•综述•

抑制HIF-1α表达的中药抗肿瘤活性成分研究进展

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摘要: 实体肿瘤的重要特征之一是缺氧, 缺氧微环境可导致缺氧诱导因子-1α (hypoxia inducible factor-1α, HIF-1α)的过度表达。HIF-1α是缺氧应答中最为关键的转录因子, 可通过激活下游基因表达促进肿瘤细胞异常增殖、肿瘤血管生成、能量代谢异常、耐药性增加、侵袭和转移。因此, 下调HIF-1α的表达是一条目前被认为治疗实体肿瘤的很有前景的途径。然而, 大多数现有的HIF-1α抑制剂的临床效果受到低效性和高毒性的限制。由此, 针对HIF-1α的过度表达研发强效安全的新型药物尤为重要。近年来, 大量研究发现多种中药化学成分可直接或间接抑制HIF-1α的激活, 在对抗低氧诱导的肿瘤进展过程方面具有广阔的前景。本综述汇总了近十年内直接或间接抑制HIF-1α表达的各种中药抗肿瘤活性成分的研究进展, 并进行总结与讨论, 以期为进一步研究作为参考。

关键词: 缺氧诱导因子-1α; 中药; 肿瘤; 缺氧; 机制

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2021)10-2689-31

Research progress of anti-tumor components of traditional Chinese medicine inhibiting the expression of HIF-1α

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Abstract: Hypoxia is one of the most significant characteristics of solid tumors. Hypoxia microenvironment can lead to the overexpression of hypoxia inducible factor-1α (HIF-1α). As the most critical transcription factor in the hypoxia response, HIF-1α activates downstream gene expression resulting in abnormal tumor cell proliferation, tumor angiogenesis, unusual energy metabolism, increased drug resistance, invasion, and metastasis. Down-regulation of HIF-1α expression is considered as a promising approach for the treatment of solid tumors, whereas the clinical efficacy of most existing HIF-1α inhibitors is restricted in low efficacy and high toxicity. Therefore, it is particularly important to develop powerful and safe novel drugs against the overexpression of HIF-1α. In recent years, numbers of studies have proved that a variety of chemical components of traditional Chinese medicine can directly or indirectly inhibit the activation of HIF-1α, which has a broad prospect in the fight against hypoxia-induced tumor progression. In this review, we summarized various anti-tumor active components of traditional Chinese medicines responsible for inhibiting the expression of HIF-1α in last ten years and analyzed the corresponding mechanism, with a view to further research as a reference.

Key words: hypoxia inducible factor-1α; traditional Chinese medicine; tumor; hypoxia; mechanism

收稿日期: 2021-01-28; 修回日期: 2021-03-12.

基金项目: 江苏省卫生健康委医学科研项目 (K2019007); 江苏省科教强卫医学重点人才项目 (ZDRCA2016036).

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DOI: 10.16438/j.0513-4870.2021-0167

癌症是全球第二大死因, 对人类健康造成严重威胁[1]。癌症初期, 肿瘤组织可以得到不间断的营养和氧气供应。但当肿瘤生长到约2～3 mm^3时将会出现血液供应不足, 导致肿瘤细胞缺氧[2,3], 进而引起缺氧诱导因子-1α (hypoxia-inducible factor 1 alpha, HIF-1α) 的过度表达。HIF-1α是HIF-1的功能亚基, 稳定的HIF-1α进入细胞核与缺氧诱导因子-1β (hypoxia-inducible factor-1β, HIF-1β) 结合, 形成HIF-1复合物。随后, HIF-1与缺氧反应元件 (hypoxia response element, HRE) 结合, 激活靶基因的转录, 从而调控恶性肿瘤的细胞增殖、血管生成、糖酵解、治疗抵抗、侵袭和转移[4]。临床研究表明, HIF-1α的过度表达是导致多种类型的癌症患者不良预后的重要因素[2]。因此, 抑制HIF-1α的表达是治疗缺氧肿瘤的有效策略。

至今, 已经报道可用于直接或间接阻断HIF-1α激活的药物有PX-478、EZN-2968、echinomycin、YC-1、topotecan和digoxin等[5-7]。然而, 目前大部分抑制剂的临床效果受到高毒性和低效性的限制[5]。因此, 针对HIF-1α的过度表达开发安全强效的新型抗肿瘤药物至关重要。近年来, 从中药中发现有活性的天然产物已成为新药研发的热点。国内外大量研究发现, 黄芩素、大黄素、雷公藤红素、小檗碱和姜黄素等多种中药化学成分可通过直接或间接抑制HIF-1α的表达发挥抗肿瘤细胞增殖、抗肿瘤血管生成、逆转糖酵解、治疗增敏、抗肿瘤侵袭和转移的作用。本综述介绍了HIF-1α与肿瘤的关系以及HIF-1的结构特点、HIF-1α表达的调控, 并汇总了近年来国内外对抑制HIF-1α表达的中药抗肿瘤活性成分的研究进展, 对它们的结构类型和调控机制进行了系统归纳、总结和讨论, 以期为未来研发抑制HIF-1α表达的新型药物提供参考。

1 HIF-1α与肿瘤进展之间的关系

大量数据显示, HIF-1α在大多数 (>70%) 类型的人类原发性癌症以及区域和远处转移中过度表达[8]。已有临床研究证实, 在乳腺癌[9]、非小细胞肺癌[10]、前列腺癌[11]、脑部肿瘤[12]、头颈部肿瘤[13]、宫颈癌[14]、结肠癌[15]、胰腺癌[16]、肝细胞癌[17]、皮肤癌[18]、胃癌[19]、食管鳞状细胞癌[20]和卵巢上皮癌[21]等多种癌症患者的肿瘤组织中, HIF-1α表达水平显著升高。这些临床研究还表明, 肿瘤组织中HIF-1α的过度表达是导致癌症患者不良预后、不良临床结果和死亡率增加的独立因素[22]。此外, HIF-1α在癌前病变部位 (如结肠腺瘤、乳腺导管原位癌和前列腺上皮内瘤变) 中也存在过度表达, 可能作为临床监测或治疗干预的癌前病变的新型生物标志物。

毫无疑问, HIF-1α信号通路与肿瘤之间存在着密切的关系 (图1)。第一, HIF-1α通过上调血管内皮生长因子 (vascular endothelial growth factor, VEGF)、干细胞因子 (stem cell factor, SCF) 和血管生成素 (angiopoietin, ANGPT) 等促血管生成因子的表达刺激了肿瘤血管的异常增生[23], 进而为肿瘤生长提供充足的血液营养物质。第二, HIF-1α的过表达促进了肿瘤细胞的侵袭和转移, 其机制在于: ①HIF-1α诱导生成的肿瘤血管具有高渗漏、高通透性和无基膜的特点, 为肿瘤细胞侵入血管并向远端器官转移提供了捷径[2]; ②HIF-1α的过表达上调了TWIST、Snail、基质金属蛋白酶 (matrix metalloproteinases, MMPs) 等因子的表达, 进而促进肿瘤细胞上皮-间充质转化 (epithelial-mesenchymal transition, EMT), 使其获得可塑性和移动性表型; ③HIF-1α还可通过激活Hedgehog、赖氨酰氧化酶 (lysyl oxidase, LOX)、核因子κB (nuclear factor κB, NF-κB) 等信号通路间接促进肿瘤的侵袭和转移[23]。第三, HIF-1α通过激活己糖激酶 (hexokinase, HK) 1、HK2、葡萄糖转运蛋白 (glucose transporter, GLUT) 1、GLUT3、3-磷酸肌醇依赖性蛋白激酶1 (3-phosphoinositide-dependent protein kinase-1, PDK1) 和乳酸脱氢酶A (lactate dehydrogenase A, LDHA) 等基因的表达对肿瘤细胞的葡萄糖代谢进行重新编程, 促进肿瘤细胞的糖酵解作用和“沃伯格效应” (Warburg effect), 保证在缺氧状态下产生足够的能量[24]。第四, HIF-1α的过度激活通过上调促红细胞生成素 (erythropoietin, EPO)、胰岛素样因子-2 (insulin-like factor-2, IGF2) 和血小板衍生生长因子 (platelet derived growth factor, PDGF) 等因子的表达, 促进了肿瘤细胞增殖。第五, HIF-1α降低了放疗、化疗和免疫治疗等抗肿瘤治疗的有效性。辐射或化疗药物诱导或产生的活性氧 (reactive oxygen species, ROS) 可通过抑制HIF-1α的泛素化降解从而导致HIF-1α的蛋白积聚。而高表达的HIF-1α通过上调VEGF和B淋巴细胞瘤/白血病-2 (B cell lymphoma/lewkmia-2, Bcl-2) 基因的表达, 下调Bcl-2相关X蛋白 (Bcl-2 associated X protein, BAX) 和caspase-3的表达发挥抗细胞凋亡和保护肿瘤血管免受辐射损伤的作用[25]。此外, HIF-1α介导了DNA损伤抑制和P-糖蛋白 (P-glycoprotein, P-gp) 引起的药物外排, 并激活了多药耐药基因1 (multi-drug resistance gene 1, MDR1) 等多药耐药表型的表达。最近的研究表明, HIF-1α通路的激活可增加程序性死亡配体1 (programmed cell death-ligand 1, PD-L1) 和细胞毒性T淋巴细胞相关蛋白4 (cytotoxic T-lymphocyte-associated protein 4, CTLA-4) 等免疫抑制分子的表达, 进而降低免疫治疗的有效性[26,27]。

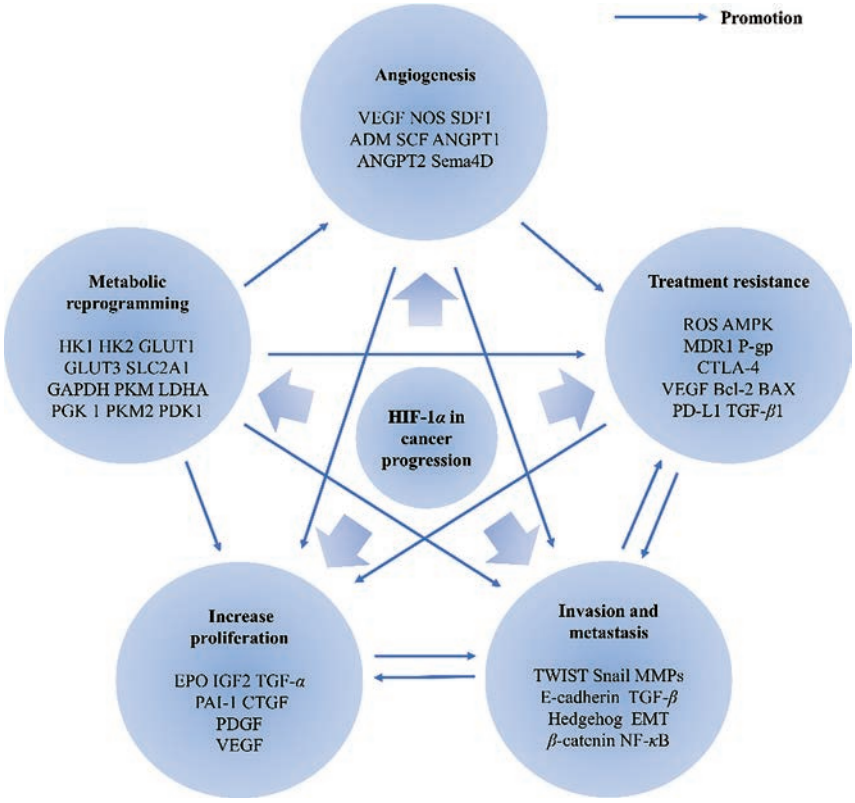


Figure 1 HIF-1α in cancer progression. HIF-1α: Hypoxia inducible factor-1α; VEGF: Vascular endothelial growth factor; NOS: Nitric oxide synthase; SDF1: Stromal cell derived factor 1; ADM: Adrenomedullin; SCF: Stem cell factor; ANGPT1: Angiopoietin 1; ANGPT2: Angiopoietin 2; Sema4D: Semaphorin 4D; ROS: Reactive oxygen species; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; MDR1: Multi-drug resistance gene 1; P-gp: P-glycoprotein; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; Bcl-2: B-cell lymphoma-2; BAX: Bcl-2 associated X protein; PD-L1: Programmed cell death-ligand 1; TGF-β: Transforming growth factor-β; MMPs: Matrix metalloproteinases; EMT: Epithelial-mesenchymal transition; NF-κB: Nuclear factor κB; EPO: Erythropoietin; IGF2: Insulin like growth factor 2; TGF-α: Transforming growth factor-α; PAI-1: Plasminogen activator inhibitor-1; CTGF: Connective tissue growth factor; PDGF: Platelet derived growth factor; HK1: Hexokinase 1; HK2: Hexokinase 2; GLUT1: Glucose transporter 1; GLUT3: Glucose transporter 3; SLC2A1: Solute carrier family 2 member 1; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; PGK1: Phosphoglycerate kinase 1; PKM2: M2-type pyruvate kinase; PDK1: 3-Phosphoinositide-dependent protein kinase-1

2 HIF-1的结构特点

HIF-1是一种异源二聚体, 主要由HIF-1α (120 kD)和HIF-1β (91～94 kD) 两个亚基构成 (图2)。HIF-1α基因定位于人类14号染色体q21～24区, 受缺氧信号的调控, 是HIF-1的活性亚基[28]。HIF-1β亚基也称芳香烃受体核转运子 (aryl hydrocarbon receptor nuclear translocator, ARNT), 基因定位于人类1号染色体q21区, 在细胞内稳定表达, 起结构性作用。二者的氨基端均含PER-ARNT-SIM (PAS) 结构和碱性的螺旋-环-螺旋 (basic-helix-loop-helix, bHLH) 构型[29], PAS基序对HIF-1 DNA亚基异源二聚体的形成起关键作用, bHLH域则有助于异源二聚体与靶基因上HRE的5'-AGCGTG-3'序列的结合。作为活性亚基的HIF-1α由826个氨基酸构成, 其两个末端是感受缺氧信号的活性调控区域, C末端有一个富含脯氨酸-丝氨酸-苏氨酸 (Pro/Ser/Thr) 的氧依赖降解结构域 (oxygen-dependent degradation domain, ODDD) 和反式激活结构域 (transactivation domain, TAD), 即C-TAD (786～826位氨基酸序列), N末端含有N-TAD (531～575位氨基酸序列)。这些结构域是缺氧诱导蛋白稳定、核定位和转录激活的调节域, 其中C-TAD发挥精细调整作用, N-TAD为激活转录所必需。它们与辅活化因子CBP和p300一起调控HIF-1α靶基因的转录, 并阻止HIF-1α的降解。稳定的HIF-1α进入细胞核并与HIF-1β结合, 形成有效的转录因子HIF-1, 随后结合到靶基因的HRE上, 从而触发细胞对多种靶基因表达的调节。

3 HIF-1α表达的调控

3.1 氧依赖的调控通路

氧依赖的羟基化降解是调控HIF-1α的最关键手段, 其主要通过脯氨酰羟化酶 (prolyl hydroxylases, PHD)/

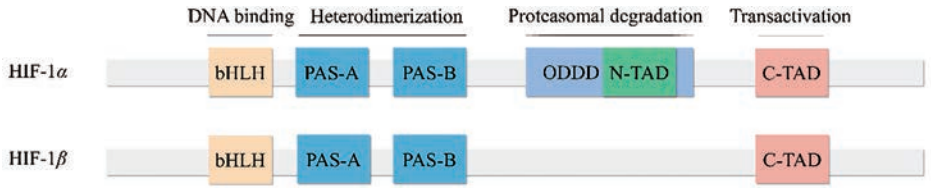


Figure 2 Structures of HIF-1α and HIF-1β. HIF-1β: Hypoxia inducible factor-1β; bHLH: Basic-helix-loop-helix; PAS-A: PER-ARNT-SIM-A; PAS-B: PER-ARNT-SIM-B; ODDD: Oxygen-dependent degradation domain; N-TAD: N-transactivation domain; C-TAD: C-transactivation domain

肿瘤抑制蛋白希佩尔林道蛋白 (Von Hippel Lindau protein, pVHL) 信号通路来进行 (图3)。在常氧状态下, HIF-1α ODDD 中的脯氨酸残基 (P402 和 P564) 会被 PHD 羟基化[6]。这种羟基化作用是通过将两个氧分子分别插入到脯氨酸和α-酮戊二酸中, 将其分解为琥珀酸和二氧化碳来实现的。随后, pVHL 与二羟基化的 HIF-1α 相结合[30], 募集泛素蛋白, 导致 HIF-1α 亚基泛素化和随后的蛋白酶体途径降解。在某些情况下, ARD1 乙酰基转移酶介导的 ODDD 中的 K532 乙酰化可促进 pVHL 依赖的 HIF-1α 降解, 而 K709 和 K674 的乙酰化则可通过稳定 HIF-1α 蛋白导致 HIF-1α 通路的上调[31]。HIF-1α 还受到 HIF 抑制因子 (factors inhibiting HIFs, FIHs) 的调节, 其可利用氧气和α-酮戊二酸进行反应, 羟化 HIF-1α C-TAD 中的天冬氨酸残基, 阻断 HIF-1α 与转录共激活子 CBP/p300 之间的相互作用。在缺氧条件下, HIF-1α 的脯氨酸残基不能发生羟基化[32]。因此, pVHL 无法与 HIF-1α 结合并将其作为 26S 蛋白酶体降解的靶点[33]。相似的, FIHs 介导的羟基化作用也会减少, 进而使 HIF 与转录共激活因子 CBP/p300 结合蛋白发生反应, 导致下游基因的表达。除氧分子外, PHD 和 FIH 还需要 Fe^{2+} 和 2-氧代戊二酸酯辅助因子才能发挥活性。而 ROS 的产生可通过将 Fe^{2+} 氧化为 Fe^{3+} 来抑制 HIF-1α 的羟基化, 进而提高 HIF-1α 的蛋白稳定性[5]。

3.2 氧不依赖的 HIF-1α 调控通路

除缺氧诱导的 HIF-1α 激活外, 还有其他信号途径参与调节 HIF-1α 蛋白的合成、稳定性和转录活性, 主要有热休克蛋白 (heat shock proteins, HSP) 信号通路、磷脂酰肌醇 3-激酶 (phosphatidylinositol 3-hydroxykinase, PI3K)/蛋白激酶 B (protein kinase B, PKB/AKT)/哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 信号通路、细胞外信号调节激酶 (extracellular signal-regulated protein kinase, ERK)/丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 信号通路等。

3.2.1 HSP 信号通路 研究表明, 有两种 HSP (HSP90 和 HSP70) 参与了 HIF-1α 的调控。HSP90 可通过与 PAS

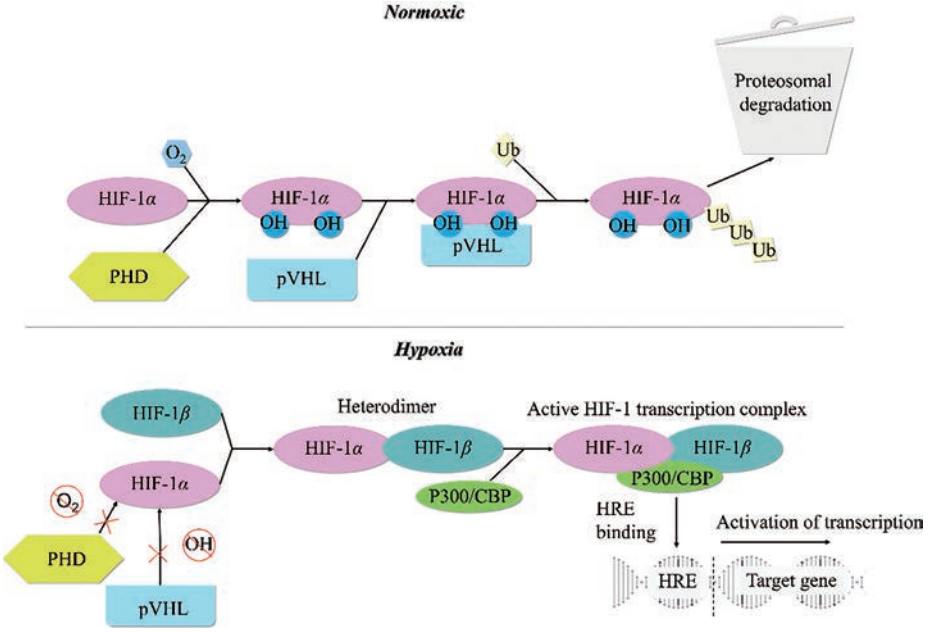


Figure 3 HIF-1α degradation, stability, and activation. PHD: Prolyl hydroxylases; pVHL: Von Hippel Lindau protein; Ub: Ubiquitin chains; HRE: Hypoxia response element

结构域结合来稳定HIF-1α, 然后被HIF-1β取代, 进而与共激活因子结合。而受体激活C激酶1 (activated C-kinase 1, RACK1) 会与HSP90竞争PAS-A结构域的结合位点, 并促进HIF-1α的泛素化降解[29]。与HSP90的调控作用相反, HSP70可募集泛素连接酶, 通过20S和26S蛋白酶体途径促进HIF-1α蛋白降解[34]。Bcl-2相关性抗凋亡基因3 (Bcl-2 associated athanogene 3, BAG3) 可通过与HSP70形成蛋白酶体复合物, 抑制HSP70蛋白对HIF-1α的降解作用, 促进HIF-1α表达。

3.2.2 PI3K/AKT/mTOR信号通路 缺氧环境会诱导PI3K/AKT/mTOR信号通路的激活, 并影响不同细胞类型中的HIF-1α的表达[35,36]。研究表明, 活化的PI3K/AKT/mTOR信号通路可通过两条途径来提高HIF-1α mRNA的翻译速率, 进而增加HIF-1α的蛋白积累: ① 促进真核翻译起始因子4E (eukaryotic translation initiation factor 4E, eIF-4E) 的磷酸化激活, 增强其与HIF-1α mRNA 5'端寡聚嘧啶核苷酸序列的结合力; ② 促进p70核糖体蛋白S6激酶 (p70 ribosomal protein S6 kinase, p70S6K) 的磷酸化, 进而激活核糖体蛋白S6 (ribosomal protein S6, rpS6)[29]。人第10号染色体缺失的磷酸酶及张力蛋白同源 (phosphatase and tensin homolog deleted on chromosome ten, PTEN) 的基因对AKT信号通路的激活具有拮抗作用。研究发现, PTEN的缺失增强了HIF-1α介导的基因表达, 而PTEN的恢复可以抑制HIF-1α的表达[37]。

3.2.3 ERK/MAPK信号通路 MAPK级联是调节增殖、分化、凋亡和应激反应等多种细胞过程的关键信号通路。而Ras/Raf/MAPK (MEK)/ERK通路是MAPK信号转导通路中最重要的信号级联, 在肿瘤细胞的生存和发展中起着至关重要的作用[38]。近年来研究表明, HIF-1α是ERK/MAPK信号通路的重要调控靶点之一。ERK包含p42和p44两个结构激酶, 均为MAPK信号通路的激酶。ERK可通过磷酸化HIF-1α的C-TAD增加其转录活性, 但对其稳定性无明显影响。此外, p42和p44 MAPK信号通路可通过磷酸化641和643位丝氨酸残基来促进HIF-1α的核积聚[5]。Ras/MAPK通路的激活还可以上调eIF4E的活性, 进而增加HIF-1α mRNA的翻译速率[39]。反之, 抑制ERK/MAPK信号通路的激活可加速HIF-1α的泛素化降解, 阻碍HIF-1α向细胞核的易位。

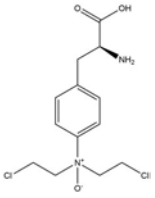
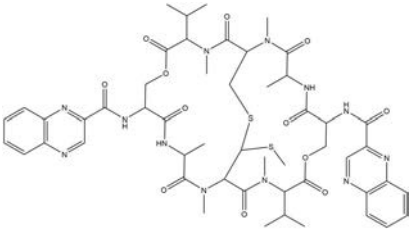
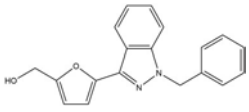
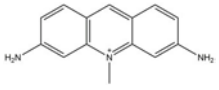
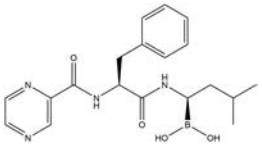
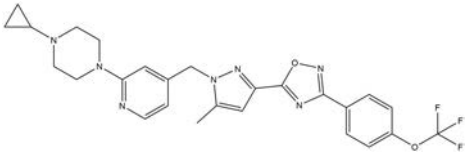
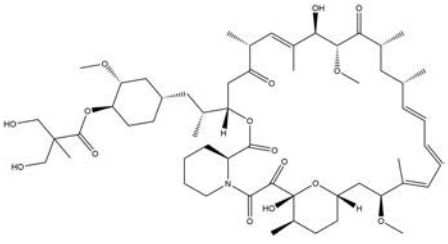
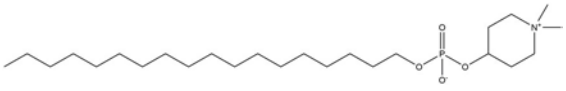
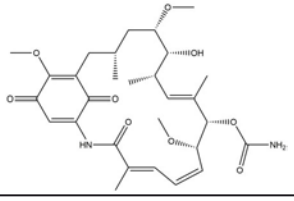
3.2.4 HIF-1α的其他调控通路 除上述信号通路外, HIF-1α的表达还受其他因子的调控。研究表明, 多种基因可对HIF-1α的氨基酸残基进行磷酸化, 干预其稳定性或转录活性[5]。如HIF-1α N-TAD中的551、555和589位丝氨酸残基可被糖原合成酶激酶-3 (glycogen synthase kinase-3, GSK-3) 磷酸化, 随后招募泛素连接酶Fbw7和USP28, 介导HIF-1α的泛素化和pVHL非依赖性蛋白酶体降解。再如, HIF-1α的PAS-B结构域的Ser-247可被蛋白激酶CK1磷酸化, 继而破坏HIF-1α/1β复合物的稳定性, 降低其转录活性。HIF-1α的稳定性或转录活性也受到非磷酸化方式的调控。比如E3泛素蛋白连接酶Mdm2可被肿瘤抑制基因p53募集以降解HIF-1α[40]。此外, 铜离子代谢结构域包含体1 [copper metabolism (murr1) domain-containing 1, COMMD1] 可通过与HIF-1α的N末端结构域进行结合与HIF-1β产生竞争作用, 随后降低HIF-1复合物的DNA结合和转录活性[41]。

4 HIF-1α抑制剂的研究现状

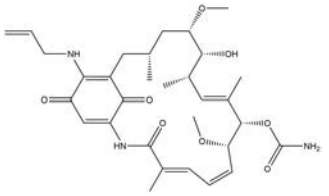
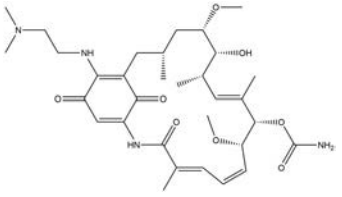
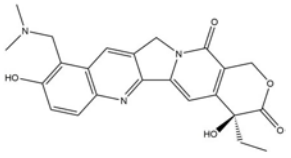
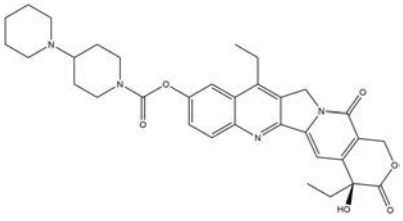
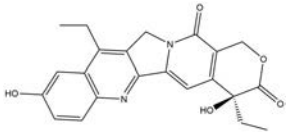
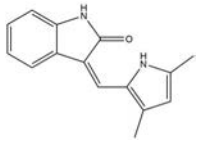
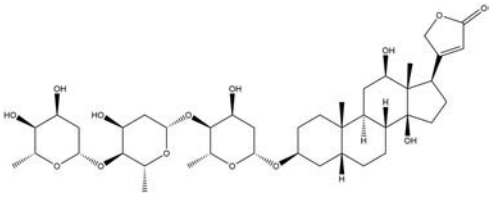
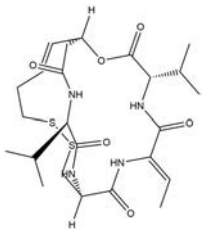
HIF-1α是治疗缺氧肿瘤的有效靶点和评估癌症患者生物学行为和预后的重要因素, 阻断HIF-1α激活的有效策略总结如下[5]: ① 降低HIF-1α的mRNA水平; ② 抑制HIF-1α蛋白的合成; ③ 促进HIF-1α蛋白的降解; ④ 抑制HIF-1α蛋白的核易位过程; ⑤ 抑制HIF-1α与HIF-1β的异源二聚体化; ⑥ 减少HIF-1与靶基因HRE的结合, 降低HIF-1α的转录活性。目前, 已开发的HIF-1α抑制剂主要分为化学合成/半合成药物、抗生素类药物和抗体类药物。其中, PX-478、EZN-2968、YC-1及其衍生物、acriflavin、echinomycin等一些化合物可特异性抑制HIF-1α的表达 (表1)。PX-478是临床第一个用于实体瘤治疗的HIF-1α抑制剂, 可在转录和翻译等多个水平下调HIF-1α的表达。EZN-2968是一种靶向HIF-1α的反义寡脱氧核苷酸, 可选择性阻断HIF-1α的mRNA表达。此外, 一些非直接靶向HIF-1α的药物也被报道具有抑制HIF-1α表达的作用, 被称为HIF-1α间接抑制剂[42], 包括HSP90拮抗剂 (如geldanamcin)、DNA拓扑异构酶1抑制剂 (如topotecan)、微管靶向药物 (如2-methoxyestradiol, 2ME2)、PI3K/AKT/mTOR抑制剂 (如temsirolimus)、蛋白酶体抑制剂 (如bortezomib)、HDAC抑制剂 (如romidepsin)、硫氧还蛋白抑制剂 (如PX-12)、酪氨酸激酶抑制剂 (如semaxanib)、蒽环类药物 (如doxorubicin)、强心苷类药物 (如digoxin) 等 (表1)[4-7,22,42,43]。此外, 已经有几种间接干预HIF-1α活性的药物被批准用于现有癌症治疗的辅助治疗[4]。

然而, 目前开发的大部分HIF-1α抑制剂的临床效果受到毒性过高和/或有效性不足的限制[5], 同时缺乏特异性。如2ME2纳米晶分散体在治疗去势抵抗性前列腺癌和转移性肾癌II期临床研究中, 由于缺乏客观效果和高毒性而被终止试验[5]。类似的, geldanamcin因在动物模型中的药理活性差和肝毒性而未能应用于

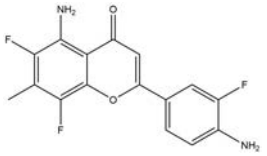
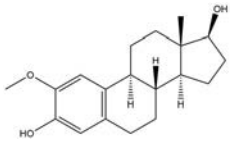
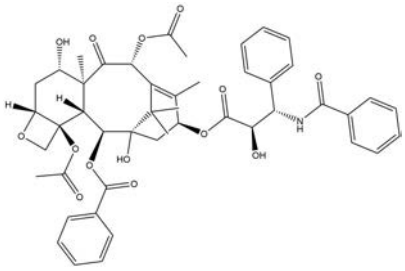
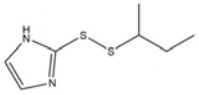
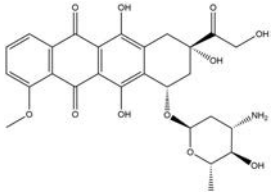
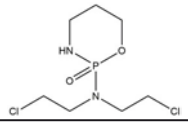
Table 1 Structures and mechanisms of some existing direct or indirect inhibitors of HIF-1α. mRNA: Messenger ribonucleic acid; FIH: Factors inhibiting HIFs; AKT: Protein kinase B; p70S6K: P70 ribosomal protein S6 kinase; S6RP: S6 ribosomal protein; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol 3-hydroxykinase; mTOR: Mammalian target of rapamycin; HSP90: Heat shock protein 90; DNA: Deoxyribonucleic acid; HDAC: Histone deacetylase; Nrf2: Nuclear factor erythroid-related factor 2; SSAT1: Spermidine/spermine-N1-acetyltransferase 1

Inhibitor	Structure	Mechanism	Ref.
PX-478		① Decrease the level of HIF-1α mRNA; ② Inhibit HIF-1α transcription and translation; ③ Modulate HIF-1α deubiquitylation	[7]
EZN-2968	—	Bind and inhibit specifically the HIF-1α mRNA expression	[6]
Echinomycin		Competitively inhibit HIF-1α binding to its target genes through sequence-specific binding to HRE	[5]
YC-1		Lower levels of HIF-1α by inducing the C-terminal HIF-1α degradation	[7]
Acriflavin		Inhibit HIF-1 dimerization by binding to the PAS-B subdomain of HIF-1α	[4]
Bortezomib		① Repress HIF-1α transcriptional activity and reinforce the FIH-mediated inhibition of p300 recruitment; ② Induce dephosphorylation of phospho-AKT, phospho-p70S6K, and phospho-S6RP, thus inactivating HIF-1α protein expression; ③ Block p44/42 MAPK phosphorylation to reduce the translocation of HIF-1α	[5,7]
BAY 87-2243		Inhibit mitochondrial production of ROS by blocking mitochondrial complex I, which subsequently reduces hypoxia-induced HIF-1α activity	[7]
Temsirolimus		Inhibit HIF-1α mRNA translation and increase HIF-1α degradation by inhibiting P13K/AKT/mTOR pathway	[5]
Perifosine		Inhibit HIF-1α mRNA translation and increase HIF-1α degradation by inhibiting P13K/AKT/mTOR pathway	[5]
Geldanamcin		Increase HIF-1α degradation and decrease in transcriptional activity by inhibiting HSP90 activity	[5]

Continued

Inhibitor	Structure	Mechanism	Ref.
Tanespimycin		Increase HIF-1α degradation and decrease in transcriptional activity by inhibiting HSP90 activity	[5]
Alvespimycin		Increase HIF-1α degradation and decrease in transcriptional activity by inhibiting HSP90 activity	[5]
Topotecan		Inhibit HIF-1α protein translation by targeting DNA topoisomerase 1	[5]
Irinotecan		Inhibit HIF-1α protein translation by targeting DNA topoisomerase 1	[5]
SN38		Inhibit HIF-1α protein translation by targeting DNA topoisomerase 1	[42]
EZN-2208	Polyethyleneglycol-SN38	Inhibit HIF-1α protein translation by targeting DNA topoisomerase 1	[6]
Semaxanib		Decrease HIF-1 DNA binding by inhibiting PI3K activity, AKT phosphorylation and p70S6K1 phosphorylation	[7]
Digoxin		Inhibit mTOR-dependent translation of HIF-1α mRNA into protein	[6]
Cetuximab	—	Inhibit mTOR-dependent translation of HIF-1α mRNA into protein	[22]
Trastuzumab	—	Inhibit mTOR-dependent translation of HIF-1α mRNA into protein	[22]
Romidepsin		Inhibit the transactivation potential of HIF-1α/p300 complex by blocking HDAC activity	[5]

Continued

Inhibitor	Structure	Mechanism	Ref.
Aminoflavone		Inhibit HIF-1α mRNA expression and almost completely block HIF-1α protein accumulation	[6]
2-Methoxyestradiol		Block HIF-1α translocation to the nucleus by disrupting cellular microtubules and inhibit HIF-1α protein translation	[5]
Taxol		Block HIF-1α translocation to the nucleus by disrupting cellular microtubules and inhibit HIF-1α protein translation	[5]
PX-12		Inhibit HIF-1α protein levels by increasing nuclear Nrf2 and SSAT1	[43]
Doxorubicin		Inhibit HIF-1 transcriptional activity by blocking its binding to DNA	[22]
Cyclophosphamide		Inhibit the expression of HIF-1α protein	[22]

临床[5]。因此, 研发下调HIF-1α表达的强效低毒的新型抗肿瘤药物至关重要。

5 抑制HIF-1α表达的中药抗肿瘤活性成分研究

中药具有悠久的历史和独特的优势, 其安全性和有效性在千百年临床实践中已得到反复验证和深入的了解。此外, 中药单体的来源更为广泛, 大大降低了新药开发的成本。近年来, 越来越多抑制HIF-1α表达的中药抗肿瘤活性成分被发掘和研究 (图4、5)。这些成分按照其结构不同可分为黄酮类、醌类、萜类、生物碱类、多酚类、皂苷类和其他类。一些中药活性成分可直接靶向HIF-1α。如海绵中分离得到的discorhabdin B、3-dihydrodiscorhabdin C等多种吡咯烷酮生物碱可阻断HIF-1α与共激活因子p300的结合[44], 宝藿苷[45]、穿心莲内酯[46]等可促进HIF-1α的蛋白降解, β-榄香烯[47]、三氧化二砷[48]等可抑制HIF-1α的mRNA表达。一些中药活性成分则通过干预PHD/VHL、HSP90、PI3K/AKT/mTOR、ERK/MAPK等上游信号通路间接影响HIF-1α的表达, 如大黄酚[49]通过阻断PI3K/AKT通路的磷酸化激活, 下调结肠癌细胞中HIF-1α的蛋白水平。此外, 槲皮素[50,51]、姜黄素[52,53]等多种中药单体既可直接抑制HIF-1α的活性, 又可阻断其上游激活通路, 多途径下调肿瘤细胞中HIF-1α的表达。

5.1 黄酮类及其糖苷

黄酮类化合物是一类广泛存在于中药中的具有2-苯基色原酮结构的活性成分, 具有丰富的药用价值。一些黄酮类物质可下调HIF-1α的表达, 对抗缺氧诱导的恶性肿瘤生长、耐药、血管生成、侵袭和转移 (表2)[45,50,51,54-70]。这里主要介绍槲皮素、木犀草素、染料木素、黄芩素及其类似物。

槲皮素是来源于银杏 (*Ginkgo biloba* L.) 等药用植物中的一种多羟基黄酮类化合物。研究发现, 槲皮素可剂量依赖性地抑制多种肿瘤细胞中缺氧诱导的HIF-1α蛋白的生物合成和下游VEGF的基因表达, 其机制与槲皮素抑制真核细胞起始因子2α (eukaryotic translation initiation factor 2α, EIF2α) 亚基的磷酸化有关[54]。槲皮素还可通过抑制结直肠癌细胞中AMPK

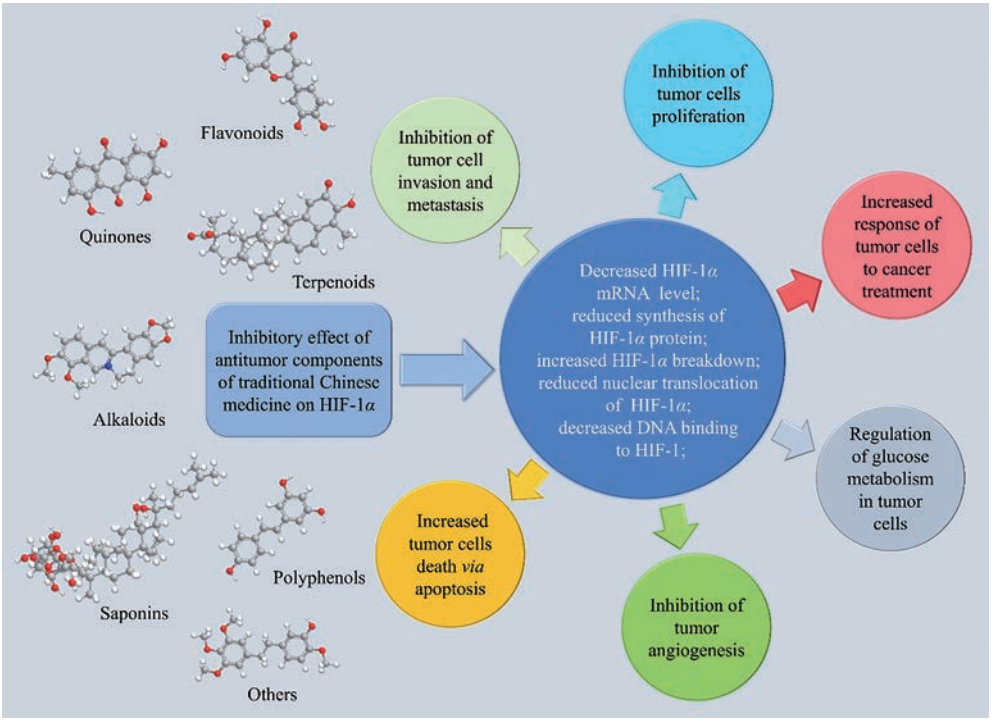
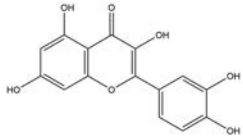
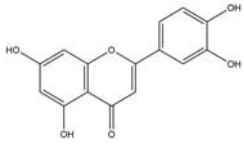
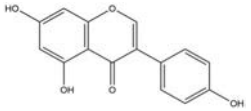
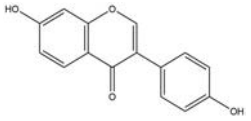
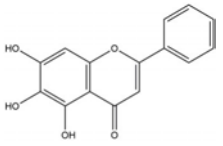
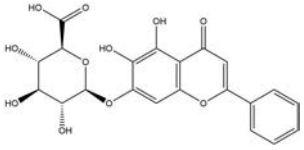
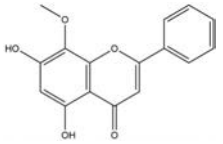
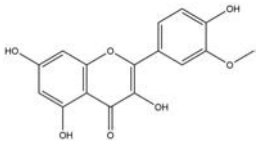
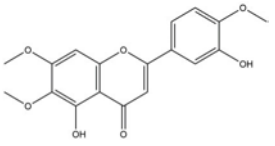
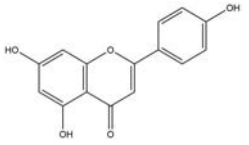
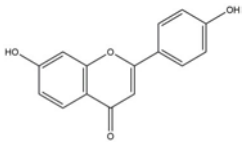
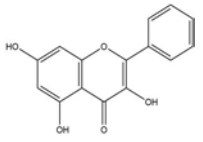
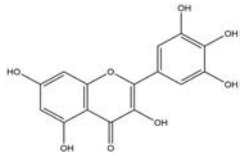


Figure 4 Inhibitory effect of antitumor components of traditional Chinese medicine on HIF-1α

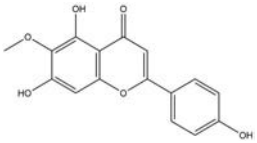
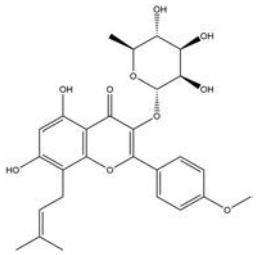
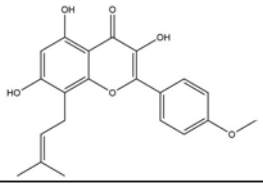
Table 2 Anti-tumor components of flavonoids of traditional Chinese medicine inhibiting the expression of HIF-1α. DOX: Doxorubicin; AP-1: Activator protein-1; Pin1: Peptidyl-prolyl isomerase NIMA-interacting 1; 5-FU: 5-Fluorouracil; HDM2: Human double minute 2; uPAR: Urokinase plasminogen activator receptor; MMP2: Matrix metalloproteinase 2; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; EMT: Epithelial-mesenchymal transition

Component	Structure	Cancer type	Mechanism	Ref.
Quercetin		Prostate cancer (LNCaP), colon cancer (CX-1), breast cancer (SkBr3)	Inhibit HIF-1α biosynthesis and VEGF gene expression by inhibiting EIF2α phosphorylation	[54]
		Colon cancer (HCT116)	Decrease the transcriptional activity of HIF-1α by inhibiting the activation of MAPK and increase the sensitivity to cisplatin and etoposide and apoptosis rate of tumor cells	[50]
		Breast cancer (4T1)	Enhance DOX toxicity to tumor cells by promoting HIF-1α degradation and reduce DOX-induced side effects	[51]
		Breast cancer (TAMR-MCF-7)	Decrease the nuclear levels of HIF-1α and c-Jun/AP-1 by inhibiting PI3K-dependent Pin1 expression, thereby inhibiting the secretion of VEGF and abnormal vascular proliferation	[55]
		Cervical cancer (A431-P, A431-III)	Increase HIF-1α degradation by pVHL pathway by decreasing the expression of UBE2S, thus inhibiting tumor metastasis and invasion	[56]
Luteolin		Lung cancer (CL1-5, 293T, LL2)	Inhibit the activation of the HIF-1α/VEGF signaling pathway by inhibiting the phosphorylation of AKT, thereby inhibiting the migration and proliferation of endothelial cells under hypoxic conditions and reducing tumor microvessel density	[57]
		Cervical cancer (A431-P, A431-III)	Increase HIF-1α degradation by pVHL pathway by decreasing the expression of UBE2S, thus inhibiting tumor metastasis and invasion	[56]
		Lung cancer (NCI-H157)	Inhibit HIF-1α transcriptional activity, VEGF expression, and STAT3 phosphorylation	[58]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
Genistein		Breast cancer (MDA-MB231, T-47D)	Down-regulate HIF-1α protein level by binding to Thr183, Ser184, Asp201, Gln203, and Arg238 residues	[59]
		Liver cancer (HCC-LM3, SMMC-7721, Hep3B, Bel-7402, Huh-7)	Block the activation of the HIF-1α/GLUT1/HK2 pathway, thereby inhibiting aerobic glycolysis and improving the sensitivity of tumor cells to chemotherapy drugs	[60]
		Prostate cancer (PC-3, C4-2B)	Inhibit the expression of APE1/Ref-1, HIF-1α, NF-κB, and have the effect of radiosensitization	[61]
Daidzein		Prostate cancer (PC-3, C4-2B)	Inhibit the expression of APE1/Ref-1, HIF-1α, NF-κB, and have the effect of radiosensitization	[61]
Baicalein		Gastric cancer (AGS)	Inhibition of hypoxia-induced AKT phosphorylation inhibits the expression of HIF-1α and glycolysis-related genes, thereby reverses hypoxia-induced 5-FU resistance	[62]
		Ovarian cancer (OVCAR-3, CP-70)	Inhibit tumor cell activity by inhibiting the gene expression of HIF-1α, c-Myc, NF-κB, and VEGF	[63]
Baicalin		Ovarian cancer (OVCAR-3, CP-70)	Inhibit tumor cell activity by inhibiting the gene expression of HIF-1α, c-Myc, NF-κB, and VEGF	[63]
Wogonin		Breast cancer (MCF-7, MDA-MB-231), liver cancer (HepG2), colon cancer (HCT116)	Increase HIF-1α protein degradation by promoting the proline hydroxylation of HIF-1α and blocking the binding of HIF-1α PAS domain to HSP90, hindering the activation of HIF-1α/VEGF axis and tumor angiogenesis	[64]
Isorhamnetin		Colon cancer (HCT116, HT29)	Inhibit ROS or hypoxia-induced HIF-1α protein accumulation and HIF-1α-dependent tumor metabolism gene transcription, thereby blocking tumor cell invasion and metastasis	[65]
Eupatorin		Lung cancer (H522)	Reduce the expression levels of HIF-1α and VEGF by inhibiting the phosphorylation activation of AKT/mTOR signal in tumor cells, thereby exerting an anti-tumor angiogenesis effect	[66]
Apigenin		Lung cancer (NCI-H157)	Inhibit HIF-1α transcriptional activity, VEGF expression, and STAT3 phosphorylation	[58]
		Ovarian cancer (OVCAR-3, A2780/CP70)	Inhibit the expression of HIF-1α and VEGF by regulating the PI3K/AKT/p70S6K1 and HDM2/p53 pathways, then hinder the formation of endothelial cells	[67]
4',7-Dihydroxyflavone		Lung cancer (NCI-H157)	Inhibit HIF-1α transcriptional activity, VEGF expression, and STAT3 phosphorylation	[58]
Galangin		Ovarian cancer (OVCAR-3, A2780/CP70)	Inhibit the expression level of HIF-1α and the secretion of VEGF by blocking the activation of p-AKT/p-70S6K pathway	[68]
Myricetin		Ovarian cancer (OVCAR-3, A2780/CP70)	Inhibit the expression level of HIF-1α and the secretion of VEGF by blocking the activation of p-AKT/p-70S6K pathway	[68]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
Hispidulin		Gallbladder cancer (GBC-SD)	Down-regulate the HIF-1α/P-gp signaling pathway by inhibiting the activation of AMPK signaling, thereby increasing the sensitivity of tumor cells to gemcitabine and 5-FU	[69]
Icariside II		Osteosarcoma (HOS)	Reduce the accumulation of HIF-1α by promoting the binding of pVHL and hydroxylated HIF-1α, and then down-regulate the levels of downstream genes such as VEGF, uPAR, ADM, MMP2	[45]
Icaritin		Glioblastoma (U87MG)	Regulate the PTEN/AKT/HIF-1α signaling pathway, thereby inhibiting the expression of extracellular matrix metalloproteinase (EMMPRIN), inhibiting tumor cell invasion and EMT	[70]

的激活显著抑制HIF-1α的转录活性, 进而降低VEGF和GLUT1的mRNA水平, 提高肿瘤细胞对顺铂和依托泊苷的敏感性和凋亡率[50]。此外, 槲皮素促进了乳腺癌细胞中HIF-1α的降解, 进而增强多柔比星 (doxorubicin, DOX) 对肿瘤细胞的细胞毒性和促凋亡作用, 同时降低DOX引起的不良反应, 延缓肿瘤生长并延长小鼠的生存时间[51]。在另一份报道中, Oh等[55]通过报告基因分析和蛋白印迹分析证实槲皮素可阻断他莫昔芬 (tamoxifen, TAM) 耐药的乳腺癌MCF-7细胞 (TAMR-MCF-7) 中HIF-1α和c-Jun/AP-1的核水平增加, 这可能归因于其抑制了PI3K依赖的Pin表达, 进而抑制VEGF的分泌和血管异常增生。

木犀草素主要存在于十字花科、天南星科、桔梗科等植物, 具有抗肿瘤、抗氧化、免疫调节、抗炎等药理作用。木犀草素是半边莲 (*Lobelia chinensis* Lour.) 中下调HIF-1α蛋白表达的主要成分, 可通过抑制AKT的磷酸化抑制HIF-1α/VEGF信号通路的激活, 从而抑制缺氧条件下内皮细胞的迁移和增殖, 降低肿瘤微血管密度[57]。最近的一份研究[56]发现木犀草素和槲皮素逆转宫颈癌EMT过程的机制可能与HIF-1α通路相关。进一步的实验表明, 这两种黄酮可能通过抑制E2S泛素连接酶 (ubiquitin E2S ligase, UBE2S) 的表达增加pVHL/PHD途径对HIF-1α的降解作用。此外, Ansó等[58]发现木犀草素能够抑制肺癌细胞中缺氧诱导的HIF-1α的激活和STAT3的磷酸化, 进而发挥降低VEGF表达的作用。

染料木素为淡豆豉 (Sojae Semen Praeparatum) 等中药中的异黄酮类有效成分。Mukund等[59]首次证明了染料木素可下调乳腺癌细胞中的HIF-1α蛋白水平, 分子对接结果显示Thr183、Ser184、Asp201、Gln203和Arg238残基是染料木素靶向HIF-1α蛋白的关键位点。染料木素对HIF-1α表达的下调作用在肝细胞癌细胞中也被证实, 同时使其下游的GLUT1和HK2失活, 从而抑制有氧糖酵解, 显著提高肿瘤细胞和荷瘤小鼠对索拉非尼的敏感性[60]。APE1/Ref-1为参与HIF-1α和NF-κB活化的一种关键蛋白, 与肿瘤放疗抵抗密切相关。而染料木素和另一种异黄酮类活性物质大豆苷元均可通过下调APE1/Ref-1的表达抑制HIF-1α和NF-κB的DNA结合活性, 阻断辐射诱导的HIF-1α和NF-κB的激活, 具有作为前列腺癌治疗的放射增敏剂的前景。有趣的是, 尽管大豆苷元的抑制作用弱于染料木素[61], 但单一使用染料木素将促进肿瘤细胞的淋巴结转移, 而与大豆苷元的联用则可抵抗这种作用。

黄芩素是中药黄芩 (Scutellariae Radix) 中分离得到的天然黄酮类化合物, 其可通过促进PTEN蛋白的积聚来抑制缺氧诱导的AKT磷酸化, 进而降低HIF-1α和糖酵解相关基因HK2、LDHA和PDK1的表达, 提高胃癌AGS细胞对5-氟尿嘧啶 (5-fuorouracil, 5-FU) 的敏感性[62]。此外, 有研究表明黄芩素和黄芩苷作用于卵巢癌OVCAR-3和CP-70细胞后, HIF-1α的mRNA表达水平显著降低, 且黄芩素表现出更强的抑制作用[63]。汉黄芩素与黄芩素结构相似, 但两者抑制HIF-1α表达的机制有所不同。Song等[64]的报道显示, 汉黄芩素可通过促进PHD/pVHL通路依赖的HIF-1α的脯氨酸羟基化和阻断HIF-1α的PAS结构域与HSP90的结合来增加HIF-1α蛋白的降解, 从而阻碍HIF-1α/VEGF轴的

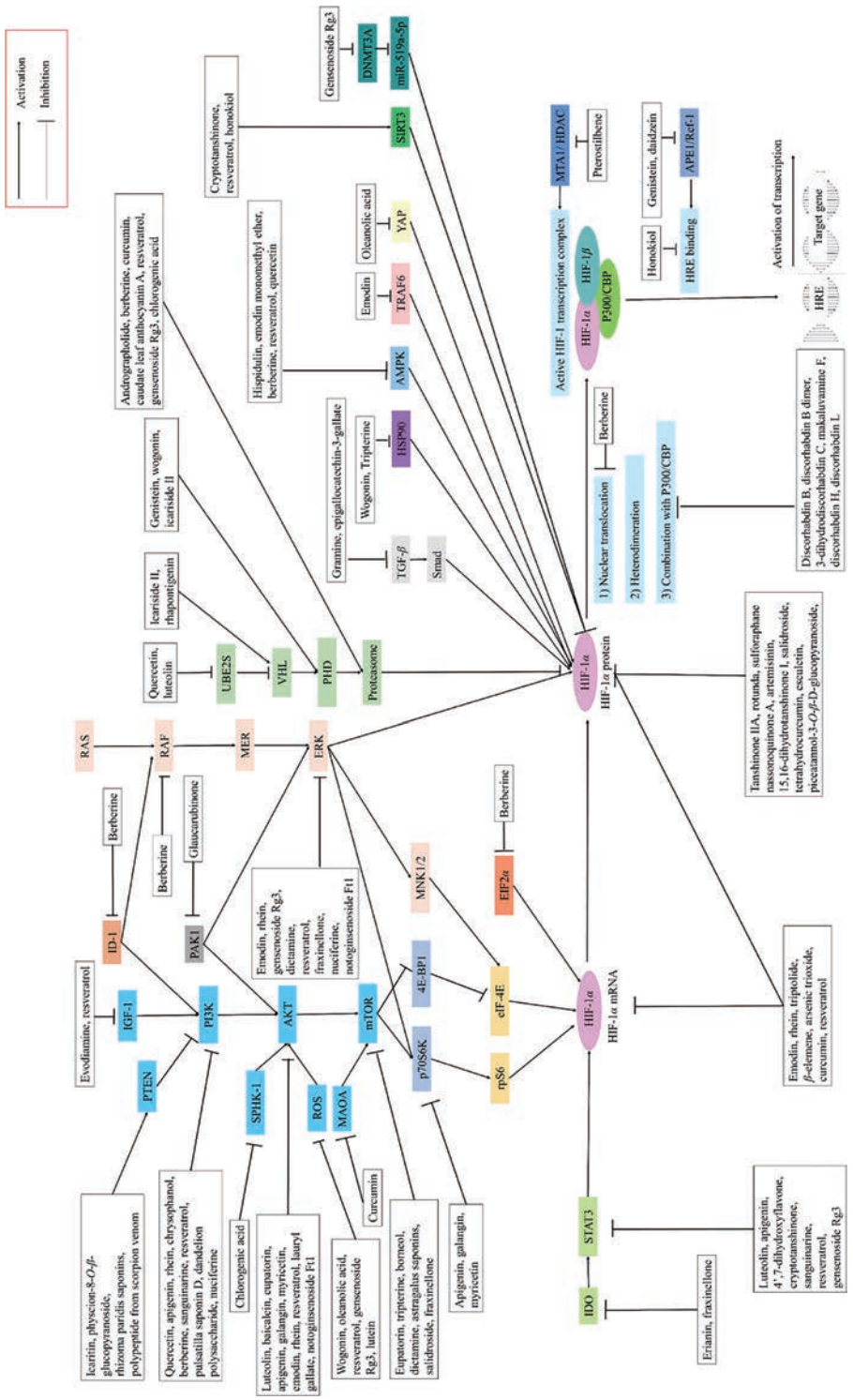


Figure 5 Anti-tumor components from traditional Chinese medicine inhibit the activation of HIF-1α in cancer treatment through different pathway. IDO: 2,3-Dioxygenase; STAT3: Signal transducer and activator of transcription 3; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; SPHK1: Sphingosine kinase-1; MAOA: Monoamine oxidase; IGF-1: Insulin-like growth factor-1; ID-1: Inhibitor of differentiation/DNA binding-1; rpS6: Ribosomal protein S6; 4E-BP1: Eukaryotic translation initiation factor 4E-bingding protein 1; eIF-4E: Eukaryotic translation initiation factor 4E; PAK1: Recombinant p21 protein activated kinase 1; ERK: Extracellular signal-regulated kinase; MNK1/2: Mitogen-activated protein kinase (MAPK)-interacting kinases 1 and 2; EIF2α: Eukaryotic translation initiation factor 2α; UBE2S: Ubiquitin E2S ligase; TRAF6: Tumor necrosis factor receptor associated factor 6; YAP: Yes-associated protein; SIRT3: Silent mating type information regulation2 homolog-3; DNMT3A: DNA methyltransferase 3A; MAT1: Menage a trois 1; APE1: Apurinic/aprimidinic endonuclease 1; Ref-1: Redox factor-1

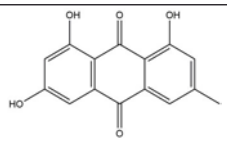
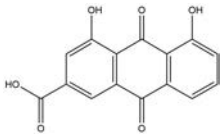
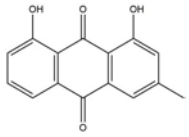
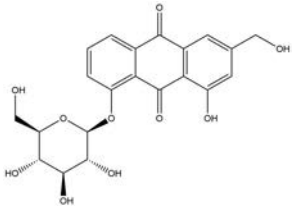
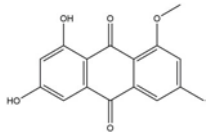
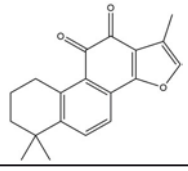
激活, 抑制多种恶性肿瘤的血管异常增生。

5.2 醌类及其糖苷

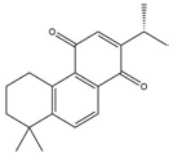
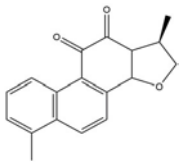
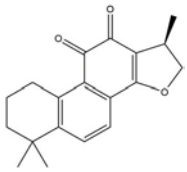
醌类化合物是一类具有醌式结构的化学成分, 主要分布在蓼科、茜草科、豆科、唇形科、紫草科等植物中。具有抑制HIF-1α表达作用的醌类化合物主要有以大黄素为代表的蒽醌类成分和以丹参酮IIA为代表的菲醌类成分 (表3)[49,71-81]。

大黄素主要来源于中药大黄 (Rhei Radix Et Rhizoma) 和虎杖 (Polygoni Cuspidati Rhizoma Et Radix)。大黄素可通过下调HIF-1α的基因和蛋白表达来调节

Table 3 Antitumor components of quinones of traditional Chinese medicine inhibiting the expression of HIF-1α. COX-2: Cyclooxygenase-2; GRB2: Growth factor receptor-bound protein 2; EGF: Epidermal growth factor; EMMPRIN: Extracellular matrix metalloproteinase; LDHA: Lactate dehydrogenase A

Component	Structure	Cancer type	Mechanism	Ref.
Emodin		Nasopharyngeal carcinoma (CNE-1)	Regulate the redox state of tumor cells by down-regulating the mRNA and protein expression of HIF-1α, and then play the role of radiosensitization	[71]
		Neuroblastoma (SH-SY5Y)	Inhibit the expression of HIF-1α, VEGF, MMPs, COX-2, Ras, GRB2, *etc*., thereby inhibiting tumor cell migration and invasion	[72]
		Thyroid cancer (8505c, SW1736)	Inhibit tumor angiogenesis and metastasis by blocking the activation of TRAF6/HIF-1α/VEGF pathway and TRAF6/CD147/MMP9 pathway	[73]
		Pancreatic cancer (AsPC-1, BxPC-3, HPAF-2, MiaPaCa2, Panc-1)	Inhibit the biosynthesis of HIF-1α protein *in vivo* and *in vitro* by decreasing phosphorylated AKT and ERK/1/2	[74]
Rhein		Colon cancer (HT29, HCT116, Colo205, SW620)	Reduce HIF-1α mRNA and protein levels to down-regulate the mRNA expression levels of immunosuppressive molecules such as PD-L1, and enhance the killing effect of effector T lymphocytes on tumor cells	[75]
		Breast cancer (MCF-7, MDA-MB-435s)	Down-regulate HIF-1α protein expression by inhibiting hypoxia-induced PI3K/AKT/ERK pathway activation, thereby reducing the secretion of VEGF and EGF	[76]
		Pancreatic cancer (AsPC-1, BxPC-3, HPAF-2, MiaPaCa2, Panc-1)	Inhibit the biosynthesis of HIF-1α protein *in vivo* and *in vitro* by decreasing phosphorylated AKT and ERK/1/2	[74]
Chrysophanol		Colon cancer (HCT116, SW480)	Reduce the expression level of HIF-1α by inhibiting the phosphorylation and activation of the PI3K/AKT signaling pathway induced by hypoxia, thereby inhibiting tumor cell invasion and metastasis	[49]
Physcion-8-*O*-*β*-glucopyranoside		Colon cancer (HCT116)	Regulate the PTEN/AKT/HIF-1α pathway to reduce the expression of EMMPRIN, Snail, Slug, and Twist, thereby inhibiting the EMT process induced by hypoxia	[77]
Emodin monomethyl ether		Colon cancer (HCT116)	Inhibit the activation of AMPK/HIF-1α pathway to down-regulate the expression of EMMPRIN and induce cell mitochondrial apoptosis	[78]
Tanshinone IIA		Breast cancer (MCF-7, HCC1937)	Inhibit the activation of HIF-1α/TWIST pathway, thereby inhibiting hypoxia-induced tumor cell EMT and DOX treatment resistance	[79]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
Rotunda nassonoquinone A		Liver cancer (AGS, Hep3B)	Dose-dependently inhibit the accumulation of HIF-1α protein and VEGF mRNA expression	[80]
15,16-Dihydrotanshinone I		Gastric cancer (AGS), liver cancer (Hep3B)	Dose-dependent inhibition of HIF-1α protein accumulation	[80]
Cryptotanshinone		Ovarian cancer (Hey, A2780)	Reduce the stability of HIF-1α protein and the expression levels of GLUT1, LDHA, and HK2 by regulating the expression of STAT3/SIRT3/HIF-1α pathway, thereby inhibiting the growth and proliferation of tumor cells induced by glycolysis	[81]

肿瘤细胞的氧化还原状态, 有效增强鼻咽癌细胞和荷瘤动物对放射治疗的敏感性, 有望成为鼻咽癌患者的一类新型放射增敏药物[71]。大黄素还可抑制人神经母细胞瘤 SH-SY5Y 细胞的迁移和侵袭, 并具有剂量和时间依赖性。其机制与大黄素抑制 HIF-1α、VEGF、MMPs、环氧合酶-2 (cyclooxygenase-2, COX-2) 等肿瘤转移和血管生成促进因子的表达相关[72]。此外, 大黄素可分别通过阻断肿瘤坏死因子受体相关因子 6 (tumor necrosis factor receptor associated factor 6, TRAF6)/HIF-1α/VEGF 和 TRAF6/CD147/MMP9 通路的激活抑制未分化甲状腺癌 (anaplastic thyroid cancer, ATC) 裸鼠异种移植和肺转移模型中的肿瘤血管生成和转移[73]。大黄酸是另一种重要的蒽醌化合物, 其作用于结直肠癌细胞后可剂量依赖性地降低 HIF-1α 的 mRNA 和蛋白水平, 进而下调程序性死亡配体-1 (programmed death-ligand 1, PD-L1)、COX-2、加连蛋白-1、IL-10 和转化生长因子-β1 (transforming growth factor-β1, TGF-β1) 等免疫抑制分子的 mRNA 表达水平, 改善肿瘤免疫微环境, 增强效应 T 淋巴细胞在缺氧条件下对肿瘤细胞的杀伤作用[75]。大黄酸还通过抑制缺氧诱导的 PI3K/AKT/ERK 通路激活进而下调 HIF-1α 的蛋白表达, 降低 VEGF 和表皮生长因子 (epidermal growth factor, EGF) 的分泌水平, 是一种有前景的抗肿瘤新生血管形成药物[76]。此外, 大黄酸和大黄素均可抑制体内外人胰腺癌细胞系中 HIF-1α 的蛋白合成, 这种抑制作用强于 PX-478 等已知的 HIF-1α 抑制剂[74]。其他具有干扰 HIF-1α 信号通路表达的蒽醌类化合物还有大黄酚[49]、芦荟大黄素-8-*O*-β-葡萄糖苷[77]和大黄素甲醚[78]。

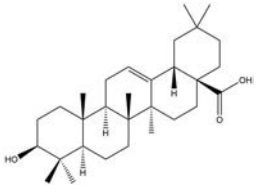
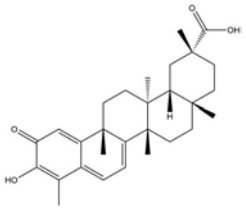
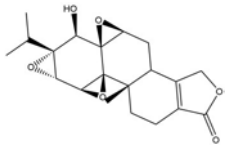
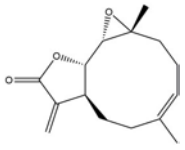
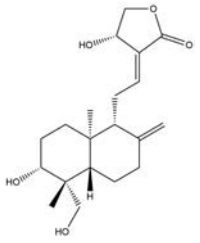
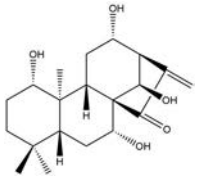
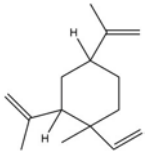
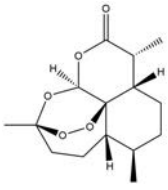
丹参酮 IIA 是从丹参 (*Salvia miltiorrhiza* Bge.) 的干燥根及根茎中分离得到的一种重要的菲醌类化合物, 其可能通过抑制 HIF-1α/TWIST 的激活进而抑制低氧诱导的乳腺癌细胞 EMT 过程及对 DOX 的治疗抵抗作用[79]。另一份研究中[80]发现丹参提取物的氯仿部位可强烈抑制低氧诱导的报告基因表达。在进一步分离得到的化合物中, 轮叶婆婆纳对醌 A 和 15,16-双氢丹参酮 I 剂量依赖性阻碍了胃癌 AGS 细胞和肝癌 Hep3B 细胞中的 HIF-1α 蛋白积累。此外, 轮叶婆婆纳对醌 A 可抑制 VEGF 的 mRNA 表达。隐丹参酮是丹参中的另一种代表性醌类活性成分, 最近的一份报道[81]显示其可调节裸鼠卵巢癌异种移植模型中信号转导和转录激活因子 3 (signal transducer and activator of transcription 3, STAT3)/SIRT3/HIF-1α 信号的表达, 显著降低 HIF-1α 的蛋白稳定性和 GLUT1、LDHA 和 HK2 的表达水平, 进而抑制糖酵解诱导的细胞生长和增殖, 具有发展为卵巢癌化疗药物的潜能。

5.3 萜类

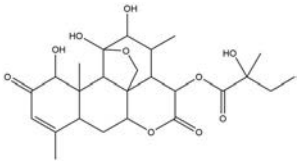
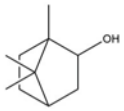
萜类中药有效成分大多存在于高等植物中, 由异戊二烯单元组成, 可分为单萜、倍半萜、二萜、三萜等。齐墩果酸、雷公藤红素等一些萜类中药单体可抑制 HIF-1α 通路的激活, 对抗缺氧诱导的肿瘤血管生成、糖酵解和远端转移 (表 4)[25,46,47,82-92]。

齐墩果酸是夏枯草 (Prunellae Spica) 等传统中药的三萜类活性成分之一。齐墩果酸可通过调控 NADPH 氧化酶 2 (NADPH oxidase 2, NOX2)/ROS 信号通路抑制 HIF-1α 表达, 诱导直肠癌细胞 G1/S 期阻滞, 抑制细胞增殖, 从而发挥其抗肿瘤作用[82]。这些结果表明, NOX2/ROS/HIF-1α 轴可能是治疗直肠癌的新靶点。

Table 4 Anti-tumor components of terpenoids of traditional Chinese medicine inhibiting the expression of HIF-1α. NOX2: NADPH oxidase; PFK1: Phosphofructokinase 1; Ang2: Angiopoietin 2; IκB: Inhibitor of NF-κB

Component	Structure	Cancer type	Mechanism	Ref.
Oleanolic acid		Colon cancer (HCT-15, HT-29)	Inhibit the expression of HIF-1α by regulating NOX2/ROS, thereby inducing tumor cell G1/S phase arrest and inhibiting cell proliferation	[82]
		Gastric cancer (MKN-45, SGC-7901)	Reduce the nuclear abundance of HIF-1α by inhibiting the activation of YAP signaling pathway, thereby inhibiting the expression of HK2 and PFK1 and blocking HIF-1α-mediated aerobic glycolysis and cell proliferation	[83]
Tripterine		Liver cancer (Hep3B, SK-Hep1), cervical cancer (HeLa)	Inhibit the expression of HIF-1α protein at the translation level by blocking the phosphorylation of mTOR/p70S6K/eIF4E and ERK signaling pathway, and down-regulate the expression of VEGF and EPO	[84]
		Liver cancer (HepG2), lung cancer (A549)	Increases the degradation of HIF-1α by inhibiting the binding of HSP90 and HIF-1α, then reduce the nuclear translocation and nuclear accumulation of HIF-1α protein	[85]
		Glioblastoma (U87)	Inhibit the activation of PI3K/AKT/mTOR signaling pathway, thereby reducing the expression of HIF-1α, CD31, VEGFR2, Ang2, and VEGFA, and inhibit tumor angiogenesis and the formation of angiogenic mimicry	[86]
Triptolide		Melanoma (A375)	Inhibit the activation of HIF-1α/EMT pathway, thereby inhibiting the invasion and metastasis of human melanoma cells	[87]
		Liver cancer (SSMC-7721)	Inhibit mRNA and protein expression of HIF-1α, HK2, PKM2, LDHA, suppressing HIF-1α-mediated glycolysis pathway	[88]
Parthenolide		Colon cancer (HCT116), glioblastoma (U87.MG), breast cancer (MDA-MB-231)	Inhibit the activation of NF-κB/HIF-1α pathway by combining with IκB kinase and preventing the degradation of IκBα (a protein that inhibits NF-κB)	[89]
Andrographolide		Liver cancer (Hep3B and HepG2)	Promote the induction of ubiquitination-mediated degradation of HIF-1α protein and reduce the expression of HIF-1α and VEGFA	[46]
Caudate leaf anthocyanin A		Liver cancer (Hep3B, Sk-hep1)	Inhibit the expression of HIF-1α protein by blocking the biosynthesis of HIF-1α, and inhibit the transcriptional activity of HIF-1α	[90]
β-Elemene		Lung cancer (A594)	Reduce the mRNA and protein expression of HIF-1α and survivin induced by radiation, thereby increasing the apoptosis rate of tumor cells under radiotherapy	[47]
Artemisinin		Breast cancer (MDA-MB-231)	High-dose artemisinin can reduce the expression levels of HIF-1α and VEGF in tumor-bearing animals, thereby inhibiting the activity of Noch1 signaling pathway and tumor development	[91]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
Glaucarubinone		Colon cancer (DLD1, HCT116, HT29, SW480, SW1222)	Down-regulate the expression of HIF-1α and β-catenin through PAK1-dependent pathways, thereby inhibiting the growth and metastasis of colorectal cancer	[92]
Borneol		Glioma (C6)	Down-regulate the expression of HIF-1α by regulating the mTORC1/eIF4E pathway, thereby down-regulating the expression of Bcl-2, and up-regulating the expression of BAX and caspase-3	[25]

此外, 齐墩果酸可通过抑制Yes相关蛋白信号通路的激活降低HIF-1α的表达和核丰度, 并抑制糖酵解限速酶HK2和磷酸果糖激酶-1 (phosphofructokinase 1, PFK1)的表达和功能活性, 从而阻断HIF-1α介导的胃癌细胞有氧糖酵解和增殖[83]。

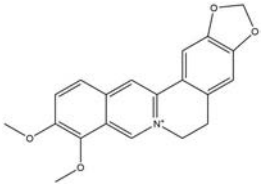
雷公藤红素为雷公藤 (*Tripterygium wilfordii* Hook. f.) 根皮中的一种五环三萜, 具有广谱的抗肿瘤作用。雷公藤红素可以在多个水平上调控HIF-1α的表达, 发挥抗肿瘤血管生成和转移的活性。雷公藤红素可阻断mTOR/p70S6K/eIF4E和ERK信号通路的磷酸化, 在翻译水平上抑制肝癌细胞和宫颈癌细胞中HIF-1α蛋白的表达, 并下调VEGF和EPO的表达[84]。此外, 雷公藤红素在常氧和缺氧条件下均可降低肝癌细胞HIF-1α的表达水平, 抑制HIF-1α蛋白的核转位和核积聚。这与雷公藤红素抑制HSP90与HIF-1α的结合, 继而增加HIF-1α的降解有关[85]。雷公藤红素还可抑制PI3K/AKT/mTOR信号通路的激活, 降低HIF-1α、CD31、VEGFR2、ANG2和VEGFA的表达, 进而抑制胶质母细胞瘤中的血管生成和血管生成拟态的形成[86]。

5.4 生物碱类

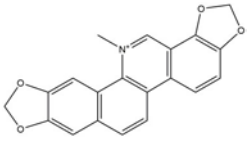
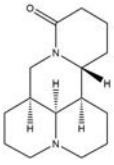
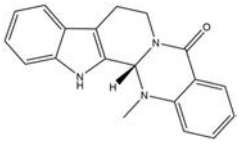
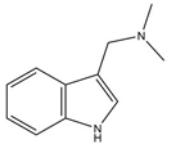
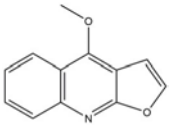
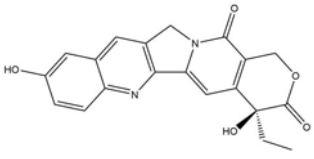
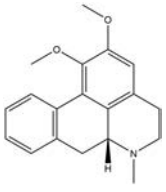
生物碱是一类含氮的碱性有机化合物, 在罂粟科、防己科、毛茛科、小檗科等植物中广泛分布。许多生物碱类中药成分被证实可显著抑制HIF-1α通路, 对抗实体瘤的恶性发展 (表5)[44,93-108]。

小檗碱是从传统中药黄连 (Coptidis Rhizoma) 中分离出的一种异喹啉类生物碱, 对肿瘤、炎症、糖尿病等疾病具有良好的治疗作用。小檗碱可通过多种机制干预HIF-1α通路的表达: ① 小檗碱可通过阻断PI3K/AKT和Raf/MEK/ERK信号通路的激活, 抑制AKT和ERK蛋白的磷酸化, 从而下调HIF-1α的转录和翻译水平[93,94]; ② 小檗碱促进了26S蛋白酶体水解途径和赖氨酸乙酰化对HIF-1α蛋白的降解作用[95]; ③ 小檗碱通过

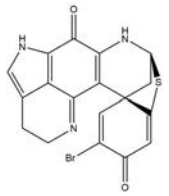
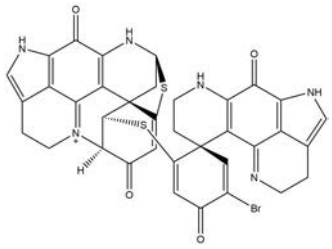
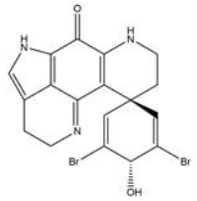
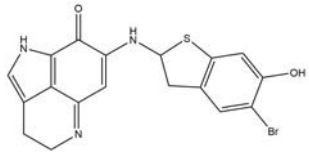
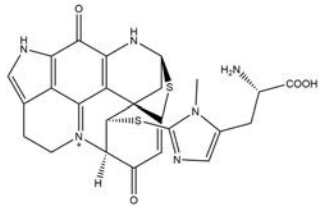
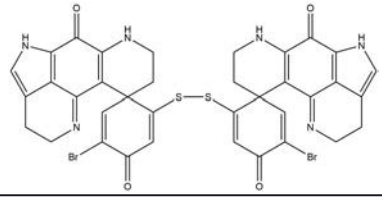
Table 5 Antitumor components of alkaloids of traditional Chinese medicine inhibiting the expression of HIF-1α. PEDF: Pigment epithelium-derived factor; ODC: Ornithine decarboxylase; OAZ1: ODC antizyme 1; GSK-3β: Glycogen synthase kinase-3β; BCRP: Breast cancer resistance protein; NF: Nuciferine

Component	Structure	Cancer type	Mechanism	Ref.
Berberine		Lung cancer (A549, H1299)	Down-regulate HIF-1α/VEGF/PEDF signal by blocking PI3K/AKT and Raf/MEK/ERK pathway activation, thereby inhibiting tumor growth and angiogenesis	[93]
		Cervical cancer (HeLa)	Down-regulate the transcription and translation levels of HIF-1α by inhibiting PI3K phosphorylation, thereby overcoming the radiation resistance of tumor cells	[94]
		Gastric cancer (SC-M1)	Promote HIF-1α degradation through 26S proteasome hydrolysis pathway and lysine acetylation	[95]
		Liver cancer (MHCC-97L, HepG2, SK-Hep1)	Inhibit the expression of HIF-1α/VEGF axis by inhibiting Id-1 gene expression, and then exerting anti-angiogenesis effect	[96]
		Colon cancer (HCT116)	Inhibit the expression of HIF-1α, ODC, C-MYC, up-regulate the expression of OAZ1 and SSAT, thereby protecting the intestinal mucosal barrier and inhibiting tumor growth	[97]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
		Prostate cancer (LNCaP, DU-145)	Inhibit the expression and nuclear translocation of HIF-1α and VEGF, thereby significantly improving the radiosensitivity of tumor cells *in vivo* and *in vitro*	[98]
		Nasopharyngeal carcinoma (CNE-1, CNE-2)	Inhibit the expression of HIF-1α and VEGF, thereby improving the sensitivity of tumor cells *in vivo* and *in vitro* to radiotherapy	[99]
		Breast cancer (MCF-7)	① Low-dose berberine can enhance the sensitivity of cells to DOX by blocking AMPK/HIF-1α/P-gp pathway; ② High-dose berberine can induce p53 activation by down-regulating the expression of AMPK/HIF-1α, and directly induce apoptosis	[100]
Sanguinarine		Breast cancer (MDA-MB-231)	Inhibit the nuclear co-localization and interaction of HIF-1α with p-STAT3-Tyr and p-STAT3-Ser, destroy the transcription complex composed of the three, and inhibit the activation of the target protein	[101]
		Liver cancer (HepG2, Hep3B, Huh-7, SK-Hep-1, Bel-7402, Bel-7404, SMMC-7721, MHCC-97H, MHCC-97L)	Inhibit HIF-1α/TGF-β signal transduction and Smad and PI3K-AKT pathway activation, thereby inhibiting tumor growth and EMT	[102]
Matrine		Colon cancer (HCT116, SW620)	Reduce HIF-1α mRNA and protein levels to inhibit the expression of GLUT1, HK2, and LDHA, thereby reversing Warburg effect and inhibit the growth of tumor cells *in vivo* and *in vitro*	[103]
Evodiamine		Colon cancer (LoVo)	Inactivate PI3K/AKT signal transduction by reducing the expression of IGF-1, thereby down-regulating the expression of HIF-1α	[104]
Gramine		Hamster buccal pouch carcinoma (induced by DMBA)	Down-regulate the expression of HIF-1α, MMP-2, MMP-9, VEGF, and VEGF-R2 by inhibiting the TGF-β/Smad signaling pathway, thereby preventing the neovascularization and remodeling of tumor extracellular matrix	[105]
Dictamine		Liver cancer (SK-Hep1), lung cancer (A549), colon cancer (HCT116)	Reduce the synthesis of HIF-1α by down-regulating the mTOR/p70S6K/eIF4E and MAPK pathway and reduce the expression of Slug protein by inhibiting the GSK-3β/Slug pathway, thereby inhibiting the abnormality of EMT markers expression	[106]
10-Hydroxycamptothecin		Liver cancer (VX2)	Inhibit the expression of HIF-1α and VEGF in liver cancer tissue after embolization, thereby inhibiting angiogenesis	[107]
Nuciferine		Colorectal adenocarcinoma (HCT-8), lung cancer (A549)	Suppress the activation of Nrf2 and HIF-1α by inhibiting PI3K/AKT/ERK pathways and further reduce the expression of P-gp and BCRP, contributing to the sensitizing effects of NF against MDR	[108]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
Discorhabdin B		Prostate cancer (LNCaP), colon cancer (HCT116, COLO205)	Block the interaction between HIF-1α and transcription co-activator p300, reduce the transcription activity of HIF and the expression of VEGF	[44]
Discorhabdin B dimer		Prostate cancer (LNCaP), colon cancer (HCT116, COLO205)	Block the interaction between HIF-1α and transcription co-activator p300, reduce the transcription activity of HIF and the expression of VEGF	[44]
3-Dihydrodiscorhabdin C		Prostate cancer (LNCaP), colon cancer (HCT116, COLO205)	Block the interaction between HIF-1α and transcription co-activator p300, reduce the transcription activity of HIF and the expression of VEGF	[44]
Makaluvamine F		Prostate cancer (LNCaP), colon cancer (HCT116, COLO205)	Block the interaction between HIF-1α and transcription co-activator p300, reduce the transcription activity of HIF and the expression of VEGF	[44]
Discorhabdin H		Prostate cancer (LNCaP), colon cancer (HCT116, COLO205)	Block the interaction between HIF-1α and transcription co-activator p300, reduce the transcription activity of HIF and the expression of VEGF	[44]
Discorhabdin L		Prostate cancer (LNCaP), colon cancer (HCT116, COLO205)	Block the interaction between HIF-1α and transcription co-activator p300, reduce the transcription activity of HIF and the expression of VEGF	[44]

下调DNA结合分化抑制因子1 (inhibitor of differentiation/DNA binding-1, Id-1) 的启动子活性抑制了其转录水平, 继而降低Id-1对HIF-1α蛋白的稳定作用[96]。小檗碱对HIF-1α通路的抑制作用显著下调了下游VEGF、PEDF、P-gp等多种基因的表达, 从而有效抑制了肿瘤生长[97]和血管生成[93], 并明显提高了前列腺癌[98]、宫颈癌[94]、鼻咽癌[99]、乳腺癌[100]等多种肿瘤细胞系对化疗或放疗的敏感性 (具体机制见表5)。这些资料表明, 小檗碱是一种具有良好前景的抗肿瘤药物, 与化疗、放疗等传统肿瘤治疗手段联用可起到协同增效的作用。

血根碱是从博落回 [*Macleaya cordata* (Willd.) R. Br.] 等罂粟科植物中发现的苯并菲啶类生物碱, 具有广谱的抗癌活性。血根碱在体内外均能抑制HIF-1α与p-STAT3-Tyr和p-STAT3-Ser的核共定位和相互作用, 破坏三者形成的转录复合体, 进而抑制VEGF等靶基因的激活和肿瘤生长[101]。缺氧可触发TGF-β和PI3K依赖的细胞外基质相关蛋白的表达或通过TGF-β的自分泌诱导EMT发生, 而TGF-β增强了HIF-1α的表达及其靶基因碳酸酐酶9 (carbonic anhydrase 9, CA9) 和VEGF的转录, 从而形成HIF-1α/TGF-β前馈通路。血根碱可显著抑制缺氧诱导的TGF-β的分泌, 阻断TGF-β诱导的HIF-1α表达增加, 有效抑制HIF-1α的核易位。此外, 血根碱还抑制了缺氧诱导的Snail易位、Smad和PI3K/AKT通路的激活, 从而抑制肿瘤生

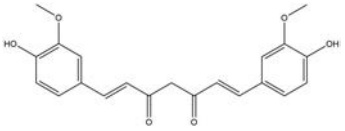
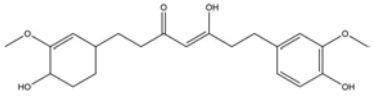
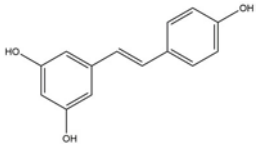
长、上皮间质转化和细胞迁移[102]。

5.5 多酚类

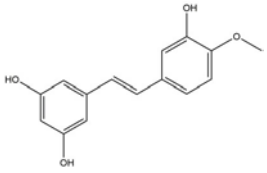
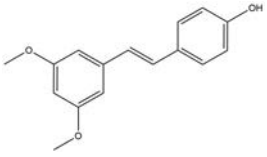
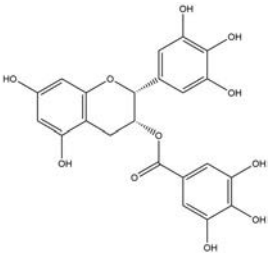
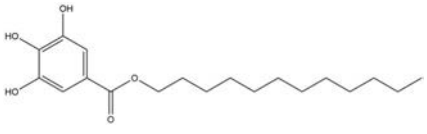
多酚类化合物是一类复杂的具有多个酚羟基的中药活性成分, 具有抗肿瘤、抗氧化、清除自由基、降血脂等作用。其中姜黄素及其类似物、白藜芦醇等已被证明可通过多种机制抑制HIF-1α的过度激活 (表6)[52,53,109-130]。

姜黄素是从姜黄 (*Curcuma longa* L.) 的干燥根茎中提取的一种多酚类多功能分子, 其含有可与蛋白质发生共价结合的α,β-不饱和二酮基团[23]。姜黄素具有抗血管生成、抗肿瘤细胞增殖[109]、促进凋亡[109]、逆转耐

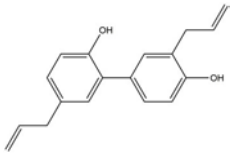
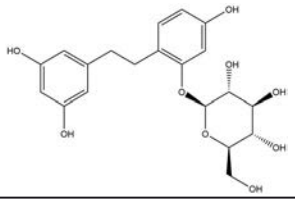
Table 6 Anti-tumor components of polyphenols of traditional Chinese medicine inhibiting the expression of HIF-1α. MCL-1: Myeloid cell leukemia 1; PARP: Poly(ADP-ribose) polymerase; CAF: Cancer-associated fibroblasts; CXCR4: C-X-C chemokine receptor type 4; IL-6: Interleukin-6; IUDR: 5-Iodo-2-deoxyuridine; CBR1: Carbonyl reductase 1; IL-1β: Interleukin-1β; SIRT1: Sirtuin 1; AR: Androgen receptor

Component	Structure	Cancer type	Mechanism	Ref.
Curcumin		Hemangioma (HemECs)	Reduce the mRNA expression of HIF-1α and MCL-1 to inhibit the expression of VEGF and promote the activation of caspase-3 and the increase of PARP lysis	[109]
		Lung cancer (A549)	Promote the degradation of HIF-1α by proteasome pathway and activate the expression of caspase-3, thereby inhibiting tumor cell proliferation, reverses drug resistance to cisplatin, and induces apoptotic death	[52]
		Prostate cancer (PC3)	Inhibit the signal transduction of MAOA/mTOR/HIF-1α pathway to block CAF-induced tumor invasion and EMT, thereby inhibiting the generation of ROS and the expression of CXCR4 and IL-6 receptors	[53]
		Breast cancer (MDA-MB231), prostate cancer (PC3)	Inhibit the expression of HIF-1α at the transcription and translation level to display anti-cell proliferation and angiogenesis effect	[110]
Tetrahydrocurcumin		Cervical cancer (CaSki)	Down-regulate the protein expression levels of HIF-1α, VEGF, and VEGFR2, resulting in reducing microvessel density in tumor models	[111]
Resveratrol		Tongue squamous cell carcinoma (SCC-9), liver cancer (HepG2)	Block the p42/44MAPK and PI3K/AKT pathway activation and promote the degradation of HIF-1α through 26S proteasome pathway to inhibit HIF-1α protein accumulation and down-regulate the expression of VEGF mRNA and protein levels	[112]
		Lung cancer (LLC), colon cancer (HT-29), breast cancer (T47D)	Reduce the ROS level of tumor cells by regulating the activity of antioxidant enzymes or the inherent ROS scavenging ability, and then inhibit the protein accumulation of HIF-1α induced by ROS, the expression of GLUT-1 and the glycolytic flux	[113]
		Nasopharyngeal carcinoma (CNE-2Z)	Down-regulate the expression of HIF-1α and Bcl-2 protein, and up-regulate the expression of caspase-3 by reducing the phosphorylation level of the pAKT1/p70S6K/p-4E-BP-1 signaling pathway and cyclin expression	[114]
		Lung cancer (A549)	Inhibit the expression of STAT3/HIF1α/VEGF pathway in non-small cell lung cancer (NSCLC) rat model	[115]
		Glioblastoma (U87MG)	Inhibit the expression and protein activity of HIF-1α, causing the S phase arrest of tumor cells and the increase of IUDR absorption, achieving radiosensitization	[116]
		Breast cancer (MCF-7)	Reduce the protein expression of HIF-1α through non-proteasome-dependent pathway, thereby inhibiting the hypoxia-induced CBR1 metabolism of doxorubicin	[117]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
		Pancreatic cancer (BxPC-3, Panc-1)	Inhibit HIF-1α protein expression and Hedgehog signaling pathway through post-transcriptional mechanism, thereby inhibiting tumor cell migration and invasion induced by hypoxia	[118]
		Osteosarcoma (Saos-2)	Interfere with the translation process of HIF-1α and promotes HIF-1α protein degradation to increased E-cadherin levels, and decrease vimentin expression	[119]
		Gastric cancer (SGC7901)	Reduce the level of HIF-1α protein to inhibit the activation of Hedgehog-related signaling pathways and the abnormal expression of EMT markers	[120]
		Ovarian cancer (A2780/CP70, OVCAR-3)	① Down-regulate HIF-1α expression by inhibiting the activation of MAPK and PI3K/AKT pathways; ② Inhibit the phosphorylation of p70S6K1, S6 ribosomal protein, 4E-BP1, eIF4E to reduce IGF-1 induced HIF-1α protein synthesis; ③ Induce degradation of HIF-1α through proteasome pathway	[121]
		Breast cancer (ASC)	Increase the binding affinity of SIRT1 and HIF-1α and inactivate the latter through Lys674 site deacetylation, thereby reducing the interaction between HIF-1α and co-activator p300 and inhibiting the transcription of aromatase genes	[122]
		Prostate cancer (LNCaP)	Reduce HIF-1α expression through non-proteasome-dependent pathway, thereby inhibiting the nuclear localization and nuclear accumulation of β-catenin and blocking β-catenin-mediated AR signaling	[123]
Rhapontigenin		Colorectal adenocarcinoma (SW620), breast cancer (MCF-7), fibrosarcoma (HT-1080), prostate cancer (LNCaP, PC-3)	Enhance the binding of hydroxylated HIF-1α to pVHL to inhibit HIF-1α protein accumulation and VEGF secretion	[124]
Pterostilbene		Prostate cancer (LNCaP)	Inhibit the signal transduction of metastasis-associated protein 1 (MTA1)/histone deacetylase (HDAC) pathway and reduce the reduction of MTA1-dependent HIF-1α, VEGF, and IL-1β, thereby making tumor cells resistant to the HDAC inhibitor SAHA treatment sensitization	[125]
Epigallocatechin-3-gallate		Lung cancer (A549)	Inhibit insulin-like growth factor-I (IGF-1)-induced HIF-1α protein accumulation and VEGF expression, resulting in anti-tumor angiogenesis effect	[126]
Lauryl gallate		Glioblastoma (U87)	Induce tumor cell apoptosis by inhibiting the expression of P-AKT, HIF-1α, HIF-2α, and β-catenin	[127]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
Honokiol		Lung cancer (H460, A549, H358, H2122)	Reduce the protein stability of its target gene HIF-1α by up-regulating the expression of SIRT3	[128]
		Colon cancer (CT269)	Improve the effect of radiotherapy and delay the tumor growth rate by reducing the transcriptional activation of HIF-1α and its coupling to HRE oligonucleotides	[129]
Piceatannol-3-*O*-*β*-*D*-glucopyranoside		Fibrosarcoma (HT-1080)	Inhibit the activation of HIF-1α/VEGF pathway under normoxia and hypoxia	[130]

药性[53]、抗侵袭和转移[53]等多种抗肿瘤活性, 其机制与姜黄素抑制HIF-1α的表达和激活caspase-3进而调控下游VEGF、P-gp、ROS、多聚腺苷二磷酸核糖聚合酶[poly(ADP-ribose) polymerase, PARP]等的基因表达水平相关。姜黄素主要从以下途径来抑制HIF-1α的表达: ① 姜黄素可在转录和翻译水平上抑制乳腺癌MDA-MB-231细胞和前列腺癌PC3细胞中HIF-1α的表达[110]; ② 姜黄素和顺铂联合治疗可促进HIF-1α的蛋白酶体途径降解, 并激活caspase-3的表达[52]; ③ 姜黄素还可通过抑制单胺氧化酶(monoamine oxidase, MAOA)/mTOR通路的信号转导阻断肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAF)诱导的HIF-1α稳定性和活性增加[53]。四氢姜黄素是姜黄素的主要代谢物之一, 其酚羟基和*β*-二酮基结构与姜黄素相似, 并具有更强的抗血管生成活性[131]。四氢姜黄素可通过下调HIF-1α、VEGF和VEGFR-2的蛋白表达水平显著降低宫颈癌动物模型中的微血管密度, 抑制肿瘤血管的异常增生[111]。

白藜芦醇(resveratrol, RES)是中药虎杖(Polygoni Cuspidati Rhizoma Et Radix)中的主要成分之一, 具有抗肿瘤、抗氧化、抗炎和免疫调节等多种活性。RES可通过抑制HIF-1α通路的激活下调VEGF、GLUT-1、羰基还原酶1 (carbonyl reductase 1, CBR1)、Bcl-2、*β*-catenin、Hedgehog信号通路以及EMT标志物的异常表达, 进而发挥抗肿瘤血管生成[112]、逆转糖酵解[113]、抗肿瘤细胞增殖[114]、促进肿瘤细胞凋亡[114,115]、治疗增敏[116,117]、抗肿瘤侵袭和转移[118-120]的作用。RES抑制HIF-1α表达的机制主要有以下几点: ① 白藜芦醇可阻断p42/44MAPK和PI3K/AKT通路的激活, 进而下调HIF-1α的表达[112]; ② 白藜芦醇促进了HIF-1α的26S蛋白酶体途径降解, 进而抑制HIF-1α蛋白积聚[112,121]; ③ 白藜芦醇可通过抑制胰岛素样生长因子-1 (insulin-like growth factor-1, IGF-1)诱导的蛋白翻译调控因子p70S6K1、S6核糖体蛋白、4E-BP1、eIF4E的磷酸化抑制HIF-1α蛋白合成[121]; ④ 白藜芦醇通过调节抗氧化酶活性或固有的ROS清除能力可降低肿瘤细胞的ROS水平, 继而抑制ROS诱导的HIF-1α的蛋白积聚[113]; ⑤ 白藜芦醇可作为sirtuin1 (Sirt1)的激动剂, 增加Sirt1与HIF-1α的结合, 使后者的Lys674位点去乙酰化失活, 进而抑制HIF-1α与共激活因子p300之间的相互作用[122]; ⑥ 白藜芦醇通过阻断STAT3的激活, 抑制下游HIF-1α的基因表达和HIF-1α功能活性[115]。总而言之, 白藜芦醇可通过多种机制下调HIF-1α通路的激活, 在对抗缺氧诱导的肿瘤进展方面具有广阔的应用前景。

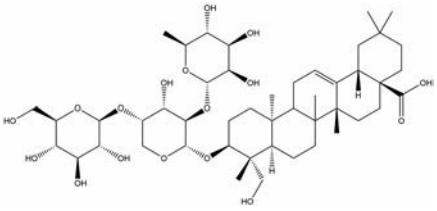
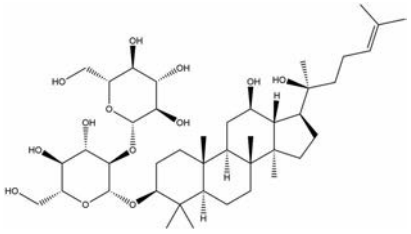
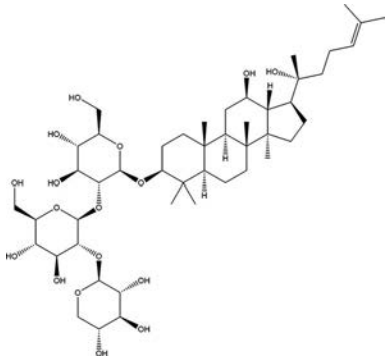
5.6 皂苷类

皂苷是一类结构复杂的螺甾烷和其相似生源的甾体化合物以及三萜类化合物的低聚糖苷, 主要存在于五加科、薯蓣科、百合科、毛茛科、桔梗科等植物中。目前已报道的抑制HIF-1α表达的皂苷类成分相对较少(表7)[132-142], 其中研究较为深入的为白头翁皂苷D和人参皂苷Rg3。

白头翁皂苷D (SB365)是从毛茛科植物白头翁[*Pulsatilla chinensis* (Bge.) Rege]中分离得到的一种抗肿瘤活性成分。Hong等[132]研究表明, SB365可有效抑制PI3K/AKT/mTOR通路激活, 继而降低HIF-1α和VEGF的表达, 显著抑制肝癌移植瘤模型的生长。Son等[133]同样发现SB365可显著降低HIF-1α和VEGF的表达而发挥抗血管生成作用, 并抑制了胰腺癌细胞的瘤球形成。小鼠体内移植实验表明, SB365通过抑制血管生成和诱导肿瘤细胞凋亡显著抑制肿瘤生长, 是治疗胰腺癌的良好候选药物。

人参皂苷Rg3是我国的名贵中药人参(Ginseng Radix Et Rhizoma)中主要的活性成分, 已经用于临床抗肿瘤治疗。近几年研究表明, Rg3可通过多种机制

Table 7 Anti-tumor components of saponins of traditional Chinese medicine inhibiting the expression of HIF-1*α*. GEM: Gemcitabine; PTX3: Pentraxin 3

Component	Structure	Cancer type	Mechanism	Ref.
Pulsatilla saponin D		Liver cancer (Huh-7 and HepG2)	Reduce the expression of HIF-1*α* and VEGF by inhibiting the PI3K/AKT/mTOR pathway, thereby inhibiting tumor growth in tumor-bearing animals	[132]
		Pancreatic cancer (PANC-1, MIAPaCa-2, BXPC-3, AsPC-1 and HPAC)	Reduce the expression of HIF-1*α* and VEGF to prevent angiogenesis, thereby inhibiting the formation of tumor balls	[133]
Gensenoside Rg3		Oesophageal carcinoma (Eca-109, 786-0)	Promote HIF-1*α* protein degradation and inhibit expression of COX-2, NF-*κ*B, phosphorylation of STAT3, and phosphorylation of ERK1/2 and JNK, thereby reducing the expression of VEGF	[134]
		Ovarian cancer (SKOV3, A2780)	Up-regulate the expression level of miR-519a-5p by reversing DNA methylation mediated by DNMT3A to inhibit the expression of HIF-1*α* and antagonize the expression of HK2 and the Warburg effect	[135]
		Ovarian cancer (SKOV3, 3AO)	Promote the degradation of HIF-1*α* by activating the ubiquitin-proteasome pathway, and then reduce the expression of HIF-1*α*, thereby inhibiting the transcription of Snail and the abnormal expression of EMT markers	[136]
		Oesophageal carcinoma (EC109, TE1, KYSE170)	Down-regulate HIF-1*α* and VEGF protein levels to enhance the radiosensitivity of tumor cells under hypoxic conditions	[137]
		Lung cancer (A549, SPCA1)	Block GEM-induced ROS-mediated activation of AKT and ERK pathways to inhibit nuclear accumulation of HIF-1*α* and NF-*κ*B and reduce the expression of drug-resistant phenotype PTX3	[138]
		Gastric cancer (GPL mice)	Down-regulate the expression of HIF-1*α*, LDH, and HK2 by inhibiting the PI3K/AKT/miRNA-21 pathway, and then relief the abnormal glycolysis in the mouse GPL model	[139]
Notoginsenoside Ft1		Breast cancer (MDA-MB-231)	Down-regulation of HIF-1*α* expression by inhibiting phosphorylation activation of AKT/mTOR/p70S6K and MAPK pathways	[140]
Rhizoma Paridis saponins	—	Liver cancer (H22)	Down-regulate the expression of PI3K/AKT/mTOR and HIF-1*α*/Myc/Ras by activating tumor suppressor genes P53 and PTEN, and further reverse tumor cell aerobic glycolysis	[141]
Astragalus saponins	—	Colon cancer (HCT 116)	Inhibit hypoxia-induced activation of mTOR/HIF-1*α*/VEGF axis to inhibit tumor angiogenesis	[142]

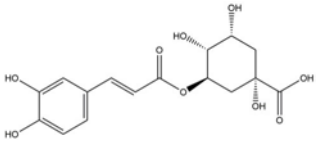
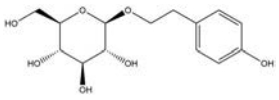
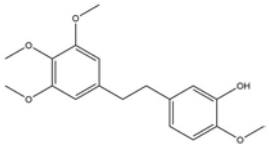
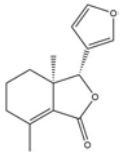
抑制HIF-1α信号通路的表达, 这可能是其发挥抗肿瘤血管生成[134,135]、抗侵袭和转移[136]以及治疗增敏作用[137]的重要机制。如Rg3可阻断吉西他滨 (gemcitabine, GEM) 诱导的ROS介导的AKT和ERK通路激活, 进而抑制肺癌细胞中HIF-1α和NF-κB的核堆积, 降低耐药表型PTX3的表达[138]。再如, Rg3可通过抑制PI3K/AKT/miRNA-21通路的激活下调HIF-1α、LDH、HK2的表达, 继而减缓小鼠胃癌前病变 (gastric precancerous lesions, GPL) 模型的糖酵解异常, 降低胃癌的发生风险[139]。此外, 人参皂苷Rg3促进了食管癌细胞中HIF-1α的蛋白降解, 显著缩短了HIF-1α蛋白的半衰期, 并抑制了缺氧诱导的COX-2、NF-κB的表达、STAT3的磷酸化以及ERK1/2和c-Jun氨基末端激酶 (C-Jun N-terminal kinase, JNK) 的磷酸化, 进而下调VEGF的表达[134]。Rg3作用于卵巢癌细胞后可抑制下游HIF-1α/HK2通路的表达和Warburg效应[135], 其机制与其抑制DNA甲基转移酶3 (DNA methyltransferase 3A, DNMT3A) 介导的miR-519a-5p前体基因启动子区域中的DNA甲基化进而上调miR-519a-5p水平有关。Rg3还可通过激活泛素-蛋白酶体途径加速HIF-1α的降解, 进而抑制Snail的转录, 促进E-钙黏素的上调和波形蛋白的下调, 进而阻断卵巢癌裸鼠异种移植模型中的EMT[136]。

5.7 其他

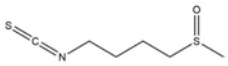
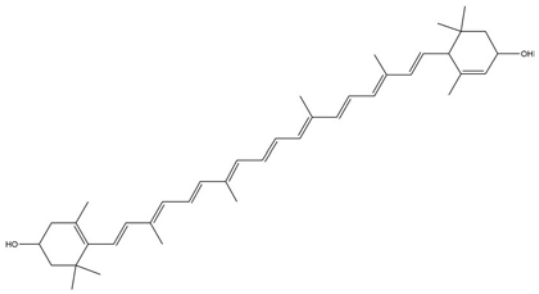
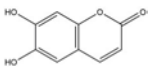
中药活性成分的种类繁多, 除了上述介绍的化合物, 绿原酸、红景天苷等化合物也发现具有一定的抑制肿瘤细胞HIF-1α通路的作用 (表8)[48,143-155]。

绿原酸是由咖啡酸的羧基和奎尼酸的羟基缩合而成的缩酚酸, 在金银花 (Lonicerae Japonicae Flos) 等中药中含量很高。绿原酸可通过促进HIF-1α的蛋白酶体途径降解抑制缺氧诱导的HIF-1α蛋白积累和转录

Table 8 Other antitumor components of traditional Chinese medicine inhibiting the expression of HIF-1α. LOXL2: Lysyl oxidase-like protein 2; JAK2: Janus kinase 2; Dll4: Delta-like ligand 4; Sox2: Sex determining region Y-box 2; OCT4: Octamer binding transcription factor 4

Component	Structure	Cancer type	Mechanism	Ref.
Chlorogenic acid		Lung cancer (A549)	Inhibit HIF-1α protein accumulation and transcriptional activity by promoting proteasome degradation of HIF-1α, and inhibit angiogenesis by inhibiting HIF-1α/AKT signal transduction	[143]
		Prostate cancer (DU145)	① Down-regulate the expression of HIF-1α by inhibiting the expression and functional activity of SPHK-1; ② Reduce the stability of HIF-1α protein and reduce the expression and secretion of VEGF by inhibiting the phosphorylation of AKT/GSK-3β pathway	[144]
Salidroside		Liver cancer (HepG2)	Inhibit the expression of HIF-1α by promoting the degradation of HIF-1α, and then significantly increase the sensitivity of tumor cells to platinum drugs and inhibit hypoxia-induced EMT	[145]
		Pancreatic cancer (BxPC-3)	Inhibit the expression and transcriptional activity of HIF-1α and reverse the tumorigenicity of BxPC-3 cells induced by LOXL2 overexpression	[146]
		Breast cancer (MCF-7)	Down-regulate the protein expression of HIF-1α/HIF-2α and inhibit the activation of mTOR pathway and tumor angiogenesis induced by hypoxia	[147, 148]
Erianin		Lung cancer (2LL)	Inhibit HIF-1α, MMP-2/-9, COX-2, IL-6, *etc.* by down-regulating indoleamine 2,3-dioxygenase (IDO)-induced phosphorylation of JAK2/STAT3	[149]
Fraxinellone		Lung cancer (A549), cervical cancer (HeLa), liver cancer (Hep3B)	① Inhibit the synthesis of HIF-1α by inhibiting mTOR/p70S6K/eIF4E and MAPK signaling pathways, ② inhibit the activation of STAT3 by inhibiting JAK1, JAK2, and Src pathways, and ③ inhibit the expression of PD-L1 by inhibiting the synergism of STAT3 and HIF-1α	[150]

Continued

Component	Structure	Cancer type	Mechanism	Ref.
Sulforaphane		Colon cance (HCT116), gastric cancer (AGS)	The expression of HIF-1α and VEGF is significantly down-regulated by affecting the stability of HIF-1α protein, thus inhibiting tumor angiogenesis and metastasis	[151]
Lutein		Breast cancer (MDA-MB-157, MCF-7)	Inhibit the expression of HIF-1α by decreasing the production of ROS, and then down-regulate the expression of NOTCH signal, hairy and enhancer of split related-1 (HES1) and EMT-related factors	[152]
Arsenic trioxide		Lung cancer (A549, SK-MES-1, NCI-H460)	Inhibit the mRNA and protein expression of HIF-1α to decrease the level of VEGF-A, and down-regulate the expression of VEGFR-2, Dll4 and Notch-1, thereby exerting the effect of anti-angiogenesis	[48]
Esculetin		Breast cancer (MDA-MB-231)	Down-regulate the expression of HIF-1α and then reduce the expression of dry related markers CD44, Nanog, Sox2, and OCT4, inhibit the proliferation of tumor cells and reduce the dryness of tumor cells	[153]
Polypeptide from scorpion venom	—	Liver cancer (H22)	Up-regulate the expression of PTEN to inhibit the expression of PI3K, p-AKT and HIF-1α, and improve the anti-angiogenic effect of 5-Fu	[154]
Dandelion polysaccharide	—	Liver cancer (Hepa1-6, H22, HepG2)	Decrease the expression of HIF-1α and VEGF by inhibiting the phosphorylation activation of PI3K and AKT	[155]

活性[143]。绿原酸还可通过抑制鞘氨醇激酶1 (sphingosine kinase-1, SPHK-1) 的表达和功能活性下调缺氧诱导的HIF-1α表达, 并通过抑制AKT/GSK-3β通路的磷酸化降低HIF-1α蛋白的稳定性, 继而下调VEGF的基因表达, 发挥抗肿瘤血管生成的作用[144]。

红景天苷主要来源于景天科植物大花红景天[*Rhodiola crenulate* (Hook. f. et Thoms.) H. Ohba] 的干燥根和根茎。红景天苷可促进HIF-1α的泛素化降解, 并通过抑制HIF-1α信号通路显著增加肝癌细胞对铂类药物的敏感性, 抑制缺氧诱导的肝细胞癌上皮−间充质转化, 有望成为一种有效的铂类药物敏化剂[145]。缺氧环境会促进肿瘤细胞中氨酰氧化酶样蛋白2 (lysyl oxidase-like protein 2, LOXL2) 的表达, 进而上调MMP的表达并诱导肿瘤细胞的增殖和侵袭。而红景天苷和HIF-1α抑制剂KC7F2处理人胰腺癌BxPC-3细胞后可明显下调HIF-1α的表达和转录活性, 进而逆转HIF-1α诱导的LOXL2过表达引起的致瘤性[146]。此外, 红景天苷和红景天提取物均可下调HIF-1α/HIF-2α的蛋白表达, 抑制乳腺癌细胞中缺氧诱导的mTOR通路的激活和肿瘤血管异常增生[147,148]。

6 总结与讨论

缺氧诱导的HIF-1α过度表达在促进肿瘤细胞异常增殖、肿瘤血管生成、能量代谢异常、耐药性增加、侵袭和转移的过程中发挥着关键作用, 并与多种类型的癌症患者的不良预后密切相关。因此HIF-1α被认为是治疗缺氧肿瘤的有效靶点和评估癌症患者生物学行为和预后的独立因素。到目前为止, 已经研发出几种药物, 包括PX-478、EZN-2968、echinomycin、YC-1等用于抑制肿瘤细胞中HIF-1α的激活。此外, 一些非直接靶向HIF-1α的药物也被报道具有抑制HIF-1α表达的作用。然而, 现有大多数HIF-1α抑制剂的临床效果受到毒性过高和/或有效性不足的限制[5], 同时缺乏特异性。所以, 研发下调HIF-1α表达的强效低毒的新型抗肿瘤药物越发重要。大量研究表明, 中药活性成分在对抗HIF-1α相关的促癌作用方面具有巨大的潜力, 可通过直接或间接抑制HIF-1α表达发挥抗肿瘤细胞增殖、抗肿瘤血管生成、逆转糖酵解、抗肿瘤侵袭和转移的作用。除此之外, 中药活性成分可通过改善HIF-1α诱导的肿瘤耐药和缺氧微环境恶化显著提高化疗[145]、放疗[61]、光动力治疗[156]和栓塞治疗[107]的肿瘤杀伤作用。

但这些天然活性成分在临床转化过程中仍然面临一定的挑战。第一, 中药活性成分对HIF-1α通路可能存在双向调节作用。这种现象在白藜芦醇[157]、15,16-双氢丹参酮I[158]、小檗碱[100,159]、槲皮素[54,160]、青蒿素[161]等化合物的抗肿瘤研究中已被报道, 提示同一中药活性成分可能会因生产厂商、肿瘤细胞系、氧气水平、给药剂量等不同对HIF-1α通路产生不同的调控方式, 意味着临床条件下将中药活性成分作为HIF-1α抑制剂来使用将变得复杂化, 需要更深一步的机制探讨。第二, 许多天然化合物存在水溶性差、结构稳定性弱、代谢快、生物利用度低、靶向性劣等问题, 导致临床转化受到限制。针对中药活性成分的自身理化性质合理设计载药系统可以有效克服以上问题。如雷公藤红素胶束[162]、Sanazole-小檗碱-氧化铁纳米粒复合物[163]、小檗碱喷雾干燥 (SD) 黏附性微粒[164]等均已被报道可显著提高所载药物的溶解度、稳定性、血药浓度和治疗特异性, 并有效抑制HIF-1α通路的表达。对天然活性先导化合物进行结构优化以改善其药理作用则是另一种新策略[110]。如HS-1793是一种合成的新型白藜芦醇类似物, 其不含白藜芦醇所具有的不稳定双键结构, 同时被证明具有更强的抗癌作用, 可通过阻断PI3K和AKT的磷酸化激活抑制HIF-1α/VEGF通路的表达[165,166]。第三, 许多基于中药活性成分的HIF-1α抑制剂的临床前研究仅停留于体外研究, 而缺乏体内实验的进一步有效验证。这是由于在小鼠中建立体内缺氧微环境存在一定的困难性和局限性, 急需开发能够简单有效研究低氧诱导的体内肿瘤病理过程的动物模型。如斑马鱼[2]具有适应低氧环境、免疫豁免特性、透明性和成本低等优势, 可能更适于作为HIF-1α抑制剂体内研究的模式动物。第四, 许多HIF-1α抑制剂未能通过临床试验的原因是对接受治疗的患者的选择是随机的, 并未准确获取血清和肿瘤组织中的HIF-1α表达水平。HIF-1α在不同肿瘤类型、进展分期以及不同区域和年龄的人群中的表达水平不同[22,167], 若能通过个体化诊疗手段选择在肿瘤组织特异性高表达HIF-1α的患者作为研究对象, 则可以更有效地评估中药活性成分对实体肿瘤的临床疗效[168]。

作者贡献: 该文章主要由史新萌收集资料和撰写; 刘玉萍提供了文章的整体思路和重要指导; 陈彦、瞿鼎、黄琳清给出了关键意见。

利益冲突: 作者声明没有任何利益冲突。

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