中药挥发油治疗脑胶质瘤的作用机制及其纳米制剂的研究进展

王佳华[1,2], 汪莲芳[1,2], 柯 刚[1,2,3], 胡鹏翼[1,2], 伍 丽[1,4], 郑 琴[1,2*], 张继稳[1,4*]

(1. 江西中医药大学现代中药制剂教育部重点实验室, 江西 南昌 330004; 2. 中药改良创新江西省重点实验室, 江西 南昌 330004; 3. 泸州市人民医院, 四川 泸州 646000; 4. 中国科学院上海药物研究所, 上海 201210)

摘要: 脑胶质瘤是最常见的中枢神经系统原发性肿瘤, 其一线治疗药物受血脑屏障阻碍, 在肿瘤部位难以达到有效剂量。中药挥发油具有高脂溶性、易穿过血脑屏障等优点, 表现出良好的抗脑胶质瘤作用。引经中药具有引药上行功效, 一些挥发油成分可通过促进化药入脑、抑制脑内药物外排、协同化药治疗等方式提高抗脑胶质瘤作用。但挥发油稳定性差, 纳米制剂如脂质体、纳米粒、自组装前药递药系统等可改善其稳定性, 并通过注射给药方式发挥治疗脑胶质瘤效果, 为挥发油治疗脑胶质瘤提供良好的应用前景。本文综述了中药挥发油及其主要成分抗脑胶质瘤的作用机制, 以及挥发油联用化疗药物及其纳米药物递送系统治疗脑胶质瘤的研究进展, 以期为中药挥发油在脑胶质瘤治疗中的应用提供参考。

关键词: 中药挥发油; 脑胶质瘤; 作用机制; 联合给药; 纳米制剂

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Researches on the anti-glioma mechanism of volatile oil from traditional Chinese medicines and nano-preparation applications

WANG Jia-hua[1,2], WANG Lian-fang[1,2], KE Gang[1,2,3], HU Peng-yi[1,2], WU Li[1,4], ZHENG Qin[1,2*], ZHANG Ji-wen[1,4*]

(*1. Key Laboratory of Modern Preparation of TCM, Ministry of Education, Jiangxi University of Chinese Medicine, Nanchang 330004, China; 2. Jiangxi Provincial Key Laboratory of Improvement and Innovation of Traditional Chinese Medicine, Nanchang 330004, China; 3. Luzhou People's Hospital, Luzhou 646000, China; 4. Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201210, China*)

Abstract: Gliomas are the most common primary tumors in the central nervous system. However, the efficacy of first-line treatments for glioma is hindered by the blood brain barrier (BBB), making it difficult to reach an effective dose at the tumor site. The volatile oil from traditional Chinese medicine have the advantages of high fat solubility and ability to penetrate the blood brain barrier, has demonstrated promising inhibitory effects on glioma. The volatile oil components of traditional Chinese medicine can improve the anti-glioma efficacy by promoting the entry of chemotherapeutic drugs into the brain, inhibiting the exocytosis of drugs within the brain and synergizing with chemical drug therapy. However, the stability of volatile oil is poor, nano-formulations including liposomes, nanoparticles, and self-assembled prodrug delivery systems, can improve their stability and exert the therapeutic efficacy. As an effective drug for the treatment of glioma, volatile oil from traditional Chinese medicine shows good prospects for application. This review summarizes the mechanisms of action of volatile oil from traditional Chinese medicine and their main components against glioma, and the research progress of volatile oil combined

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*通讯作者 Tel: 86-791-87118658, E-mail: zhengqin912006@163.com;
Tel: 86-21-68077837, E-mail: jwzhang@simm.ac.cn
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with chemotherapeutic drugs or designed as nano-drug delivery systems for glioma therapy, with a view to providing reference for the application of volatile oil from traditional Chinese medicine in the treatment of glioma.

Key words: volatile oil from traditional Chinese medicine; glioma; mechanism of action; co-administration; nano-formulation

脑胶质瘤是一种源于脑神经胶质细胞的原发性肿瘤, 通常以血管增生和坏死为特征, 其预后性极差, 中位生存期仅为14.6～16.6个月[1]。目前, 脑胶质瘤的主要治疗策略是手术切除, 术后放疗和化疗。治疗脑肿瘤的化疗药物如卡莫司汀、伊立替康和贝伐珠单抗等, 通常受肿瘤的异质性、血脑屏障 (blood brain barrier, BBB) 和耐药性等影响, 限制药物有效进入脑肿瘤[2,3]。替莫唑胺 (temozolomide, TMZ) 是治疗胶质瘤的一线药物, 但其半衰期短, 靶向性差, BBB透过率不高, 药物通常加大给药剂量, 以较高浓度才能进入中枢神经系统和肿瘤部位, 长期服用易造成肿瘤耐药性和全身毒副作用, 严重影响其治疗效果[4,5]。因此, 为脑胶质瘤开发新的治疗策略具有重要意义。

中药挥发油常见的植物来源包括伞形科、唇形科、芸香科和百合科, 富含萜类、脂肪族及芳香族等多种成分[6], 展现出抗炎、抗氧化和抗肿瘤等多种药理作用, 其中合江佛手挥发油、大蒜素和β-榄香烯等已被证实具有抑制脑胶质瘤的作用[7-9]。富含挥发油的引经中药或其活性成分, 如川芎挥发油、β-细辛醚、薄荷醇和麝香酮等, 具有引药上行功效, 可通过调节BBB通透性或促进药物入脑的方式, 增强其他药物在脑组织分布[10-12]。将这类挥发油与化疗药物联合使用, 可提高化疗药物在脑内的富集度, 增强抗肿瘤效果, 并降低其给药剂量, 从而减少毒副作用。尽管中药挥发油具有潜在的治疗效果, 但其稳定性差, 易受光、热、氧气等因素的影响, 限制其实际应用[13]。纳米递药系统为解决挥发油的缺陷提供了新的机遇, 如脂质体、纳米粒和仿生纳米技术等, 能够有效改善挥发油的稳定性和靶向性[14]。

本文对近年来中药挥发油及其活性成分抗脑胶质瘤作用机制、与化疗药物联用和纳米制剂用于胶质瘤的治疗进行综述, 为中药挥发油的应用和药物递送提供参考。

1 中药挥发油抗脑胶质瘤作用机制

中药挥发油及其活性成分通过诱导细胞凋亡和细胞周期阻滞、抑制细胞增殖和侵袭转移、调节细胞自噬以及抑制血管生成等不同机制展现出抗脑胶质瘤作用 (图1、表1[7-9,15-31])。

1.1 诱导肿瘤细胞凋亡和细胞周期阻滞

细胞凋亡是胶质瘤中最重要的细胞死亡形式, 包括内源性途径和外源性途径。凋亡相关蛋白B淋巴细胞瘤-2 (B-cell lymphoma-2, Bcl-2)、Bcl-2相关X蛋白 (Bcl-2-associated X protein, Bax) 和半胱氨酸天冬氨酸蛋白酶 (cysteinyl aspartate specific proteinase, caspases) 是参与内源性途径的主要调控因子[32,33]。Yang等[7]发现低质量浓度β-榄香烯 (10 μg·mL^{-1}) 通过提高C6细胞p53蛋白水平, 降低核纤层蛋白B1表达, 诱导衰老相关分泌表型 (senescence-associated secretory phenotype, SASP) 的表达, 进而促进细胞衰老, 而高质量浓度的β-榄香烯 (100 μg·mL^{-1}) 能显著增加caspase-3水平, 诱

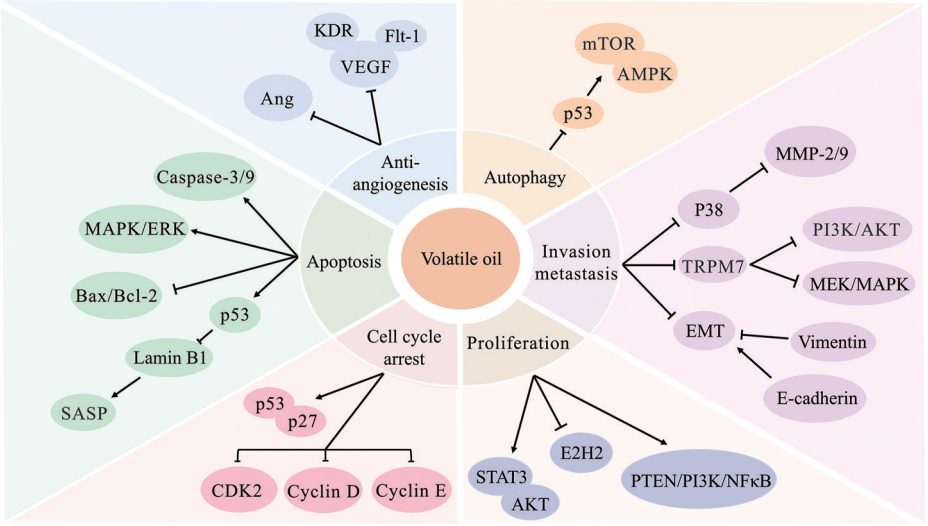

Figure 1 Anti-glioma mechanism of volatile oil from traditional Chinese medicine and their active ingredients

Table 1 Anti-glioma mechanism of volatile oil from traditional Chinese medicine and their active ingredients

Mechanism	Compound	Experimental model	Relevant pathway	Ref.
Induce tumor cell apoptosis and cell cycle arrest	*β*-Elemene	C6	Up-regulated expression of p53, SASP and caspase-3; down-regulated expression of Lamin B1 and YAP/CDK6 signaling pathways	[7]
	Volatile oil of Hejiang Bergamot	U87	Down-regulated expression of Bcl-2/Bax	[8]
	Allicin	U87	Inhibit Bcl-2, activated Bax and MAPK/ERK signaling pathway	[9]
	Citral	A172/U87	Activated caspase-3 and caspase-9; inhibit expression of MRP1	[15]
	Carvacrol	DBTRG-05	Up-regulated expression of caspase-3 and $[Ca^{2+}]_i$	[16]
	β-Asarone	U251	Cell cycle arrest in G1 phase; inhibit hnRNP A2/B1 expression	[17]
	Tea tree oil	U87	Cell cycle arrest in G0/G1 phase; up-regulated expression of TNFR1, RIP and TRADD	[18]
Inhibit tumor cell proliferation	MCEO/PALD/EPER1	U87	Up-regulated expression of PTEN/PI3K/NF*κ*B; inhibit AKT signaling pathway	[19]
	Volatile oil of *L. multiflora* and *O. basilicum*	SF-767 SF-763	Activated STAT3 signaling pathway Activated STAT3 and AKT signaling pathway	[20]
	Perillyl alcohol	U87	Inhibit Ras signaling pathway	[21]
	Curcumol	U251/A172	Suppressing FOXD2-As1-mediated EZH2 activation	[22]
Inhibit tumor cell invasion and metastasis	Allicin	U87	Down-regulated expression of MMP-2 and MMP-9	[23]
	Carvacrol	U87	Inhibit TRPM7, PI3K/Akt, MEK/MAPK signaling pathways; down-regulated expression of MMP2; up-regulated expression of p-cofilin	[24]
	β-Asarone	U251	Inhibit EMT expression; down-regulated expression of MMP-9 and p-STAT3	[25]
	Ligustilide	T98	Down-regulated expression of RhoA	[26]
	Volatile oil of turmeric	SH-SY5Y	–	[27]
Induce tumor cell autophagy	Volatile oil of *Acorus gramineus*	A172	Activate AMPK/mTOR signaling pathways; decrease the activity of p53	[28]
Anti-angiogenesis	*α* & *α*/*β*-Thujone	U87/C6	Down-regulated expression of VEGF and Ang-4	[29]
	Volatile oil of Hejiang Bergamot	U87	Inhibit VEGF/Flt-1/KDR protein express	[30]
	Volatile oil of *Ligusticum chuanxiong*	U87	Inhibit EGFR/VECF-A signaling pathways	[31]

导细胞凋亡。体内实验结果表明, 在C6肿瘤裸鼠模型中, *β*-榄香烯 (100 mg·kg^{-1}) 治疗后的肿瘤体积较对照组显著减小, 其机制主要是通过降低Yes相关蛋白 (Yes-associated protein, YAP)/细胞周期蛋白依赖性激酶6 (cyclin-dependent kinase 6, CDK6) 信号通路诱导体内胶质瘤细胞衰老, 从而抑制肿瘤生长。合江佛手挥发油 (25、50、100 μg·mL^{-1}) 和大蒜素 (90 μmol·L^{-1}) 具有促进U87细胞凋亡作用, 其机制与下调Bcl-2, 上调Bax, 降低Bcl-2/Bax比值有关, 其中大蒜素还能通过激活丝裂原活化蛋白激酶 (mitogen activated protein kinase, MAPK)/细胞外调节蛋白激酶 (extracellular regulated protein kinase, ERK) 通路参与肿瘤细胞凋亡[8,9]。香蜂草挥发油 (36.8 μg·mL^{-1}) 及其活性成分柠檬醛 (18.4、36.8 μg·mL^{-1}) 通过激活caspase-3和caspase-9, 从而诱导A172细胞凋亡, 同时还发现柠檬醛 (16.9、28.1 μg·mL^{-1}) 可抑制A172细胞多药耐药相关蛋白1的表达, 从而降低胶质瘤细胞的耐药性[15]。此外, 香芹酚 (200、400、600 μmol·L^{-1}) 也能通过激活caspase-3表达诱导胶质瘤细胞凋亡[16]。

细胞周期阻滞与细胞凋亡密切相关, 通过调控相关周期蛋白 (cyclin) 和CDK因子, 阻滞细胞周期进程并诱导细胞死亡。异质核糖核蛋白A2/B1能降低胶质母细胞瘤的活力, 对其生长、存活和侵袭具有关键作用[34]。*β*-细辛醚 (480 μmol·L^{-1}) 通过上调细胞周期蛋白依赖性激酶抑制剂p27, 下调CDK2、cyclin D和cyclin E, 使细胞阻断在G1期。此外, *β*-细辛醚 (120～480 μmol·L^{-1}) 还可通过抑制异质核糖核蛋白A2/B1, 促进Bcl-x的选择性剪接, 诱导U251细胞凋亡[17]。研究发现, 用0.025%茶树油处理U87细胞, 可通过降低CDK2、增加p27和p53的表达, 诱导胶质瘤细胞在G0/G1期停滞, 并激活肿瘤坏死因子 (TNFR-1、RIP-1和TRADD), 诱导U87细胞坏死, 促进细胞凋亡[18]。

综上可知, 中药挥发油及其活性成分参与多种途径促进胶质瘤细胞死亡, 通过下调相关凋亡蛋白Bcl-2/Bax的比值, 激活caspase-3和caspase-9的表达和调控MAPK/ERK信号通路, 激活肿瘤坏死因子诱导细胞凋亡。此外, 还能通过调节p27、p25、cyclin、CDK2等因子诱导细胞阻滞。

1.2 抑制肿瘤细胞增殖

挥发油通过不同途径调节细胞转导通路, 抑制

胶质瘤细胞过度增殖发挥抗肿瘤作用。研究发现，薄荷挥发油 (16.263 μg·mL^{-1}) 及其主要成分紫苏醛 (14.888 μg·mL^{-1})、1,2-紫苏醛环氧化物 (15.087 μg·mL^{-1}) 能有效增强蛋白酪氨酸磷酸酶基因 (protein tyrosine phosphatase gene, PTEN)、磷脂酰肌醇 3-激酶 (phosphatidylinositol 3-kinase, PI3K)、核转录因子 *κ*B (nuclear factor kappa-B, NF-*κ*B) 的表达，降低蛋白激酶 B (protein kinase B, AKT) 表达，从而抑制 U87 细胞增殖[19]。多花乳香和罗勒精油 (0.3 mg·mL^{-1}) 通过激活信号转导子和转录激活子 3 (signal transducer and activator of transcription 3, STAT3) 抑制 SF-767 细胞的增殖，而在 SF-763 细胞中，STAT3 和 AKT 途径被共同激活发挥抗增殖作用[20]。紫苏醇可通过下调大鼠肉瘤蛋白 (rat sarcoma protein, Ras) 信号通路抑制胶质瘤细胞增殖[21]。莪术醇 (20、40 μg·mL^{-1}) 可通过抑制长链非编码 RNA (long non-coding RNA, lncRNA) FOXD2-AS1 诱导的 EZH2 活性，发挥抑制胶质瘤细胞增殖转移作用。通过建立 U251/TMZ 耐药型裸鼠模型，每 3 天腹腔注射莪术醇 (20 mg·kg^{-1})，结果发现，莪术醇在体内能有效地抑制胶质瘤细胞增殖、转移，具有自我更新能力和 TMZ 耐药性[22]。此外，石菖蒲挥发油[35]、金丝桃挥发油[36]在体外均具有抑制胶质瘤细胞增殖的作用。挥发油及其活性成分能够通过调节 PTEN/PI3K/AKT/NF*κ*B、STAT3/AKT、Ras 等信号通路和降低 lncRNA 表达抑制胶质瘤细胞增殖。

1.3 抑制肿瘤细胞侵袭转移

胶质瘤细胞侵袭和转移是肿瘤复发主要原因。基质金属蛋白酶 (matrix metalloproteinase, MMP) 中的 MMP-2 和 MMP-9 能通过降解细胞外基质增加神经胶质瘤细胞中侵袭性[37]。Cai 等[23]研究发现，大蒜素 (< 8 μg·mL^{-1}) 呈剂量依赖性抑制 U87 细胞的侵袭能力，作用机制与调节 p38 信号的通路活性从而下调 MMP-2 和 MMP-9 的表达有关。香芹酚 (500 μmol·L^{-1}) 通过降低 MMP-2、增加肌动蛋白磷酸化、抑制瞬时受体电位通道 7 活性以及 PI3K/Akt 和丝裂原活化蛋白激酶激酶 (mitogen-activated protein kinase kinase, MEK)/MAPK 信号通路抑制 U87 细胞的迁移和侵袭[24]。上皮−间充质转化 (epithelial-mesenchymal transformation, EMT) 是上皮细胞转化为间充质表型细胞的过程，EMT 的典型特征是上皮细胞减少或遗失和间充质标志物增加，使肿瘤细胞更容易发生侵袭和转移[38,39]。Li 等[25]研究发现，*β*-细辛醚 (60 μmol·L^{-1}) 通过上调 E-钙黏蛋白 (E-cadherin) 和下调波形蛋白 (vimentin) 水平，阻断 EMT 发生，同时下调 MMP-9 和 p-STAT3 表达，从而抑制 U251 细胞迁移、侵袭和黏附。藁本内酯 (5 μmol·L^{-1}) 通过下调 *Ras* 同源基因家族成员 A (ras homolog gene family member A, RhoA) 抑制 T98 细胞迁移[26]。此外，姜黄挥发油 (160 mg·L^{-1}) 也具有抑制 SH-SY5Y 肿瘤侵袭作用[27]。因此，挥发油活性成分主要通过下调 MMP-2、MMP-9 和 RhoA 的表达，抑制 PI3K/Akt、MEK/MAPK 信号通路，逆转 EMT 进程，从而抑制胶质瘤细胞侵袭和转移。

1.4 诱导肿瘤细胞自噬

自噬诱导已成为胶质瘤细胞死亡的重要替代途径[40]。中药挥发油能够通过调节腺苷酸活化蛋白激酶 (adenosine monophosphate-activated protein kinase, AMPK)/哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 信号通路诱导胶质瘤细胞自噬。例如，石菖蒲挥发油 (100 μmol·L^{-1}) 通过下调 p53 蛋白水平进一步增强 AMPK/mTOR 信号通路诱导 A172 细胞自噬，在 U251 细胞中通过激活 AMPK 非依赖性 mTOR 通路诱导自噬，此外，自噬的阻断增强了 A172 和 U251 细胞的促凋亡作用，表明石菖蒲挥发油能诱导凋亡细胞死亡和保护性自噬[28]。

1.5 抗血管生成

缺氧是胶质瘤主要病理特征之一，其会产生假栅栏状肿瘤坏死细胞，这些细胞具有高度迁移、促血管生成和耐药性等表现[41]。肿瘤缺氧因子是调控促血管生成基因表达的重要因素。受缺氧调节的血管内皮生长因子 (vascular endothelial growth factor, VEGF) 和血管生成素 (angiopoietin, Ang) 是促进新血管生成的关键信号，其在胶质瘤内高度表达[42]。*α*-侧柏酮 (300 μg·mL^{-1}) 和 *α*/*β*-侧柏酮 (200 μg·mL^{-1}) 可通过降低 U87 和 C6 细胞的 VEGF 和 Ang-4 水平，发挥抗肿瘤血管生成作用[29]。Han 等[30]发现合江佛手挥发油 (25 mg·kg^{-1}) 在 U87 肿瘤裸鼠中具有显著抗肿瘤作用，其机制是通过减少 VEGF 及其受体 1 (fms-like tyrosine kinase 1, Flt-1)、受体 2 (kinase insert domain containing receptor, KDR) 表达，从而抑制肿瘤内皮细胞的增殖、迁移和小管形成。川芎挥发油 (1.56×10^{-3}、6.25×10^{-3} μL·mL^{-1}) 可通过下调富含亮氨酸重复序列和免疫球蛋白样结构域 2，进而下调表皮生长因子受体 (epidermal growth factor receptor, EGFR) 和 VEGF-A 表达，从而抑制 U87 细胞血管生成[31]。由此可知，中药挥发油通过调控 VEGF 及其受体、EGFR 和 Ang 因子，抑制新血管生成，改善肿瘤区域缺氧，为治疗胶质瘤抗血管生成提供新策略。

2 中药挥发油协同化药治疗脑胶质瘤

由于脑胶质瘤受 BBB 和耐药性的影响，使单一化疗药物疗效有限，中药与化疗药物联用具有提高疗效、避免全身毒性和减小肿瘤耐药性的效果[43,44]。BBB 是

由脑毛细血管内皮细胞之间的紧密连接形成的生理屏障, 它在阻碍有害物质进入脑内的同时也限制了化疗药物递送至中枢神经系统, 因此增强BBB的通透性以促进化疗药物入脑发挥药效至关重要[45]。P糖蛋白(P-glycoprotein, P-gp) 属于ATP结合盒转运蛋白家族, 位于肿瘤细胞表面, 是介导肿瘤耐药的主要蛋白, 能将药物泵出细胞外, 降低细胞内药物浓度使肿瘤产生耐药性, 中药活性成分在P-gp介导的中药化药相互作用中会改变化学药物的疗效、逆转肿瘤多药耐药[46,47]。

引经中药挥发油成分具有引药上行和芳香走窜功效, 可促进化药透过BBB将药物直接运输至病灶和抑制P-gp外排功能提高化疗药物在脑内蓄积, 从而增强抗肿瘤作用。Shuai等[10]在C6胶质瘤原位模型中发现, 川芎挥发油可通过下调紧密连接蛋白-5 (claudin-5) 和闭合蛋白 (occludin) 表达, 促进TMZ透过BBB, 并通过抑制P-gp蛋白增加TMZ在脑和肿瘤中富集。Wu等[11]通过体内研究发现, TMZ和川芎挥发油联合给药能显著抑制肿瘤生长, 且与挥发油剂量呈正相关, 体外机制研究表明川芎挥发油可通过抑制P-gp蛋白表达, 促进TMZ跨膜转运, 增强TMZ在脑和肿瘤中浓度, 从而提高胶质瘤的治疗效果。Wang等[12,48]发现*β*-细辛醚、苏合香挥发油和麝香酮, 可通过降低P-gp、多药耐药基因1的表达, 促进TMZ透过细胞膜同时降低肿瘤细胞的耐药性, 从而增强TMZ治疗胶质瘤的作用。

研究发现, 部分中药挥发油与化疗药物联用具有协同抗肿瘤作用。*β*-榄香烯是温郁金挥发油中主要活性成分, 具有透过BBB和逆转肿瘤多药耐药性的能力。Zhang等[49]通过体外BBB模型发现, *β*-榄香烯具有促TMZ透过BBB的能力。体内实验发现, TMZ与*β*-榄香烯联用能显著抑制胶质瘤生长, 全身毒性小, 且耐受性良好, 提示两药具有协同抗肿瘤作用。Feng等[50]在U87/GSLC肿瘤裸鼠中发现, TMZ和*β*-榄香烯联合治疗对胶质瘤干样细胞抑制作用显著优于TMZ, 表明两药联用具有协同抗肿瘤效果。此外, *β*-榄香烯和吉非替尼联用显著增强了吉非替尼对U251和U87细胞的抑制作用, 其作用机制与下调AKT/ERK信号通路, 诱导caspase-3切割多聚ADP核糖聚合酶, 上调自噬相关蛋白becline1有关[51]。异呋喃二烯 (isofuranodiene, IFD) 是从马芹挥发油中提取的一种倍半萜化合物。Brunetti等[52]体外研究发现, 与单独IFD或TMZ相比, IFD和TMZ联合治疗具有更高的细胞毒性, 表明IFD和TMZ对肿瘤的生长抑制具有协同作用, 其机制可能与胶质瘤细胞DNA损伤有关。胶质纤维酸性蛋白、神经元特异性烯醇化酶和神经纤毛蛋白-1是胶质瘤最重要的肿瘤标志物, 它们在诊断和预后方面具有较高的特异性和敏感性。*β*-细辛醚与TMZ联用能显著降低这些肿瘤标志物, 且较单一药物治疗表现出更好的效果, 具有协同抗肿瘤作用[53]。

中药挥发油协同化药治疗不仅能增强疗效、降低化药的剂量和全身毒副作用, 还具有逆转肿瘤多药耐药作用, 为脑胶质瘤提供新的治疗途径。中药挥发油与化药联合治疗胶质瘤作用机制见表2。

3 中药挥发油治疗脑胶质瘤纳米制剂研究

中药挥发油在肿瘤治疗方面已广泛研究, 但其不稳定性和溶解性差等缺陷限制了其在医药领域的应用[14]。随着技术的不断进步, 纳米制剂的出现为克服这些限制提供了新的可能性。通过将挥发油与脂质纳米载体、纳米粒、自组装前药递药系统和纳米海绵等纳米载体结合或经修饰, 可以提高其稳定性和靶向性, 并实现缓释[54]。

3.1 脂质纳米载体

脂质纳米载体具有毒性低、可降解以及在不破坏BBB前提下将药物递送到脑组织病灶等特点。此外, 经配体修饰的脂质纳米载体可特异性结合BBB或血脑肿瘤屏障 (blood-brain tumor barrier, BBTB) 上高表达的受体, 实现主动靶向胶质瘤, 是胶质瘤药物递送系统常用的纳米制剂[55]。

3.1.1 普通脂质体 脂质体是脂类分子或脂类在水中自发形成的双分子层结构[56]。将挥发油包裹于脂质双分子层结构中可以实现挥发油固化, 以增强其物理稳定性, 提高治疗胶质瘤的效果, 但脂质体半衰期短、载药量较低、制备工艺复杂、储存时易发生药物渗漏和融

Table 2 Anti-glioma mechanism of volatile oil from traditional Chinese medicine combined with chemotherapeutic drugs. TMZ: Temozolomide; IFD: Isofuranodiene

Combined drug	Relevant pathway	Ref.
TMZ: volatile oil of *Ligusticum chuanxiong*	Down-regulated expression of P-gp, claudin-5 and occludin	[10,11]
TMZ: volatile oil of Styrax/Musk	Inhibit P-gp and MDR1express	[12]
TMZ: *β*-asarone	Down-regulated expression of P-gp, MDR1, GFAP, NRP-1, NSE markers for glioma expression	[12,48,53]
TMZ: *β*-elemene	Inhibit the proliferation of GSLC	[50]
Gefitinib: *β*-elemene	Inhibit AKT/ERK signaling pathways; induce caspase-3 and PARP cleavage, up-regulated expression of becline 1 protein	[51]
TMZ: IFD	Induce ROS-dependent DNA damage	[52]

合现象。Detoni等[57]采用薄膜水化法制备花椒精油脂质体, 有效提高了花椒精油的热稳定性, 体外实验表明, 载药脂质体比游离花椒精油更显著降低GL-15细胞活性, 诱导细胞凋亡。

3.1.2 长循环脂质体 长循环脂质体是在脂质体表面修饰亲水性聚合物或糖脂类化合物, 可穿透肿瘤的血管内皮细胞, 以减少单核吞噬细胞系统对脂质体的摄入, 延长药物在血液中循环, 提高药物在体内分布。经聚乙二醇或其衍生物修饰的长循环脂质体, 为其提供较大的空间位阻并掩盖其表面疏水性结合位点, 使脂质体结构更加稳定[58]。但其存在制备复杂、生产成本高等不足。

Kang等[59]采用薄膜水化法, 基于DSPE-PEG2000构建以麝香酮和RI7217小鼠单克隆抗体共修饰的多烯紫杉醇 (docetaxel, DTX) 长循环脂质体 (RI-LP-M-DTX)。麝香酮作为芳香开窍药物可以改变BBB的通透性, 以促进其和其他药物进入大脑[60], 与RI7217协同修饰增强了DTX对U87细胞肿瘤深部区域的穿透和摄取, 促进药物在脑内的吸收, U87原位肿瘤裸鼠模型药效实验结果发现, RI-LP-M-DTX组抗肿瘤效果最佳, 较生理盐水组的中位生存期延长1.6倍, 具有良好的抗肿瘤效果。长循环脂质体能够利用自身结构修饰, 并借助肿瘤的高通透性和滞留效应, 提高挥发油活性成分在肿瘤部位的分布。

3.1.3 仿生纳米脂质体 仿生纳米载体因其具有再现天然材料功能的优势而被广泛开发, 基于肿瘤细胞膜的仿生纳米药物, 具有特异性识别靶部位、靶组织和靶细胞的特性, 可以有效提高药物针对胶质瘤的选择性积累[61]。但仿生纳米药物存在致病风险、载体不稳定且不易控制、难以大规模生产等问题。

Li等[62]采用高速剪切法联合探头超声法, 将共载榄香烯 (elemene, ELE) 和卡巴他赛 (cabazitaxel, CTX) 的复合脂质体 (ELE/CTX@LIP) 与转铁蛋白 (Tf) 缀合形成Tf-ELE/CTX@LIP, Tf可通过抑制P-gp外排, 提高脂质体BBB渗透率, 为进一步提高脂质体的靶向性, 将RG2神经胶质瘤细胞的细胞膜蛋白包埋到脂质体中, 构建活性靶向仿生脂质体 (Tf-ELE/CTX@BLIP)。经细胞膜蛋白修饰的脂质体对RG2细胞摄取率显著高于C6和U251细胞, 且巨噬细胞RAW264.7对其吞噬率最低, 表明仿生脂质体具有显著的同源靶向和免疫逃逸特性。RG2原位胶质瘤裸鼠模型药效实验结果显示, Tf-ELE/CTX@BLIP组的中位生存期较ELE/CTX@BLIP和Tf-ELE/CTX@LIP组高6.5%和10.0%, 表现出显著的抗神经胶质瘤作用。

3.1.4 纳米结构脂质载体 纳米结构脂质载体是由固体和液体脂质混合物组成的脂质基质制成的纳米颗粒[63]。其具有高负载能力、提高药物稳定性、控制药物释放等优点, 但储存过程中易出现结晶和药物泄漏等问题。Dana等[64]采用热高压均质法制备大蒜油纳米结构脂质载体, 与游离大蒜油相比, 大蒜油纳米结构脂质载体显著抑制U87细胞的侵袭和迁移。通过建立体外BBB模型并结合U87细胞, 测定大蒜油和大蒜油纳米结构脂质载体对BBB渗透性和U87细胞活力的影响, 结果显示大蒜油纳米结构脂质载体处理的U87细胞活力为73.8%, 而大蒜油处理后的活力为95.2%, 提示大蒜油纳米结构脂质载体可以有效地穿过BBB, 比游离大蒜油具有更高的治疗效果。Ahmed等[65]采用乳液−低温固化法制备负载紫苏醇纳米结构脂质载体, 细胞增殖实验显示, 紫苏醇纳米结构脂质载体比游离紫苏醇更能显著降低ANGM-CSS和A127细胞的IC_{50}, 具有抑制胶质瘤细胞增殖作用。

3.2 纳米粒

纳米粒具有优异的生物降解性、高稳定性、良好的生物相容性和低毒性, 它可以通过表面改性进一步增强纳米粒的靶向性, 从而延长患者的生存期, 为脑胶质瘤的治疗提供了一种新的前景[66]。

3.2.1 聚合物纳米粒 聚合物纳米粒是由生物可降解的大分子聚合物合成[67]。其具有良好的生物相容性和生物降解性, 但其存在载药量低、粒子易聚集等缺点[68]。壳聚糖是一种天然聚合物, 它的黏附特性使纳米粒能够跨内皮和上皮迁移。Li等[69]合成一种基于壳聚糖的丁香酚纳米粒 (Eu-Cs), 体外研究显示, Eu-Cs能促进酸性细胞器形成, 并下调NF-κB蛋白表达, 从而诱导C6细胞自噬, 且在转化生长因子-β存在下, Eu-Cs能显著降低MMP-9、锌指转录因子、尿激酶型纤溶酶原激活物和VEGF的表达, 发挥抑制胶质瘤转移和诱导细胞凋亡作用。

3.2.2 蛋白纳米粒 基于蛋白的纳米载体因其自身存在丰富的羟基、氨基和羧基适用于化学修饰, 具有可生物降解、易于代谢、毒性低等特点, 但结构变化可能改变天然蛋白质的原始性质, 且存在产率低的问题[70]。Liang等[71]将天然促渗剂麝香酮和薄荷醇修饰牛血清白蛋白纳米粒, 有效地增强纳米粒在脑部积累, 这与纳米粒亲脂性和内吞作用的增加、下调紧密连接蛋白-1 (zonula occludens-1, ZO-1) 和occludin蛋白, 以及通过松果体途径绕过BBB有关。Gao等[72]成功制备了一种负载10-羟基喜树碱的薄荷醇修饰酪蛋白纳米粒 (HCPT-M-CA-NP), 肿瘤球体穿透和体内成像验证了薄荷醇修饰的蛋白纳米粒比未修饰的纳米粒表现出更高的脑肿瘤分布, 在C6原位裸鼠模型药效实验中发

现, 与游离10-羟基喜树碱或HCPT-CA-NP治疗的胶质瘤小鼠相比, 经薄荷醇修饰的纳米粒能显著延长小鼠的中位生存期, 可增强10-羟基喜树碱的抗胶质瘤作用和安全性。因此, 将天然脑渗透剂与蛋白跨膜转运的能力相结合, 能更好地促进纳米粒透过BBB, 使药物安全有效地递送到脑胶质瘤区域, 从而提高治疗效果。

3.3 自组装前药递药系统

自组装前药是将药物通过氢键、π-π堆积和范德华力等非共价键自组装形成的缀合物, 其可增强药物稳定性, 提高药代动力学特性, 降低对组织的非特异性毒性[73]。但自组装前药的设计需考虑药物是否具有合适的反应官能团 (如羟基、胺、羧酸和羰基)、母体药物是否能有效再生而无毒副产物等问题。

Wang等[74]通过醛胺缩合反应合成色胺 (tryptamine, Try)−桂皮醛 (cinnamaldehyde, CA), 采用O/W乳液溶剂蒸发法进一步构建pH响应性小分子纳米前药 (Try-CA-NPs)。由于席夫碱的形成, 使Try-CA-NPs在24 h内的血浆胺氧化酶和H_2O_2中结构保持不变, 有效提高Try-CA血液循环稳定性。体外细胞实验表明, Try-CA-NPs可以通过Try介导的细胞摄取、有效的药物释放、内体逃逸以及Try-CA之间的协同作用, 显著促进SH-SY5Y细胞凋亡。Try-CA-NPs能将CA/Try (1.908、2.587 h)半衰期延长至10.566 h, 且安全性良好。表明Try-CA-NPs比Try/CA能更稳定地保留在血液中, 使其在体内保持高脂溶性以克服BBB在脑内高效蓄积, 且无明显全身毒性, 有利于胶质瘤的治疗。

自组装前药在自组装过程中能够将挥发油锚定在载体或药物分子中的官能团, 以提高药物的稳定性, 并利用肿瘤微环境促进药物释放, 发挥治疗胶质瘤的作用。此外, 将两种药物混合递送可能存在单个抗癌药物生物分布不均匀的缺陷, 而药物−药物缀合的方法可以避免这类问题, 并控制时间和空间双重药物递送。

3.4 纳米海绵

纳米海绵是含有微小空隙和网状网络的胶体海绵状结构, 具有调控药物释放、增强肿瘤摄取等特点[75]。但纳米海绵制备方法复杂、处理困难、制备成本高和潜在的生物衍生污染物。Yapa等[76]设计了一种用于增强紫苏醇递送神经胶质瘤细胞的肽纳米海绵 [(D-POH)10K20]。利用天冬氨酸侧链上的羧基将紫苏醇与肽共价结合, 随后将生物素与肽的N-末端缀合以实现靶向递送。(D-POH)10K20可通过血脑屏障转运至神经胶质瘤细胞, 体外实验显示, K20修饰能增强纳米海绵对GL26细胞摄取, 与游离紫苏醇相比, 紫苏醇肽纳米海绵能有效抑制小鼠神经胶质瘤细胞。

4 展望与挑战

脑胶质瘤具有高度侵袭性和浸润性, 术后复发率高, 使其治疗成为一项巨大的挑战。其难治性受到多种因素的影响, 包括肿瘤的异质性、BBB的存在以及药物耐药性等。目前, 一线抗胶质瘤药物面临靶向性差、毒副作用大和耐药性等问题。中药挥发油具有毒副作用小和易透过BBB的特性, 可通过多种途径诱导胶质瘤细胞死亡, 发挥抗肿瘤作用。此外, 具有引药上行功效的中药挥发油成分, 可以通过改善BBB通透性、抑制P-gp外排以减少药物泵出脑组织或肿瘤, 进而协同化疗药物增强其抗肿瘤效果。因此, 中药挥发油与化疗药物联用可成为抗脑胶质瘤有效途径。纳米递药系统在肿瘤治疗中已有广泛研究, 这些系统通过表面功能化修饰和主动靶向策略等方式, 能够实现良好的挥发油靶向功能, 并增强其稳定性和渗透性, 从而提高抗肿瘤效果。综上, 中药挥发油作为治疗或辅助治疗药物为脑胶质瘤提供一种有效的治疗策略。

中药挥发油在脑胶质瘤治疗中展现出良好的应用前景, 但仍存在若干问题需深入探讨。首先, 挥发油治疗脑胶质瘤的机制研究局限于诱导细胞凋亡、抑制细胞增殖、抗侵袭转移和抗血管生成, 在以后的研究中可从诱导肿瘤自噬与调节肿瘤微环境等方面进行深入探究, 完善对挥发油体内外疗效的评估体系; 其次, 引经中药挥发油不仅能抑制肿瘤生长, 还可作为促渗剂诱导化疗药物和纳米制剂入脑以增强化药疗效, 但目前相关研究有限, 对此应深入剖析中医理论挖掘更多引经挥发油“药辅合一”的双重作用[77], 并结合多学科阐明其机制, 扩大挥发油应用价值。纳米制剂制备工艺较为复杂, 生产成本高昂, 长期储存可能出现药物外漏现象, 使其产业化受到一定限制, 目前挥发油纳米制剂治疗胶质瘤给药方式主要集中于静脉注射或腹腔注射, 较为单一。为推进中药挥发油纳米制剂在脑胶质瘤中的转化应用, 可从挥发油中挖掘更多活性成分并将其转化为药物, 结合不同给药途径如静脉注射和经鼻给药, 开发更多安全、有效、方便的剂型。此外, 挥发油纳米制剂的制备应在提高质量控制的同时综合考虑简化制备工艺、控制成本使其易于产业化, 促进其在脑胶质瘤治疗中的应用。

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