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进展评述
Reviews

雷公藤红素抗肿瘤作用及机制研究进展

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摘 要： 雷公藤红素是我国传统中药雷公藤中的天然活性成分，具有抗类风湿、抗炎、抗肿瘤等多种生物学活性。近年来，雷公藤红素由于低毒、多靶点、广谱性等优势，在抗肿瘤治疗中备受关注。雷公藤红素可以通过调控PI3K/AKT、NF-κB、MAPK和STAT3等多种信号通路抑制肿瘤增殖、侵袭和转移，诱导肿瘤细胞凋亡。综述了雷公藤红素的抗肿瘤作用及机制，以期促进雷公藤红素的深入研究与应用。

关键词： 雷公藤红素；细胞凋亡；信号通路；抗肿瘤

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Progress on Celastrol in Anti-tumor Effects and Mechanism

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Abstract: Celastrol is one of the natural active ingredient in traditional Chinese medicine *Tripterygium wilfordii*, which has many biological activities such as anti-rheumatoid, anti-inflammatory, anti-tumor and so on. In recent years, celastrol has attracted much attention in anti-tumor therapy due to its advantages of low toxicity, multiple targets and broad spectrum. Celastrol can inhibit tumor proliferation, invasion and metastasis, and induce tumor cell apoptosis via regulating various signaling pathways such as PI3K/AKT, NF-κB, MAPK and STAT3 pathway. This paper summarized the anti-tumor effects and mechanism of celastrol, in order to provide reference for the future research.

Key words: celastrol; apoptosis; signaling pathway; anti-tumor

雷公藤红素（celastrol）属于五环三萜类化合物，分离自传统中药雷公藤或南蛇藤的根皮、茎和叶，分子量为450.61，易溶于乙醇、三氯甲烷、二甲基亚砜等有机溶剂[1]。雷公藤红素是卫矛科植物雷公藤和南蛇藤的主要活性成分之一，其具有较强的免疫调节、抗炎、抗病原微生物、抗肿瘤等药理学活性[2-4]。近年来传统中药及其活性成分因低毒、高效、低耐药等优点，在抗肿瘤研究中得到了广泛关注。雷公藤红素对肝癌、乳腺癌、前列腺癌、骨髓瘤、胶质瘤等多种肿瘤具有广谱的药理学活性[5-6]。因此，本文主要对雷公藤红素的抗肿瘤作用及其机制进行了总结，以期为雷公藤红素在抗肿瘤中的应用提供理论参考。

1 雷公藤红素的抗肿瘤作用

癌症的进展是一个复杂的多步骤过程，其与细胞周期的失控、细胞凋亡、原发肿瘤的血管生成、侵袭周围基质和迁移到远处器官产生转移密切相关。细胞周期具有高度调节和协调的生命机制，以确保细胞的连续分裂和细胞内物质的精确复制。细胞周期相关蛋白的改变会导致正常细胞分裂异常，这是癌症和其他疾病的重要诱因之一[7]。Qian等[8]研究表明雷公藤红素可显著抑制

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*c-Myc*基因表达，诱导骨肉瘤SW1353细胞发生G_2/M期阻滞，并通过线粒体途径促进细胞凋亡。在人胃癌BGC-823和MGC-803细胞中雷公藤红素通过下调*miR-21*表达，抑制p27蛋白的降解，引起G_2/M细胞周期阻滞[9]。

肿瘤转移是指肿瘤细胞从原发病灶侵入淋巴、血管或体腔等，经血流和淋巴流带到其他部位或器官继续生长。肿瘤细胞的侵袭是指肿瘤细胞脱离原发部位，穿越基底膜并向周围间质浸润性生长，尚未进入局部毛细血管或淋巴管的阶段，侵袭是肿瘤转移的组成部分[10]。雷公藤红素通过抑制丝/苏氨酸蛋白激酶（protein serine/threonine kinase，ROCK2）介导的细胞骨架与细胞膜之间的连接蛋白Ezrin处Thr567位点的磷酸化，从而调控肝癌细胞MHCC97H、Huh7和HepG2的迁移和转移[11]。基质金属蛋白（MMP-9）参与各种癌细胞的侵袭，雷公藤红素通过抑制核因子κB（nuclear factor-kappa B，NF-κB）介导的MMP-9表达，从而抑制乳腺癌细胞MCF-7的侵袭和迁移[12]。

肿瘤的血管生成在其生长和转移中具有重要作用，肿瘤的发生与发展对血管生成具有依赖性，主要表现为新生血管为肿瘤提供营养成分，肿瘤细胞又经血管转移[13]。血管生成是肿瘤的主要驱动力，研究表明雷公藤红素纳米微粒靶向作用于缺氧诱导的低氧诱导因子-1α/血管内皮生长因子（hypoxia inducible factor-1α/vascular endothelial growth factor，HIF-1α/VEGF）通路，抑制视网膜母细胞瘤SO-Rb50生长和血管生成[14]。Gao等[15]发现雷公藤红素通过抑制结肠癌HT-29和HCT116细胞中一氧化氮合酶（NOS）的活性及血管生成中关键基因（*TYMP*、*CDH5*、*THBS2*、*LEP*、*MMP9*和*TNF*）和蛋白质（IL-1、MMP-9、PDGF、Serpin E1和TIMP-4）的表达调控血管生成，发挥对结肠癌细胞增殖和迁移的抑制活性。此外，雷公藤红素可靶向作用于蛋白激酶B/雷帕霉素靶蛋白（protein kinase B/mammalian target of rapamycin，AKT/mTOR）通路激活核糖体蛋白S6激酶1（ribosomal protein S6 kinase，P70S6K），从而抑制人前列腺癌PC3细胞的生长和血管生成[16]。

细胞凋亡是在多种基因相互调控下进行的程序性死亡过程，其中内源性凋亡包括线粒体和内质网应激途径；外源性凋亡即死亡受体途径。细胞凋亡在肿瘤的发展中意义重大，雷公藤红素通过上调人骨肉瘤U-2OS细胞中促凋亡蛋白Bcl-2关联X蛋白（Bel-2 associated X，Bax）和细胞色素C（cytochrome C，CytC）的表达，改变Bax/Bcl-2的比率，诱导细胞凋亡，从而抑制U-2OS细胞的增殖[17]。研究发现，雷公藤红素可通过激活线粒体途径和Fas/FasL介导的途径诱导人非小细胞癌A549细胞的凋亡[18]。

2 雷公藤红素的抗肿瘤机制

2.1 调控PI3K/AKT信号通路

磷脂酰肌醇3激酶/蛋白激酶B通路（phosphatidylinositol 3 kinase/protein kinase B pathway，PI3K/AKT）对细胞的生长、凋亡、代谢和增殖等多种生理功能具有重要调控作用，是肿瘤细胞中最常见的异常激活途径，同时也是一种很有吸引力的治疗靶点[19-20]。Zhu等[21]研究表明，雷公藤红素通过下调PTEN/PI3K/AKT（PTEN蛋白/磷脂酰肌醇3激酶/蛋白激酶B）信号通路，增强半胱氨酸蛋白酶-3，9酶（cysteinyl aspartate specific proteinase，Caspase-3，9）活性，提高Bax/Bcl-2的比值，进而抑制胆管癌CCA细胞增殖，诱导肿瘤细胞凋亡；同时体内研究表明，雷公藤红素能够抑制小鼠胆管癌的侵袭与转移。肿瘤血管生成和血管生成拟态（vasculogenic mimicry，VM）被认为是胶质母细胞瘤（glioblastoma，GBM）生长和转移过程中维持肿瘤营养供给的主要过程。雷公藤红素能够阻断PI3K/AKT/mTOR信号通路，抑制胶质瘤U87和U251细胞的生长、迁移和侵袭，破坏VM的形成[22]。miR-21过表达可显著提高结肠癌HCT-116细胞增殖活力，抑制细胞凋亡，降低BCL-2表达，增加Bax蛋白表达，降低Caspase-3活性。雷公藤红素可通过下调*miR-21*和磷脂酰肌醇3激酶/蛋白激酶B/糖原合成酶激酶-3（PI3K/AKT/GSK-3β）信号通路，抑制结肠癌HCT-116细胞增殖有效逆转了*miR-21*的作用[23]。Yao等[24]研究发现，雷公藤红素可通过下调*miR-21*表达及PI3K、AKT、p65和核因子κB抑制剂（inhibitor of NF-κB，IκBα）磷酸化水平，抑制人胃癌MKN45细胞PTEN/PI3K/AKT通路的活化，诱导肿瘤细胞凋亡。此外，雷公藤红素还可通过下调PI3K/AKT信号通路抑制直肠癌MMP3和MMP7、乳腺癌MCF-7、黑色素瘤B16细胞增殖、侵袭和转移诱导肿瘤细胞凋亡[25-27]。

2.2 调控NF-κB信号通路

NF-κB为一种重要的核转录因子，参与多种复杂的生物过程，包括免疫调节、炎症、细胞增殖

和凋亡等[28-30]。NF-κB在多种肿瘤中组成型过表达，如骨髓瘤、乳腺癌、卵巢癌和前列腺癌等[31]。雷公藤红素通过抑制人骨髓瘤U266细胞NF-κB信号通路过表达，诱导细胞周期阻滞于G_0/G_1期，使肿瘤细胞发生凋亡[32]。Yan等[33]研究发现雷公藤红素通过阻断乳腺癌MDA-MB-468和MDA-MB-231细胞NF-κB信号通路降低白细胞介素-6（interleukin-6，IL-6）表达水平，抑制细胞的增殖、迁移和侵袭，进而发挥抗肿瘤作用。雷公藤红素通过抑制IκBα磷酸化、IκBα降解和p65积累，阻断NF-κB信号通路和降低NF-κB靶蛋白基质金属蛋白酶（MMP9）表达，进而发挥对卵巢癌SKOV-3和OVCAR-3细胞的迁移和侵袭抑制作用[34]。在前列腺癌PC-3细胞中，雷公藤红素能够下调IκBα、IKKα（kappa B抑制因子激酶α亚基）、p50和p65蛋白的表达，促进抗凋亡蛋白Mcl-1的降解并激活促凋亡蛋白Noxa，阻断IL-6的表达，使细胞周期阻滞在G_0/G_1期，抑制肿瘤细胞的增殖、迁移和侵袭[35-36]。

2.3 调控MAPK信号通路

丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）信号通路在胞外信号向胞内传导过程中发挥着重要作用。MAPK主要由c-Jun氨基末端激酶（c-Jun N-terminal kinases，JNK）、细胞外调节蛋白激酶（extracellular signal-regulated kinases，ERK）、p38丝裂原活化蛋白激酶（p38mitogen activated protein kinases，p38）通路组成，与肿瘤的发生和发展关系密切[37]。Hong等[38]研究发现雷公藤红素通过激活p38 MAPK信号通路，下调黏着斑激酶FAK的磷酸化程度，阻断了人肺癌95-D和小鼠黑色素瘤B16F10胞外基质的黏附，进而抑制粘着斑依赖性的细胞迁移和侵袭。此外，雷公藤红素通过上调p38 MAPK和ERK通路诱导鼻咽癌细胞周期阻滞在G_2/M期，并诱导内源性和外源性凋亡途径介导的细胞凋亡，发挥抗肿瘤的作用[39]。在人多发性骨髓瘤RPMI-8226细胞中，雷公藤红素通过激活JNK通路并抑制PI3K通路，降低Caspase-8、Caspase-9、Caspase-3活化程度，阻碍促凋亡蛋白Bid、NDA修复酶PARP裂解以及降低抗凋亡蛋白的表达，抑制肿瘤细胞增殖，诱导其凋亡[23]。

2.4 调控STAT3信号通路

信号转导子和转录激活子3（signal transducers and activators of transcription 3，STAT3）是一种信号转导和转录激活因子，主要参与肿瘤的发生发展和对放化疗及靶向药物的耐药。STAT3在炎症和免疫调控过程中与泌尿生殖系统、胃肠道、肺、卵巢和脑肿瘤等多种疾病密切联系，使STAT3成为一种治疗肿瘤的理想候选策略[40]。Li等[41]研究发现，雷公藤红素处理卵巢癌SKOV3细胞后，通过抑制Pin1蛋白的表达，导致周期蛋白*CyclinD1*、*CDK2*和*CDK4*基因表达下调，使细胞周期阻滞于G_2/M期；上调Caspase-3、Caspase-8和Bax以及下调Bcl-2诱导细胞凋亡；同时雷公藤红素下调干细胞标记物CD44、Nanog、Klf4和Oct4的表达，减少CD44和CD24细胞群；下调AKT、STAT3、P38、JNK、P65和IL-6的表达，发挥抗肿瘤的作用。此外，雷公藤红素可通过调节*miR-24*和*miR-181b*的表达，降低人肺癌A549细胞STAT3的磷酸化水平和Bcl-2/Bax比值，抑制细胞增殖和诱导细胞凋亡[42]。而在肝癌HCC细胞系中，雷公藤红素对STAT3激活的抑制导致JAK2失活，引起G_1期细胞周期阻滞，诱导细胞凋亡[43]。

2.5 调控细胞凋亡途径

细胞凋亡即细胞程序性死亡，是机体为维持内环境稳定而进行的主动消亡过程。细胞凋亡对机体的生长代谢、免疫防御、细胞分化、神经系统损伤、肿瘤等进程具有十分重要的意义[44]。肿瘤细胞凋亡与内源性凋亡通路和外源通路的异常表达密切相关[45]。线粒体是生命活动的直接供能者，在细胞凋亡过程中线粒体结构发生重塑，外膜通透性增加，Cyt C通过释放不可逆地激活下游Caspases蛋白参与细胞凋亡过程[46]。Chen等[47]研究表明雷公藤红素通过抑制急性早幼粒白血病细胞（HL-60和NB-4）中半胱氨酸代谢，增加活性氧（reactive oxygen species，ROS）水平，激活线粒体凋亡途径诱导细胞凋亡。雷公藤红素能够下调血管紧张1型受体（angiotensin type 1 receptor，AT1R）的表达，阻断线粒体呼吸链，抑制了血管紧张素Ⅱ（AngⅡ）依赖的肝癌HepG2细胞的增殖。这与雷公藤红素增加了ROS和NO水平、导致细胞损伤、激活线粒体凋亡途径有关[48]。

内质网是细胞中修饰和分泌蛋白的主要细胞器，在持续而强烈的刺激下内质网应激（ERS）被激活，ERS导致错误和未折叠蛋白过度积累并触发未折叠蛋白反应，启动细胞凋亡[49]。内质网应激可通过调控肿瘤细胞的增殖、凋亡和迁移等影响肿瘤的进程。Chen等[50]研究表明雷公藤红素通过抑制内质网应激相关蛋白（Bip、PERK、p-PERK、IRE1α、calnexin、PDI、Erol-Lα）、线粒体凋

亡相关蛋白和自噬相关蛋白的表达水平诱导人骨肉瘤HOS细胞凋亡。雷公藤红素可引起HepG2和Bel7402细胞G_2/M期静止，抑制肝癌细胞增殖并通过ERS和UPR激活内源性凋亡通路[51]。雷公藤红素能够上调Bip、CHOP、XBP1s和IRE1等蛋白的表达，增加内质网应激靶基因如BIM的转录，诱导Bax易位进入线粒体，最终激活宫颈癌HeLa细胞内质网和线粒体凋亡途径[52]。

死亡受体途径与肿瘤的转归关系密切，在经典的外源性凋亡途径中Fas和FasL结合，将信号传递到胞内，激活相应的Caspase蛋白，诱导肿瘤细胞凋亡。Fas和FasL异常表达，可引起正常细胞凋亡过程的抑制和低分化细胞存活，诱发肿瘤的产生[53-54]。Cha等[55]研究表明雷公藤红素通过上调死亡受体5（death receptor 5，DR5）、Caspase-8，Caspase-3和PARP蛋白的表达水平，激活胶质瘤细胞死亡受体途径，抑制肿瘤细胞增殖，诱导细胞凋亡。雷公藤红素除能够通过线粒体途径诱导鼻咽癌HONE-1和NPC-039细胞凋亡外，还可以上调TNF受体超家族成员（TNRSF）1A和10B，激活Fas死亡结构域，导致细胞周期G_1期和G_2/M期阻滞，诱导细胞凋亡[56]。而在人乳腺癌MDA-MB-231、MCF-7和T47D细胞中雷公藤红素通过下调细胞存活蛋白cFLIP、IAP-1、Bcl-2、Bcl-xL、Survivin和XIAP表达水平，上调细胞表面肿瘤坏死因子相关凋亡诱导配体（tumor necrosis factor-related apoptosis inducing ligand，TRAIL）DR5和DR4的表达，激活TRAIL诱导的肿瘤细胞凋亡[57]。

2.6 其他途径

雷公藤红素除对肿瘤中上述信号通路有调控作用外，对其他通路也具有显著的作用。雷公藤红素能降低乳腺癌MDA-MB-231、BT20和PD-TN-BC细胞中Notch-1的活性及其下游靶蛋白DNA结合蛋白（hairy enhancer of split，HES-1）和HES相关家族bHLH转录因子（HES related family bHLH transcription factor with YRPW motif 1，HEY-1）的表达，抑制Notch信号通路，进而靶向干预乳腺癌的发生和转移[58]。Wang等[59]研究发现雷公藤红素能够增强热休克转录因子1（heat shock transcription factor 1，HSF1）表达，激活丝氨酸/苏氨酸激酶1-AMP激活蛋白激酶（LKB1-AMPKα）途径，进一步磷酸化Hippo通路效应因子（yes-associated protein，YAP）导致β-catenin降解，最终激活Wnt/β-catenin通路，发挥抗结肠癌HCT116和SW480作用。雷公藤红素与组蛋白去乙酰化酶类抗肿瘤药SAHA（伏立诺他）联合应用后，两种药物通过抑制NF-κB和E-钙粘蛋白，互相增敏，发挥联合增效作用[60]。雷公藤红素通过调控Ca^{2+}MKKβ-AMPK-mTOR信号转导、内质网应激和未折叠蛋白反应（unfolded protein response，UPR），诱导肿瘤细胞凋亡和自噬性死亡[61]。雷公藤红素能够下调mTOR信号通路，抑制顺铂耐药胃癌细胞SGC7901/DDP细胞的增殖，诱导细胞凋亡，降低耐药基因的表达，发挥降低肿瘤细胞耐药性的作用[62]。

3 展望

雷公藤红素作为传统中药雷公藤的有效活性成分，在抗肿瘤方面的药理作用得到了广泛认可，有望开发为新型的抗肿瘤药物。研究表明，雷公藤红素能够有效地抑制肿瘤细胞增殖、迁移和侵袭，影响细胞周期和肿瘤血管的形成，表现出良好的抗肿瘤活性。然而，由于雷公藤红素溶解性较差并具有一定的神经毒性和胃肠道反应，成为制约雷公藤红素临床应用的主要瓶颈。而雷公藤活性成分纳米给药系统的研发，成功地解决了溶解性差和神经毒性问题[2,63]。对雷公藤红素结构的改造有效克服了水溶性差、生物利用度低、胃肠道反应等缺点[64-65]。随着对传统中药有效活性成分的抗肿瘤机制的深入研究，中药作为天然的抗肿瘤药物具有广阔的研究和应用前景。

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