

中药活性成分逆转肿瘤多药耐药及协同增效作用的研究进展



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【摘要】肿瘤多药耐药 (MDR) 是导致化疗与靶向治疗失败的重要原因。近年来, 中药活性成分由于其“多成分-多靶点-低毒性”的特点, 在逆转 MDR 和增强化疗疗效方面展现出独特优势。本文系统综述了 MDR 的关键分子机制, 重点探讨了黄芩素、姜黄素、丹参酮等典型活性成分在抑制药物外排泵、重建凋亡稳态、干扰 DNA 修复通路及改善肿瘤免疫微环境等方面的作用。研究表明, 这些成分不仅能够独立发挥逆转耐药的作用, 还可与常用化疗药物协同增效, 显著提升抗肿瘤综合疗效。本综述为中药改善肿瘤耐药研究提供了理论支持, 并为多靶点联合干预策略的构建与优化提供了新思路。

【关键词】肿瘤多药耐药; 中药活性成分; 协同增效; 分子机制

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Research progress on the synergistic effects of active components from traditional Chinese medicine in reversing tumor multidrug resistance

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【Abstract】Multidrug resistance (MDR) is a major cause of failure in chemotherapy and targeted therapy. In recent years, active components of traditional Chinese medicine (TCM), characterized by their "multi-component, multi-target, and low-toxicity" properties, have shown unique advantages in reversing MDR and enhancing the efficacy of chemotherapy. This review systematically summarizes the key molecular mechanisms of MDR, with a focus on representative active components such as baicalein, curcumin, and tanshinone. These compounds have been shown to inhibit drug efflux pumps, restore apoptotic homeostasis, interfere with DNA repair pathways, and modulate the tumor immune microenvironment. Evidence indicates that these components not only exert independent effects in reversing resistance but also act synergistically with conventional chemotherapeutic agents, significantly improving overall antitumor efficacy. This review provides theoretical support for the application of TCM in MDR research and offers new perspectives for the development and optimization of multi-target combination strategies.

【Keywords】Tumor multidrug resistance; Active components of traditional Chinese medicine; Synergistic effect; Molecular mechanism

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肿瘤多药耐药 (multidrug resistance, MDR) 是导致癌症治疗失败的主要因素之一, 其主要表现为癌细胞对多种结构和作用机制不同的抗肿瘤药物产生交叉耐药性^[1]。MDR 的形成是一个多因素、多机制协同作用的过程, 核心机制主要包括三磷酸腺苷 (adenosine triphosphate, ATP) 结合盒转运蛋白 (ATP-binding cassette transporters, ABC) 如 P-糖蛋白 (P-glycoprotein, P-gp)、乳腺癌耐药蛋白等的过度表达, 导致药物外排增强; 细胞凋亡程序的抑制, 使癌细胞逃避免疫清除; DNA 损伤修复机制的异常激活, 提高细胞对药物诱导损伤的耐受能力; 以及肿瘤微环境 (tumor microenvironment, TME) 中免疫抑制、低氧、酸性、促炎状态等因素的综合干扰^[2]。此外, DNA 甲基化、组蛋白修饰、非编码 RNA 等表观遗传异常亦在 MDR 发生中起到重要调控作用^[3]。这些改变相互交织, 构建出一个高度复杂、动态可塑的耐药网络, 严重削弱了化疗及靶向治疗的疗效。

目前临床主要通过加大药物剂量、调整用药方案或联合逆转剂 (如 P-gp 抑制剂、凋亡诱导剂、信号通路抑制剂等) 方式尝试逆转 MDR 表型^[4]。尽管上述策略在一定程度上改善了部分患者的治疗反应, 但普遍存在疗效不稳定、不良反应大、作用靶点局限等问题, 难以有效覆盖 MDR 网络的复杂调控机制。因此, 亟需开发具有多靶点、低毒性、协同增效的新型耐药逆转干预策略。

传统中医药在肿瘤治疗中已有长期应用基础, 具有扶正祛邪、抗肿瘤、缓解毒副反应、延缓耐药进展等综合作用。近年来, 越来越多研究集中于中药活性成分在 MDR 逆转中的潜力。大量证据表明, 中药来源的天然产物凭借“多成分-多靶点-多通路”的药理特性, 能够同时干预多个耐药相关通路, 重塑肿瘤细胞的药物敏感性^[5]。其中, 黄酮类、生物碱类、萜类、多酚类及香豆素类等活性成分在调控药物外排泵表达、促进凋亡、抑制 DNA 修复、改善肿瘤免疫微环境等方面展现出显著效果^[6]。此外, 部分活性成分如姜黄素、白藜芦醇等已进入临床前或临床研究阶段, 并在与化疗药物联合应用中展现出良好的协同疗效和安全性^[7]。相比传统化学抑制剂, 中药活性成分具有低毒性、良好耐受性等优势, 成为当前逆转耐药研究的重要方向之一。

1 直接靶向耐药相关蛋白

1.1 抑制 ABC 转运泵

药物转运蛋白是 MDR 发展的关键分子驱动因素, 其通过 ATP 依赖的主动外排机制显著降低细胞内化疗药物浓度。常见的 ABC 家族成员包括 P-gp、乳腺癌耐药蛋白 (breast cancer resistance protein, BCRP/ABCG2)、多药耐药相关蛋白 1 (multidrug resistance-associated protein 1, MRP1/ABCC1) 以及肺耐药相关蛋白 (lung resistance-related protein, LRP) 等^[8]。尤其是 P-gp, 作为 ABC 转运蛋白的代表, 是多种肿瘤中 MDR 的核心介导因素之一。该蛋白能够识别多种结构类型的抗癌药物, 并将其主动泵出细胞外, 从而显著降低药物在癌细胞内的有效浓度^[9-11]。

目前, P-gp 的过表达已在多种耐药性恶性肿瘤中被证实。传统中药在逆转 P-gp 介导的耐药中展现出独特优势。一方面, 中药活性成分可作为底物类似物与化疗药物竞争结合 P-gp 的药物结合位点, 阻断药物外排; 另一方面, 可通过抑制 ATP 酶活性, 剥夺泵功能所需的能量来源或者在转录、翻译、蛋白稳定性层面下调 P-gp 的表达水平, 改变 P-gp 构象, 从而间接抑制其泵出功能^[12]。Alopecurone B (ALOB) 是一种从苦参中分离得到的黄酮类化合物, 苦参具有清热燥湿、杀虫止痒等传统功效。Xia 等^[13]研究表明, ALOB 可下调 P-gp 的表达水平, 促进阿霉素 (doxorubicin, DOX) 在骨肉瘤耐药株 MG-63/DOX 细胞核内的积聚, 从而增强 DOX 诱导的细胞凋亡。丹参素可以降低多药耐药基因 1 和 B 淋巴细胞瘤-2 (B-cell lymphoma-2, Bcl-2) 的表达诱导凋亡, 在体外有效杀伤多药耐药肿瘤细胞^[14]。甾体皂苷类薯蓣皂苷通过双重调控 P-gp 蛋白转录合成与泛素化降解途径逆转耐药, 即靶向蛋白激酶 B (protein kinase B, Akt) / 磷酸化 p38 丝裂原活化蛋白激酶 (mitogen-activated protein kinases, MAPK) / 糖原合成酶激酶 3 β (glycogen synthase kinase 3 beta, GSK3 β) 信号网络, 抑制 Akt、c-Jun 氨基端激酶 (c-Jun N-terminal kinase, JNK)、细胞外信号调节激酶 (extracellular signal-regulated kinase, ERK) 及 GSK3 β 位点磷酸化, 阻断 P-gp 基因转录激活。通过增强 E3 泛素连接酶与 P-gp 的结合, 促进 P-gp Lys48 位点多聚泛素化修饰^[15]。

1.2 调控药物代谢酶

药物代谢是药物的生物转化过程,通常由药物代谢酶介导,在肿瘤耐药中通过多种机制发挥作用,包括 I 相酶如细胞色素 P450 酶 (cytochrome P450, CYP) 对药物的氧化、还原或水解代谢,降低药物活性; II 相酶如谷胱甘肽转移酶 (glutathione S-transferase, GST)、葡萄糖醛酸转移酶 (UDP-glycosyltransferase, UGT) 通过结合反应促进药物解毒和排出; III 相酶通过外排泵减少细胞内药物蓄积。这些酶的异常表达或活性改变导致化疗药物代谢加速或清除增强,从而削弱药效,是肿瘤耐药的重要机制之一^[16]。中药天然成分可通过选择性调节 CYP450 酶家族及非 P450 酶系等的活性,重塑 TME 中的药物代谢平衡,进而逆转耐药。雷公藤可以选择性抑制 CYP3A4 及 CYP2C19/CYP2D6,减少化疗药物代谢失活^[17]。黄芩素通过激活芳烃受体,诱导 CYP1A1/1A2 活性以增强部分前药的激活效率,同时抑制 CYP3A 降低药物降解,增加环磷酸胺活化^[18]。丹参酮通过上调 CYP1A2 的蛋白和 mRNA 表达,促进依托泊苷等依赖该酶活化的前药转化为活性形式,弥补耐药细胞中代谢激活不足的缺陷^[19]。

2 间接调控耐药信号通路

2.1 表观遗传调控

表观遗传调控通过改变组蛋白修饰 (如组蛋白去乙酰化酶 4 抑制剂恢复乙酰化水平) 和 DNA 甲基化状态 (如逆转耐药基因的低甲基化),重新激活抑癌基因并抑制促耐药基因的表达,从而增强肿瘤细胞对化疗药物的敏感性^[20]。中药活性成分可以通过调控表观遗传,联合传统化疗有效逆转多药耐药。

盐酸小檗碱是一种天然异喹啉生物碱,虽然单独抗菌活性较弱,但能显著增强多重耐药菌对抗生素的敏感性,甚至逆转其对替加环素、舒巴坦钠、美罗培南和环丙沙星等药物的耐药性。其机制涉及 *adeB* 基因的表达与 AdeB 转运蛋白结合,减少 AdeABC 泵对抗生素的排出,从而减少药物外排^[21]。小檗碱还能通过下调 RAD51 蛋白表达和磷酸化水平,破坏 DNA 损伤修复机制,削弱肿瘤基因组稳定性^[22]。盐酸小檗碱可以靶向结合磷脂酰肌醇 3-激酶 (phosphatidylinositol-3 kinase, PI3K) 催化亚基,阻断下游 Akt/哺乳动物雷帕

霉素靶蛋白 (mammalian target of rapamycin, mTOR) 磷酸化,以此增强肝癌细胞对索拉非尼敏感性^[23]。白藜芦醇直接结合 XPA 蛋白,阻断其与损伤 DNA 的结合能力,导致顺铂诱导的 DNA 交联修复失败^[24]。

2.2 TME 重塑

TME 是由癌细胞、癌症相关成纤维细胞 (cancer-associated fibroblasts, CAFs)、免疫细胞 (如骨髓来源的抑制性细胞和肿瘤相关巨噬细胞)、细胞外基质及缺氧-酸性-氧化应激网络组成的动态生态系统。TME 通过炎症微环境、缺氧等物理屏障,以及代谢重编程和免疫逃逸协同驱动上皮-间充质转化和多药耐药^[25-26]。而中药活性成分的多靶点干预策略可以通过抑制或激活自噬,改变 TME 的缺氧、酸性和氧化应激状态,增强药物敏感性。丹参酮 IIA 可以抑制 CAFs 的血小板衍生生长因子受体 β /ERK1/2 通路,减少血小板源性生长因子-BB 和趋化因子 2 的分泌,削弱 CAFs 对癌细胞耐药性的支持作用^[27]。抑制下游 Janus 激酶 1 和 2,促进血管完整性和原位灌注来抑制肿瘤生长,改善免疫抑制性微环境,与 PD-1 单克隆抗体联合治疗时,表现出更强的免疫激活表型^[28]。人参皂苷 Rg₃ 可以通过逆转免疫抑制状态,将促肿瘤的 M2 型巨噬细胞重新极化为抗肿瘤的 M1 型,抑制髓源性抑制细胞和白细胞介素-6/信号传导及转录激活蛋白 (signal transducer and activator of transcription, STAT3) /p-STAT3 信号通路,减少 M2 巨噬细胞的浸润及其介导的耐药性,从而改善免疫抑制性 TME。同时减少肿瘤相关成纤维细胞和胶原纤维,破坏肿瘤的纤维化结构,降低细胞外基质的屏障作用,增强药物渗透性^[29]。

图 1 和表 1 中汇总了不同种类的中药在肿瘤耐药上的作用机制及应用。其中黄酮类和多酚类成分是抑制 ABC 转运泵的主要代表,而黄酮类和皂苷类则在药物代谢酶调控中作用突出;不同类别成分的作用机制相互补充,为构建“多成分-多靶点”的联合逆转策略提供了坚实的分子基础。

3 协同增效的配伍策略

3.1 中药-化疗药协同

中药活性成分与化疗药物的协同配伍不仅可通过直接抑制耐药蛋白表达及调控凋亡通路以增强化疗敏感性,还涉及铁死亡诱导、免疫微环境

调控等新兴机制，从而在多维度克服多药耐药并减轻毒副作用^[52]。例如，低剂量表没食子儿茶素与 DOX 联用可抑制 Nrf2 介导的抗氧化通路，增强氧化应激并促进药物内化，显著提升对 A549 耐药肺癌细胞的杀伤效果^[53]。黄芩苷则通过扰乱细胞内铁稳态，激活 p53/SLC7A11/GPX4 信号轴并促进脂质过氧化，从而诱发铁死亡，增强 5-FU 对乳腺癌细胞的化疗敏感性^[54–55]。葛根素能够抑制上皮-间质转化进程并下调 ABCB1 外排泵功能，有效逆转乳腺癌对奥沙利铂的耐药表型，联合应用显著抑制肿瘤转移并提升体内抗肿瘤效果^[56]。综上，中药活性成分通过多靶点、多机制协同化疗药物，不仅显著提高肿瘤细胞对药物的

响应能力，还有助于降低系统毒性，为逆转 MDR 提供了有效的联合策略。

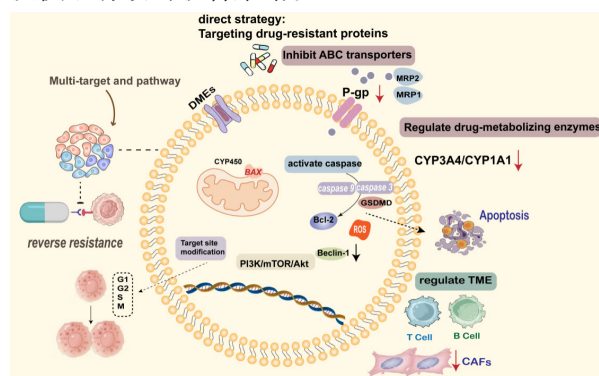


图1 中药活性成分逆转MDR的主要机制
Figure 1. The main mechanism of MDR reversal by active ingredients in TCM

表1 部分中药活性成分及其耐药机制

Table 1. Some active ingredients of TCM and their resistance mechanisms

中药活性成分	成分类别	主要来源	耐药机制	参考文献
倍半萜香豆素	萜类及其衍生物	防风、前胡等	抑制ABCC (MRP1/ABCC1) 外排泵，减少化疗药物外流	[30]
雷公藤甲素		雷公藤	特异性结合P-gp跨膜结构域Leu884/Lys887位点，通过构象锁定抑制药物转运	[31]
白桦脂酸		白桦树皮	通过疏水口袋结合P-gp核昔结合域，竞争性抑制ATP水解活性	[32]
紫草素		紫草	产生ROS，使紫杉醇对耐药的人卵巢癌细胞的治疗作用增敏的非P-gp独立机制	[33]
姜黄素	多酚类	姜黄	下调Wnt/β-catenin通路，抑制ABCB1基因启动子活性	[34]
白藜芦醇		虎杖	抑制HIF-1α通路改善缺氧微环境；通过ROS超载诱导DNA损伤累积；抑制核苷酸切除修复通路，下调P-gp蛋白表达；通过miR-122-5p靶向Bcl-2，参与细胞周期阻滞	[35]
表没食子儿茶素		绿茶	调制的P-gp的作用，增加化疗剂DOX的耐药KB-A1细胞的细胞内累积	[36]
槲皮素	黄酮类	槐花	通过调控ERK/JNK磷酸化诱导凋亡，同时抑制ABCB1糖蛋白膜转运效率	[37]
异鼠李素		沙棘	DNA损伤和调节DOX耐药乳腺癌中的 AMPK/mTOR/p70S6K 信号通路诱导细胞周期停滞和凋亡	[38]
柚皮苷		枳壳	下调P-gp、MRP，抑制NF-κB	[39]
木犀草素		菊花	下调Nrf2、MRP1、P-gp、GST-pi表达，增加细胞内DOX浓度	[40]
芹菜素		黄芩	抑制ABC转运蛋白ATP酶活性 (P-gp、MDR1表达)	[41]
黄芪多糖	皂苷/多糖类	黄芪	通过TLR4/MyD88信号诱导M2向M1巨噬细胞极化，重塑免疫抑制性微环境调节miR-16/NF-κB信号通路，从而影响MDR1和P-gp170的水平	[42]
三七皂苷		三七	通过ERK/Akt通路改变HepG2/DOX细胞耐药性	[43]
重楼皂苷		重楼	联合后降低和EMT有关的蛋白质波形蛋白的表达，以及增加钙粘蛋白的表达，表明联合组抑制EMT的形成	[44]
淫羊藿苷		淫羊藿	通过lncRNANEAT1/TGF-β/SMAD2、PTEN/Akt通路逆转DNA甲基化耐药表型，同时抑制EMT进程	[45–46]
苦参碱	生物碱类	苦参	非竞争性抑制P-gp和MRP1功能，增加DOX胞内浓度	[47]
小檗碱		黄连	抑制同源重组修复关键蛋白RAD51，增强顺铂对DNA损伤的不可逆性	[48]
蛇床子素		蛇床子	抑制PI3K/Akt/mTOR通路，减少P-gp翻译合成	[49]
植酸	其他类	谷物、豆类	与P-gp外排通道的芳香族残基 (Phe335/Tyr310) 结合，诱导构象变化抑制药物转运	[50]
川穹嗪		川芎	川穹嗪可下调ABCB1、ABCC1和ABCG2的表达水平，此可能为逆转A549/DDP细胞对顺铂耐受性的机制之一。	[51]

注：ROS：活性氧 (reactive oxygen species)；β-catenin：β-连锁蛋白；HIF：低氧诱导因子 (hypoxia-inducible factor)；AMPK：AMP 活化蛋白激酶 (AMP-activated protein kinase)；NF-κB：核因子κB (nuclear factor kappa-B)；Nrf2：核因子-红细胞2相关因子2 (nuclear factor erythroid 2-related factor 2)；TLR4：Toll样受体4 (Toll-like receptor 4)；MyD88：髓样分化因子88 (myeloid differentiation primary response protein 88)；TGF-β：转化生长因子-β (transforming growth factor-β)。

3.2 中药-靶向药协同

靶向药物虽在肿瘤治疗中展现出高特异性，但长期使用易引发耐药和毒副作用。中药活性成分可通过多靶点调控与靶向药物形成协同效

应^[57]。人参皂苷 Rg₃ 联合厄洛替尼可以通过抑制表皮生长因子受体/PI3K/Akt 通路，增强厄洛替尼的治疗效果^[58]。熊果酸可以促进髓样细胞白血病 1 蛋白的蛋白酶体降解、抑制 SLC7A11 诱导铁

死亡增加索拉菲尼的化疗敏感性,表现出协同效应^[59]。黄腐酚与奥希替尼联合治疗破坏 USP9X 与 Ets-1 之间的相互作用,抑制 Ets-1 在 Thr38 位点的磷酸化并促进其降解,从而靶向 Ets-1/c-Met 信号通路,诱导耐药细胞发生内源性凋亡,在体内内外均显著恢复了奥希替尼耐药非小细胞肺癌细胞对奥希替尼的敏感性^[59]。

3.3 纳米载药协同增效

随着纳米技术在药物传递领域的深入研究,纳米共递送系统为联合抗肿瘤治疗提供了新策略。纳米载体通过调控粒径、优化结构及表面功能化修饰,可实现高效载药、延长体内循环时间,并借助增强渗透与滞留效应或主动靶向机制,显著提升药物在肿瘤组织中的富集与滞留。该类系统不仅可改善药物的溶解性、稳定性和生物利用度,还能通过协同增效、逆转多药耐药和减轻系统毒性,显著增强抗肿瘤疗效^[60]。

研究显示,纳米葛根素可通过调控 Akt/基质金属蛋白酶 9 (matrix metalloproteinase 9, MMP-9) 信号通路、抑制 NSUN2 介导的 RNA 甲基化、阻断 Akt/血管内皮生长因子 A/MMP-9 轴,进而重塑免疫抑制性 TME,增强 HepG2 细胞对 DOX 的敏感性,逆转化疗耐药^[61]。Baek 等^[62]开发了一种共载姜黄素与紫杉醇的多功能脂质纳米粒,通过在表面修饰叶酸配体实现针对肿瘤细胞上叶酸受体的主动靶向,该策略显著增强细胞内药物积累并有效逆转 MDR。此外,共载白藜芦醇与紫杉醇的纳米系统可显著抑制 P-gp 的表达,增加药物在耐药细胞内的蓄积,减少外排,从而有效逆转 MDR^[63]。综上所述,纳米共递送系统不仅显著提升了天然活性成分与化疗药物的协同抗肿瘤效果,还在一定程度上克服了传统化疗中常见的耐药性和毒副作用问题,展现出广阔的临床转化前景,是未来抗肿瘤药物研发的重要方向之一。

4 结语

MDR 治疗选择包括联合治疗、靶向治疗、药物递送系统、耐药机制抑制和免疫治疗。当耐药机制受到抑制时,癌细胞通过适应替代耐药机制或途径获得耐药性^[64]。为了有效对抗耐药性,需要全面了解与 MDR 相关的多种机制。中药活性成分在逆转 MDR 方面展现出显著的协同增效潜力,通过多靶点逆转耐药,优于单一靶点的化学抑制剂。配

伍策略需结合“直接抑制外排+信号通路调控+递药技术优化”。未来需加强基于患者的个性化用药验证,推动中药增敏剂纳入联合治疗方案。这些多途径、多靶点的协同作用,不仅为逆转 MDR 提供了新策略,还减轻了化疗的毒副作用,展现了中药在肿瘤综合治疗中的独特优势。未来研究需进一步结合临床验证,以推动其转化应用。

参考文献

- 1 Tannock IF. Tumor physiology and drug resistance[J]. *Cancer Metastasis Rev*, 2001, 20(1-2): 123-132. DOI: [10.1023/a:1013125027697](#).
- 2 Vasan N, Baselga J, Hyman DM. A view on drug resistance in cancer[J]. *Nature*, 2019, 575(7782): 299-309. DOI: [10.1038/s41586-019-1730-1](#).
- 3 Correia AL, Bissell MJ. The tumor microenvironment is a dominant force in multidrug resistance[J]. *Drug Resist Updat*, 2012, 15(1-2): 39-49. DOI: [10.1016/j.drug.2012.01.006](#).
- 4 Chen T, Xiao Z, Liu X, et al. Natural products for combating multidrug resistance in cancer[J]. *Pharmacol Res*, 2024, 202: 107099. DOI: [10.1016/j.phrs.2024.107099](#).
- 5 Zou JY, Chen QL, Luo XC, et al. Natural products reverse cancer multidrug resistance[J]. *Front Pharmacol*, 2024, 15: 1348076. DOI: [10.3389/fphar.2024.1348076](#).
- 6 李克仙. 马齿苋中黄酮类及生物碱类的研究进展[J]. *药物资讯*, 2023, 12(4): 317-337. [Li KX. Research progress on flavonoids and alkaloids in *Portulaca oleracea* L.[J]. *Pharmacy Information*, 2023, 12(4): 317-337.] DOI: [10.12677/PI.2023.124040](#).
- 7 Wang S, Yang S, Yang X, et al. Research progress of traditional Chinese medicine monomers in reversing multidrug resistance of breast cancer[J]. *Am J Chin Med*, 2023, 51(3): 575-594. DOI: [10.1142/S0192415X23500283](#).
- 8 Hanssen KM, Haber M, Fletcher JL. Targeting multidrug resistance-associated protein 1 (MRP1)-expressing cancers: beyond pharmacological inhibition[J]. *Drug Resist Updat*, 2021, 59: 100795. DOI: [10.1016/j.drug.2021.100795](#).
- 9 Fan J, To KKW, Chen ZS, et al. ABC transporters affects tumor immune microenvironment to regulate cancer immunotherapy and multidrug resistance[J]. *Drug Resist Updat*, 2023, 66: 100905. DOI: [10.1016/j.drug.2022.100905](#).
- 10 Levchenko A, Mehta BM, Niu X, et al. Intercellular transfer of P-glycoprotein mediates acquired multidrug resistance in tumor cells[J]. *Proc Natl Acad Sci U S A*, 2005, 102(6): 1933-1938. DOI: [10.1073/pnas.0401851102](#).
- 11 Tian Y, Lei Y, Wang Y, et al. Mechanism of multidrug resistance to chemotherapy mediated by pglycoprotein (review)[J]. *Int J Oncol*, 2023, 63(5): 119. DOI: [10.3892/ijo.2023.5567](#).
- 12 Dong J, Qin Z, Zhang WD, et al. Medicinal chemistry strategies to discover P-glycoprotein inhibitors: an update[J]. *Drug Resist Updat*, 2020, 49: 100681. DOI: [10.1016/j.drug.2020.100681](#).
- 13 Xia YZ, Ni K, Guo C, et al. Alopecurone B reverses doxorubicin-resistant human osteosarcoma cell line by inhibiting P-glycoprotein

- and NF- κ B signaling[J]. *Phytomedicine*, 2015, 22(3): 344–351. DOI: [10.1016/j.phymed.2014.12.011](https://doi.org/10.1016/j.phymed.2014.12.011).
- 14 Miao ZH, Tang T, Zhang YX, et al. Cytotoxicity, apoptosis induction and downregulation of MDR-1 expression by the anti-topoisomerase II agent, salvicine, in multidrug-resistant tumor cells[J]. *Int J Cancer*, 2003, 106(1): 108–115. DOI: [10.1002/ijc.11174](https://doi.org/10.1002/ijc.11174).
 - 15 赵劲竹. 薯蓣皂苷通过抑制 P-gp 表达并促进其降解逆转肿瘤耐药及 EMT 进程的研究 [D]. 郑州: 郑州大学, 2022. DOI: [10.27466/d.cnki.gzzdu.2022.005820](https://doi.org/10.27466/d.cnki.gzzdu.2022.005820).
 - 16 Wang J, Yu L, Jiang H, et al. Epigenetic regulation of differentially expressed drug-metabolizing enzymes in cancer[J]. *Drug Metab Dispos*, 2020, 48(9): 759–768. DOI: [10.1124/dmd.120.000008](https://doi.org/10.1124/dmd.120.000008).
 - 17 周锦屏, 张蕊, 师少军, 等. 雷公藤对药物代谢酶和转运体的调控作用研究进展 [J]. *中国医院药学杂志*, 2020, 40(14): 1595–1599. [Zhou JP, Zhang R, Shi SJ, et al. Advances in the modulation of Tripterygium on drug metabolizing enzyme and transporter[J]. *Chinese Journal of Hospital Pharmacy*, 2020, 40(14): 1595–1599.] DOI: [10.13286/j.1001-5213.2020.14.19](https://doi.org/10.13286/j.1001-5213.2020.14.19).
 - 18 Chan HY, Chen ZY, Tsang DS, et al. Baicalein inhibits DMBA–DNA adduct formation by modulating CYP1A1 and CYP1B1 activities[J]. *Biomed Pharmacother*, 2002, 56(6): 269–275. DOI: [10.1016/s0753-3322\(02\)00192-0](https://doi.org/10.1016/s0753-3322(02)00192-0).
 - 19 Tian QT, Ding CY, Song SS, et al. New tanshinone I derivatives S222 and S439 similarly inhibit topoisomerase I/II but reveal different p53-dependency in inducing G2/M arrest and apoptosis[J]. *Biochem Pharmacol*, 2018, 154: 255–264. DOI: [10.1016/j.bcp.2018.05.006](https://doi.org/10.1016/j.bcp.2018.05.006).
 - 20 Hayashi T, Konishi I. Correlation of anti-tumour drug resistance with epigenetic regulation[J]. *Br J Cancer*, 2021, 124(4): 681–682. DOI: [10.1038/s41416-020-01183-y](https://doi.org/10.1038/s41416-020-01183-y).
 - 21 Li X, Song Y, Wang L, et al. A potential combination therapy of berberine hydrochloride with antibiotics against multidrug-resistant *Acinetobacter baumannii*[J]. *Front Cell Infect Microbiol*, 2021, 11: 660431. DOI: [10.3389/fcimb.2021.660431](https://doi.org/10.3389/fcimb.2021.660431).
 - 22 Hou D, Xu G, Zhang C, et al. Berberine induces oxidative DNA damage and impairs homologous recombination repair in ovarian cancer cells to confer increased sensitivity to PARP inhibition[J]. *Cell Death Dis*, 2017, 8(10): e3070. DOI: [10.1038/cddis.2017.471](https://doi.org/10.1038/cddis.2017.471).
 - 23 吴泽明, 黄欣慧, 彭琴, 等. 盐酸小檗胺通过调控自噬和 PI3K/Akt/mTOR 信号通路改善索拉非尼耐药的机制 [J]. *中国实验方剂学杂志*, 2024, 30(14): 78–88. [Wu ZM, Huang XH, Peng Q, et al. Berberine hydrochloride ameliorates sorafenib resistance by regulating autophagy and PI3K/Akt/mTOR Signaling pathway[J]. *Chinese Journal of Experimental Formula*, 2024, 30(14): 78–88.] DOI: [10.13422/j.cnki.syfx.20240701](https://doi.org/10.13422/j.cnki.syfx.20240701).
 - 24 Choi CY, Lim SC, Lee TB, et al. Molecular basis of resveratrol-induced resensitization of acquired drug-resistant cancer cells[J]. *Nutrients*, 2022, 14(3): 699. DOI: [10.3390/nu14030699](https://doi.org/10.3390/nu14030699).
 - 25 Li Z, Yin P. Tumor microenvironment diversity and plasticity in cancer multidrug resistance[J]. *Biochim Biophys Acta Rev Cancer*, 2023, 1878(6): 188997. DOI: [10.1016/j.bbcan.2023.188997](https://doi.org/10.1016/j.bbcan.2023.188997).
 - 26 Erin N, Grahovac J, Brozovic A, et al. Tumor microenvironment and epithelial mesenchymal transition as targets to overcome tumor multidrug resistance[J]. *Drug Resist Updat*, 2020, 53: 100715. DOI: [10.1016/j.drug.2020.100715](https://doi.org/10.1016/j.drug.2020.100715).
 - 27 Mao D, Wang H, Guo H, et al. Tanshinone IIA normalized hepatocellular carcinoma vessels and enhanced PD-1 inhibitor efficacy by inhibiting ELTD1[J]. *Phytomedicine*, 2024, 123: 155191. DOI: [10.1016/j.phymed.2023.155191](https://doi.org/10.1016/j.phymed.2023.155191).
 - 28 Zhang YZ, Lai HL, Huang C, et al. Tanshinone IIA induces ER stress and JNK activation to inhibit tumor growth and enhance anti-PD-1 immunotherapy in non-small cell lung cancer[J]. *Phytomedicine*, 2024, 128: 155431. DOI: [10.1016/j.phymed.2024.155431](https://doi.org/10.1016/j.phymed.2024.155431).
 - 29 Zhu Y, Wang A, Zhang S, et al. Paclitaxel-loaded ginsenoside Rg₃ liposomes for drug-resistant cancer therapy by dual targeting of the tumor microenvironment and cancer cells[J]. *J Adv Res*, 2023, 49: 159–173. DOI: [10.1016/j.jare.2022.09.007](https://doi.org/10.1016/j.jare.2022.09.007).
 - 30 Kasaian J, Mosaffa F, Behravan J, et al. Modulation of multidrug resistance protein 2 efflux in the cisplatin resistance human ovarian carcinoma cells A2780/RCIS by sesquiterpene coumarins[J]. *Phytother Res*, 2016, 30(1): 84–89. DOI: [10.1002/ptr.5504](https://doi.org/10.1002/ptr.5504).
 - 31 Yi JM, Huan XJ, Song SS, et al. Triptolide induces cell killing in multidrug-resistant tumor cells via CDK7/RPB1 rather than XPB or p44[J]. *Mol Cancer Ther*, 2016, 15(7): 1495–1503. DOI: [10.1158/1535-7163.MCT-15-0753](https://doi.org/10.1158/1535-7163.MCT-15-0753).
 - 32 Saeed MEM, Mahmoud N, Sugimoto Y, et al. Betulinic acid exerts cytotoxic activity against multidrug-resistant tumor cells via targeting autocrine motility factor receptor (AMFR)[J]. *Front Pharmacol*, 2018, 9: 481. DOI: [10.3389/fphar.2018.00481](https://doi.org/10.3389/fphar.2018.00481).
 - 33 Wang Z, Yin J, Li M, et al. Combination of shikonin with paclitaxel overcomes multidrug resistance in human ovarian carcinoma cells in a P-gp-independent manner through enhanced ROS generation[J]. *Chin Med*, 2019, 14: 7. DOI: [10.1186/s13020-019-0231-3](https://doi.org/10.1186/s13020-019-0231-3).
 - 34 Xu T, Guo P, He Y, et al. Application of curcumin and its derivatives in tumor multidrug resistance[J]. *Phytother Res*, 2020, 34(10): 2438–2458. DOI: [10.1002/ptr.6694](https://doi.org/10.1002/ptr.6694).
 - 35 Zhang W, Jiang H, Chen Y, et al. Resveratrol chemosensitizes adriamycin-resistant breast cancer cells by modulating miR-122-5p[J]. *J Cell Biochem*, 2019, 120(9): 16283–16292. DOI: [10.1002/jcb.28910](https://doi.org/10.1002/jcb.28910).
 - 36 Qian F, Wei D, Zhang Q, et al. Modulation of P-glycoprotein function and reversal of multidrug resistance by (–)-epigallocatechin gallate in human cancer cells[J]. *Biomed Pharmacother*, 2005, 59(3): 64–69. DOI: [10.1016/j.biopha.2005.01.002](https://doi.org/10.1016/j.biopha.2005.01.002).
 - 37 Li S, Zhao Q, Wang B, et al. Quercetin reversed MDR in breast cancer cells through down-regulating P-gp expression and eliminating cancer stem cells mediated by YB-1 nuclear translocation[J]. *Phytother Res*, 2018, 32(8): 1530–1536. DOI: [10.1002/ptr.6081](https://doi.org/10.1002/ptr.6081).
 - 38 Yang T, Xiao Y, Liu S, et al. Isorhamnetin induces cell cycle arrest and apoptosis by triggering DNA damage and regulating the AMPK/mTOR/p70S6K signaling pathway in doxorubicin-resistant breast cancer[J]. *Phytomedicine*, 2023, 114: 154780. DOI: [10.1016/j.phymed.2023.154780](https://doi.org/10.1016/j.phymed.2023.154780).
 - 39 He J, Zhang HP. Research progress on the anti-tumor effect of Naringin[J]. *Front Pharmacol*, 2023, 14: 1217001. DOI: [10.3389/fphar.2023.1217001](https://doi.org/10.3389/fphar.2023.1217001).
 - 40 周欣宇, 李京敏, 张婷, 等. 木犀草素对白血病 K562/ADR 细胞多药耐药的逆转作用及机制研究 [J]. *天津医药*, 2023, 51(12): 1321–1325. [Zhou XY, Li JM, Zhang T, et al. Study on the mechanism of luteolin reversing multidrug resistance in leukemia K562/ADR cells[J]. *Tianjin Pharmaceutical*, 2023, 51(12): 1321–1325.] DOI: [10.11958/20230722](https://doi.org/10.11958/20230722).

- 41 乐伊婕, 曹建国, 杨小红, 等. 芹菜素对 MHCC97H 源性球细胞对 5-氟尿嘧啶敏感性的影响 [J]. 中南药学, 2024, 22(6): 1566–1571. [Le YJ, Cao JG, Yang XH, et al. Apigenin up-regulates expression of miR-34a-5p and enhances sensitivity to fluorouracil in MHCC97H-derived spheres[J]. Central South Pharmacy, 2024, 22(6): 1566–1571.] DOI: [10.7539/j.issn.1672-2981.2024.06.025](https://doi.org/10.7539/j.issn.1672-2981.2024.06.025).
- 42 Zhou L, Liu Z, Wang Z, et al. Astragalus polysaccharides exerts immunomodulatory effects via TLR4-mediated MyD88-dependent signaling pathway *in vitro* and *in vivo*[J]. Sci Rep, 2017, 7: 44822. DOI: [10.1038/srep44822](https://doi.org/10.1038/srep44822).
- 43 冯晓异, 魏宁顺, 赵微, 等. 三七总皂苷通过 ERK/Akt 通路改变 HepG2/阿霉素细胞耐药性 [J]. 中国实验方剂学杂志, 2021, 27(2): 52–59. [Feng XY, Wei NY, Zhao W, et al. Effect of notoginseng total saponins on changing multidrug resistance in HepG2/adriamycin cells through ERK/Akt Signaling[J]. Chinese Journal of Experimental Formulae, 2021, 27(2): 52–59.] DOI: [10.13422/j.cnki.syfx.20202121](https://doi.org/10.13422/j.cnki.syfx.20202121).
- 44 吕盼盼. 重楼皂苷联合顺铂抗肺癌作用机制研究 [D]. 天津: 天津科技大学, 2021. DOI: [10.27359/d.cnki.gtqgu.2021.000069](https://doi.org/10.27359/d.cnki.gtqgu.2021.000069).
- 45 Xu B, Jiang C, Han H, et al. Icaritin inhibits the invasion and epithelial-to-mesenchymal transition of glioblastoma cells by targeting EMMPRIN via PTEN/Akt/HIF-1 α signalling[J]. Clin Exp Pharmacol Physiol, 2015, 42(12): 1296–1307. DOI: [10.1111/1440-1681.12488](https://doi.org/10.1111/1440-1681.12488).
- 46 Song B, Wei F, Peng J, et al. Icaritin regulates emt and stem cell-like character in breast cancer through modulating lncRNA NEAT1/TGF β /SMAD2 signaling pathway[J]. Biol Pharm Bull, 2024, 47(2): 399–410. DOI: [10.1248/bpb.b23-00668](https://doi.org/10.1248/bpb.b23-00668).
- 47 Zhou BG, Wei CS, Zhang S, et al. Matrine reversed multidrug resistance of breast cancer MCF-7/ADR cells through PI3K/AKT signaling pathway[J]. J Cell Biochem, 2018, 119(5): 3885–3891. DOI: [10.1002/jcb.26502](https://doi.org/10.1002/jcb.26502).
- 48 孙梦瑶, 王丹丹, 吴秋雪, 等. 吴茱萸碱、小檗碱对 SGC-7901/DDP 耐药性及耐药相关蛋白的影响 [J]. 世界科学技术-中医药现代化, 2019, 21(2): 197–203. [Sun MY, Wang DD, Wu QX, et al. Effects of evodiamine and berberine on DDP resistance and drug resistance-related proteins of SGC-7901/DDP[J]. World Science & Technology-Modernization of Traditional Chinese Medicine, 2019, 21(2): 197–203.] DOI: [10.11842/wst.2019.02.008](https://doi.org/10.11842/wst.2019.02.008).
- 49 Wang H, Jia XH, Chen JR, et al. Osthole shows the potential to overcome P-glycoprotein-mediated multidrug resistance in human myelogenous leukemia K562/ADM cells by inhibiting the PI3K/Akt signaling pathway[J]. Oncol Rep, 2016, 35(6): 3659–3668. DOI: [10.3892/or.2016.4730](https://doi.org/10.3892/or.2016.4730).
- 50 Tian Z, Zhao J, Zhao S, et al. Phytic acid-modified CeO₂ as Ca²⁺ inhibitor for a security reversal of tumor drug resistance[J]. Nano Res, 2022, 15(5): 4334–4343. DOI: [10.1007/s12274-022-4069-0](https://doi.org/10.1007/s12274-022-4069-0).
- 51 王小梅, 薛春苗, 王艳梅, 等. 川芎嗪对人非小细胞肺癌耐药细胞株 A549/DDP 的相关 ATP 结合盒转运体表达水平的影响 [J]. 山东中医药大学学报, 2023, 47(1): 64–70. [Wang XM, Xue CM, Wang YM, et al. Effects of Tetramethylpyrazine on expression levels of ATP-binding cassette transporters in human non-small cell lung cancer drug-resistant cell line A549/DDP[J]. Journal of Shandong University of Traditional Chinese Medicine, 2023, 47(1): 64–70.] DOI: [10.16294/j.cnki.1007-659x.2023.01.013](https://doi.org/10.16294/j.cnki.1007-659x.2023.01.013).
- 52 Li B, Shao H, Gao L, et al. Nano-drug co-delivery system of natural active ingredients and chemotherapy drugs for cancer treatment: a review[J]. Drug Deliv, 2022, 29(1): 2130–2161. DOI: [10.1080/10717544.2022.2094498](https://doi.org/10.1080/10717544.2022.2094498).
- 53 Datta S, Sinha D. Low dose epigallocatechin-3-gallate revives doxorubicin responsiveness by a redox-sensitive pathway in A549 lung adenocarcinoma cells[J]. J Biochem Mol Toxicol, 2022, 36(4): e22999. DOI: [10.1002/jbt.22999](https://doi.org/10.1002/jbt.22999).
- 54 Shehata NH, Okda TM, Omran GA, et al. Baicalin; a promising chemopreventive agent, enhances the antitumor effect of 5-FU against breast cancer and inhibits tumor growth and angiogenesis in Ehrlich solid tumor[J]. Biomed Pharmacother, 2022, 146: 112599. DOI: [10.1016/j.biopha.2021.112599](https://doi.org/10.1016/j.biopha.2021.112599).
- 55 Shao L, Zhu L, Su R, et al. Baicalin enhances the chemotherapy sensitivity of oxaliplatin-resistant gastric cancer cells by activating p53-mediated ferroptosis[J]. Sci Rep, 2024, 14(1): 10745. DOI: [10.1038/s41598-024-60920-y](https://doi.org/10.1038/s41598-024-60920-y).
- 56 Chen X, Zhou Z, Zhang Z, et al. Puerarin inhibits EMT induced by oxaliplatin via targeting carbonic anhydrase XII[J]. Front Pharmacol, 2022, 13: 969422. DOI: [10.3389/fphar.2022.969422](https://doi.org/10.3389/fphar.2022.969422).
- 57 Yarla NS, Bishayee A, Sethi G, et al. Targeting arachidonic acid pathway by natural products for cancer prevention and therapy[J]. Semin Cancer Biol, 2016, 40–41: 48–81. DOI: [10.1016/j.semcancer.2016.02.001](https://doi.org/10.1016/j.semcancer.2016.02.001).
- 58 Jiang J, Yuan Z, Sun Y, et al. Ginsenoside Rg₃ enhances the anti-proliferative activity of erlotinib in pancreatic cancer cell lines by downregulation of EGFR/PI3K/Akt signaling pathway[J]. Biomed Pharmacother, 2017, 96: 619–625. DOI: [10.1016/j.biopha.2017.10.043](https://doi.org/10.1016/j.biopha.2017.10.043).
- 59 Fan YJ, Pan FZ, Cui ZG, et al. The antitumor and sorafenib-resistant reversal effects of ursolic acid on hepatocellular carcinoma via targeting ING5[J]. Int J Biol Sci, 2024, 20(11): 4190–4208. DOI: [10.7150/ijbs.97720](https://doi.org/10.7150/ijbs.97720).
- 60 Ma Y, Wang R, Liao J, et al. Xanthohumol overcomes osimertinib resistance via governing ubiquitination-modulated Ets-1 turnover[J]. Cell Death Discov, 2024, 10(1): 454. DOI: [10.1038/s41420-024-02220-y](https://doi.org/10.1038/s41420-024-02220-y).
- 61 Shang Q, Liu W, Leslie F, et al. Nano-formulated delivery of active ingredients from traditional Chinese herbal medicines for cancer immunotherapy[J]. Acta Pharm Sin B, 2024, 14(4): 1525–1541. DOI: [10.1016/j.apsb.2023.12.008](https://doi.org/10.1016/j.apsb.2023.12.008).
- 62 Baek JS, Cho CW. A multifunctional lipid nanoparticle for co-delivery of paclitaxel and curcumin for targeted delivery and enhanced cytotoxicity in multidrug resistant breast cancer cells[J]. Oncotarget, 2017, 8(18): 30369–30382. DOI: [10.18632/oncotarget.16153](https://doi.org/10.18632/oncotarget.16153).
- 63 陈聪慧, 纪雅文. 共载紫杉醇与白藜芦醇靶向纳米粒逆转肿瘤多药耐药性机制及效果研究 [J]. 中国药理学杂志, 2023, 58(22): 2079–2084. [Chen CH, Ji YW. Mechanism and activity of reversing multidrug resistance by paclitaxel and resveratrol co-loaded targeting nanoparticles[J]. Chinese Pharmaceutical Journal, 2023, 58(22): 2079–2084.] DOI: [10.11669/cpj.2023.22.009](https://doi.org/10.11669/cpj.2023.22.009).
- 64 Musyuni P, Bai J, Sheikh A, et al. Precision medicine: Ray of hope in overcoming cancer multidrug resistance[J]. Drug Resist Updat, 2022, 65: 100889. DOI: [10.1016/j.drug.2022.100889](https://doi.org/10.1016/j.drug.2022.100889).

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