

抑制缺氧诱导因子-1 α 改善卵巢癌化疗耐药的进展

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摘要: 缺氧诱导因子-1 α (HIF-1 α) 是卵巢癌的一个关键调节因子, 可通过多种机制促进卵巢癌细胞对化疗的耐药性, 并且在一定程度上与卵巢癌患者的不良预后相关。直接或间接抑制 HIF-1 α 的表达或活性的药物可以提高卵巢癌细胞对化疗的反应性。全文就抑制 HIF-1 α 改善卵巢癌化疗耐药方面的研究进展作一综述。

主题词: 缺氧诱导因子-1 α ; 卵巢癌; 抑制; 化疗耐药

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Research Progress on Inhibiting Hypoxia-inducible Factor-1 α in Improving Chemoresistance of Ovarian Cancer

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Abstract: Hypoxia-inducible factor-1 α (HIF-1 α) is one of the key regulators of ovarian cancer, which can induce the resistance of ovarian cancer cells to chemotherapy through a variety of mechanisms, and is related to the poor prognosis of ovarian cancer patients to a certain extent. Drugs that directly or indirectly inhibit the expression or activity of HIF-1 α can improve the responsiveness of ovarian cancer cells to chemotherapy. This article reviews the latest research progress on inhibition of HIF-1 α in improving chemotherapy resistance in ovarian cancer.

Subject words: hypoxia-inducible factor-1 α ; ovarian cancer; inhibition; chemotherapy resistance

卵巢癌是女性生殖系统恶性肿瘤之一, 发病率居生殖系统肿瘤第三位, 死亡率则居首位^[1]。目前, 卵巢癌的主要治疗方案是积极的肿瘤细胞减灭术, 结合以铂和紫杉醇为基础的化疗^[2]。贝伐单抗或聚二磷酸腺苷核糖聚合酶抑制剂的维持治疗可以延长患者无进展生存期 (progression free survival, PFS), 而非总生存期 (overall survival, OS)^[3-4]。虽然大部分卵巢癌患者对含铂化疗非常敏感, 但是超过 70% 的患者会在大约 3 年内复发, 并且缓解间期逐渐缩短, 最终发展为铂耐药型卵巢癌, 导致超过 75% 的晚期卵巢癌患者在诊断后 1 年内死亡^[5-6]。

由于快速失控的增殖限制了氧气的供应, 血液

供应不足或缺氧几乎是所有实体瘤的典型肿瘤微环境特征^[7]。肿瘤细胞在适应缺氧的同时, 会导致更具侵袭性和治疗抗性的肿瘤表型, 最终导致患者预后不良^[8]。低氧主要通过稳定缺氧诱导因子 (hypoxia-inducible factor-1 α , HIF-1 α) 激活缺氧依赖的信号转导通路。在常氧条件下, HIF-1 α 氧依赖降解结构域 (oxygen dependent degradation domain, ODDD) 的两个脯氨酸残基被脯氨酰羟化酶 2 (prolyl hydroxylase 2, PHD2) 羟基化, 同时 ODDD 区域的赖氨酸残基被乙酰转移酶-1 (acetyltransferase 1, ARD1) 乙酰化, 触发 HIF-1 α 与 pVHL E3 连接酶复合体的结合, 导致其通过泛素-蛋白酶体途径降解^[9]。HIF-1 α 也受 HIF 抑制因子 (factor inhibiting HIF, FIH) 的功能调节, FIH 对 HIF-1 α 的天冬酰胺羟基化通过阻断 p300/CBP 共激活因子向 COOH 末端反式激活结构域 (COOH-terminal transactivation domain, CAD) 的募集

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来抑制其转录活性^[10]。在缺氧时,HIF-1 α 亚基变得稳定,并易位到细胞核,与 HIF-1 β 结合形成 HIF-1 异二聚体,作为转录因子发挥作用^[11]。通过转录多个基因,HIF-1 α 激活影响肿瘤发生、进展和转移的关键点,这些基因编码与遗传不稳定性、永生性、细胞增殖、免疫逃逸、血管生成、代谢重编程、侵袭和治疗抗性有关的关键蛋白^[12]。肿瘤大小、恶性腹腔积液的存在和血管密度均促进了卵巢癌缺氧区域的存在。因此,抑制 HIF-1 α 将会是治疗卵巢癌的新途径^[13-14]。

1 HIF-1 α 对卵巢癌预后的预测价值

与正常卵巢组织相比,人卵巢癌组织中 HIF-1 α 表达升高。HIF-1 α 在临床晚期、低分化卵巢癌和淋巴结转移患者中过表达^[15]。HIF-1 α 高表达可能是卵巢癌预后较差的指标。在晚期和低分化卵巢癌中,与 HIF-1 α 弱阳性或阴性的患者相比,HIF-1 α 强阳性表达患者 OS 降低;在肿瘤细胞减灭不佳的患者中,与 HIF-1 α 阴性患者相比,HIF-1 α 阳性患者的无进展间期(progression-free interval,PFI)缩短 7.5 个月^[16]。然而,也有研究认为单独 HIF-1 α 蛋白过表达对卵巢癌的预后并没有影响,只有在与非功能性 p53 组合时才能表明预后不佳^[17]。一项荟萃分析显示,HIF-1 α 高表达与患者的 OS、无病生存期(disease-free survival,DFS)、PFS、癌症特异性生存期(cancer-specific survival,CSS)、无复发生存期(relapse-free survival,RFS)和无转移生存期(metastasis-free survival,MFS)显著性缩短相关^[18]。

2 HIF-1 α 对卵巢癌化疗反应的影响

HIF-1 α 对卵巢癌预后的影响,部分体现在其与化疗反应相关。对 60 例浆液性卵巢癌(serous ovarian carcinoma,SOC)患者进行长达 36 个月的随访显示,低表达 HIF-1 α 与对化疗的良好反应相关,并且患者成功治疗后复发率降低^[19]。

迄今为止,HIF-1 α 已被证明通过多个机制促进卵巢癌细胞耐药性的发生:①诱导细胞周期停滞:由于大多数抗癌药物主要对快速分裂的细胞有效,耐药性产生部分是由于癌细胞中的细胞周期停滞。缺氧诱导卵巢癌细胞中核 HIF-1 α 的表达并增加其转

录活性,从而诱导细胞 G₀/G₁ 期停滞,促进对紫杉醇的抗性^[20]。②诱导卵巢癌干细胞(cancer stem cells,CSCs)样特性:CSCs 是一群具有高致瘤能力的自我更新细胞,比肿瘤内的其他细胞更能抵抗常规疗法^[21]。缺氧条件下,HIF-1 α 通过激活核因子 κ B(nuclear factor-kappa B,NF- κ B) 信号通路增加去乙酰化酶 1(sirtuin 1,SIRT1)的表达促进 CSCs 样特征^[22]。因此,卵巢癌细胞对氟尿嘧啶和顺铂的抵抗增加。③诱导细胞自噬发生:自噬是一种细胞存活的生理机制,被肿瘤细胞有效利用以避免细胞死亡和诱导耐药性^[23]。缺氧条件下 HIF-1 α 诱导的自噬有助于卵巢癌细胞对顺铂的抵抗^[24]。④调节癌症代谢:HIF-1 α 的敲低可以将耐药癌细胞中的有氧糖酵解重定向到线粒体氧化磷酸化,产生过量的活性氧(reactive oxygen species,ROS)导致细胞死亡,以此来改善顺铂耐药卵巢癌细胞对顺铂的反应^[25]。

3 抑制 HIF-1 α 的药物在改善卵巢癌化疗耐药中的应用

3.1 小分子抑制剂

3.1.1 喜树碱及其衍生物

人类 DNA 拓扑异构酶 I(topoisomerase I,Top1)是喜树碱(camptothecin,CPT)及其衍生物的唯一靶点,CPT 对 Top1 的抑制扰乱了启动子和转录基因处的 RNA 聚合酶 II(RNA polymerase II,Pol II)密度,有利于 Pol II 从活细胞中 HIF-1 α 基因的启动子近端暂停位点逃逸,造成 HIF-1 α mRNA 可变剪接的共转录改变^[26]。CRLX101 是一种含有喜树碱的纳米颗粒药物偶联物,可以持续将活性 CPT 输送到癌细胞中,同时减少全身暴露。在晚期转移性卵巢癌的临床前小鼠模型中,较低剂量 CRLX101 显著性降低 HIF-1 α 表达。尽管与载体相比,贝伐单抗单药治疗未显示出任何抗肿瘤疗效或生存获益,但低剂量 CRLX101 和贝伐单抗组合使用显著性降低转移性肿瘤负荷,并将中位生存延长 47 d^[27]。一项针对复发性卵巢癌患者的 II 期开放标签单臂临床试验研究评估了 CRLX101 作为单一疗法以及与贝伐单抗联合治疗的有效性,其中纳入部分铂类难治性、耐药性患者,结果显示 27 例接受单药 CRLX101 治疗的患者 PFS 为 4.5 个月,临床获益率(clinical benefit

rate, CBR)为68%,总有效率(overall response rate, ORR)为11%;在34例接受CRLX101联合贝伐单抗治疗的患者中,PFS为6.5个月,CBR提高到95%,ORR提高到18%^[28]。

拓扑替康(topotecan, TPT)是CPT的衍生物,目前用于卵巢癌的二线治疗^[29]。TPT抑制HIF-1 α 表达的主要机制为:①TPT不影响HIF-1 α 降解,而是影响其翻译;②抑制HIF-1 α 蛋白积累需要Top1抑制;③TPT抑制HIF-1 α 蛋白积累需要RNA转录,而非DNA复制^[30]。在卵巢癌细胞中,TPT已被证明靶向驻留在HIF-1 α mRNA上的Top1,阻碍HIF-1 α 翻译。由于缺氧条件下HIF-1 α 与p53结合后p53的转录功能受到抑制,TPT介导的HIF-1 α 缺失可以恢复p53的功能,从而逆转卵巢癌细胞对顺铂和紫杉醇的耐药性,促进细胞凋亡^[31]。

3.1.2 YC-1

YC-1,即3-(5'-羟甲基-2'-呋喃基)-1-甲苯,是一种针对HIF-1 α 的抗癌药物。机制上,YC-1已被证明在翻译后水平下调HIF-1 α ^[32-33]。YC-1通过靶向HIF-1 α 氨基酸720~780区域或通过抑制MDM2加速HIF-1 α 降解。除了下调HIF-1 α 之外,YC-1还能刺激FIH与HIF-1 α 的CAD结合,从而阻止p300与CAD结合,导致HIF-1 α 功能抑制^[34]。YC-1与顺铂联合作用可以促进卵巢癌细胞凋亡和周期阻滞,从而发挥协同抗肿瘤作用^[35]。通过抑制HIF-1 α 、YC-1可以使铂耐药卵巢癌细胞重新对顺铂敏感^[36]。

3.1.3 2-甲氧基雌二醇

2-甲氧基雌二醇(2-methoxyestradiol, 2-ME2)是雌二醇的天然代谢产物,其诱导HIF-1 α 表达的失调依赖于微管解聚与转录后翻译^[37]。由于口服药物生物利用度和代谢程度低,一项II期临床试验评估了2-ME2纳米晶体®分散体在复发、铂耐药或难治性卵巢癌患者中的安全性和有效性,16例可评估患者中有5例病情稳定时间超过3个月,其中2例患者病情稳定时间超过1年,CBR达31.3%^[38]。

3.2 从植物中提取的天然化合物

3.2.1 黄芩提取物

黄芩是一种常见的中草药,黄芩提取物(extract of *Scutellaria baicalensis*, SbE)在预防和治疗多种恶性肿瘤方面具有一定的临床疗效^[39]。通过失活PI3K/AKT和MEK/ERK途径抑制HIF-1 α 的合成以

及促进蛋白酶体和溶酶体途径对HIF-1 α 的降解,SbE在卵巢癌细胞中抑制HIF-1 α 的积累,进而逆转卵巢癌细胞对顺铂的耐药性^[40-41]。此外,SbE和顺铂联合治疗可以通过诱导自噬的发生显著性抑制顺铂耐药性卵巢癌细胞系的细胞活力^[42]。FV-429是汉黄芩的衍生物,是从黄芩中提取的主要成分之一,具有多种抗癌活性^[43]。在缺氧条件下,FV-429可以干扰c-Src的表达和磷酸化,随后抑制STAT3核易位及其与HIF-1 α 的结合,通过增加G₂/M阻滞逆转卵巢癌紫杉醇抗性^[44]。

3.2.2 茶皂素 E1

茶皂素已被证明具有包括免疫调节和抗肿瘤活性在内的多种药理作用^[45]。茶皂素E1(theasaponin E1, TSE1)比茶种子中存在的其他皂苷单体具有更高的生物活性。TSE1可以明显抑制来自铂耐药卵巢癌细胞系中的醛脱氢酶(aldehyde dehydrogenase, ALDH)阳性细胞的干细胞特征,包括球体形成能力、迁移能力和干细胞标志表达,具有改善卵巢癌细胞抗性的潜力^[46]。TSE1可以降低Delta样蛋白4(delta-like protein 4, Dll4)和Jagged1(JAG1)的表达,从而抑制Notch1途径;而Notch1途径可以使共济失调毛细血管扩张突变蛋白(ataxia telangiectasia-mutated protein, ATM)失活^[47]。TSE1诱导的ATM的激活上调磷酸酶张力蛋白同源物(phosphatase and tensin homolog, PTEN)的表达,降低AKT及其下游蛋白HIF-1 α 的磷酸化,在顺铂耐药的卵巢癌细胞系中具有明显的增殖抑制作用^[48]。

3.2.3 杨梅叶原花色素

杨梅叶原花色素(bayberry leaves proanthocyanidin, BLPs)是在杨梅叶中提取的含量丰富的原花色素(proanthocyanidins, PAs),具有很强的抗氧化能力和抗增殖能力^[49]。与TSE1相似,BLPs能降低卵巢癌细胞活力、减少ALDH⁺群体和干性相关蛋白的表达,对抗化疗的卵巢癌细胞的生长产生抑制作用^[50]。BLPs降低ROS水平并靶向AKT/mTOR/p70S6K/4E-BP-1信号通路降低HIF-1 α 和VEGF表达,从而抑制血管生成;还能通过降低c-Myc、cyclin D1和CDK4的表达来诱导细胞G₁期停滞,对顺铂耐药的卵巢癌细胞产生强烈的生长抑制作用^[51]。

3.2.4 余甘子提取物

余甘子是一种果实植物,因其药用价值而得到

认可,在传统医学中用于治疗包括癌症在内的多种疾病^[52]。卵巢癌的特征是基因组学多样性,这些突变和异质性增加了其治疗抗性^[53]。实验证实,余甘子提取物治疗可以抑制耐药突变高级别浆液性卵巢癌(high-grade serous epithelial ovarian cancer,HGSOC)的细胞生长,并调节转移途径的关键分子[HIF-1 α 、胰岛素生长因子受体1(growth factor receptor 1,IGF1R)、SNAIL1和E-钙黏蛋白(E-cadherin)],使携带p53、BRCA1/2基因突变的铂和紫杉醇耐药HG-SOC细胞对化疗敏感,并减弱其恶性特征^[54]。因此,余甘子提取物是一种潜在的辅助治疗剂,可用于治疗耐药、突变、异质性卵巢癌。

3.3 从动物中提取的化合物

蟾蜍灵是一种类似地高辛的C-24类固醇,是中药蟾酥、蟾蜍皮肤和腮腺毒腺提取物中的主要生物反应成分^[55]。由于其在包括卵巢癌在内的多种癌细胞系中的促凋亡作用,被用作抗肿瘤制剂^[56-57]。在卵巢癌细胞中,蟾蜍灵抑制mTOR的激活,降低HIF-1 α 水平,并且有效地抑制异种移植瘤生长^[56]。由于低水平的HIF-1 α 与卵巢癌患者对顺铂治疗的反应增强相关,蟾蜍灵与顺铂联合用于卵巢癌有望增强对顺铂治疗的敏感性,最终延长患者的生存期。

4 总结与展望

HIF-1 α 已被证实在卵巢癌耐药的多个途径中占据重要位置。HIF-1 α 可以作为卵巢癌患者开始化疗时筛查的生物标志物,低水平HIF-1 α 表达的患者会从治疗中获益更多。因此,直接或间接抑制HIF-1 α 的疗法均可以有效地增加肿瘤对化疗的敏感性,抑制肿瘤的进展,延长患者生存期。目前,已经有几种药物正在进行临床试验,但种类十分有限,疗效不一。尽管其机制尚不完全清楚,但抑制HIF-1 α 表达水平的动植物衍生产品具有低毒性的抗肿瘤作用,可与化疗联合以提高卵巢癌患者对化疗的敏感性。

参考文献:

- [1] Siegel RL,Miller KD,Fuchs HE,et al. Cancer statistics, 2021[J]. CA Cancer J Clin,2021,71(1):7-33.
- [2] Armstrong DK,Alvarez RD,Bakkum-Gamez JN,et al. Ovarian cancer,version 2.2020,NCCN clinical practice

- guidelines in oncology[J]. J Natl Compr Canc Netw,2021,19(2):191-226.
- [3] González-Martín A,Pothuri B,Vergote I,et al. Niraparib in patients with newly diagnosed advanced ovarian cancer [J]. N Engl J Med,2019,381(25):2391-2402.
- [4] Ray-Coquard I,Pautier P,Pignata S,et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer [J]. N Engl J Med,2019,381(25):2416-2428.
- [5] Yang L,Xie HJ,Li YY,et al. Molecular mechanisms of platinum-based chemotherapy resistance in ovarian cancer [J]. Oncol Rep,2022,47(4):82.
- [6] Nowak M,Klink M. The role of tumor-associated macrophages in the progression and chemoresistance of ovarian cancer[J]. Cells,2020,9(5):1299.
- [7] Jing X,Yang F,Shao C,et al. Role of hypoxia in cancer therapy by regulating the tumor microenvironment[J]. Mol Cancer,2019,18(1):157.
- [8] Roma-Rodrigues C,Mendes R,Baptista PV,et al. Targeting tumor microenvironment for cancer therapy[J]. Int J Mol Sci,2019,20(4):840.
- [9] Jaakkola P,Mole DR,Tian YM,et al. Targeting of HIF-1 α to the von Hippel-Lindau ubiquitylation complex by O₂-regulated prolyl hydroxylation[J]. Science,2001,292(5516):468-472.
- [10] Lando D,Peet DJ,Whelan DA,et al. Asparagine hydroxylation of the HIF transactivation domain a hypoxic switch [J]. Science,2002,295(5556):858-861.
- [11] Lee JW,Bae SH,Jeong JW,et al. Hypoxia-inducible factor (HIF-1) α : its protein stability and biological functions [J]. Exp Mol Med,2004,36(1):1-12.
- [12] Miranda-Galvis M,Teng Y. Targeting hypoxia-driven metabolic reprogramming to constrain tumor progression and metastasis[J]. Int J Mol Sci,2020,21(15):5487.
- [13] Klemba A,Bodnar L,Was H,et al. Hypoxia-mediated decrease of ovarian cancer cells reaction to treatment: significance for chemo- and immunotherapies[J]. Int J Mol Sci,2020,21(24):9492.
- [14] Pereira M,Matuszewska K,Jamieson C,et al. Characterizing endocrine status,tumor hypoxia and immunogenicity for therapy success in epithelial ovarian cancer [J]. Front Endocrinol(Lausanne),2021,12:772349
- [15] Shen W,Li HL,Liu L,et al. Expression levels of PTEN, HIF-1 α ,and VEGF as prognostic factors in ovarian cancer [J]. Eur Rev Med Pharmacol Sci,2017,21(11):2596-2603.
- [16] Daponte A,Ioannou M,Mylonis I,et al. Prognostic significance of hypoxia-Inducible factor 1 alpha (HIF-1 alpha)

- expression in serous ovarian cancer: an immunohistochemical study[J]. *BMC Cancer*, 2008, 8: 335.
- [17] Birner P, Schindl M, Obermair A, et al. Expression of hypoxia-inducible factor 1 α in epithelial ovarian tumors: its impact on prognosis and on response to chemotherapy[J]. *Clin Cancer Res*, 2001, 7(6): 1661–1668.
- [18] Han S, Huang T, Hou F, et al. The prognostic value of hypoxia-inducible factor-1 α in advanced cancer survivors: a meta-analysis with trial sequential analysis[J]. *Ther Adv Med Oncol*, 2019, 11: 1758835919875851.
- [19] Alabiad M, Harb O, Mandour D, et al. Prognostic and clinicopathological implications of expression of Beclin-1 and hypoxia-inducible factor 1 α in serous ovarian carcinoma: an immunohistochemical study[J]. *Pol J Pathol*, 2021, 72(1): 23–38.
- [20] Huang L, Ao Q, Zhang Q, et al. Hypoxia induced paclitaxel resistance in human ovarian cancers via hypoxia-inducible factor 1 α [J]. *J Cancer Res Clin Oncol*, 2010, 136(3): 447–456.
- [21] Najafi M, Mortezaee K, Majidpoor J. Cancer stem cell (CSC) resistance drivers[J]. *Life Sci*, 2019, 234: 116781.
- [22] Qin J, Liu Y, Lu Y, et al. Hypoxia-inducible factor 1 α promotes cancer stem cells-like properties in human ovarian cancer cells by upregulating SIRT1 expression[J]. *Sci Rep*, 2017, 7(1): 10592.
- [23] Zamame Ramirez JA, Romagnoli GG, Kaneno R. Inhibiting autophagy to prevent drug resistance and improve anti-tumor therapy[J]. *Life Sci*, 2021, 265: 118745.
- [24] Long F, Liu W, Jia P, et al. HIF-1 α -induced autophagy contributes to cisplatin resistance in ovarian cancer cells[J]. *Pharmazie*, 2018, 73(9): 533–536.
- [25] Ai Z, Lu Y, Qiu S, et al. Overcoming cisplatin resistance of ovarian cancer cells by targeting HIF-1-regulated cancer metabolism[J]. *Cancer Lett*, 2016, 373(1): 36–44.
- [26] Baranello L, Bertozzi D, Fogli MV, et al. DNA topoisomerase I inhibition by camptothecin induces escape of RNA polymerase II from promoter-proximal pause site, antisense transcription and histone acetylation at the human HIF-1 α gene locus[J]. *Nucleic Acids Res*, 2010, 38(1): 159–171.
- [27] Pham E, Birrer MJ, Eliasof S, et al. Translational impact of nanoparticle-drug conjugate CRLX101 with or without bevacizumab in advanced ovarian cancer[J]. *Clin Cancer Res*, 2015, 21(4): 808–818.
- [28] Krasner CN, Campos SM, Young CL, et al. Sequential phase II clinical trials evaluating CRLX101 as monotherapy and in combination with bevacizumab in recurrent ovarian cancer[J]. *Gynecol Oncol*, 2021, 162(3): 661–666.
- [29] Alshammari MK, Alghazwani MK, Alharbi AS, et al. Nanoplatfor for the delivery of topotecan in the cancer milieu: an appraisal of its therapeutic efficacy[J]. *Cancers (Basel)*, 2022, 15(1): 65.
- [30] Rapisarda A, Uranchimeg B, Sordet O, et al. Topoisomerase I-mediated inhibition of hypoxia-inducible factor 1: mechanism and therapeutic implications[J]. *Cancer Res*, 2004, 64(4): 1475–1482.
- [31] Parmakhtiar B, Burger RA, Kim JH, et al. HIF inactivation of p53 in ovarian cancer can be reversed by topotecan, restoring cisplatin and paclitaxel sensitivity[J]. *Mol Cancer Res*, 2019, 17(8): 1675–1686.
- [32] Kim HL, Yeo EJ, Chun YS, et al. A domain responsible for HIF-1 α degradation by YC-1, a novel anticancer agent[J]. *Int J Oncol*, 2006, 29(1): 255–260.
- [33] Lau CK, Yang ZF, Lam CT, et al. Suppression of hypoxia inducible factor-1 α (HIF-1 α) by YC-1 is dependent on murine double minute 2 (Mdm2)[J]. *Biochem Biophys Res Commun*, 2006, 348(4): 1443–1448.
- [34] Li SH, Shin DH, Chun YS, et al. A novel mode of action of YC-1 in HIF inhibition: stimulation of FIH-dependent p300 dissociation from HIF-1 α [J]. *Mol Cancer Ther*, 2008, 7(12): 3729–3738.
- [35] 周筠, 洪莉, 黄金玲, 等. YC-1 增强顺铂对卵巢癌 A2780s 细胞的增殖抑制和促凋亡作用[J]. *中国临床药理学杂志*, 2019, 35(2): 137–139.
- [35] Zhou Y, Hong L, Huang JL, et al. YC-1 enhanced the anti-proliferation and pro-apoptosis effects of cisplatin in oophoroma A2780s cells[J]. *The Chinese Journal of Clinical Pharmacology*, 2019, 35(2): 137–139.
- [36] Li Z, Zhou W, Zhang Y, et al. ERK regulates HIF1 α -mediated platinum resistance by directly targeting PHD2 in ovarian cancer[J]. *Clin Cancer Res*, 2019, 25(19): 5947–5960.
- [37] Mooberry SL. Mechanism of action of 2-methoxyestradiol: new developments[J]. *Drug Resist Updat*, 2003, 6(6): 355–361.
- [38] Matei D, Schilder J, Sutton G, et al. Activity of 2 methoxyestradiol(Panzem NCD) in advanced, platinum-resistant ovarian cancer and primary peritoneal carcinomatosis: a Hoosier Oncology Group trial[J]. *Gynecol Oncol*, 2009, 115(1): 90–96.
- [39] Banik K, Khatoon E, Harsha C, et al. Wogonin and its analogs for the prevention and treatment of cancer: a systematic review[J]. *Phytother Res*, 2022, 36(5): 1854–1883.
- [40] Hussain I, Waheed S, Ahmad KA, et al. Scutellaria

- baicalensis targets the hypoxia-inducible factor-1 α and enhances cisplatin efficacy in ovarian cancer[J]. J Cell Biochem, 2018, 119(9):7515–7524.
- [41] Xing F, Sun C, Luo N, et al. Wogonin increases cisplatin sensitivity in ovarian cancer cells through inhibition of the phosphatidylinositol 3-Kinase (PI3K)/Akt pathway[J]. Med Sci Monit, 2019, 25:6007–6014.
- [42] Choi BY, Joo JC, Lee YK, et al. Anti-cancer effect of scutellaria baicalensis in combination with cisplatin in human ovarian cancer cell[J]. BMC Complement Altern Med, 2017, 17(1):277.
- [43] Hu P, Wang J, Qing Y, et al. FV-429 induces autophagy blockage and lysosome-dependent cell death of T-cell malignancies via lysosomal dysregulation[J]. Cell Death Dis, 2021, 12(1):80.
- [44] Guo Q, Lu L, Liao Y, et al. Influence of c-Src on hypoxic resistance to paclitaxel in human ovarian cancer cells and reversal of FV-429[J]. Cell Death Dis, 2018, 8(1):e3178.
- [45] Khan MI, Karima G, Khan MZ, et al. Therapeutic effects of saponins for the prevention and treatment of cancer by ameliorating inflammation and angiogenesis and inducing antioxidant and apoptotic effects in human cells[J]. Int J Mol Sci, 2022, 23(18):10665.
- [46] Jia LY, Xia HL, Chen ZD, et al. Anti-proliferation effect of theasaponin E₁ on the ALDH-positive ovarian cancer stem-like cells[J]. Molecules, 2018, 23(6):1469.
- [47] Adamowicz M, Vermezovic J, d'Adda di Fagagna F. NOTCH1 inhibits activation of ATM by impairing the formation of an ATM-FOXO3a-KAT5/Tip60 complex[J]. Cell Rep, 2016, 16(8):2068–2076.
- [48] Li B, Tong T, Ren N, et al. Theasaponin E(1) inhibits platinum-resistant ovarian cancer cells through activating apoptosis and suppressing angiogenesis[J]. Molecules, 2021, 26(6):1681.
- [49] Zhang S, Yu Z, Sun L, et al. An overview of the nutritional value, health properties, and future challenges of Chinese bayberry[J]. Peer J, 2022, 10:e13070.
- [50] Zhang Y, Chen S, Wei C, et al. Dietary compound proanthocyanidins from Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves attenuate chemotherapy-resistant ovarian cancer stem cell traits via targeting the Wnt/ β -catenin signaling pathway and inducing G1 cell cycle arrest[J]. Food Funct, 2018, 9(1):525–533.
- [51] Zhang Y, Chen S, Wei C, et al. Dietary compound proanthocyanidins from Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves inhibit angiogenesis and regulate cell cycle of cisplatin-resistant ovarian cancer cells via targeting Akt pathway[J]. J Funct Foods, 2018, 40:573–581.
- [52] Gantait S, Mahanta M, Bera S, et al. Advances in biotechnology of *Emblia officinalis* Gaertn. syn. *Phyllanthus emblica* L.: a nutraceuticals-rich fruit tree with multifaceted ethnomedicinal uses[J]. 3 Biotech, 2021, 11(2):62.
- [53] Konishi I, Abiko K, Hayashi T, et al. Peritoneal dissemination of high-grade serous ovarian cancer: pivotal roles of chromosomal instability and epigenetic dynamics [J]. J Gynecol Oncol, 2022, 33(5):e83.
- [54] De A, De A, Sharma R, et al. Sensitization of carboplatin- and taxol-resistant high-grade serous ovarian cancer cells carrying p53, BRCA1/2 mutations by *emblica officinalis* (Amla) via multiple targets[J]. J Cancer, 2020, 11(7):1927–1939.
- [55] Soumoy L, Ghanem GE, Saussez S, et al. Bufalin for an innovative therapeutic approach against cancer[J]. Pharmacol Res, 2022, 184:106442.
- [56] Su S, Dou H, Wang Z, et al. Bufalin inhibits ovarian carcinoma via targeting mTOR/HIF- α pathway [J]. Basic Clin Pharmacol Toxicol, 2021, 128(2):224–233.
- [57] Dou L, Zou D, Song F, et al. Bufalin suppresses ovarian cancer cell proliferation via EGFR pathway[J]. Chin Med J (Engl), 2021, 135(4):456–461.