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抗肝癌天然产物的研究进展

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摘　要:肝癌是临床上常见的恶性肿瘤,目前仍没有有效的治疗手段。随着近年来对天然产物的研究进一步加深,越来越多的具有很好的抗肝癌活性的化合物被发现,这为新一代肝癌治疗药物的发展指明了新的方向。本文主要从抑制癌细胞增殖、诱导凋亡、细胞周期阻滞、诱导自噬、抑制癌细胞侵袭、调节耐药性、免疫功能调节、抑制肿瘤血管生成等八个方面综述了天然产物的抗肝癌作用,并对抗肝癌天然产物的应用前景进行展望。

关键词:肝癌;天然产物;活性化合物

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Review of Natural Products against Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma, with no effective treatment, is a common clinical malignancy. However, with the further study in natural products, more and more compounds with good anti-hepatoma activity were found, which represents a new direction for the development of new hepatocarcinoma therapeutic drugs. In this paper, the anti-hepatocarcinoma activity which are inhibiting cell proliferation, inducing apoptosis, cell cycle arrest, induction of autophagy, inhibition of metastasis, regulation of drug resistance, regulation of immune function and inhibition of angiogenesis has been reviewed, as well as the prospects of anti-hepatoma natural products.

Key words: hepatocellular carcinoma; natural products; active compounds

原发性肝癌是常见的消化道恶性肿瘤之一,由于其病因及确切分子机制尚不完全清楚,发病隐匿,早期诊断较困难,发现时多数已处于中晚期,因此预后性极差,而且其发病率和死亡率呈逐渐上升趋势,已成为仅次于胃癌和食道癌的第三大常见恶性肿瘤。对于肝癌的治疗,手术切除是最根本的方法,但对于无法手术切除,特别是伴有肝外转移的患者,有效的方法极少,临床治疗十分棘手。另外,肝癌的放射治疗和药物化疗也不能明显延长患者的生命,且都有严重的副作用。近 10 年来,随着对肝癌基础研究的深入,以及肝癌相关发生发展信号转导通路的逐渐明确,以索拉非尼(Sorafenib)为代表的分子靶向药物在进展期肝癌治疗中日益受到重视并广泛应用,延长了进展期肝癌的生存时间,但遗憾的是,至今未再有新的相关靶向药物被批准用于临床。近些年天然产物研究在抗肝癌方面取得了不少成绩,许多具有良好抗肝癌活性的化合物被发现,这些活性化合物为新一代抗肝癌药物的研发指明了新的方向。因此本文主要根据抗肝癌天然产物的作用进行综述,并展望其发展前景。

1　抑制癌细胞增殖的活性化合物

肝癌作为恶性肿瘤的主要特征就是癌细胞能无限增殖,因此抑制肝癌细胞增殖也是肝癌治疗的目的之一。从中药丹参中分离出的丹酚酸 B 能通过下调细胞色素氧化酶 CYP3A4 和 CYP1A2,以及上调谷胱甘肽硫转移酶(GST)来抑制 HepG2 肝癌细胞增殖[1]。《本草经疏》中记载:黄药根,解少阴之热,相火自不妄动而喉痹瘳矣。蛇犬咬毒,亦血分受热所伤故也,苦寒能凉血,得土气之厚者,又能解百毒也。从黄独的根中提取的甾体皂苷对 SMMC-7721 肝癌细胞和 Bel-7402 肝癌细胞的增殖有显著抑制作用[2]。从温郁金中分离的 β-榄香烯[3] 和从九节龙中得到的化合物九节龙皂苷 I[4],以及分离自两头尖的化合物银莲花素 A[5] 都能抑制 H22 肿瘤生长,其中 β-榄香烯能增强组蛋白 H1 的表达。

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从靛蓝中分离的吲哚-3-乙腈-4-甲氧基-2-C-β-D-吡喃葡萄糖苷能显著抑制 HepG2 肝癌细胞的增殖[6]。中药赶黄草具有利水除湿,祛瘀止痛的的功效,从其中提取的化合物吗啉-7-*O*-[3-*O*-甲酰基-4,6-六羟基联苯酰基]-β-葡萄糖和 Thonningianin A 能抑制 SMMC-7721 肝癌细胞增殖[7]。刺梨,可供食用及药用,能解暑消食,其含有的三萜类化合物具有体外抗 SMMC-7721 肝癌细胞增殖的作用,其机制可能通过下调 Bad mRNA 的表达而诱导细胞分化[8]。姜黄素,主要存在于传统中药材莪术,郁金,姜黄,菖蒲中,具有明显的剂量依赖性抗人 HepG2 肝癌细胞增殖的作用,可以直接或间接的影响人肝癌细胞中野生型 P53 蛋白表达量从而调节凋亡基因 Bax 的表达[9]。黄连、黄柏、三颗针中都含有黄连素,其抑制细胞增殖、诱导细胞凋亡和细胞周期阻滞与 α-线粒体依赖性通路有关[10]。《全国中草药汇编》中记载:南蛇藤的根和藤能祛风活血,消肿止痛,从其中分离的化合物南蛇藤醇通过激活应激活化蛋白激酶、蛋白激酶 B 和抗凋亡蛋白表达下调抑制细胞增殖和触发细胞凋亡,并通过降低细胞周期蛋白 D1 和细胞周期蛋白 E 水平来抑制肝肿瘤细胞的生长[11]。异荭草苷通过增加细胞内活性氧的水平抑制肝癌细胞增殖[12]。熊果酸抑制肝癌细胞增殖的作用机制可能与 B 淋巴细胞瘤-2 基因和凋亡抑制基因 Survivin 表达下调有关[13]。肉桂醛抑制 HepG2 肝癌细胞的增殖与调节 p21 和周期蛋白依赖性激酶的蛋白表达有关[14]。从月腺大戟中分离得到的 Ebracteolatain A 和 Ebracteolatain B 能抑制 HepG2 细胞的增殖,可能与线粒体介导的凋亡相关[15]。4-乙酰羟基喹诺酮 B 通过影响人体抑癌基因 p53,以及 p21 和 p27 的表达水平抑制 HepG2 细胞的增殖[16]。山姜素通过上调磷酸化丝裂原活化蛋白激酶 MKK7(p-MKK7)的表达水平,抑制 HepG2 细胞增殖并阻滞 G_0/G_1 期的细胞[17]。藤黄酸通过降低癌基因 c-MYC 的表达、下调端粒酶亚单位(hTERT)转录和降低端粒酶活性来抑制 SMMC-7721 增殖[18]。山楂酸[19]和科罗索酸[20]对人肝癌 HepG2 细胞、人肝癌 Huh7 细胞的增殖均有一定的抑制作用。鞣花酸通过抑制肿瘤相关基因 Ct BP、Stathmin 和环氧化酶 2(COX-2)的表达抑制 HepG2 细胞增殖并诱导其凋亡[21]。柴胡是中医治疗肝病最常用的中药之一,柴胡皂甙 d 是从中药柴胡中分离提取的有效单体成分,在 HepG2 和 Hep3B 细胞中通过上调 p53、I 型跨膜糖蛋白 Fas/APO-1、与细胞膜结合的 Fas 配体(mFasL)和可溶性 Fas 配体(sFasL)和 Bax,下调核转录因子 NF-κB 和癌基因 Bcl-XL 来达到抑制癌细胞增殖的作用[22]。高良姜通过诱导内质网应激来抑制癌细胞的增殖[23]。

2 诱导癌细胞凋亡的活性化合物

藤黄酮 F 通过上调 PLC/PRF/5 细胞中的 Caspase-3 和 DNA 修复酶(PARP)表达来诱导凋亡[24]。厚朴酚通过促进 caspase-3, caspase-8, caspase-9 的活化和 Bcl-2 蛋白表达下调诱导细胞凋亡[25]。甘草黄酮诱导 Huh7 肝癌细胞凋亡与 p38 分裂原激活的蛋白激酶(p38MAPK)和 JNK 1/2 途径有关[26]。黄樟油素能诱导细胞凋亡、抑制肿瘤细胞生长[27]。蓝萼素通过诱导减少 Bcl-2 和增加 Bax 从而使 HepG2 细胞凋亡[28]。α-楝子素通过抑制 p38 MAPK 途径诱导 SK-Hep-1 肝癌细胞中的线粒体依赖性凋亡[29]。异甘草素诱导肝癌细胞凋亡的作用与上调 Bax,下调 Bcl-2 表达,增加 cyt-c 从而导致 Caspase-3 活化有关[30]。在 HepG2 细胞中冬凌草甲素诱导的细胞凋亡与氧化应激有关[31]。鬼臼毒素通过 Bax 依赖性途径诱导癌细胞凋亡[32,33]。蛇葡萄素诱导 HepG2 肝癌细胞的凋亡涉及到胱天蛋白酶级联的活化,包括 caspase-3,caspase-8 和 caspase-9;同时增加死亡受体 4,死亡受体 5 的表达水平,并减少 Bcl-2 蛋白的表达,导致 Bax/Bcl-2 比率的增加;细胞色素 c 从线粒体释放;降低 iNOS 和 COX-2 的水平等[34]。紫草素通过调节活性氧诱导肝癌细胞凋亡[35]。齐墩果酸能明显抑制肝癌细胞的生长,诱导细胞凋亡,其机制可能是通过激活凋亡线粒体信号通路而实现的;此外齐墩果酸能够抑制 Hep3B 肝癌细胞株增殖[36]。氯化两面针碱对 SMMC-7721 肝癌细胞的生长有明显抑制作用,其能抑制 DNA 拓扑异构酶活性以及 P125 蛋白的表达、调控肿瘤细胞生长相关基因的表达、诱导细胞周期阻滞 G_2/M 期[37]。10-羟基喜树碱呈时间-剂量依赖性诱导凋亡,并干扰细胞周期[38]。桑皮素通过抑制信号传导与转录激活因子(STAT3)和 NF-κB 信号通路,下调整联蛋白 b1 的水平,降低线粒体膜电位(MMP)来诱导肝癌细胞凋亡[39]。丹皮酚通过刺激白细胞介素-2(IL-2)和肿瘤坏死因子 α(TNF-α)产生而诱导癌细胞凋亡[40]。从苦参中提取的化合物 Leachianone A 诱导 HepG2 肝癌细胞凋亡[41]。泡番

荔枝辛通过减少细胞内环磷酸腺苷(cAMP)和环磷酸鸟苷(cGMP)水平来诱导凋亡[42]。澳洲茄边碱诱导的细胞凋亡可能与瘤坏死因子受体(TNFR)-I 和瘤坏死因子受体-II 上调有关[43]。杨梅素通过激活线粒体途径诱导 HepG2 细胞凋亡[44]。牛蒡子苷元诱导的凋亡与线粒体介导的途径和 Fas/FasL 相关途径相关,同时伴随有 PI3K/p-Akt 通路的失活、p53 蛋白的积累和 NF-κB 核易位的抑制[45]。香叶木甙通过激活 HA22T 肝癌细胞中的蛋白磷酸酶 2A 诱导细胞凋亡[46]。金雀异黄素通过 p53 信号通路诱导肝癌细胞凋亡[47]。紫杉醇通过调节细胞凋亡抑制基因 Bcl-2 和细胞凋亡促进基因 Bax 诱导肝癌 SMMC-7721 细胞凋亡[48]。二氢杨梅素通过激活 p53 依赖性凋亡途径促进癌细胞凋亡[49]。Tatariside F 诱导的凋亡与 Bax 和 p53 的蛋白表达上调和 Bcl-2 的下调有关[50]。

3 诱导癌细胞自噬的活性化合物

细胞自噬,是细胞器和蛋白质被螯合并随后通过与溶酶体融合而降解的过程,被认为是肝癌治疗的靶标。长春新碱能诱导 HepG2 细胞自噬性凋亡,并可以通过升高 SMMC-7721 细胞内的活性氧含量,氧化损伤线粒体膜,降低线粒体跨膜电位强度,使线粒体膜内外通透更容易,使细胞色素(cyt-c)等一系列促凋亡的因子被释放出,诱导细胞凋亡[51]。重楼皂苷 VII 通过抑制磷脂酰肌醇 3-激酶(PI3Ks)信号通路和激活 c-Jun 氨基末端激酶(JNK)通路诱导 HepG2 细胞自噬死亡[52]。6-姜烯酚能够诱导活性氧和内质网应激相关蛋白的产生并激活 HepG2 细胞自噬,此外,还可引起细胞周期停滞在 G2/M 期,诱导肝癌细胞凋亡[53]。齿孔酸诱导自噬相关蛋白 LC3-I 转化为 LC3-II 和大量自噬体/自溶酶体形成[54]。防己诺林碱通过 p53/sestrin2/AMPK 信号转导诱导肝癌细胞自噬死亡[55]。

4 阻滞癌细胞增殖周期的活性化合物

癌细胞具有不受控制的增殖周期,停止细胞增殖周期是理想的癌症治疗方法之一。分离自蟾酥的蟾毒配基 B 酯通过上调细胞有丝分裂相关基因 Aurora A 和细胞周期蛋白依赖性激酶 cdc25、CDK1、细胞周期蛋白 A 以及细胞周期蛋白 B1 表达,下调 p53 和 p21 表达,诱导细胞周期阻滞在 G_2/M 期[56]。白藜芦醇能通过增加诱导型一氧化氮合酶和内皮型一氧化氮合酶的表达和活性使细胞滞留在 G_1 期来诱导细胞凋亡[57]。水飞蓟宾能诱导 HepG2 细胞的细胞周期阻滞在 G_1 期和 Hep3B 细胞的细胞周期阻滞在 G_2/M 期,这与细胞周期蛋白 D1、细胞周期蛋白 D3、细胞周期蛋白 E、细胞周期蛋白依赖性激酶-2 和细胞周期蛋白依赖性激酶 CDK4 表达减少以及细胞周期蛋白抑制基因 Kip1/p27 表达增加有关[58]。槲皮素通过诱导 p53 依赖性细胞周期阻滞和凋亡来抑制肝癌细胞的生长,且与时间和浓度正相关[59]。丹参酮 II-A 诱导 SMMC-7721 细胞的细胞周期阻滞 G_0/G_1 期,这与 Fas,p53,Bax 的上调以及 Bcl-2 的表达和 c-myc 的下调相关[60,61]。橄榄苦甙诱导的细胞增殖周期阻滞与 p53、p21、CDK1 的调控和细胞周期蛋白 B1 的表达水平有关[62]。木犀草素通过诱导 G_1/S 期阻滞,增加 Bax 水平,下调抗凋亡蛋白 Bcl-2 的水平,进而激活半胱氨酸天冬氨酸蛋白酶 3(caspase-3),降低线粒体膜电位,最终导致细胞凋亡[63]。肿柄菊中含有的 TagitininC 能诱导 caspase-3 和 caspase-8 的活化,诱导 G_1/S 期停滞[64]。白头翁皂苷 B4 诱导肝癌细胞周期 G2/M 期阻滞[65]。大蒜素诱导肝癌细胞周期 G_0/G_1 期阻滞,其分子机制涉及上调 Bax、caspase-3 表达,抑制肝癌细胞血管内皮生长因子(VEGF) mRNA 和细胞间黏附分子-1(ICAM-1) mRNA 转录[66]。斑蝥素诱导肝癌细胞周期 G_2/M 期阻滞并可诱导细胞凋亡[67]。吉马酮的通过诱导细胞周期阻滞 G_2/M 期,并促进 p53 的表达[68]。DICO,从马蹄莲获得的一种新型的非芳香 B 环黄酮,通过 ROS(reactive oxygen species)介导的线粒体途径诱导细胞周期阻滞在 G_2/M[69]。洋菝葜皂甙元诱导 HepG2 肝癌细胞周期阻滞在 G2/M 期,从而导致其凋亡[70]。Taiwanin A 可以作为新类型的微管损伤剂,通过激活 p53 来阻止细胞周期进程和诱导细胞凋亡[71]。

5 抑制癌细胞侵袭的活性化合物

中草药化合物已经显示出抑制肝癌细胞转移的作用,如粘附、侵袭和转移。姬松茸发酵乙醇提取物中的 Blazeispirol A、Blazeispirol C 能抑制 SK-Hep1 和 HA22T/VGH 细胞侵袭,同时其通过上调 Bax 表达,下调 Bcl-2 表达,促进 caspase-3,caspase-9 和 PARP 的活化来诱导癌细胞凋亡[72]。黄芩素通过降低蛋白激酶 α(CPKCα)和 p38 蛋白的磷酸化水平来抑制低分化肝癌细胞的侵袭[73]。人参皂苷 IH901

通过降低 VEGF/bFGF 的表达来抑制肝癌细胞的侵袭转移[74]。苦参素能下调 MMP-9 和 NF-κB 并抑制肝癌细胞侵袭[75]。紫草素通过波形蛋白,MMP-2 和 MMP-9 的下调抑制肝癌细胞的迁移[76]。青蒿素通过使 MMP2 下调、Cdc42(癌细胞转移所需的关键蛋白)和 E-钙粘蛋白上调以及促进 p38 和细胞外调节蛋白激酶(ERK1/2)的磷酸化来抑制肝癌细胞转移[77]。白藜芦醇[78,79]和桔梗皂苷 D[80]也能抑制肝癌细胞粘附,迁移,侵袭。

除了单一化合物之外,可以组合多种草药成分。例如黄芪和丹参提取物是一种含有黄芪苷,黄芪多糖和丹酚酸的草药组分配方,能通过调节 TGF-β/Smad 信号(调控干细胞活性和器官形成)抑制转化生长因子-β1(TGFβ1)介导的肝癌 HepG2 细胞侵袭[81]。

6 抑制血管生成的活性化合物

血管生成,从现有血管产生的新血管过程在肿瘤生长和转移中起关键作用,已被认为是肝癌的潜在靶标。桔梗皂苷 D 通过改善免疫功能,抑制血管生成,能够显著抑制 H22 肿瘤生长[82]。淫羊藿苷抗增殖的作用机制可能与它的抗血管生成有关[83]。马缨移衣黄酮能抑制血管内皮生长因子的产生和抑制血管生成,同时激活 caspase-3 和诱导癌细胞凋亡[84]。羟基红花黄色素 A 通过阻断 ERK/MAPK 和 NF-κB 信号通路抑制肝细胞癌的血管生成[85]。马先蒿甙 G 也能抑制人肝癌中血管生成[86]。

7 调节耐药性的活性化合物

寻求有效的活性成分来逆转耐药性已成为肝癌研究的重点研究领域。苦参素能逆转肝癌细胞耐药性,并能抑制肝癌细胞增殖、诱导肝癌细胞分化、抑制端粒酶活性、阻滞细胞周期、调节免疫功能、抑制肝癌血管内皮细胞增殖,促进肝癌细胞凋亡[87]。黄芪多糖通过上调 IL-1α,IL-2,IL-6 和 TNF-α 以及下调 IL-10 和 MDR1(与肿瘤细胞多药耐药相关的基因),增强阿霉素在 H22 肝癌中的抗肿瘤作用[88]。卵黄素 A 是一种从黄芩中分离得到的化合物,能显著抑制整合素 β1,逆转耐药性,并增强紫杉醇对耐药性 HepG2 肝癌细胞的凋亡诱导作用[89]。

除了逆转耐药性外,一些化合物对耐药性肝癌细胞具有直接作用。耳草酮 A 通过激活 caspase-3,caspase-7 和 caspase-9 诱导耐药性肝癌细胞凋亡[90]。从白芷中分离得到的化合物异戊-2-烯氧呋豆素通过诱导蛋白酶体依赖性 Mcl-1 降解释放 Bak 和 Bax,引发耐药性肝癌细胞凋亡[91]。

8 调节免疫功能的活性化合物

抗癌细胞免疫的主要细胞群包括 CD4 + T 辅助细胞(Th)和 CD8 + T 淋巴细胞。CD4 + Th1 细胞产生细胞因子,如 IL-2 和 IFN-γ,引起细胞介导的免疫或吞噬细胞依赖性炎症。CD4 + Th2 细胞分泌细胞因子,如 IL-4 和 IL-6,与体液免疫相关。抗原呈递细胞,如树突状细胞和巨噬细胞,加工抗原以引导 CD4 + 和 CD8 + T 细胞产生抗原特异性免疫应答。紫草素能有效增加 CD3 + 和 CD19 + 淋巴细胞,改善肝细胞 Hep A22 的自然杀伤活性,促进淋巴细胞转化和 IL-2 产生[92]。天麻素通过上调 NF-κB,IL-2 和 Bcl-2 在 CD4 + T 细胞中的表达,增强 CD8 + T 细胞对 H22 肝癌细胞的细胞毒性[93]。源于 CD4 + Th0 细胞的 CD4 + CD25 + 调节性 T 细胞(Tregs)能促进 TGF-β 和 Foxp3 表达。Treg 可能产生 IL-10,并且起免疫调节剂的作用。甘草多糖能下调 Treg、细胞因子 IL-10、TGF-β 和 Foxp3 的表达,并增加 H22 肿瘤小鼠血清中 IL-2 和 IL-12p70 水平[94]。

综上所述,天然产物对肝细胞癌具有多重作用,包括抑制癌细胞增殖、诱导凋亡、细胞周期阻滞、诱导自噬、抑制癌细胞侵袭、调节耐药性、调节免疫功能、抑制肿瘤血管生成等,为进一步开发新药提供了依据。同时,一种植物可以含有多种抗癌活性化合物,例如郁金含有姜黄素,大黄素和 β-榄香烯;一种天然产物可能对肝癌具有多重作用,如川陈皮素能显著抑制 H22 移植瘤的生长;在 SMMC-7721 细胞中能下调 COX-2 的表达,上调 Bax 和 caspase-3 的表达;还能诱导细胞周期 G2 阻滞[95]。

我国具有丰富的天然产物资源,以中药为主,近年来的研究表明许多中药复方有良好的抗肝癌作用,如改善患者症状体征、调节免疫、减毒增效及提高生存质量,因此可从这些中药中提取中药单体用于抗肝癌药物研究。中药在中国应用了几千年,具有广泛的临床实践资料,且中药具有天然的优势,因此可以结合现代药学理论和生物技术,完善实验研究方法和体系,从多靶点、多途径、多学科加强对抗肝癌中药活性成分的筛选以及作用机制的探讨,为研发抗肝癌药物奠定基础。此外,中药联用能同时

作用于多个靶点,能产生更加有效和更加持久的治疗效果,也不失为一种抗肝癌天然产物的利用手段。随着对肝癌研究的逐步深入,人们对其发生发展机制和相关信号通路的逐步明确,结合计算机辅助药物设计,基于相关受体、配体和受体配体复合物构建药效团筛选抗肝癌先导化合物,或对天然产物进行结构修饰使之更具成药性,进而研发出高效的肝癌治疗药物,具有良好的发展前景。

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