# 体外代谢体系中中药及其成分对肝脏CYP450代谢酶抑制作用的研究进展

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**摘要**: 细胞色素P450 (CYP450) 是肝微粒体中参与体内I相代谢反应的酶, 临床上90%以上的药物都经CYP450氧化代谢, 其被诱导或抑制是引起药物相互作用的主要机制。通过离体器官、细胞或酶系统进行的体外代谢研究以其精准、简化等特点近年来发展迅速。中药的体外代谢研究可推断药物可能的代谢途径和参与代谢的CYP450酶, 研究药物的相互作用, 更好地解释中药及其成分的作用机制, 促进临床合理用药。本文就中药、中药成分、中药提取物在不同种属肝微粒体中对CYP450代谢酶活性的抑制作用进行综述, 以期为中药−中药、中药−化学药物之间相互作用研究提供借鉴与参考。

**关键词**: 细胞色素P450; 中药; 体外代谢; 肝微粒体; 药物相互作用

**中图分类号**: R917 **文献标识码**: A **文章编号**: 0513-4870(2022)02-0303-10

# Review of the *in vitro* inhibitory effects of traditional Chinese medicine and its components on CYP450 enzymes in liver microsomes

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**Abstract**: Cytochrome P450s (CYP450) is a superfamily of phase I metabolic enzymes, which participates in more than 90% of drug oxidation. The induction or inhibition of CYP450s is the main mechanism of drug-drug interaction. In recent years, *in vitro* metabolism studies conducted through isolated organs, cells, or enzyme systems have developed rapidly, due to their precision and simplicity. Therefore, profiles of the *in vitro* metabolism studies of traditional Chinese medicines can infer the possible metabolic pathways of drugs, predict the potential drug interactions, and may enhance the rational use of drugs in clinic. This article reviews the *in vitro* inhibitory effects of traditional Chinese medicine, ingredients, and extracts on the activities of CYP450 enzymes in the liver microsomes, which can provide a reference for further researches on the interaction between Chinese medicine and chemical medicine.

**Key words**: cytochrome P450; traditional Chinese medicine; *in vitro* metabolism; liver microsome; drug-drug interaction

细胞色素P450 (CYP450) 是指含血红素的蛋白质在一氧化碳存在的还原性状态下, 最大吸收波长在450 nm的一类能够催化大多数药物和其他亲脂性外源性物质的主要代谢酶家族。CYP450代谢酶在体内广泛分布, 以肝脏、小肠含量最高。人类CYP450代谢

收稿日期: 2021-09-18; 修回日期: 2021-11-03.
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DOI: 10.16438/j.0513-4870.2021-1384

酶分为18个家族和44个亚家族, 其中CYP1/2/3家族中的代谢酶 (CYP1A2、CYP2C9、CYP2C19、CYP2D6、CYP2E1和CYP3A4) 参与临床上90%以上药物的I相代谢过程, 其他家族在代谢内源性物质方面发挥重要的作用[1,2]。CYP450代谢酶的表达和活性受多种因素影响, 如年龄、性别、遗传、环境及病理因素等, 其活性被抑制可导致经其代谢的药物在体内代谢减慢, 暴露量增加, 从而增大不良反应发生概率, 对于前药而言则会导致药物疗效减弱。CYP450代谢酶具有泛底物性和底物交叉性, 底物与活性中心非特异性结合会导致药物的代谢动力学发生改变, 从而引起药物−药物之间相互作用[3]。

随着中西医结合治疗的发展, 中药方剂及中成药与化学药品联合使用不断增多, 中药−化学药物之间的相互作用及不良反应数量也逐渐上涨。中药成分按照其母核结构可分为生物碱类、黄酮类、萜类、苷类等。目前中药对CYP450代谢酶影响的研究方法主要有探针药物法、体外孵育法 (肝微粒体及重组P450酶)、计算机软件模拟筛选法[4,5]。探针药物法是指通过底物的特定氧化代谢途径来确定体内外特异性代谢酶活性的一种CYP酶−底物配对的检测方法, 分为体内探针药物法及体外探针药物法[6], 体内探针药物法是指给予机体一定量的探针药物后以其代谢物和原形药物之间的比例或速率来衡量代谢酶活性的变化, 在研究代谢酶与疾病之间的关系及药物之间在机体内的相互作用具有更高的价值。

由于体内研究影响因素颇多, 中药代谢及其机制研究受限。体外模型, 尤其是以肝微粒体为核心的药物代谢模型具有专属性强、灵敏度高等特点[7], 在提高药物疗效、促进安全合理用药等方面具有重要意义。本文就目前以肝微粒体为体外代谢模型, 开展中药及其成分对主要CYP450代谢酶的抑制作用进行综述。

## 1 CYP1A2

CYP1家族由CYP1A1、1A2、1B1组成, 其中CYP1A2约占总P450的13%～15%[8], 参与代谢临床上大多数药物如咖啡因、非那西丁、氯氮平、茶碱、普萘洛尔、维拉帕米、哌唑嗪、杜洛西汀等[9]。其中非那西丁、咖啡因和茶碱常作为模型底物评价CYP1A2代谢酶的体内活性。在超过45%的新药体外研究中, 非那西丁-*O*-去甲基化反应作为检测CYP1A2活性最常用的探针反应[10]。部分中药及其成分对CYP1A2抑制作用见表1[11-26]。

根据《FDA药物相互作用研究指南》体内相互作用的可能性通过 $R = [I] / K_i$ ([I] 代表作用部位抑制剂的浓度, $K_i$为抑制剂常数) 表示, $R > 1$表明很有可能发生药物间的相互作用。当由体外数据定量预测体内相互作用发生的可能性时, 可以通过$K_i$值进行初步筛选, 数值越小, 外推至体内发生相互作用的可能性越大。测定半数抑制浓度 ($IC_{50}$) 值可快速初步了解药物对代谢酶是否具有强抑制作用, $IC_{50}$值越小说明抑制作用越强。若 $IC_{50} < 1.00$ μmol·L$^{-1}$, 初步表明药物对该代谢酶的抑制能力强; 若 $IC_{50} > 50$ μmol·L$^{-1}$则表明药物对该代谢酶抑制作用较弱, 外推至体内时由于药物抑制该代谢酶的活性而引起的药物相互作用可能性较小[27]。在所列举的中药及其成分中, 对CYP1A2代谢酶的活性抑制作用较强的分别是丹红注射液 ($IC_{50} = 0.036$ μmol·L$^{-1}$), 大叶茜草素 ($IC_{50} = 1.03$ μmol·L$^{-1}$) 和甘草酚 ($IC_{50} = 2.2$ μmol·L$^{-1}$)。

**Table 1** Inhibition of traditional Chinese medicine and its components on CYP1A2. HLM: Human liver microsome; RLM: Rat liver microsome; -: Not obtained

| Category | Name | Source | *In vitro* model | $IC_{50}/K_i$ | Inhibition type | Ref. |
|---|---|---|---|---|---|---|
| Flavone | Kurarinone | *Sophora flavescens* | HLM | 13.64 μmol·L$^{-1}$ | Competitive | [11] |
| | Kaempferitrin | *Vepris heterophylla* | HLM | 20.56 μmol·L$^{-1}$ | Competitive | [12] |
| | Diosmetin | *Teucrium* | HLM | 2.6 μmol·L$^{-1}$ | − | [13] |
| The other compound | Isofraxidin | Umbelliferae | HLM | 23.01 μmol·L$^{-1}$ | Competitive | [14] |
| | Honokiol | *Magnolia officinalis* | RLM | 1.6 μmol·L$^{-1}$ ($K_i$) | Mixed | [15] |
| | Magnolol | *Magnolia officinalis* | RLM | 1.62 ± 0.423 μmol·L$^{-1}$ | Non-competitive | [16] |
| | Psoralidin | *Psoraleacorylifolia* | HLM | 1.818 ± 0.22 μmol·L$^{-1}$ | Non-competitive | [17] |
| | Glycyrol | *Glycyrrhiza uralensis* | HLM | 2.2 μmol·L$^{-1}$ | Competitive | [18] |
| | Mollugin | *Rubia cordifolia* | HLM | 1.03 μmol·L$^{-1}$ | Competitive | [19] |
| | Astragaloside IV | Radix Astragali | RLM | 45 μmol·L$^{-1}$ | Competitive | [20] |
| Traditional Chinese medicine extracts | *Corydalis saxicola* Bunting total alkaloids extract | *Corydalis saxicola* Bunting | RLM | 38.08 mg·mL$^{-1}$ | Non-competitive | [21] |
| | Huanglian extract | *Coptis chinensis* Franch | HLM | 36.8 μg·mL$^{-1}$ | − | [22] |
| | Danshen ethanolic extract | *Salvia miltiorrhiza* Bunge | HLM | 2.91 μg·mL$^{-1}$ | Competitive | [23] |
| | | | RLM | 8.49 μg·mL$^{-1}$ | Competitive | |
| Chinese patent medicine | Qingfei Paidu decoction | − | HLM | 174.4 ± 7.7 μg·mL$^{-1}$ | − | [24] |
| | Huosu Yangwei oral liquid | − | HLM | 0.314 8 mg·mL$^{-1}$ | − | [25] |
| | Danhong injection | *Salvia miltiorrhiza* Bunge | HLM | 0.793% | − | [26] |

## 2 CYP2C

CYP2C家族占人类肝脏总P450的30%左右, 主要包括CYP2C8、2C9、2C19, 能代谢20%以上的药物和内源性化合物[28]。CYP2C8约占肝脏总P450的7%, 底物主要包括抗肿瘤药物 (紫杉醇)、降糖药物 (瑞格列奈和吡格列酮)、降脂药物 (氟伐他汀)、抗疟药物 (阿莫地喹) 等60多种临床常用药物, 常用紫杉醇-6-羟基化检测CYP2C8代谢酶的活性[29]。CYP2C9占肝脏总P450的20%左右, 临床上15%的药物经其代谢, 底物主要有糖尿病治疗药物 (格列美脲)、降压药 (氯沙坦)、抗癫痫药物、非甾类抗炎药物 (双氯芬酸)[30], 双氯芬酸-4-羟基化用于检测CYP2C9活性[29]。虽然CYP2C19在肝脏的表达仅占肝脏总P450代谢酶的1%, 但能参与临床上10%左右的药物代谢。代谢底物主要包括质子泵抑制剂 (奥美拉唑、泮托拉唑等)、抗抑郁药 (舍曲林、氟西汀)、镇静催眠药 (地西泮、苯巴比妥)、抗血小板药物 (氯吡格雷)[31], 美酚妥英-4-羟基化常作为探针反应用于检测CYP2C19代谢酶活性。部分中药及其成分对CYP2C抑制作用见表2[12,15,18,24,25,32-55]。

对CYP2C9抑制作用最强的中药成分是甘草酚 ($IC_{50}$ = 0.13 μmol·L$^{-1}$), 对CYP2C19抑制作用最强的中药成分是黄酮类的二氢丹参酮 ($IC_{50}$ = 0.1 μmol·L$^{-1}$)。二氢丹参酮是丹参中主要的醌类脂溶性化合物之一, 体外抗肿瘤活性明显, 可通过抑制细胞增殖、促进细胞凋亡、诱导细胞分化等机制发挥抗肿瘤作用[56]。目前二氢丹参酮尚未作为单一成分成药, 已经上市的中药注射剂丹参注射液中二氢丹参酮含量较低, 故目前由于二氢丹参酮抑制体内CYP2C19代谢酶活性而引起的药物相互作用的可能性较小。随着二氢丹参酮在抗肿瘤方面的研究不断进展, 其单独成药的可能性也不

**Table 2** Inhibition of traditional Chinese medicine and its components on CYP2C. HRC: Human recombinant CYP

| Category | Name | Source | CYP2C | *In vitro* model | $IC_{50}$ | Inhibition type | Ref. |
|---|---|---|---|---|---|---|---|
| Alkaloid | Epiberberine | Rhizoma Coptidis | CYP2C9 | HLM | 8.18 μmol·L$^{-1}$ | Anti-competitive | [32] |
| | Phellodendrine | *Phellodendri* | CYP2C9 | HLM | 16.30 μmol·L$^{-1}$ | Competitive | [33] |
| | Sophocarpine | *Sophora* | CYP2C9 | HLM | 15.96 μmol·L$^{-1}$ | Competitive | [34] |
| Flavone | Kaempferitrin | *Vepris heterophylla* | CYP2C9 | HLM | 16.42 μmol·L$^{-1}$ | Competitive | [12] |
| | Cynaroside | *Angelica keiskei* | CYP2C9 | HLM | 16.58 μmol·L$^{-1}$ | Competitive | [35] |
| Terpenoid | Pachymic acid | *Poria* | CYP2C9 | HLM | 27.95 μmol·L$^{-1}$ | Competitive | [36] |
| | Alantolactone | *Helenium* | CYP2C9 | HLM | 36.82 μmol·L$^{-1}$ | – | [37] |
| | Dihydrotanshinone | *Salvia miltiorrhiza* | CYP2C19 | HLM | 0.1 μmol·L$^{-1}$ | Mixed | [38] |
| | Miltirone | *Salvia miltiorrhiza* | CYP2C9 | HLM | 8.61 μmol·L$^{-1}$ | Competitive | [39] |
| | Celastrol | *Tripterygium wilfordii* | CYP2C11 | RLM | 10.2 μmol·L$^{-1}$ | Competitive | [40] |
| The other compound | Osthole | *Angelica* | CYP2C9 | HLM | 5.736 μg·mL$^{-1}$ | Competitive | [41] |
| | | | CYP2C11 | RLM | 11.33 μg·mL$^{-1}$ | Non-competitive | |
| | Honokiol | *Magnolia officinalis* | CYP2C11 | RLM | 16.5 μmol·L$^{-1}$ | Mixed | [15] |
| | Rosmarinic acid | Rosemary | CYP2C9 | HRC | 39.6 μmol·L$^{-1}$ | Mixed | [42] |
| | | | CYP2C9 | HLM | 76.89 μmol·L$^{-1}$ | – | [43] |
| | Sauchinone | *Saururus chinensis* | CYP2C19 | HLM | 3.60 μmol·L$^{-1}$ | Non-competitive | [44] |
| | Shikonin | Boraginaceae | CYP2C9 | HLM | 1.01 μmol·L$^{-1}$ | Mixed | [45] |
| | | | CYP2C11 | RLM | 2.36 μmol·L$^{-1}$ | Mixed | |
| | Bergenin | *Bergenia purpurascens* | CYP2C9 | HLM | 15.11 μmol·L$^{-1}$ | Competitive | [46] |
| | Glycyrol | *Glycyrrhiza uralensis* | CYP2C9 | HLM | 0.13 μmol·L$^{-1}$ | Competitive | [18] |
| | Cajaninstilbene acid | *Pigeonpea* | CYP2C9 | HLM | 31.3 μmol·L$^{-1}$ | Competitive | [47] |
| | Curculigoside | *Curculigo* | CYP2C8 | HLM | 11.93 μmol·L$^{-1}$ | Competitive | [48] |
| | Catalpol | Rehmanniae Radix | CYP2C9 | HLM | 14.69 μmol·L$^{-1}$ | Competitive | [49] |
| Traditional Chinese medicine extract | *Tinospora cordifolia* extracts | – | CYP2C9 | HLM | 127.55 μg·mL$^{-1}$ | – | [50] |
| | Ethanol extract of *Descurainia sophia* seeds | *Descurainia sophia* | CYP2C9 | HLM | 25.8 ± 1.9 μg·mL$^{-1}$ | Mixed | [51] |
| | | | CYP2C19 | HLM | 38.7 ± 1.7 μg·mL$^{-1}$ | Mixed | |
| | Danshen ethanolic extract | *Salvia miltiorrhiza* Bunge | CYP2C19 | HLM | 30.9 μg·mL$^{-1}$ | Competitive | [38] |
| | *Marsdenia tenacissima* extract | *Marsdenia tenacissima* | CYP2C9 | HLM | 12.68 mg·mL$^{-1}$ | – | [52] |
| | | | CYP2C19 | HLM | 25.48 mg·mL$^{-1}$ | – | |
| | Sophora flavescens extract | *Sophora favescens* | CYP2C8 | HLM | 1.42 μg·mL$^{-1}$ | – | [53] |
| | | | CYP2C9 | HLM | 13.6 μg·mL$^{-1}$ | Competitive | |

Continued

| Category | Name | Source | CYP2C | *In vitro* model | $IC_{50}$ | Inhibition type | Ref. |
|---|---|---|---|---|---|---|---|
| | | | CYP2C19 | HLM | 19.1 μg·mL$^{-1}$ | − | |
| | *Labisia pumila* extracts | *Labisa pumila* | CYP2C8 | HLM | 2.39 μg·mL$^{-1}$ | Non-competitive | [54] |
| | | | CYP2C9 | HLM | 0.56 μg·mL$^{-1}$ | Competitive | |
| | | | CYP2C19 | HLM | 4.1 μg·mL$^{-1}$ | Non-competitive | |
| Chinese patent medicine | Qingfei Paidu decoction | − | CYP2C8 | HLM | 337.7 ± 43.3 μg·mL$^{-1}$ | − | [24] |
| | | − | CYP2C9 | HLM | 706.8 ± 71.1 μg·mL$^{-1}$ | − | |
| | Bovis Calculus Artifactus | Bovis Calculus | CYP2C11 | RLM | 3.71 μmol·L$^{-1}$ | − | [55] |
| | Huosu Yangwei oral liquid | − | CYP2C8 | HLM | 1.191 mg·mL$^{-1}$ | − | [25] |
| | | − | CYP2C9 | HLM | 1.815 mg·mL$^{-1}$ | − | |
| | | − | CYP2C19 | HLM | 1.272 mg·mL$^{-1}$ | − | |

断增大, 对于其在体内对CYP2C19代谢酶活性的抑制作用而引起的药物相互作用也不容忽视。

迷迭香酸在不同的体外模型中对CYP2C9抑制程度也不同, 在人肝微粒体 (HLM) 中 $IC_{50}$ = 76.89 μmol·L$^{-1}$, 在基因重组酶系 (HRC) 中 $IC_{50}$ = 39.6 μmol·L$^{-1}$。基因重组酶系与人体内相同酶的丰度差异较大, 只能用来对药物代谢进行细节化的研究, 其实验得到的结果不能外推到人体代谢。因此, 在HRC中迷迭香酸对CYP2C9抑制作用更明显, $IC_{50}$值相比于HLM也更小, 显示出更强的抑制作用。

## 3 CYP2D6

CYP2D6仅占肝脏总P450含量的2%～4%, 但能参与25%左右的临床常用药物的代谢[57], 其代谢底物主要包括抗抑郁药 (氟西汀、丙咪嗪、度洛西汀等)、抗心律失常药物 (普罗帕酮、美西律、利多卡因等)、抗高血压药物如$\beta$受体阻断剂 (普萘洛尔)、抗组胺药物 (氯雷他定、异丙嗪、特非那定)、抗病毒药物 (茚地那韦)[58], 常用右美沙芬-*O*-去甲基化作为检测CYP2D6代谢酶活性的探针反应[59]。部分中药及其成分对CYP2D6抑制作用见表3[24,25,32,43,45,60-65]。

丹红注射液对CYP2D6代谢酶活性的抑制作用最强 ($IC_{50}$ = 0.144 μmol·L$^{-1}$)。丹红注射液由丹参和红花两味中药组成, 主要功效为活血化瘀、舒脉通络, 临床广泛用于治疗冠心病、心绞痛、心肌梗死、脑血栓等心脑血管疾病, 常与阿司匹林、氯吡格雷、阿托伐他汀钙注射液等合用[66]。由于CYP2D6参与代谢的底物涉及大多数心血管系统药物如$\beta$受体阻断剂等, 故在联合使用丹红注射液治疗急性心肌梗死、冠心病、充血性心力衰竭时应注意中药所引起的药物相互作用, 谨慎使用。

## 4 CYP2E1

CYP2E1占肝脏中CYP450总量的7%, 能代谢大多数内源性小分子化合物和药物, 代谢底物主要包括对乙酰氨基酚、氯唑沙宗、苯、四氯化碳等[67]。常用氯唑沙宗-6-羟基化作为检测CYP2E1代谢酶活性的探针反应。部分中药及其成分对CYP2E1抑制作用见表4[13,14,25,26,36,43,46,49,62,63,68-74]。

CYP2E1可活化肝毒性物质及前致癌物质, 参与多种疾病的发生。所列举的中药及其成分中金合欢素 ($IC_{50}$ = 12.36 μmol·L$^{-1}$) 对CYP2E1代谢酶抑制作用较强。金合欢素是一种天然黄酮类化合物, 具有抗炎、抗氧化、抗肿瘤等广泛的药理活性[75]。研究表明, 金合欢素可以有效地抑制CYP1B1代谢酶的活性, 阻止雌

**Table 3** Inhibition of traditional Chinese medicine and its components on CYP2D6

| Category | Name | Source | *In vitro* model | $IC_{50}$ | Inhibition type | Ref. |
|---|---|---|---|---|---|---|
| Alkaloid | Peimine | *Fritillaria ussuriensis* | HLM | 22.46 μmol·L$^{-1}$ | Competitive | [60] |
| | Epiberberine | Rhizoma Coptidis | HLM | 11.86 μmol·L$^{-1}$ | Anti-competitive | [32] |
| | Lupanine | *Blue cohosh* | HLM | 10.00 μmol·L$^{-1}$ | − | [61] |
| Flavone | Dihydromyricetin | *Ampelopsis grossedentata* | HLM | 22.69 μmol·L$^{-1}$ | Competitive | [62] |
| Terpenoid | Ganoderic acid A | *Ganoderma lucidum* | HLM | 21.83 μmol·L$^{-1}$ | Competitive | [63] |
| The other compound | Anemarsaponin BII | *Anemarrhena asphodeloides* Bunge | HLM | 16.26 μmol·L$^{-1}$ | Competitive | [64] |
| | Acetylshikonin | *Lithospermum erythorhizon* | HLM | 2.6 μmol·L$^{-1}$ | − | [45] |
| Traditional Chinese medicine extract | Lotus leaf alcoholic extract | *Nelumbo nucifera* Gaertn | HLM | 12.05 μg·mL$^{-1}$ | − | [65] |
| | Lotus leaf alcoholic extract - alkaloid fraction | *Nelumbo nucifera* Gaertn | HLM | 0.96 μg·mL$^{-1}$ | Competitive | |
| | Lotus leaf alcoholic extract - flavonoid fraction | *Nelumbo nucifera* Gaertn | HLM | 139.40 μg·mL$^{-1}$ | Competitive | |
| Chinese patent medicine | Qingfei Paidu decoction | − | HLM | 125 3 ± 105.7 μg·mL$^{-1}$ | − | [24] |
| | Huosu Yangwei oral liquid | − | HLM | 2.642 mg·mL$^{-1}$ | − | [25] |
| | Danhong injection | *Salvia miltiorrhiza* Bunge | HLM | 0.676% | − | [43] |

**Table 4** Inhibition of traditional Chinese medicine and its components on CYP2E1

| Category | Name | Source | *In vitro* model | $IC_{50}$ | Inhibition type | Ref. |
|---|---|---|---|---|---|---|
| Flavone | Acacetin | *Lygodium japonicum* | RLM | 12.36 μmol·L$^{-1}$ | Competitive | [68] |
| | Baicalin | Radix Scutellariae | RLM | 103.5 μmol·L$^{-1}$ | Competitive | [69] |
| | Kaempferol | *Lysimachia clethroides* Duby | RLM | 60.26 ± 2.54 μmol·L$^{-1}$ | – | [70] |
| | Dihydromyricetin | *Ampelopsis grossedentata* | HLM | 25.74 μmol·L$^{-1}$ | Competitive | [62] |
| | Diosmetin | *Teucrium* | HLM | 20.5 μmol·L$^{-1}$ | – | [13] |
| Terpenoid | Catalpol | Rehmanniae Radix | HLM | 22.4 μmol·L$^{-1}$ | Competitive | [49] |
| | Friedelin | *Maytenus ilicifolia* | HLM | 22.54 μmol·L$^{-1}$ | Competitive | [71] |
| | Ganoderic acid A | *Ganoderma lucidum* | HLM | 28.35 μmol·L$^{-1}$ | Competitive | [63] |
| | Pachymic acid | *Poria* | HLM | 24.22 μmol·L$^{-1}$ | Competitive | [36] |
| | Bergenin | *Bergenia purpurascens* | HLM | 22.83 μmol·L$^{-1}$ | Competitive | [46] |
| | Isofraxidin | Umbelliferae | HLM | 15.98 μmol·L$^{-1}$ | Competitive | [14] |
| | Eleutheroside B | *Acanthopanax senticosus* | HLM | 193.20 μmol·L$^{-1}$ | Mixed | [72] |
| | Eleutheroside E | *Acanthopanax senticosus* | HLM | 188.36 μmol·L$^{-1}$ | Mixed | |
| Traditional Chinese medicine extract | Herbal extract of Jingyin granules | – | HLM | 810.0 ± 154.4 μg·mL$^{-1}$ | – | [73] |
| | Danshen water extract | *Salvia miltiorrhiza* Bunge | RLM | 1.07 mg·mL$^{-1}$ | Mixed | [74] |
| Chinese patent medicine | Danhong injection | *Salvia miltiorrhiza* Bunge | HLM | 0.917% | – | [26] |
| | Danhong injection | *Salvia miltiorrhiza* Bunge | HLM | 1.10% | – | [43] |
| | Huosu Yangwei oral liquid | – | HLM | 1.062 mg·mL$^{-1}$ | – | [25] |

激素致癌代谢产物的生成, 从而预防肿瘤的发生[76]。随着对金合欢素生物活性及作用机制的不断探索, 其能否通过抑制CYP2E1活性, 减少致癌代谢物质的生成, 从而预防肿瘤的发生, 成为一种有效的抗肿瘤药物, 还需要进一步的实验验证。

$IC_{50}$值取决于代谢体系中底物浓度及酶浓度等因素, 例如丹红注射液在所汇总的两篇文献中$IC_{50}$值分别为0.197%[26] (底物氯唑沙宗浓度为40 μmol·L$^{-1}$, 肝微粒体浓度为0.25 mg·mL$^{-1}$) 和1.10%[43] (氯唑沙宗浓度为50 μmol·L$^{-1}$, 肝微粒体浓度为0.3 mg·mL$^{-1}$), 因此在比较同一化合物对同一代谢酶在不同实验室的抑制结果时应保持实验条件一致。

## 5 CYP3A

CYP3A是广泛分布于机体各个组织, 主要包括CYP3A4、3A5、3A7、3A43四个亚家族, 是人类肝脏和小肠中CYP450含量最多的一个家族, 其中CYP3A4约占肝脏总P450含量的50%左右, 小肠中大约含有40% CYP3A4[77], 迄今为止, 已有超过50%的治疗药物被CYP3A4代谢, 如钙通道阻滞剂 (硝苯地平)、抗肿瘤药物 (多烯紫杉醇、环磷酰胺、他莫昔芬) 等[78], 咪达唑仑是一种短效苯二氮䓬类镇静催眠药物, 经CYP3A代谢酶催化生成1-OH咪达唑仑, 是测定体内外CYP3A最常用的探针底物之一[79]。部分中药及其成分对CYP3A的抑制作用见表5[12,14,16,32-37,40,44,46-49,52,55,60,62-64,71,80-99]。

**Table 5** Inhibition of traditional Chinese medicine and its components on CYP3A

| Category | Name | Source | CYP3A | *In vitro* model | $IC_{50}$ | Inhibition type | Ref. |
|---|---|---|---|---|---|---|---|
| Alkaloid | Cornin | *Verbena officinalis* | CYP3A4 | HLM | 9.20 μmol·L$^{-1}$ | Non-competitive | [80] |
| | Epiberberine | Rhizoma Coptidis | CYP3A4 | HLM | 81.5 μmol·L$^{-1}$ | – | [32] |
| | Peimine | *Fritillaria ussuriensis* | CYP3A4 | HLM | 13.43 μmol·L$^{-1}$ | Non-competitive | [60] |
| | Phellodendrine | *Phellodendri chinensis* cortex | CYP3A4 | HLM | 14.98 μmol·L$^{-1}$ | Non-competitive | [33] |
| | Sophocarpine | *Sophora* | CYP3A4 | HLM | 12.22 μmol·L$^{-1}$ | Non-competitive | [34] |
| | Brucine | *Strychnos nuxvomica* L. | CYP3A4 | HLM | 0.77 μmol·L$^{-1}$ | Competitive | [81] |
| Flavone | Astilbin | *Smilacis glabrae* Roxb | CYP3A4 | HLM | 2.63 μmol·L$^{-1}$ | Non-competitive | [82] |
| | lysionotin | *Lysionotus* | CYP3A4 | HLM | 13.85 μmol·L$^{-1}$ | Non-competitive | [83] |
| | Kaempferitrin | *Justicia spicigera* | CYP3A4 | HLM | 13.87 μmol·L$^{-1}$ | Non-competitive | [12] |
| | Cynaroside | *Angelica keiskei* | CYP3A4 | HLM | 15.88 μmol·L$^{-1}$ | Non-competitive | [35] |
| | Dihydromyricetin | *Ampelopsis grossedentata* | CYP3A4 | HLM | 14.75 μmol·L$^{-1}$ | Non-competitive | [62] |
| | Licochalcone A | *liquorice* | CYP3A4 | HLM | 2.77 μmol·L$^{-1}$ | Competitive | [84] |
| | Puerarin | Puerariae Radix | CYP3A4 | HLM | 15.5 ± 3.9 μmol·L$^{-1}$ | – | [85] |
| | Acacetin | *Lygodium japonicum* | CYP3A1 | RLM | 58.46 μmol·L$^{-1}$ | Mixed | [86] |
| | Apigenin | *Lygodium* root | CYP3A1 | RLM | 8.20 μmol·L$^{-1}$ | – | |
| | Chrysin | *Propolis* | CYP3A4 | HLM | 2.5 ± 0.6 μmol·L$^{-1}$ | – | [87] |
| | Myricetin | *Myricaceae* | CYP3A4 | HLM | 20.29 μmol·L$^{-1}$ | Non-competitive | [88] |
| | | | CYP3A2 | RLM | 27.14 μmol·L$^{-1}$ | Mixed | |

Continued

| Category | Name | Source | CYP3A | *In vitro* model | $IC_{50}$ | Inhibition type | Ref. |
|---|---|---|---|---|---|---|---|
| | Isobavachalcone | Fructus Psoraleae | CYP3A4 | HLM | 35.20 μmol·L$^{-1}$ | Competitive | [89] |
| | Methylophiop-ogonanone A | *Ophiopogon japonicas* | CYP3A | HLM | 2.75 μmol·L$^{-1}$ | − | [90] |
| Terpenoid | Ganoderic acid A | *Ganoderma lucidum* | CYP3A4 | HLM | 15.05 μmol·L$^{-1}$ | Non-competitive | [63] |
| | Catalpol | Rehmanniae Radix | CYP3A4 | HLM | 14.27 μmol·L$^{-1}$ | Non-competitive | [49] |
| | Friedelin | *Maytenus ilicifolia* | CYP3A4 | HLM | 10.79 μmol·L$^{-1}$ | Non-competitive | [71] |
| | Glycyrrhetinic acid | *Licorice* | CYP3A4 | HLM | 1.53 μmol·L$^{-1}$ | − | [91] |
| | Alantolactone | *Helenium* | CYP3A4 | HLM | 3.599 μmol·L$^{-1}$ | Non-competitive | [37] |
| | Celastro | *Trypterygium wilfordi* Hook | CYP3A2 | RLM | 23.2 μmol·L$^{-1}$ | Mixed | [40] |
| | Dihydrotanshinone | *Danshen* | CYP3A2 | RLM | 56.1 μmol·L$^{-1}$ | − | [92] |
| Phenol | Curculigoside | *Curculigo orchioides* | CYP3A4 | HLM | 9.47 μmol·L$^{-1}$ | Competitive | [48] |
| The other compound | Anemarsaponin BII | *Anemarrhena asphodeloides* | CYP3A4 | HLM | 13.67 μmol·L$^{-1}$ | Non-competitive | [64] |
| | Pachymic acid | *Poria* | CYP3A4 | HLM | 15.04 μmol·L$^{-1}$ | Non-competitive | [36] |
| | Isofraxidin | *Umbelliferae* | CYP3A4 | HLM | 15.49 μmol·L$^{-1}$ | Non-competitive | [14] |
| | Sauchinone | *Saururaceae* | CYP3A4 | HLM | 0.207 μmol·L$^{-1}$ | Non-competitive | [44] |
| | Bergenin | *Bergenia purpurascens* | CYP3A4 | HLM | 14.39 μmol·L$^{-1}$ | Non-competitive | [46] |
| | Sodium tanshinone IIA sulfonate | *Danshen* | CYP3A4 | HLM | 6.4 μmol·L$^{-1}$ | Competitive | [93] |
| | Cajaninstilbene acid | *Pigeonpea* | CYP3A4 | HLM | 28.3 μmol·L$^{-1}$ | − | [47] |
| | Gomisin B | *Schisandra chinensis* | CYP3A4 | HLM | 0.76 μmol·L$^{-1}$ | − | [94] |
| | Gomisin C | | CYP3A4 | HLM | 0.059 ± 0.03 μmol·L$^{-1}$ | − | [95] |
| | Magnolol | *Magnolia officinalis* | CYP3A | RLM | 35.0μmol·L$^{-1}$ | Competitive | [16] |
| Traditional Chinese medicine extract | Huang-Lian-Jie-Du-decoction-total flavonoids | − | CYP3A1 | RLM | 4.24 μg·mL$^{-1}$ | − | [96] |
| | Huang-Lian-Jie-Du-decoction-total alkaloids | − | CYP3A1 | RLM | 2.61 μg·mL$^{-1}$ | − | |
| | *Marsdenia tenacissima* extract | *Marsdenia tenacissima* | CYP3A4 | HLM | 11.25 mg·mL$^{-1}$ | − | [52] |
| | Danshen extract | *Salvia miltiorrhiza* Bunge | CYP3A4 | HLM | 136 μg·mL$^{-1}$ | Competitive | [97] |
| | | | CYP3A1 | RLM | 748 μg·mL$^{-1}$ | Competitive | |
| Chinese patent medicine | Bovis Calculus Artifactus | Bovis Calculus | CYP3A1 | RLM | 0.17 μmol·L$^{-1}$ | − | [55] |
| | Dengzhan Shengmai capsule | − | CYP3A1 | RLM | 0.02 mg·mL$^{-1}$ | − | [98] |
| | Salvianolate | − | CYP3A4 | HLM | 1.438 mg·L$^{-1}$ | Non-competitive | [99] |

生物碱类中对CYP3A代谢酶活性抑制作用最强的是马钱子碱 ($IC_{50}$ = 0.77 μmol·L$^{-1}$), 马钱子碱是传统中药马钱子的主要有效成分, 其含量占马钱子总生物碱的30%～40%, 具有显著的镇痛、抗炎、抗肿瘤作用[100]。目前国内外有关报道已经能从细胞水平、分子水平等方面解释其作用机制, 有关马钱子碱的研究趋势是如何将其开发成安全、有效的药用新剂型, 充分发挥其药理作用。在将其开发成新剂型时的临床前药物研究, 应充分考虑其对CYP3A4代谢酶活性的抑制作用。

木脂素类中五味子乙素和五味子丙素对CYP3A4抑制作用最强, $IC_{50}$值分别为0.76 μmol·L$^{-1}$和0.059 ± 0.03 μmol·L$^{-1}$。五味子为木兰科植物五味子的干燥成熟果实, 主要含有木脂素、挥发油类、黄酮类、萜类等活性成分, 药理研究表明具有保护肝脏、镇静催眠、降血糖、抗氧化及增强免疫力抗肿瘤等作用, 木脂素为五味子中主要的特征性活性成分, 约占8%[101]。研究表明, 五味子乙素连续3天灌胃给药后, 大鼠体内CYP3A4探针底物咪达唑仑药动学发生显著变化, 咪达唑仑的血药浓度−时间曲线下面积 (AUC) 增大约60%, 咪达唑仑经CYP3A4代谢产物羟基咪达唑仑的AUC降低[102]。目前有五味子胶囊、参芪五味子片等由五味子做成的著名中成药, 有健脾安神、益气宁心等功效, 常用于一些疾病的辅助治疗, 故在与经CYP3A4代谢的药物合用时应注意由中药所引起的药物相互作用。

## 6 结语

近年来, 中西医联合治疗已经成为治疗疾病的常用方法, 尤其对于一些慢性疾病如高血压、糖尿病等在化学药物治疗的同时经常合用一些中成药。中药或其成分对肝脏中CYP450代谢酶活性产生抑制作用会直接影响该代谢酶底物的药动学过程, 从而对其药效产生影响。由于体内实验受干扰因素较多, 无法完全阐明由中药引起的不良反应机制及代谢机制, 限制了其在探究中药及其成分与CYP450代谢酶之间相互作用

方面的应用。肝微粒体的体外代谢研究对于明确中药及其成分的代谢途径、阐明中药配伍使用达到增效减毒的代谢机制、探究中药或其成分对肝微粒体中相关代谢酶的影响, 以阐明其不良反应的机制有着积极的作用。

同时对于中药代谢探究仍有不足, 如未能从蛋白结构与分子结构层面上解释其抑制原理等。因此, 还需发展相应技术和研究方法, 结合体内实验深入探究中药的物质组成和结果特征并在此基础上阐明其作用机制, 减少由中药与CYP450代谢酶相互作用引起的药物不良反应, 从而促进中医药的现代化发展。

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**利益冲突**: 本文无任何利益冲突问题。

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