍生物是临床解除剧烈疼痛的主要药物, 全世界使用量最大的强效镇痛剂[1]。然而, 若使用不当, 这些生物碱及相关中药也会对机体产生一定甚或较强的毒性, 影响其临床应用。大量研究表明, 这些生物碱的药效或毒副作用, 除少数表现为对机体的直接作用外, 大多与其在体内的代谢过程及暴露水平相关, 是原型药物与代谢物共同作用的结果。因此, 本文查阅2020年版《中华人民共和国药典》收录的“有毒”中药中所含生物碱类成分, 综合近20年来的中外文献, 按不同结构类型的代表性生物碱的代谢途径、相关的药物代谢酶等进行归纳、评述, 以期为含有此类成分中药的临床用药的安全性和有效性提供参考, 也为相关药物的研发提供依据。

1 《中华人民共和国药典》中含生物碱类成分“有毒”中药的收录情况

查阅2020年版《中华人民共和国药典》, 对其中收录的“有毒”中药进行归纳总结, 在收录的83种“有毒”中药中, 以生物碱为主要药效/毒性成分者达17种 (表1), 如“大毒”中药马钱子、马钱子粉含有大量吲哚类生物碱, 川乌、草乌含双酯型生物碱, 罂粟壳、北豆根含异喹啉类生物碱; 进一步对相关复方进行统计, 2020年版《中华人民共和国药典》中收录含此类“有毒”中药的复方共170种, 以含二萜类、吲哚类、异喹啉类生物碱为主要活性/毒性成分的中药复方居多, 分别为88、32、32种。

2 生物碱的代谢途径及代谢机制

代谢是大部分外源性药物从体内消除的主要方式。有毒生物碱代谢可分为以下三种情况: ① 代谢解毒/减毒, 如马钱子中士的宁在体内经细胞色素P450酶 (cytochrome P450 enzyme, CYP450) 催化I相代谢生成氮氧化物从而减毒[2,3]。② 代谢活化致毒, 如蝙蝠葛碱被代谢成亲电活性中间体甲基醌, 可发生II相代谢生成谷胱甘肽结合物而耗竭细胞内谷胱甘肽致毒[4], 或与蛋白结合进一步诱发毒性[5]。③ 代谢生成活性代谢物, 如罂粟壳中吗啡经葡萄糖醛酸化酶 (UDP-glucuronosyltransferase, UGTs) 催化II相代谢生成吗啡-6-葡萄糖醛酸结合物, 从而发挥镇痛、止咳、止泻药效[6,7]。

2.1 乌头类生物碱毒性及其代谢机制 乌头类生物碱为二萜类生物碱, 以乌头碱 (aconitine) 为代表性成分, 主要来源于乌头类中药, 包括川乌、草乌、附子等。乌头碱为双酯型生物碱, 既是乌头类中药的主要有效成分, 也是其毒性成分, 可导致肝毒性、心脏毒性、神经毒性等[8,9]。临床数据显示口服乌头碱0.2 mg即可引发中毒, 2～5 mg即可致死, 死亡原因主要与心律失常和呼吸衰竭有关。乌头碱等双酯型生物碱可被逐级水解生成毒性较低的单酯型生物碱和几乎无毒的胺醇型生物碱[10,11]。临床应用中乌头类中药材常以炮制品入药, 以达到炮制解毒的目的。

肝微粒体体外代谢研究表明乌头碱代谢存在一定的种属差异: 在大鼠肝微粒体中, 乌头碱经由CYP3A1/2和CYP1A1/2催化共产生6个去甲基化物和脱氢化物[12]; 而在人的肝微粒中, 乌头碱主要经CYP3A4/5和CYP2D6催化发生去甲基化等反应, 生成脱氢化物、羟化物、去甲基化物等I相代谢物[13]。Sui等[14]以家兔口服给药乌头碱, 在家兔胃内容物中鉴定出14种代谢产物, 主要包括羟基化物、脱氧化物、去甲基化物和长链脂肪酸酯化物等。目前对于乌头碱的II相代谢研究尚无报道。乌头碱通过代谢降低毒性的主要代谢途径如图1。

2.2 莨菪烷类生物碱毒性及代谢机制 莨菪烷类生物碱由莨菪烷上的3位-羟基与有机酸类缩合成酯, 多

Table 1 Toxic traditional Chinese medicines with recorded in Chinese Pharmacopoeia (ChP 2020). [a]Preparations officially recorded in ChP 2020; - no related preparations

Traditional Chinese medicine	Toxicity degree	Active/toxic alkaloid	Preparations involved [a]
Strychni Semen	Poisonous	Indole alkaloids	15 preparations, including Renqing Mangjue, Dieda Zhentong Gao, Tongbi Pian, Shenjin Huoluo Wan, Shenjindan Jiaonang, Shufenghuoluo Wan, Maqianzi San, Tongbi Jiaonang, Wanling Wuxiang Gao, Shexiang Dieda Fengshi Gao, Fenghan Shuangliguai Pian, Shangshi Zhitong Gao, Tianmeng Koufuye, Tianmeng Jiaonang, and Fufang Futianwu Pian
Strychni Semen Pulveratum	Poisonous	Indole alkaloids	10 preparations, including Jiufen San, Fengshi Maqian Pian, Pingxiao Pian, Pingxiao Jiaonang, Shangke Jiegu Pian, Yujin Yinxie Pian, ShujinWan, Shufeng Dingtong Wan, Yaotongning Jiaonang, and Biqi Jiaonang
Aconiti Radix	Poisonous	Diterpenoid alkaloids	13 preparations, including GoupiGao, Tianhe Zhuifeng Gao, Anyang Jingzhi Gao, Shenjin Huoluo Wan, Awei Huapi Gao, Mugua Wan, Yanghe Jiening Gao, Shexiang Zhentong Gao, Shaolin Fengshi Dieda Gao, Qingyu Piwen Dan, Wanling Wuxiang Gao, Dingchuan Gao, and Yaoaitiao
Aconiti Radix Cocta	Toxic	Diterpenoid alkaloids	18 preparations, including Fengshi Gutong Pian, Fengshi Gutong Jiaonang, Fenghan Shuangliguai Pian, Fugui Gutong Pian, Fugui Gutong Jiaonang, Fugui Gutong Keli, Huoxue Zhuangjin Wan, Shexiang Fengshi Jiaonang, Guci Xiaotong Pian, Qufeng Shujin Wan, Zhuifeng Tougu Wan, Jintongxiao Ding, Xiaohuoluo Wan, Fufang Yangjiao Pian, Tongbi Jiaonang, Tongbi Pian, Guci Wan, and Zhonghua Dieda Wan
Aconiti Kusnezoffii Radix	Poisonous	Diterpenoid alkaloids	9 preparations, including Tianhe Zhuifeng Gao, Shaolin Fengshi Dieda Gao, Shangshi Zhitong Gao, Anyang Jingzhi Gao, Yanghe Jiening Gao, Awei Huapi Gao, GoupiGao, Qushang Xiaozhong Ding, and Dieda Zhentong Gao
Aconiti Kusnezoffii Radix Cocta	Toxic	Diterpenoid alkaloids	25 preparations, including Sanqi Pian, Sanqi Shangyao Jiaonang, Sanqi Shangyao Keli, Sanqi Xueshangning Jiaonang, Xiaojin Wan, Xiaojin Pian, Xiaojin Jiaonang, Xiaohuoluo Wan, Mugua Wan, Fengshi Gutong Pian, Fengshi Gutong Jiaonang, Fenghan Shuangliguai Pian, ZhengguShui, Shenjin Hluuoo Wan, Guci Wan, Guci Xiaotong Pian, Fufang Futianwu Pian, Zhuifeng Tougu Wan, Qufeng Zhitong Wan, Qufeng Zhitong Pian, Qufeng Zhitong Jiaonang, Qufeng Shujin Wan, Jintongxiao Ding, and Qiangli Tianma Duzhong Wan
Hyoscyami Semen	Poisonous	Tropane alkaloids	2 preparations, including Kuiyangsan Jiaonang and Xuanning Chaji
Berberidis Radix	Toxic	Isoquinoline alkaloids	-
Sophorae Tonkinensis Radix et Rhizoma	Toxic	Pyridine alkaloids	10 preparations, including Kouyanqing Wan, Yunxiang Qufeng Zhitong Ding, Qingyu Piwen Dan, FufangYigan Wan, Guilin Xiguashuang, Qingyan Runhou Wan, Qingge Wan, Houjiling Pian, Houjiling Jiaonang, Biyanling Pian
Chelidonii Herba	Toxic	Isoquinoline alkaloids	-
Physochlainae Radix	Toxic	Tropane alkaloids	1 preparation, Huashanshen Pian
Aconiti Lateralis Radix Praeparata	Toxic	Diterpenoid alkaloids	23 preparations, including Renshen Zaizao Wan, Tianma Wan, Wumei Wan, Shengbai Heji, Zaizao Wan, Yanghe Jiening Gao, Fuzi Lizhong Wan, Fuzi Lizhong Pian, Fugui Gutong Pian, Fugui Gutong Jiaonang, Fugui Gutong Keli, Guben Tongxue Keli, Dingchuan Gao, Shenfu Qiangxin Wan, Qianlieshu Wan, Jisheng Shenqi Wan, Guifu Dihuang Koufuye, Guifu Dihuang Wan, Guifu Dihuang Jiaonang, Yishenling Keli, Tongbi Pian, Tongbi Jiaonang, and Weidakang Koufuye
Daturaeflos	Toxic	Tropane alkaloids	5 preparations, including Zhichuanling Zhusheye, Huazhi Shuan, Zhuanggu Shenjin Jiaonang, Ruyi Dingchuan Pian, and Henggu Gushangyu Heji
Papaveris Pericarpium	Toxic	Isoquinoline alkaloids	17 preparations, including Ermu Ansou Wan, Zhisou Huatan Wan, Keke Pian, Changweining Pian, Pipa Zhike Ruanjiaonang, Pipa Zhike Jiaonang, Pipa Zhike Keli, Guchang Zhixie Jiaonang, Jingwanhong Ruangao, Kechuanning Koufuye, Fufang Manshanhong Tangjiang, Yangshen Baofei Wan, Xiaoyan Zhike Pian, Qiangli Pipa Jiaonang, Qiangli Pipa Gao, Qiangli Pipa Lu, and Juhong Huatan Wan
Menispermi Rhizoma	Small Poisonous	Isoquinoline alkaloids	4 preparations, including Xiaoer Qingre Zhike Heji, Beidougen Pian, Beidougen Jiaonang, Qingguo Wan
Zanthoxyli Radix	Small Poisonous	Isoquinoline alkaloids	11 preparations, including Sanjiu Weitai Jiaonang, Sanjiu Weitai Keli, ZhengguShui, Fuyanjing Jiaonang, Changweishi Jiaonang, Gongyanping Pian, Gongyanping Diwan, Qushang Xiaozhong Ding, Xiaozhong Zhitong Ding, Dieda Zhentong Gao, and Biyan Qingdu Keli
Evodiae Fructus	Small Poisonous	Indole alkaloids	7 preparations, including Danguixiang Keli, Zuojin Wan, Zuojin Jiaonang, Huatuo Zaizao Wan, Biling Weitong Keli, Fufang Huangliansu Pian, and Xuanshi Yaoshui

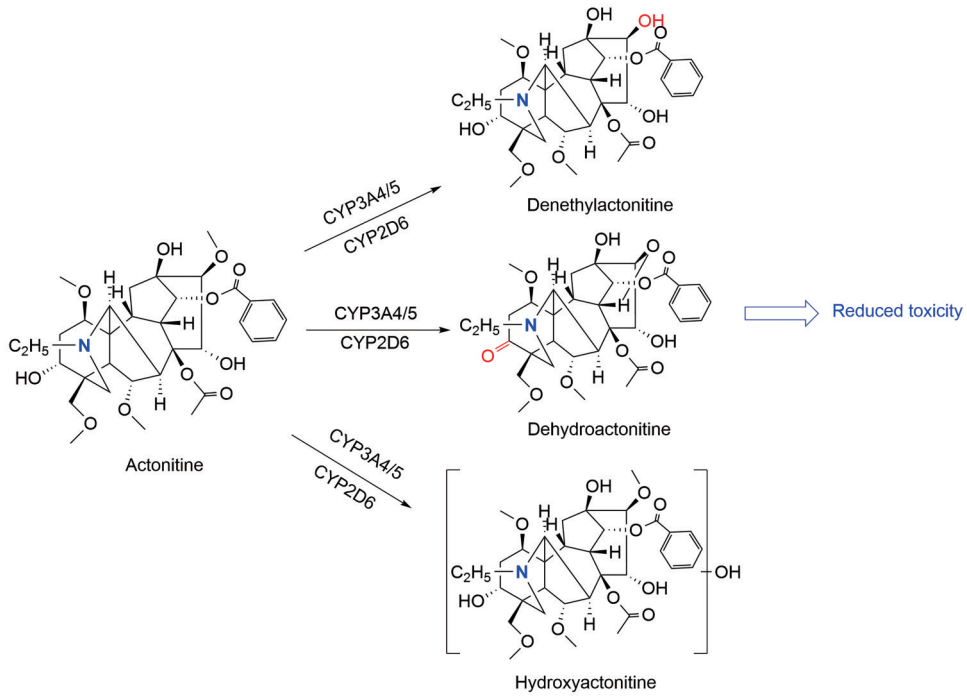

Figure 1 The major detoxification pathway of aconitine by human CYP450s

数分布于茄科曼陀罗属、天仙子属、颠茄属、山莨菪属、茄属等 14 属中[15,16], 以阿托品 (atropine) 为代表性成分。有毒中药天仙子、洋金花、华山参均含此类生物碱。莨菪烷类生物碱为M胆碱受体拮抗剂, 临床上在治疗痉挛疼痛、咳喘等病症方面具有独特的疗效。但该类生物碱毒性强, 误服过量可引起神经毒性[16-18]。阿托品通过麻痹副交感神经的神经末梢, 产生典型的毒蕈碱样作用, 进而产生中枢抗胆碱作用; 毒性严重者可因血压下降、呼吸衰竭死亡。阿托品最低致死量成人为80～130 mg, 儿童约为10 mg[19]。

Chen 等[20]发现阿托品经大鼠肝微粒体代谢生成脱水产物和去甲基化产物。在厌氧条件下, 阿托品与富含肠内菌的大鼠肠内容物共孵育, 生成脱水产物及水解产物, 即脱水阿托品、托品和托品酸[21]。大鼠口服灌胃阿托品可发生去甲基化、水解、氧化和磺酸化、葡萄糖醛酸化等反应[22], 在尿液和粪便中共鉴定到15个代谢物, 包括9个I相代谢物和6个II相代谢物。但是, 志愿者口服阿托品后, 在尿液中仅发现去甲基阿托品、阿托品氮氧化物、托品和托品酸共4个代谢物, 但未发现II相代谢物[23]。阿托品在人和大鼠体内代谢的差异表明其代谢存在一定的种属差异, 需要开展深入的研究, 以更有利于其临床应用。

2.3 异喹啉类生物碱毒性及代谢机制 异喹啉类生物碱是最大的一类生物碱, 以异喹啉或四氢异喹啉为母核, 广泛分布于罂粟科、巴比特科、毛茛科、防己科中。有毒中药三颗针、白屈菜、罂粟壳、北豆根、两面针中均含有异喹啉类生物碱。

吗啡 (morphine) 是罂粟壳的主要生物碱成分, 属吗啡烷类。吗啡为阿片受体激动剂, 具有显著的镇痛、镇咳作用, 由于其长效、强大的镇痛效能被长期应用于临床, 并被世界卫生组织推荐为镇痛药物, 广泛应用于终末期癌症疼痛及各种中重度非癌症疼痛[24], 但其具有麻醉性、毒性和成瘾性[25]。吗啡在人体内主要经肝脏 UGT2B7 催化代谢生成吗啡-3-葡萄糖醛酸结合物和吗啡-6-葡萄糖醛酸结合物[26] (图 2), 其中吗啡-6-葡萄糖醛酸结合物为镇痛药效物质[1,27,28], 而吗啡-3-葡萄糖醛酸结合物可通过 Toll 样受体 4 和白介素 1 增强患者的痛感[29]。对 47 名口服吗啡的终末期患者进行群体药代动力学研究[30], 发现吗啡代谢符合二室模型而两个葡萄糖醛酸结合物符合一室模型, 且因终末期患者肾脏排泄功能下降, 两个葡萄糖醛酸结合物均在体内大量蓄积。据报道, 吗啡-6-葡萄糖醛酸化代谢物可穿过肾损伤患者的血脑屏障, 引起极度镇静, 从而导致昏迷[31]。因此, 此类药物的临床使用必须谨慎, 充分考虑患者的病理/生理状态, 特别是对于临床需要腹膜透析的患者应慎用吗啡作为镇痛剂。罂粟壳中另一种异喹啉类生物碱可待因 (codeine) 经 CYP2D6 催化发生 *O*-脱甲基而代谢为吗啡[6,7], 进一步代谢为葡萄糖醛酸结合物, 发挥镇痛、止咳、止泻药效。

小檗碱 (berberine) 为原小檗类生物碱, 是三颗

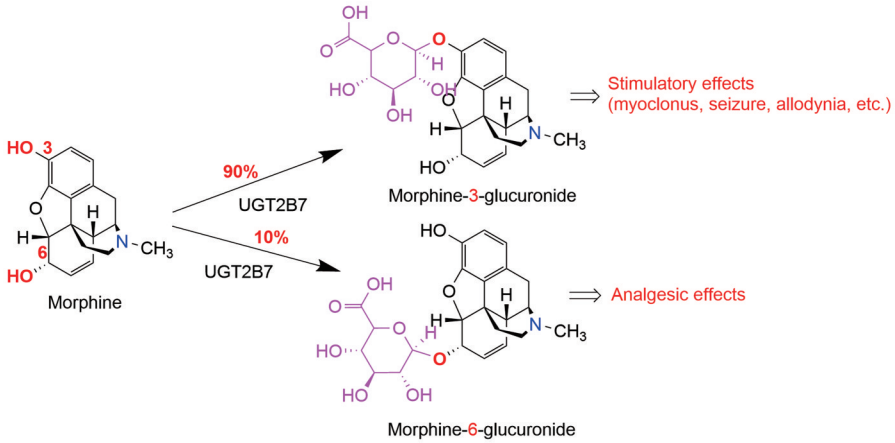

Figure 2　Glucuronidation of morphine by UGT2B7

针的主要活性成分。小檗碱临床应用广泛, 但也有研究表明其存在潜在的不良反应[32]。Kheir 等[33]报道小鼠静脉注射和腹腔注射小檗碱的半数致死量 (median lethal dose, LD_{50}) 分别为 9.04、57.61 mg·kg^{-1}; 但小鼠口服给药小檗碱的毒性相对较低, 在 83.2 g·kg^{-1} 下小鼠的死亡率仅为 30%, 这可能与小檗碱口服生物利用度低有关。关于小檗碱的代谢研究较多, 在人体和实验动物体内发现了多个代谢物[34]。大鼠灌胃小檗碱后在尿液、胆汁和粪便中共发现 16 个代谢物, 包括 10 个 I 相代谢物和 6 个 II 相代谢物; 其中去甲基化产物 (小檗红碱、芬氏唐松草定碱、去甲基小檗碱) 和还原产物 (药根碱) 是其主要代谢物[35,36]。Qiu 等[37]在大鼠尿液和人的尿液中分别分离得到 5 个、7 个代谢物, 主要为小檗碱代谢物的磺酸化物和葡萄糖醛酸化物。小檗碱在 CYP1A2、CYP2D6、CYP3A4 代谢酶的催化下 (图 3), 参与去甲基化、羟基化等 I 相代谢[38,39], 代谢物继而在葡萄糖醛酸转移酶 UGT1A1、UGT2B1 及 SULTs 的参与下完成 II 相代谢, 形成极性强的葡萄糖醛酸化物和磺酸化物从而排出体外[40]。

北豆根中含多种生物碱类成分, 双苄基四氢异喹啉型生物碱蝙蝠葛碱 (dauricine)、蝙蝠葛苏林碱 (daurisoline) 为其含量最高的生物碱, 具有抗心律失常、抗肿瘤等药理作用[41,42]。但有研究报道小鼠腹腔注射 150 mg·kg^{-1} 蝙蝠葛碱后可致明显肺损伤[43]。蝙蝠葛碱在大鼠体内可发生去甲基化、脱氢、脱甲氧基、羟化、葡萄糖醛酸化、磺酸化、谷胱甘肽结合反应[5,44]。在

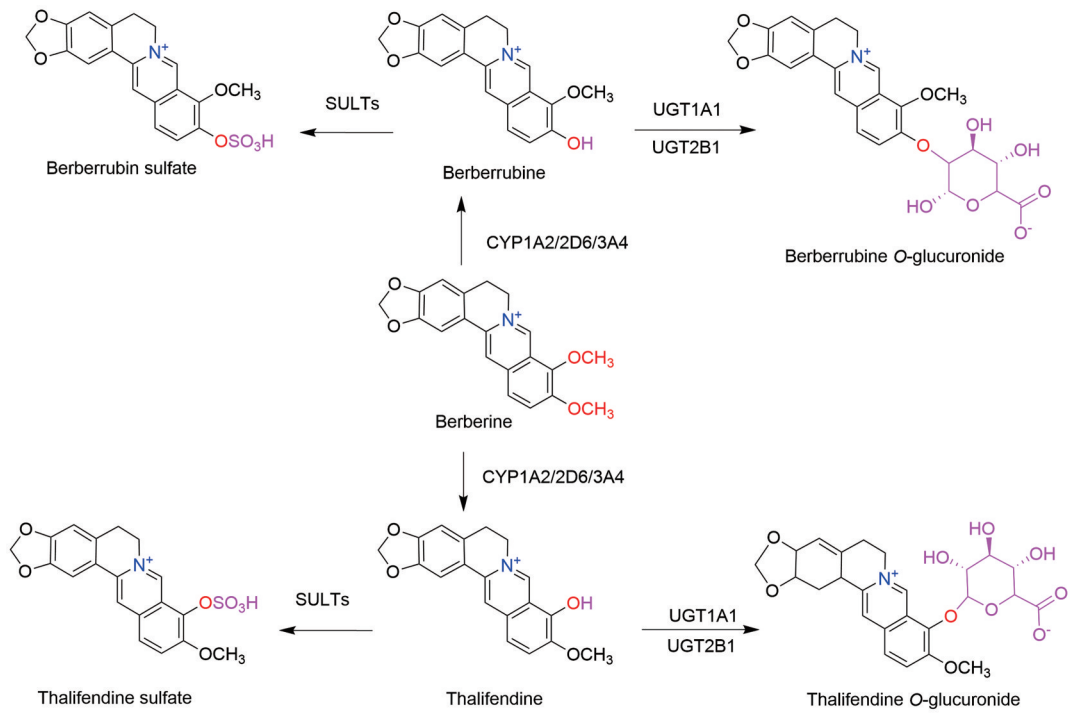

Figure 3　The major metabolic pathways for detoxification of berberine

人肝微粒体中也鉴定到了以上代谢物, 研究者[5]利用人重组单酶和体外抑制剂进一步确证CYP3A4是催化蝙蝠葛碱代谢活化进而生成谷胱甘肽结合物的关键酶。蝙蝠葛碱的结构中含有对亚甲基苯酚基团, 被代谢成亲电活性中间体甲基醌, 可与谷胱甘肽偶联耗竭谷胱甘肽 (图4), 从而引起毒性[5]。此外, 该活性中间体甲基醌还可与蛋白结合, 进一步诱发毒性[4]。

此外, 临床报道白屈菜可导致临床溶血性贫血、急性肝炎等[45,46]。白屈菜碱 (chelidonine) 是白屈菜中苯并菲啶类生物碱活性成分, 由多种CYP450酶 (CYP3A4、CYP1A2、CYP2C19和CYP2D6) 催化发生氧化反应[47]; 可生成脱亚甲基化代谢物, 其含有的酚羟基易被氧化为醌类化合物, 可与谷胱甘肽巯合生成醌−硫醚, 造成肝脏内谷胱甘肽耗竭, 具有潜在的肝毒性[48,49]。然而, 白屈菜碱在肝脏中生物利用度极低 (低于1%)[50,51], 可能需要服用较高剂量才能导致毒性。体外研究表明氯化两面针碱 (nitidine chloride) 具有肝细胞毒性、肾细胞毒性、发育毒性以及心脏毒性等不良反应[52,53], 但尚未有体内毒性的研究报道。迄今为止对于氯化两面针碱的体内外代谢报道为空白。

2.4 吲哚类生物碱毒性及代谢机制 吲哚类生物碱是生物碱中结构类型多、结构复杂、化合物数目最多的一类生物碱。大毒中药马钱子、马钱子粉中所含士的宁 (strychnine)、马钱子碱 (brucine) 以及小毒中药吴茱萸中所含吴茱萸碱 (evodiamine)、吴茱萸次碱 (rutaecarpine) 均属于吲哚类生物碱。

士的宁 (strychnine)、马钱子碱 (brucine) 为马钱子、马钱子粉的主要活性成分, 占马钱子生物碱成分的80%[2]。现代研究表明士的宁、马钱子碱具有显著的抗炎镇痛、抗肿瘤、调节免疫、中枢神经系统兴奋等广泛的药理作用[54]。然而两者既是有效成分也是有毒成分, 治疗剂量与中毒剂量接近, 中毒可导致抽搐惊厥、横纹肌溶解等神经系统毒性和肾毒性[55]。研究者[56]比较了小鼠口服士的宁和马钱子碱的毒性, 发现其LD_{50}分别为3.3 mg·kg^{-1}、233.0 mg·kg^{-1}。Zhu等[57]研究表明小鼠单次口服马钱子碱的为189.9 mg·kg^{-1}, 腹腔注射马钱子碱的LD_{50}为55.2 mg·kg^{-1}。总的说来, 士的宁毒性较强, 是马钱子碱的10～20倍。士的宁被吸收进入血液循环后, 如图5, 主要经CYP3A4催化氮氧化反应[58,59], 生成士的宁氮氧化物 (strychnine *N*-oxide); 氮氧化物毒性小于原型且具有良好的活性, 是其主要的代谢物。此外, CYP2C9、CYP1A2、CYP2C19和CYP2D6酶也参与了士的宁的代谢[60,61]。除氮氧化物外, 士的宁的代谢物还包括羟化物[62]和葡萄糖醛酸化物[63,64]。Li等[63,64]利用肝微粒体对其II相代谢研究发现, 士的宁仅在人肝微粒中生成1个葡萄糖醛酸化物 (图5), 而在大鼠肝微粒体中未发现此代谢物, 进一步利用重组单酶及特异性抑制剂实验确定该反应由UGT1A4催化。马钱子碱也可由UGT1A4催化葡萄糖醛酸化代谢。由于UGT1A4的表达存在种属差异, 在大鼠、小鼠中为不表达的假基因[65,66], 这可能导致士的宁和马钱子碱在不同种属中量−毒−效的差异, 亟需采用合适的整体动物模型来开展体内量−毒−效关系研究, 以进一步保障其临床用药安全性与有效性。

以吴茱萸碱和吴茱萸次碱为代表的生物碱类成分是吴茱萸的主要药效成分, 具有抗癌、抗炎镇痛、抗血

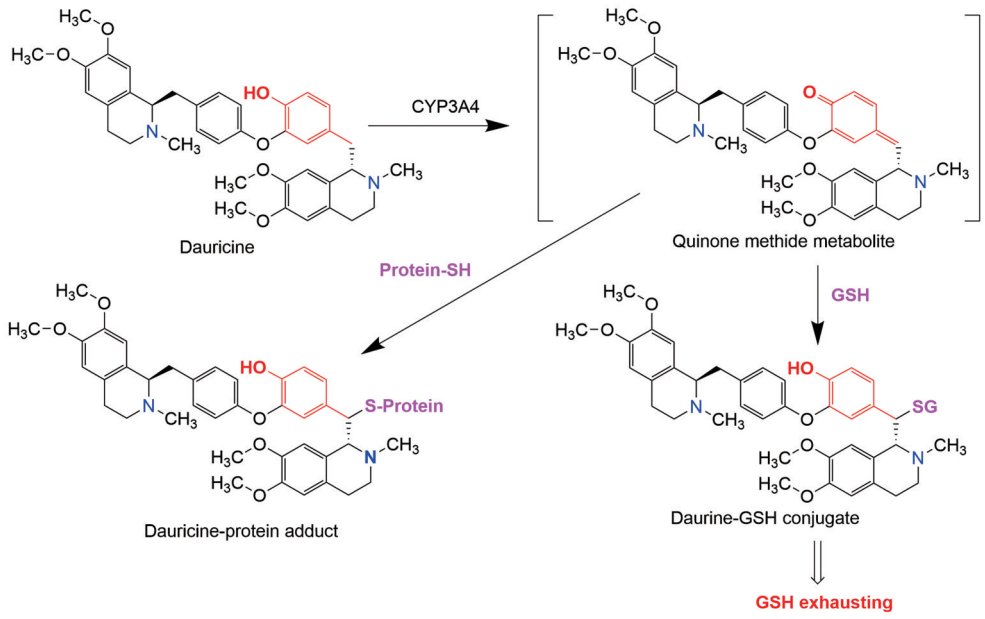

Figure 4 Proposed metabolic pathways of dauricine responsible for its toxicity

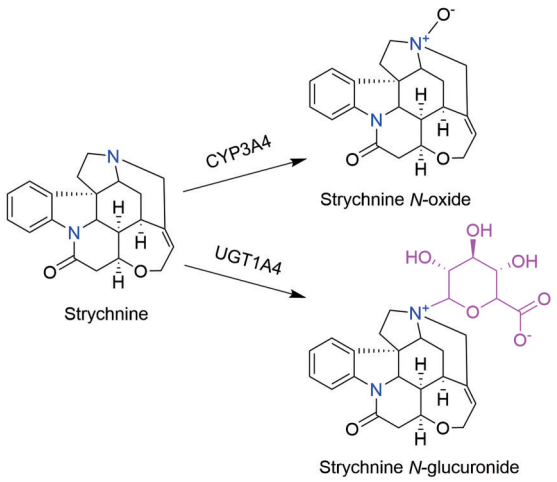

Figure 5　Major metabolic pathways for detoxification of strychnine. The formation of strychnine-*N*-glucuronide is catalyzed by UGT1A4, which is a pseudogene in experimental rodents (i. e., mice and rats)

栓、保肝及心血管系统等作用[67,68], 但也具有潜在的肝毒性、心血管毒性等[69,70]。低浓度吴茱萸碱和吴茱萸次碱 (小于 5 μmol·L^{-1}) 即可致人肝细胞 L02 的存活率显著下降[71]。小鼠静脉注射吴茱萸碱、吴茱萸次碱的 LD_{50} 分别为 77.79、65.00 mg·kg^{-1}[72]。小鼠单次静脉注射吴茱萸次碱 20 mg·kg^{-1}即可导致免疫抑制, 明显降低小鼠脾脏重量[73]。目前研究表明, 吴茱萸碱和吴茱萸次碱的毒性与代谢活化相关, 两者可被 CYP450 酶活化脱氢后形成亲电中间体从而产生毒性[74-76]。Zhang 等[77]在人肝微粒体和人原代肝细胞中分别鉴定到 12 个、19 个代谢物, 包括 12 个 I 相代谢物、7 个 II 相代谢物, 主要为氧化、去甲基化、脱氢、葡萄糖醛酸化和谷胱甘肽结合反应产物。吴茱萸次碱在人肝微粒中主要经 CYP1A2、CYP2D6、CYP3A4 代谢酶发生羟基化反应生成羟化物[78]。利用大鼠进行吴茱萸次碱体内代谢研究, 鉴定到 9 个 I 相代谢物、8 个 II 相代谢物, 主要为羟化、葡萄糖醛酸化及磺酸化反应产物[79,80]。

2.5　吡啶类生物碱毒性及代谢机制　吡啶类生物碱主要来源于鸟氨酸合成途径, 该类生物碱结构简单, 数目较少。有毒中药中仅有山豆根含有吡啶类生物碱, 其中苦参碱 (matrine) 和氧化苦参碱 (oxymatrine) 是山豆根质量控制的指标成分, 氧化苦参碱是苦参碱的氮氧化物, 二者均为弱碱性化合物, 具有较强的亲水性和极性。但二者也被认为是山豆根的毒性成分, 可能引起神经毒性、肝毒性等[81,82]。小鼠静脉给药苦参碱和氧化苦参碱, 其 LD_{50} 分别为 83.24、214.22 mg·kg^{-1}[83]。相比而言, 苦参碱更易透过生物膜[84]。氧化苦参碱口服给药后可经 CYP450 酶 (主要为 CYP3A4) 代谢生成苦参碱, 被认为是苦参碱的前体药物[85,86]。

3　总结与展望

生物碱类成分是中药中含量丰富的一类化合物, 药理活性强, 作用范围广, 具有广阔的应用和开发前景; 但由于其结构的特殊性, 部分生物碱既是中药的有效成分也是毒性成分, 限制了此类生物碱的深入研究和开发利用, 对含此类生物碱中药临床应用的安全性和有效性也提出了更高的要求。本文对 2020 年版《中华人民共和国药典》收录的“有毒”中药统计发现以生物碱类成分为药效/毒性物质基础的中药占比达 25%, 涉及复方制剂百余种, 对于此类中药及相关制剂的应用应予以高度重视。

药物发挥疗效及临床用药安全性与药物代谢密切相关, 通过对“有毒”中药中含有的生物碱类成分的代谢研究进行归纳总结发现此类化合物经 CYP450 酶、UGTs、SULTs 等多种代谢酶调控, I 相代谢主要包括氮氧化、羟化、脱水、脱氢、去甲基化、水解反应等, II 相代谢主要包括葡萄糖醛酸化、磺酸化、谷胱甘肽结合反应等。目前大部分研究集中于去甲基化、羟基化、脱氢等 I 相反应, 对于 II 相代谢的研究报道较少。加强活性/毒性生物碱的 II 相代谢研究对于有毒中药的致毒机制、减毒策略及相关临床疾病的诊断、预后、治疗均具有重要意义。然而药物代谢酶存在较大的种属差异, 也会造成有毒中药毒性种属差异。如 II 相葡萄糖醛酸化酶 UGT1A4、UGT2B4 在常用的实验模型小鼠、大鼠中均为不表达的假基因[65,87], 可能造成基于这些模型的临床前药代-药效/毒代-毒性数据与临床观察的差异[88]。有研究者[89]观察到高剂量下布洛芬在人源化 UGT1s 小鼠中的暴露量明显高于野生型小鼠, 且更快引发了血清转氨酶的升高。本课题组[90]前期也证明与野生型小鼠比较, 人源化 UGT1A4 小鼠对毒性生物碱千里光碱更加耐受, 与 UGT1A4 可特异性催化千里光碱发生葡萄糖醛酸化代谢[91,92]密切相关。药物的药效/毒性通常是体内多种代谢酶共同作用的结果, 选择合适的模型或构建人源化模型进行整体水平的药物临床前研究, 将为此类中药及复方的创新研发、临床合理用药提供更加科学的指导。

复方配伍是中医药的用药特点, 中药配伍后, 药与药之间会呈现种种变化关系。随着“君、臣、佐、使”配伍理念的发展与应用, 配伍后的中药复方不仅发挥着增强药效的作用, 同时也具有减毒、降低不良反应的作用。其减毒增效机制主要与增加药效成分生物利用度、改善靶器官药物分布及抑制相关酶对活性成分的代谢速率等体内过程密切相关[93]。药物-药物相互作用影响其代谢可能将改变其药效或毒性。甘草配伍马

钱子通过诱导CYP3A4代谢酶从而提高马钱子碱和士的宁的代谢使其毒性降低[94]。附子配伍芍药、干地黄能够诱导CYP1A2、CYP3A4酶活性, 加快附子主要毒性成分乌头碱的代谢过程, 进而降低附子毒性[95,96]。“十八反”中甘遂与甘草同用, 川乌与瓜蒌同用而致中毒[97]等; 延胡索配伍马钱子加重马钱子的毒性[98]等。然而, 目前对于此类生物碱成分的代谢酶的研究不足, 明确催化药物发生代谢的关键酶及药物-酶之间的关系对于复方配伍、药物−药物相互作用、致毒/减毒的研究及临床中西医联合用药和合理化用药提供有价值的理论依据。

临床防治疾病, 通常需要采用合理的配伍形式, 以增强疗效, 降低或消除毒副作用, 扩大应用范围, 全面照顾病情。若配伍不合理, 则会减效、增毒, 影响临床的安全性和有效性[99]。因此, 面对此类中药的应用, 临床合理用药尤为关键, 兼以炮制、调剂、配伍、剂量、品种变换等方法而增效减毒。建议在临床使用时首先应该严格辨证论治, 控制其适用范围与使用剂量, 减少多种药物同时使用; 其次要辨别中药饮片的真伪如同名异物、同物异名, 严格科学进行炮制或配伍以达到减毒或增效的目的; 制定不同“有毒”中药中毒后抢救的应急预案, 熟悉其毒性成分、中毒机制和解毒措施[100]; 也要重视对此类中药的科学研究动态, 掌握“有毒”中药的药理毒性、药代等方面的最新研究进展, 在传统中医药炮制、调剂、配伍、剂量、品种变换等理论与方法进行传承与创新, 以实现增效减毒, 从而充分发挥“有毒”中药的临床疗效, 保证用药安全、合理用药。

作者贡献: 陈岩负责文献检索整理分析及论文撰写; 唐莹莹负责文献检索; 杨莉负责文章选题; 熊爱珍、王峥涛负责文章选题、修改及校对文章。

利益冲突: 本文无利益冲突。

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