

鸦胆子素D抗肿瘤作用机制的研究进展

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[摘要] 恶性肿瘤严重威胁着人类的生命健康。放疗和化疗是目前临床治疗晚期肿瘤的常规方法,由于放疗对机体不良反应严重、化疗常引起肿瘤耐药性和细胞增殖抑制作用等问题,其预后和疗效不尽人意。因此寻找新型安全有效的抗肿瘤药物、阐明药物抗肿瘤分子作用机制是临床治疗肿瘤和改善患者生活质量的有效措施。源于中草药及天然产物的有效活性成分因其具多靶点、多途径的抗肿瘤药理活性特点,且其对机体不良反应小等优点而逐渐成为抗肿瘤药物研发的热点。鸦胆子素D是从鸦胆子果实中提取的一类四环三萜类化合物,不仅具有抗炎、抗疟、抗寄生虫等多种药理学活性作用,其抗肿瘤活性尤为显著。药理学研究发现,鸦胆子素D可通过靶向不同的信号通路来调控肺癌、肝癌、胰腺癌、肠癌等多种癌细胞的增殖、凋亡、侵袭和迁移等多种细胞生理活动;鸦胆子素D还可与其他化疗药物联用提高肿瘤细胞对化疗药物的敏感性,从而减轻化疗的不良不良反应。临床应用实践已表明,含有鸦胆子素D的鸦胆子油乳注射液在肿瘤治疗的有效性和安全性方面具有显著的优越性。虽鸦胆子素D的抗肿瘤药理学活性研究较多、临床功效作用显著,然而鸦胆子素D的具体抗肿瘤分子机制仍不清楚,且缺乏对现有鸦胆子素D抗肿瘤作用机制研究的系统性综述。因此,笔者依据近年来国内外对鸦胆子素D的研究,从肿瘤细胞的增殖、凋亡、转移和侵袭、糖代谢过程、自噬以及化疗敏感性等6个方面对鸦胆子素D抗肿瘤作用及相关分子机制的研究进行综述,以期对鸦胆子素D的抗肿瘤药物研发和临床应用提供药理学依据和科学参考。

[关键词] 鸦胆子素D; 抗肿瘤; 作用机制; 研究进展; 信号通路

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Anti-tumor Mechanisms of Bruceine D: A Review

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[Abstract] Malignant tumors seriously threaten human life and health. Radiotherapy and chemotherapy are the conventional methods for the clinical treatment of advanced tumors. The prognosis and efficacy are still far from satisfactory due to the radiotherapy has serious adverse effects on the body and the chemotherapy often causes problems such as tumor resistance and cell proliferation inhibition. Therefore, the search for new, safe, and effective anti-tumor drugs and the elucidation of their molecular mechanisms are effective measures for

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clinical treatment of tumors and improvement of patients' quality of life. Active ingredients derived from Chinese herbal medicines and natural products have gradually become a hot spot in the research and development of anti-tumor drugs due to their multi-target and multi-channel anti-tumor pharmacological activity characteristics and their advantages such as less adverse reaction on the body. Bruceine D is a class of tetracyclic triterpenoids extracted from the fruit of the Chinese herbal medicine *Brucea Fructus*, with anti-inflammatory, anti-malarial, anti-parasitic, and other pharmacological activities, and its anti-tumor activity is particularly significant. Pharmacological studies have found that bruceine D can regulate various cellular physiological activities such as proliferation, apoptosis, invasion, and migration of lung cancer, liver cancer, pancreatic cancer, intestinal cancer, and other cancer cells by targeting different signaling pathways. Bruceine D can be used in combination with other chemotherapeutic drugs to improve the sensitivity of tumor cells to chemotherapeutic drugs, thereby reducing the adverse effect of chemotherapy. Clinical application practice has shown that *Brucea Fructus* oil emulsion injection containing bruceine D has significant advantages in the efficacy and safety of tumor treatment. Although there are many studies on the antitumor pharmacological activity of bruceine D and its clinical efficacy is significant, the specific antitumor molecular mechanism of bruceine D is still unclear, and there is a lack of systematic review on the existing antitumor mechanism of bruceine D. Therefore, based on the research on bruceine D in China and abroad in recent years, this paper reviewed the anti-tumor effect and related molecular mechanisms of bruceine D from six aspects, namely, tumor cell proliferation, apoptosis, metastasis and invasion, glucose metabolism process, autophagy, and chemotherapy sensitivity. This paper is expected to provide a pharmacological basis and scientific reference for the antitumor drug development and clinical application of bruceine D.

[Keywords] bruceine D; anti-tumor; mechanism; research progress; signaling pathway

恶性肿瘤是导致人类死亡的主要原因之一^[1]。目前常用的肿瘤治疗手段主要有手术、放疗、化疗等。但大部分癌症晚期患者确诊时已不具备手术治疗条件,而放、化疗又往往伴随着严重的不良反应,给患者带来不可逆的损伤,严重影响患者治疗后的生活质量^[2]。因此寻找新型安全有效的抗肿瘤药物、阐明药物的相关抗肿瘤作用及分子机制迫在眉睫。

近年来,中药已成为抗肿瘤药物的重要来源。许多中药有效活性成分能显著降低肿瘤放化疗中产生的不良反应、延长患者生存期、改善患者生活质量^[3],正在成为肿瘤治疗药物研究领域的热点。鸦胆子,又称苦参子、老鸦胆,为苦木科植物鸦胆子 *Brucea javanica* 的干燥成熟果实。鸦胆子具有清热解毒、截疟、止痢等众多功效,可用于热毒血痢、疟、疟疾、鸡眼等疾病的治疗^[4-5]。在现代药理学的研究中,鸦胆子已被证明具有抗肿瘤特性^[6]。在临床中,鸦胆子已广泛用于肝癌^[7]、胃癌^[8]、宫颈癌^[9]、肺癌^[10]、结直肠癌^[11]、乳腺癌^[12]、食管癌^[13]和膀胱癌^[14]的治疗中。鸦胆子素D(BD)是从鸦胆子中分离提取的一种四环三萜类化合物,除具有抗炎、抗疟、抗阿米巴原虫活性外,其抗肿瘤作用更为显著^[15]。研

究表明,BD可通过靶向不同的信号通路来调控乳腺癌^[16]、胰腺癌^[17]、肺癌^[18]等多种癌细胞的增殖、凋亡、侵袭和迁移等多种细胞生理活动。此外,研究已证实BD与其他化疗药物如阿霉素^[19]、吉西他滨^[20]、紫杉醇^[21-22]联用时可显著增强肿瘤细胞在治疗中对化疗药物的敏感性,提高抗肿瘤效果。虽然目前关于BD抑制肿瘤作用的研究较多,但其具体抗肿瘤分子作用机制尚不完全清楚。本文依据近年来国内外对BD的研究,从肿瘤细胞的增殖、凋亡、转移和侵袭、糖代谢过程、自噬及化疗敏感性等方面总结梳理了BD抗肿瘤作用机制^[18-67],以期为BD抗肿瘤药物研发及其临床应用提供一定的理论基础和参考依据。

1 BD的提取及理化性质

BD主要从鸦胆子全株、种子、茎和根等部位分离提取获得,提取方法有水提取法和有机溶剂提取法^[23-28]。其中水提取法操作简单,但得率较低,故该方法很少使用^[23]。有机溶剂提取法中主要包括丙酮提取法^[24-25]、甲醇提取法^[26-27]和乙醇提取法^[28],这些提取方法主要是将鸦胆子粉碎,用有机溶剂提取后,经硅胶柱和高效液相色谱法分离纯化出BD,其中提取效率最高的是乙醇提取法。BD是一种不溶

于水,可溶于乙醇、甲醇等多种有机溶剂的白色针状结晶,化学式为 $C_{20}H_{26}O_9$ ^[28]。现代药理学研究表明BD具有抗肿瘤、降血糖、抗病毒、抗寄生虫、抗炎和抗菌等多种药理活性^[6]。

2 鸦胆子素D的抗肿瘤作用

依据近年来国内外研究,从肿瘤细胞的增殖、凋亡、转移和侵袭、糖代谢过程、自噬及化疗敏感性等方面总结BD抗肿瘤作用机制^[18-67],见表1。

表1 鸦胆子素D的抗肿瘤作用

Table 1 Anti-tumor activities of bruceine D

肿瘤分型	细胞系	机制	分子靶点	文献
骨肉瘤	MNNG/HOS、MG-63、U-2OS、Saos-2	抑制增殖	Cyclin D ₁ ↓, Cyclin-E ↓, CDK2 ↓, CDK4 ↓, JAK2 ↓, p-JAK2 ↓, p-STAT3 ↓, SHP1 ↑	[31]
	143B HOS	抑制迁移和侵袭	N-cadherin ↓, MMP-2 ↓, MMP-9 ↓	
		诱导自噬	LC3B I ↓, LC3B II ↑	[67]
胃癌	HGC27、MKN45	抑制增殖	Linc01667 ↓, miR-138-5p ↑, CDK2 ↓, Cyclin E ₁ ↓, Cyclin E ₂ ↓	[19]
		化疗敏感性	C-PARP ↑, cleaved Caspase-3 ↑	
肝癌	Huh7、Hep3B	促进细胞凋亡	β-catenin ↓, Jagged1 ↓, Hes1 ↓, LEF1 ↓, Survivin ↓, c-Myc ↓, Cyclin D ₁ ↓	[48]
	HepG2、Huh7	抑制糖代谢	ICAT ↓, β-catenin ↓, HIF-1α ↓	[63]
	Hep3B	促进细胞凋亡	miR-95 ↓, CUGBP2 ↑	[50]
肺癌	A549	抑制增殖	FZ-2 ↓, Cyclin D ₁ ↓, c-Myc ↓, Survivin ↓, β-catenin ↓, LRP5/6 ↓, Axin2 ↓, ABCG2 ↓	[18]
	A549	促进细胞凋亡	Bcl-2 ↓, pro-Caspase-8 ↓, pro-Caspase-3 ↓, Bak ↑, XIAP ↓, Bax ↑, ROS ↑, PARP ↓, Bcl-xL ↓	[37]
	H460、A549	促进细胞凋亡	Bcl-2 ↓, Bax ↑, p-JNK ↑, PARP ↓, Caspase-3 ↓, cleaved Caspase-3 ↑	[38]
	PC9、H1975	促进细胞凋亡	p-JNK ↓	[47]
	H1299	抑制迁移和侵袭	E-cadherin ↑, N-cadherin ↓, Twist ↓, Snail ↓, β-catenin ↓, MMP7 ↓	[54]
	A549、NCI-H292	诱导自噬	LC3 II/I ↑, Atg7 ↑, p62 ↓	[66]
乳腺癌	MCF-7、MDA-MB-231	促进细胞凋亡	p-p38 MAPK ↑, p-JNK ↑, NF-κB ↓, Bid ↓, tBid ↑, pro-Caspase-3 ↓, pro-Caspase-8 ↓, Bcl-xL ↓, XIAP ↓	[43]
	MDA-MB-231	抑制迁移和侵袭	Vimentin ↓, β-catenin ↓, E-cadherin ↑, PI3K ↓, p-Akt ↓	[55]
	MDA-MB-231	抑制糖代谢	PI3K ↓, p-Akt ↓	[60]
胰腺癌	Capan-2	促进细胞凋亡	Bcl-2 ↓, Caspase-9 ↑, Caspase-3 ↑	[39]
	PANC-1	促进细胞凋亡	Bcl-2 ↓, Caspase-3 ↑, XIAP ↓, Bak ↑, Caspase-8 ↑, Caspase-9 ↑, p-NF-κB p65 ↓, NF-κB ↓, p-p38 MAPK ↑, IκB-α ↑, p-IκB-α ↓	[44]
	Capan-2	促进细胞凋亡	Bcl-2 ↓, Caspase-3 ↑, Bak ↑, Caspase-8 ↑, Caspase-9 ↑, p38 MAPK ↑	[45]
	Capan-2	化疗敏感性	Caspase ↑, p-JNK ↑	[21]
	Miapaca-2、Capan-2	化疗敏感性	Nrf2 ↓, Caspase-3 ↓, Caspase-9 ↓, NQO1 ↓, AKR1B10 ↓, Keap1 ↓, HO-1 ↓, PARP ↓, γGCSm ↓	[20]
白血病	K562	促进细胞凋亡	Cyto-c ↑, PARP ↓, p-Akt ↓, p-ERK ↓, Caspase-9 ↑, Caspase-3 ↑	[40]
结肠癌	HT29	促进细胞凋亡	JNK ↓, p-JNK ↑	[46]
人视网膜母细胞瘤	Y79	促进细胞凋亡	miR-155 ↓, Bcl-2 ↓, Bax ↑, Caspase-3 ↑	[51]
卵巢癌	SKOV3、A2780	化疗敏感性	cleaved Caspase-3 ↑, Bcl-2 ↓, Bax ↓, p-JNK ↑, p-STAT3 ↓	[22]

注: ↑.升高; ↓.降低

2.1 抑制肿瘤细胞增殖 恶性肿瘤的特征是异常的细胞增殖^[29],因此抑制肿瘤细胞增殖是抗肿瘤的有效策略。BD可通过调节不同细胞信号传导途径来抑制肿瘤细胞的异常增殖。Janus激酶2(JAK2)/

信号转导及转录激活因子3(STAT3)信号通路在细胞增殖、凋亡、侵袭、迁移及免疫应答等活动中发挥重要作用^[30]。在骨肉瘤MNNG/HOS、U-20s细胞中,BD通过上调JAK2、磷酸化(p)-STAT3的表达,

下调负调节因子含SH2结构域的蛋白酪氨酸磷酸酶1(SHP1)的表达来阻滞JAK2/STAT3途径^[31],从而抑制骨肉瘤细胞的增殖。Wnt/ β -连环蛋白(β -catenin)途径与胚胎发育和肿瘤发生过程中细胞增殖、侵袭和迁移有关^[32]。BD可通过Wnt/ β -catenin途径抑制肺癌A549细胞的增殖,其具体分子机制是BD通过促进 β -catenin磷酸化,进而阻滞 β -catenin入核,促使下游靶蛋白细胞周期蛋白D₁(Cyclin D₁)、c-核蛋白类基因(c-Myc)和Axis抑制蛋白2(Axin2)的表达下调而抑制肺癌细胞的增殖^[18]。最新研究表明,BD还可通过干预长链非编码RNA(lncRNAs)的表达来抑制细胞增殖,如LI等^[19]研究发现BD可以通过Linc01667/miR-138-5p/Cyclin E₁途径抑制胃癌HGC27、MKN45细胞的增殖,体内实验也表明BD可显著抑制胃癌细胞的致瘤性。细胞的异常增殖可能源于细胞周期控制的丧失^[33],在乳腺癌MDA-MB-231细胞中,BD通过诱导G₀/G₁细胞周期的阻滞来抑制细胞增殖^[34]。

2.2 诱导肿瘤细胞凋亡 细胞凋亡是所有多细胞生物中器官发生、细胞增殖和维持组织稳态不可或缺的自杀过程,亦是去除受损和异常细胞所必需的^[35]。在哺乳动物细胞中,导致凋亡的信号级联主要分为两大类,内源性线粒体途径和外源性死亡受体途径^[36]。已有研究证实,BD可通过线粒体介导的凋亡途径诱导肿瘤细胞凋亡。BD可通过上调促凋亡蛋白B细胞淋巴瘤-2(Bcl-2)相关X蛋白(Bax)表达,下调抑凋亡蛋白Bcl-2、胱天蛋白酶(Caspase)-3前体(pro-Caspase-3)、pro-Caspase-8和聚腺苷二磷酸核糖聚合酶(PARP)的表达,激活肺癌细胞H460、A549中线粒体介导的凋亡途径,从而诱导细胞凋亡^[37-38];同样在胰腺癌中,BD通过下调Bcl-2的表达、上调胱天蛋白酶-9(Caspase-9)和Caspase-3表达来诱导癌细胞Capan-2凋亡^[39]。BD亦可通过激活线粒体凋亡途径即上调Caspase-3、Caspase-9的表达、降低线粒体膜电位来诱导人慢性髓性白血病K562细胞的凋亡^[40]。BD还可通过调节其他癌症相关信号通路来促进细胞凋亡。丝裂原活化蛋白激酶(MAPK)信号通路参与细胞的多种生理过程,如细胞增殖、凋亡、转移和侵袭^[41]。p38丝裂原活化蛋白激酶(p38 MAPK)和Jun氨基末端激酶(JNK)是MAPK超家族的成员,他们可参与细胞凋亡的调控^[42]。BD可以通过激活JNK、p38 MAPK信号通路诱导肿瘤细胞凋亡。在乳腺癌MCF-7、MDA-MB-231细胞中,BD可通过上调p38

MAPK、JNK的磷酸化水平来激活MAPK信号通路诱导细胞凋亡^[43]。当BD作用于胰腺癌PANC-1细胞时,不仅可以通过激活p38 MAPK信号通路促进癌细胞凋亡,还可通过激活核转录因子- κ B(NF- κ B)进而下调抗凋亡基因Bcl-2的表达,从而促进癌细胞凋亡^[44-45]。BD亦可通过抑制JNK信号通路来诱导结肠癌HT29细胞^[46]和肺癌细胞^[47]凋亡。此外,研究表明BD还可通过抑制Wnt信号通路中 β -catenin的核积累、下调Notch信号通路中齿状蛋白1(Jagged1)的表达促进肝癌细胞Huh7、Hep3B的细胞凋亡^[48]。微小RNA(miRNA)是一类高度保守的内源性非编码单链RNA分子,平均长度约为22个核苷酸,其异常表达与肿瘤细胞的增殖、凋亡、迁移和耐药性密切相关^[49]。在一项关于肝癌的研究中发现,BD在体内外可通过下调miR-95、上调促凋亡蛋白RNA结合蛋白2(CUGBP2)的表达来诱导细胞凋亡^[50]。BD还可通过抑制miR-155来下调Bcl-2、上调Caspase-3、Bax的表达,进而促进人视网膜母细胞瘤Y79细胞发生凋亡^[51]。

2.3 抑制肿瘤细胞侵袭和转移 侵袭转移是恶性肿瘤发生发展过程中的重要因素,亦是肿瘤患者死亡的主要原因^[52]。上皮间质转化(EMT)是指上皮细胞向间充质细胞的形态学改变,是肿瘤细胞侵袭转移的重要机制。发生EMT时,上皮细胞失去细胞极性、细胞间黏附和对基底膜的附着作用,运动和迁移能力增强,最终导致肿瘤细胞广泛侵袭和转移^[53]。BD对EMT的进程有显著影响。当BD作用于肺癌细胞H1299时,可使EMT标记物E-钙黏蛋白(E-cadherin)的表达上调、N-钙黏蛋白(N-cadherin)、扭曲蛋白(Twist)、锌指转录因子(Snail)和 β -catenin的表达下调,进而抑制癌细胞的转移和侵袭^[54]。在乳腺癌MDA-MB-231细胞中,BD亦可通过上调E-cadherin、下调波形蛋白(Vimentin)的表达来阻断EMT过程;同时磷脂酰肌醇3-激酶(PI3K)和磷酸化蛋白激酶B(p-Akt)的表达下调,表明BD也可通过PI3K/Akt信号通路抑制乳腺癌细胞的迁移侵袭^[55]。细胞外基质和基底膜的降解在癌细胞的侵袭和转移中占据重要地位,而这一过程是通过各种蛋白水解酶的参与来实现的,如基质金属蛋白酶(MMPs)^[56]。在骨肉瘤体内异种移植瘤实验中,BD可通过下调MMP-2和MMP-9的表达来抑制肿瘤细胞的迁移侵袭,且对小鼠的心脏、肝脏和肾脏组织均无明显的器官损伤^[31]。

2.4 抑制糖代谢 糖代谢异常是恶性肿瘤的重要

特征,与肿瘤的发生发展、侵袭及转移有密切联系^[57]。大多数实体肿瘤细胞在很大程度上依赖有氧糖酵解产生能量来适应其异质的微环境,这种现象被称为 Warburg 效应^[58]。PI3K/Akt 信号传导途径的激活和缺氧诱导因子-1 α (HIF-1 α)的表达上调可促进糖酵解的发生^[59]。有研究表明,BD 通过抑制 PI3K/Akt 途径减少乳腺癌 MDA-MB-231 细胞中葡萄糖消耗量和乳酸生成量,即通过抑制有氧糖酵解过程来抑制肿瘤细胞的生长^[60]。在低氧条件下,BD 可通过下调 HIF-1 α 的表达来抑制糖代谢过程,进而抑制肝癌 HepG2、Huh7 细胞的增殖和异种移植瘤的生长,且小鼠模型未出现显著的体质量减轻和不良作用^[61]。

2.5 诱导肿瘤细胞自噬 自噬是一种自我降解过程,也是细胞防御机制的关键。自噬可通过不同的分子机制促进或抑制肿瘤进展,其功能与肿瘤组织类型、分期和遗传背景有关^[62]。在肿瘤发生的早期,自噬可以阻止肿瘤的发生、增殖、侵袭和转移;而在晚期肿瘤中,自噬可能有助于肿瘤生存、增殖、转移和对治疗药物的耐药性,所以调节肿瘤细胞自噬是肿瘤治疗的一种新的潜在方法^[63-64]。自噬相关蛋白微管相关蛋白 1 轻链 3(LC3)以 LC3 I、LC3 II 两种形式存在,而自噬体形成的关键是 LC3 I 向 LC3 II 转化^[65]。用 BD 处理肺癌 A549、NCI-H292 细胞,在电镜下可观察到细胞内有大量的自噬体和自溶体液泡积累,其自噬的发生与 LC3 II / I 和自噬相关蛋白 7(Atg7)的表达上调、自噬蛋白 P62 的表达下调有关^[66]。在骨肉瘤细胞中,BD 通过上调 LC3B-II 蛋白的表达和细胞内自噬体的生成、下调 LC3B-I 蛋白的表达来诱导骨肉瘤细胞 143B 发生自噬^[67]。

2.6 增加化疗药物敏感性 肿瘤细胞对化疗药物的不敏感性是肿瘤治疗中的一个难题,而在临床治疗过程中,中药与化疗药物联合使用可以明显提高化疗药物的抗肿瘤作用,减轻化疗的不良反应,因此中药与化疗药物的联用被广泛关注^[68]。BD 可以辅助多种化疗药物对肿瘤细胞的杀伤作用,达到增强化疗药物杀死肿瘤细胞的效果。吉西他滨是用于治疗胰腺导管腺癌(PDAC)的一线化疗药物,但临床上经常遇到化疗耐药的问题。核转录因子 E₂ 相关因子 2(Nrf2)是一种氧化应激反应性转录因子,是 PDAC 对化疗产生耐药性和预后不良的重要因素。在体内外生物学模型中,BD 通过促进 Nrf2 蛋白的降解和抑制其下游靶基因表达来抑制 Nrf2

信号途径,增强胰腺癌细胞对吉西他滨的化疗敏感性^[20]。在胰腺癌 Capan-2 细胞中,BD 可通过上调 p-JNK 和裂解胱天蛋白酶-3(cleaved Caspase-3)的表达、下调 Bcl-2、PARP、Caspase-3 和 JNK 的表达从而增强紫杉醇诱导肿瘤细胞凋亡的作用^[21];同样在卵巢癌中,BD 可通过上调 p-JNK 和 cleaved Caspase-3 的表达、下调 Bcl-2、Bax 和 p-STAT3 的表达从而增强紫杉醇诱导肿瘤细胞 SKOV3、A2780 的凋亡^[22]。BD 亦可通过上调 cleaved Caspase-3 和凋亡蛋白 PARP 的表达来增强胃癌 HGC27、MKN45 细胞对阿霉素的敏感性^[19]。

3 讨论

越来越多的抗肿瘤研究表明,天然活性产物是未来寻找新的抗肿瘤候选药物的可行途径^[69-70]。鸦胆子是一种重要的中药,广泛用于治疗各种肿瘤和炎症疾病。鸦胆子油乳注射液(BJOEI)是源自鸦胆子成熟果实中的一种提取物,已在临床治疗中作为一种辅助治疗手段展示了其在肿瘤治疗的有效性和安全性方面的优越性^[71-73]。

从鸦胆子中提取的生物活性成分 BD 同样具有显著的抗肿瘤疗效,其潜在分子机制如图 1 所示,① BD 通过 JAK2/STAT3 和 Wnt/ β -catenin 途径抑制肿瘤细胞增殖。② BD 通过 Linc01667/miR-138-5p/Cyclin E₁ 途径抑制肿瘤细胞的增殖。③ BD 通过 MAPK、Wnt、Notch 信号通路和线粒体凋亡途径诱导肿瘤细胞凋亡。④ BD 通过阻断 EMT 和 PI3K/Akt 途径,使肿瘤细胞的侵袭和迁移受到抑制。

然而,现阶段 BD 抗肿瘤作用机制及临床应用仍有待完善,首先,BD 抗肿瘤机制的研究多以离体细胞实验为主,缺乏动物体内实验和肿瘤治疗效果的临床研究,未来应建立更多动物模型,在体内验证相关作用机制,更加系统地阐明 BD 在不同人类肿瘤细胞中的作用机制及安全性,以便为 BD 在抗肿瘤临床应用中提供更多依据,从而为抗肿瘤药物研发指明新方向。其次,BD 的口服生物利用度低、体内代谢快的特点限制了其在临床中的应用^[74-75],有研究利用新型给药系统改善了这一不足,DOU 等^[76]发现一种由中链甘油三酯、聚乙二醇 15 羟基硬脂酸酯、丙二醇和 BD 组成的自纳米乳化给药系统,可显著提高 BD 的生物利用度并延长其终末半衰期,这为 BD 的临床应用提供了新的见解。随着新型给药系统研究的不断深入及成熟,相信未来将会为 BD 的临床应用提供更多可能,也会带来令人期待、兴奋的 BD 临床抗肿瘤效果。

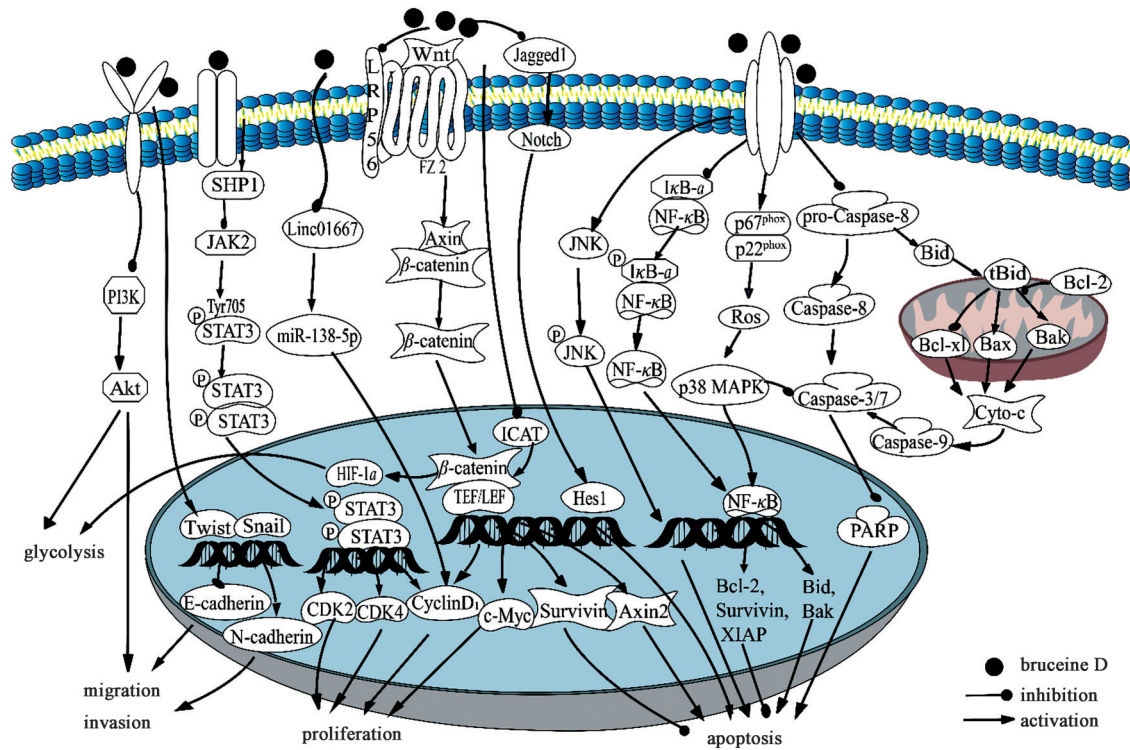


图1 鸦胆子素D抗肿瘤信号通路

Fig 1 Anti-tumor signaling pathway map of bruceine D

[参考文献]

[1] SUNG H, FERLAY J, SIEGEL R L, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249.

[2] CAZZANIGA M, BONANNI B. Breast cancer chemoprevention: Old and new approaches[J]. J Biomed Biotechnol, 2012, doi: 10.1155/2012/985620.

[3] 李小江, 邱明歆, 孔凡铭, 等. 中药有效成分抗肿瘤活性及作用机制研究进展[J]. 中草药, 2020, 51(9): 2587-2592.

[4] KIM I H, TAKASHIMA S, HITOTSUYANAGI Y, et al. New quassinoids, javanicolides C and D and javanicosides B-F, from seeds of *Brucea javanica*[J]. J Nat Prod, 2004, 67(5): 863-868.

[5] YAN Z, GUO G F, ZHANG B. Research of *Brucea javanica* against cancer[J]. Chin J Integr Med, 2017, 23(2): 153-160.

[6] ZHANG J, XU H, DOU Y, et al. *Brucea javanica* major constituents from and their pharmacological actions[J]. Front Pharmacol, 2022, doi: 10.3389/fphar.2022.853119.

[7] 李欣依, 王其美, 邓湘生, 等. 经肝动脉灌注鸦胆子油乳注射液联合碘油栓塞治疗中晚期原发性肝癌的临床研究[J]. 湖南中医杂志, 2020, 36(8): 5-7, 17.

[8] 沈丹萍, 郑中显, 程亮, 等. 鸦胆子油乳注射液联合替吉奥、阿帕替尼治疗晚期胃癌的临床研究[J]. 临床和实验医学杂志, 2022, 21(9): 945-948.

[9] 彭飞辉, 李莉. 鸦胆子油乳注射液治疗宫颈癌及改善放疗不良反应效果分析[J]. 临床药物治疗杂志, 2022, 20(4): 26-31.

[10] 李志路, 杨督, 何文静, 等. 鸦胆子油乳注射液联合培美曲塞+顺铂化疗在非小细胞肺癌中的应用效果[J]. 癌症进展, 2022, 20(7): 672-675.

[11] 裴东明, 冀叶, 李震. 鸦胆子油乳联合卡培他滨、奥沙利铂对老年晚期结直肠癌患者免疫功能及肿瘤转移浸润的影响[J]. 世界临床药物, 2021, 42(5): 369-374.

[12] 谷田露, 毛琳. 鸦胆子油乳联合新辅助化疗治疗局部晚期乳腺癌患者的疗效及对病灶基因表达的影响[J]. 中国药物经济学, 2020, 15(11): 44-47.

[13] 赖奕静, 廖泽飞, 王耿杰. 鸦胆子油乳注射液联合化疗对中晚期食管癌患者淋巴细胞CD4⁺、CD8⁺的影响[J]. 世界中医药, 2019, 14(11): 3016-3019.

[14] 姜丰泽, 蒋思雄, 田丰, 等. 鸦胆子油乳联合常规化疗方案对局部晚期膀胱癌患者的疗效观察及免疫功能的影响[J]. 中华保健医学杂志, 2019, 21(1): 24-27.

[15] ZHAO L, LI C, ZHANG Y, et al. Phytochemical and biological activities of an anticancer plant medicine: *Brucea javanica* [J]. Anticancer Agents

- Med Chem, 2014, 14(3):440-458.
- [16] TIAN S, JING R, ZHANG W. Network-based approach to identify the antiproliferative mechanisms of bruceine D in breast cancer from the cancer genome atlas [J]. Front Oncol, 2020, doi: 10.3389/fonc.2020.01001.
- [17] 王飞达,王兆洪,张跃,等. 鸦胆子素D对人胰腺癌细胞株 Panc-1 体外增殖的抑制作用[J]. 浙江医学, 2015,37(12):1019-1021.
- [18] 沈孝云,波拉提·马卡比力,吴孟华,等. 鸦胆子素D调控肺癌干细胞干性分子的研究[J]. 中药材,2019,42(5):1160-1163.
- [19] LI L, DONG Z, SHI P, et al. Bruceine D inhibits cell proliferation through downregulating Linc01667/microRNA-138-5p/Cyclin E₁ axis in gastric cancer[J]. Front Pharmacol, 2020, doi: 10.3389/fphar.2020.584960.
- [20] ZHANG J, XU H X, CHO W, et al. Brucein D augments the chemosensitivity of gemcitabine in pancreatic cancer via inhibiting the Nrf2 pathway[J]. J Exp Clin Cancer Res,2022,41(1):90.
- [21] 黄玉玉,饶明君,谭笔琴,等. 鸦胆子素D联合紫杉醇对胰腺癌 Capan-2 细胞增殖的抑制作用及机制研究[J]. 中国药房,2019,30(6):789-795.
- [22] YAN Z, JIN Z, SUI H, et al. Bruceine D sensitizes human ovarian cancer cells to paclitaxel through JNK and STAT3 signal regulation [J]. Rev Bras Farmacogn, 2022, 32(2):257-265.
- [23] MAN F, CHOO C. Safety assessment of standardized aqueous *Brucea javanica* extract in rats [J]. J Ethnopharmacol, 2018, doi: 10.1016/j.jep.2017.12.040.
- [24] CHUMKAEW P, SRISAWAT T. Antimalarial and cytotoxic quassinoids from the roots of *Brucea javanica* [J]. J Asian Nat Prod Res, 2017, 19(3) : 247-253.
- [25] HUANG Y, CHEN L, HE L, et al. Herbicidal activity and bioactive components of *Brucea javanica* (L.) Merr. residue [J]. Arab J Chem, 2021, doi: 10.1016/j.arabjc.2021.103228.
- [26] ZHAN Y, TAN T, QIAN K, et al. *Brucea javanica* quassinoids from seeds of and their anticomplement activities[J]. Nat Prod Res, 2020, 34(8):1186-1191.
- [27] HE X, WU J, TAN T, et al. Quassinoids from *Brucea javanica* and attenuates lipopolysaccharide-induced acute lung injury by inhibiting PI3K/Akt/NF- κ B pathways[J]. Fitoterapia, 2021, doi:10.1016/j.fitote.2021.104980.
- [28] CHUMKAEW P, PECHWANG J, SRISAWAT T. Two new antimalarial quassinoid derivatives from the stems of *Brucea javanica* [J]. J Nat Med, 2017, 71(3):570-573.
- [29] HANAHAN D, WEINBERG R A. Hallmarks of cancer: The next generation[J]. Cell, 2011, 144(5): 646-674.
- [30] KISSELEVA T, BHATTACHARYA S, BRAUNSTEIN J, et al. Signaling through the JAK/STAT pathway, recent advances and future challenges [J]. Gene, 2002, 285(1):1-24.
- [31] WANG S, HU H, ZHONG B, et al. Bruceine D inhibits tumor growth and stem cell-like traits of osteosarcoma through inhibition of STAT3 signaling pathway[J]. Cancer Med, 2019, 8(17):7345-7358.
- [32] NUSSE R, CLEVERS H. Wnt/ β -catenin signaling, disease, and emerging therapeutic modalities [J]. Cell, 2017, 169(6):985-999.
- [33] KIPREOS E T, VAN D H S. Developmental control of the cell cycle: Insights from caenorhabditis elegans [J]. Genetics, 2019, 211(3): 797-829.
- [34] 张贺,姜大庆. 鸦胆子素D对乳腺癌MDA-MB-231细胞增殖与凋亡及细胞周期的影响[J]. 陕西中医, 2019,40(11):1495-1497.
- [35] KUMAR S, SHARMA G, CHAKRABORTY C, et al. Regulatory functional territory of PLK-1 and their substrates beyond mitosis [J]. Oncotarget, 2017, 8(23):37942-37962.
- [36] WANG Q, FROLOVA A I, PURCELL S, et al. Mitochondrial dysfunction and apoptosis in cumulus cells of type I diabetic mice [J]. PLoS One, 2010, doi:10.1371/journal.pone.0015901.
- [37] XIE J, LAI Z, ZHENG X, et al. Apoptosis induced by bruceine D in human non-small-cell lung cancer cells involves mitochondrial ROS-mediated death signaling [J]. Int J Mol Med, 2019, 44(6) : 2015-2026.
- [38] TAN B, HUANG Y, LAN L, et al. Bruceine D induces apoptosis in human non-small cell lung cancer cells through regulating JNK pathway [J]. Biomed Pharmacother, 2019, doi: 10.1016/j.biopha.2019.109089.
- [39] LIU L, LIN Z, LEUNG P S, et al. Involvement of the mitochondrial pathway in bruceine D induced apoptosis in Capan-2 human pancreatic adenocarcinoma cells [J]. Int J Mol Med, 2012, 30(1):93-99.
- [40] ZHANG J, LIN M, TUNG H, et al. Bruceine D

- induces apoptosis in human chronic myeloid leukemia K562 cells via mitochondrial pathway [J]. *Am J Cancer Res*, 2016, 6(4):819-826.
- [41] PARK H B, BAEK K H. E3 ligases and deubiquitinating enzymes regulating the MAPK signaling pathway in cancers [J]. *Biochim Biophys Acta Rev Cancer*, 2022, 1877(3):188736.
- [42] ICHIJO H, NISHIDA E, IRIE K, et al. Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways [J]. *Science*, 1997, 275(5296):90-94.
- [43] MOHAN C, LIEW Y, JUNG Y, et al. Brucein D modulates MAPK signaling cascade to exert multifaceted anti-neoplastic actions against breast cancer cells [J]. *Biochimie*, 2021, doi: 10.1016/j.biochi.2021.01.009.
- [44] LAU S T, LIN Z X, LEUNG P S. Role of reactive oxygen species in brucein D-mediated p38-mitogen-activated protein kinase and nuclear factor-kappaB signalling pathways in human pancreatic adenocarcinoma cells [J]. *Br J Cancer*, 2010, 102(3):583-593.
- [45] LAU S, LIN Z X, LIAO Y H, et al. Bruceine D induces apoptosis in pancreatic adenocarcinoma cell line PANC-1 through the activation of p38-mitogen activated protein kinase [J]. *Cancer Lett*, 2009, 281(1):42-52.
- [46] 郑艳艳,陈晶晶,王兆洪. 鸦胆子素D对结肠癌HT29细胞株增殖的抑制及诱导其凋亡的机制[J]. *医学研究杂志*, 2017, 46(12):85-89.
- [47] 田姗,曹霞,李翔,等. 鸦胆子素D对非小细胞肺癌细胞生物学行为的影响及其机制[J]. *山东医药*, 2020, 60(34):61-64.
- [48] CHENG Z, YUAN X, QU Y, et al. Bruceine D inhibits hepatocellular carcinoma growth by targeting β -catenin/jagged1 pathways [J]. *Cancer Lett*, 2017, doi:10.1016/j.canlet.2017.06.014.
- [49] XU X, TAO Y, SHAN L, et al. The role of microRNAs in hepatocellular carcinoma [J]. *J Cancer*, 2018, 9(19):3557-3569.
- [50] XIAO Z, CHING C S, HAN LI C, et al. Role of microRNA-95 in the anticancer activity of brucein D in hepatocellular carcinoma [J]. *Eur J Pharmacol*, 2014, 728:141-150.
- [51] QIN D, AINIWAER X, PAN H, et al. Effect of bruceine D on microRNA-155 expression and proliferation and apoptosis of human retinoblastoma cells [J]. *Nanosci Nanotech Let*, 2020, 12(2): 178-183.
- [52] MARX V. Tracking metastasis and tricking cancer [J]. *Nature*, 2013, 494(7435):133-136.
- [53] YEUNG K T, YANG J. Epithelial-mesenchymal transition in tumor metastasis [J]. *Mol Oncol*, 2017, 11(1): 28-39.
- [54] SHEN X, SU C, YAN Y, et al. A study on the mechanism of bruceine D in the treatment of non-small cell lung cancer H1299 cells [J]. *WJTCM*, 2020, doi: 10.4103/wjtc.wjtc_42_20.
- [55] LUO C, WANG Y, WEI C, et al. The anti-migration and anti-invasion effects of bruceine D in human triple-negative breast cancer MDA-MB-231 cells [J]. *Exp Ther Med*, 2020, 19(1):273-279.
- [56] NELSON A R, FINGLETON B, ROTHENBERG M L, et al. Matrix metalloproteinases: Biologic activity and clinical implications [J]. *J Clin Oncol*, 2000, 18(5):1135-1149.
- [57] 刘福乐,王钢. HIF-1 α 调控恶性肿瘤糖代谢的相关机制及研究进展 [J]. *中国医学创新*, 2021, 18(27): 173-176.
- [58] GHANEM N, EL-BABA C, ARAJI K, et al. The pentose phosphate pathway in cancer: Regulation and therapeutic opportunities [J]. *Chemotherapy*, 2021, 66(5/6):179-191.
- [59] SEMENZA G L. HIF-1: Upstream and downstream of cancer metabolism [J]. *Curr Opin Genet Dev*, 2010, 20(1):51-56.
- [60] 王雨,罗璨,吉兆宁. 鸦胆子苦素D通过PI3K/Akt信号通路抑制人乳腺癌MDA-MB-231细胞的能量代谢研究 [J]. *蚌埠医学院学报*, 2020, 45(5):561-565.
- [61] HUANG R, ZHANG L, JIN J, et al. Bruceine D inhibits HIF-1 α -mediated glucose metabolism in hepatocellular carcinoma by blocking ICAT/ β -catenin interaction [J]. *Acta Pharm Sin B*, 2021, 11(11): 3481-3492.
- [62] ANTUNES F, ERUSTES A G, COSTA A J, et al. Autophagy and intermittent fasting: The connection for cancer therapy? [J]. *Clinics (Sao Paulo)*, 2018, 73(suppl 1):e814s.
- [63] WHITE E. Deconvoluting the context-dependent role for autophagy in cancer [J]. *Nat Rev Cancer*, 2012, 12(6):401-410.
- [64] LEONARDI L, SIBÉRIL S, ALIFANO M, et al. Autophagy modulation by viral infections influences tumor development [J]. *Front Oncol*, 2021, doi: 10.3389/fonc.2021.743780.
- [65] SATOH K, TAKEMURA Y, SATOH M, et al. Loss of

- FYCO1 leads to cataract formation[J]. *Sci Rep*, 2021, 11(1):13771.
- [66] FAN J, REN D, WANG J, et al. Bruceine D induces lung cancer cell apoptosis and autophagy via the ROS/ MAPK signaling pathway *in vitro* and *in vivo*[J]. *Cell Death Dis*, 2020, 11(2): 126.
- [67] 郑颖,王刚阳,陈瑞玲,等. 探讨鸦胆子素D对骨肉瘤细胞增殖、凋亡与自噬的作用[J]. *中国骨与关节杂志*, 2017, 6(6):433-438.
- [68] 张微,钱晓萍,刘宝瑞. 中药与化疗药物的协同作用[J]. *中国中西医结合杂志*, 2007, 27(10):952-956.
- [69] WU J, YI J, WU Y, et al. 3, 3'-Dimethylquercetin inhibits the proliferation of human colon cancer RKO cells through inducing G₂/M cell cycle arrest and apoptosis[J]. *Anticancer Agents Med Chem*, 2019, 19(3):402-409.
- [70] KIM C, KIM B. Anti-cancer natural products and their bioactive compounds inducing ER stress-mediated apoptosis: A review [J]. *Nutrients*, 2018, doi:10.3390/nu10081021.
- [71] WANG X, WANG H, CAO L, et al. *Brucea javanica* efficacy and safety of oil emulsion injection in the treatment of gastric cancer: A systematic review and Meta-analysis [J]. *Front Nutr*, 2021, doi: 10.3389/ fnut. 2021. 784164.
- [72] XU C, GUO X, ZHOU C, et al. Brucea javanica oil emulsion injection (BJOEI) as an adjunctive therapy for patients with advanced colorectal carcinoma: A protocol for a systematic review and Meta-analysis[J]. *Medicine (Baltimore)*, 2020, 99(27):e21155.
- [73] WANG J, YE H, DONG Y. Effects of javanica oil emulsion injection combined with radiotherapy versus radiotherapy alone on the efficacy and safety in patients with esophageal cancer: A pooled analysis of 1269 cases[J]. *J Buon*, 2017, 22(4):985-995.
- [74] MAN F, CHOO C Y. HPLC-MS/MS method for bioavailability study of bruceines D & E in rat plasma [J]. *J Chromatogr B Analyt Technol Biomed Life Sci*, 2017, 1063:183-188.
- [75] ZHANG Y, ZHEN Y, ZHANG Y, et al. Development and validation of a sensitive LC-MS/MS assay for quantification of bruceine D in rat plasma [J]. *Biomed Chromatogr*, 2016, 30(11):1873-1876.
- [76] DOU Y X, ZHOU J T, WANG T T, et al. Self-nanoemulsifying drug delivery system of bruceine D: A new approach for anti-ulcerative colitis [J]. *Int J Nanomedicine*, 2018, 13:5887-5907.

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