

莪术油化学成分、抗肿瘤作用及制剂研究进展^Δ

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摘要 莪术油是从莪术中提取的挥发油, 化学成分主要以单萜(包括 α -蒎烯、 β -蒎烯等)、倍半萜(包括 β -榄香烯、莪术醇、莪术二酮等)为主, 对卵巢癌、宫颈癌、结直肠癌、肺癌、肝癌等多种恶性肿瘤具有较好的治疗作用。莪术油主要通过调控血管内皮生长因子、核因子 κ B、信号转导及转录激活因子3等信号通路, 发挥抑制肿瘤血管生成、抑制肿瘤细胞增殖、诱导肿瘤细胞凋亡、阻滞细胞周期等作用。目前, 莪术油因难溶于水、稳定性差等缺点限制了其在临床上的应用, 现代制剂研究则采用新技术将其制备成脂质体、微球、微乳/纳米乳等, 从而改善了莪术油的溶解性和稳定性。本文归纳总结了国内外近年来莪术油化学成分、抗肿瘤作用及制剂研究进展, 可为莪术油在抗肿瘤方面的应用及制剂研发提供理论依据。

关键词 莪术油; 化学成分; 抗肿瘤; 制剂

Research progress on the chemical components, anti-tumor effects and preparations of zedoary turmeric oil

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ABSTRACT Zedoary turmeric oil, volatile oil extracted from zedoary turmeric, composed mainly of monoterpenes (including α -pinene, β -pinene, etc.) and sesquiterpenes (including β -elemene, zedoary alcohol, zedoary ketone, etc.), and has been used in clinical practice to treat various malignant tumors such as ovarian cancer, cervical carcinoma, colorectal cancer, lung cancer and liver cancer. Zedoary turmeric oil regulates vascular endothelial growth factor and nuclear factors- κ B, signal transducers and activator of transcription 3 signaling pathways to play a role in inhibiting tumor angiogenesis, inhibiting tumor cell proliferation, inducing tumor cell apoptosis, and blocking cell cycle. However, due to its insolubility in water and poor stability, its clinical application is limited; the application of new formulations and technologies such as liposomes, microspheres, and nanoemulsion improves the solubility and stability of zedoary turmeric oil. This paper summarizes recent research progress on the chemical composition, anti-tumor effects, and formulations of zedoary turmeric oil, both domestically and internationally, providing a reference for further expanding the clinical application and formulation development of zedoary turmeric oil in the anti-tumor field.

KEYWORDS zedoary turmeric oil; chemical components; anti-tumor; preparation

莪术是姜科植物蓬莪术 *Curcuma phaeocaulis* VaL.、广西莪术 *C. kwangsiensis* S. G. Lee et C. F. Liang 或温郁金 *C. wenyujin* Y. H. Chen et C. Ling 的干燥根茎, 始载于

唐代《药性论》, 亦被载于《新修本草》《开宝本草》《本草图经》等后世书籍。莪术性温、味苦、辛, 归肝、脾二经, 具有行气破血、消积止痛的功效, 可用于癥瘕痞块、瘀血经闭、胸痹心痛、食积胀痛等症的治疗, 对鼻咽癌、食管癌、肝癌等多种肿瘤类疾病具有良好疗效^[1]。莪术油是莪术干燥根茎经水蒸气蒸馏提取的挥发油, 其中 β -榄香烯^[2]、莪术醇^[3]、吉马酮^[4]等萜类化学成分已被证实具有显著的抗肿瘤活性, 这些成分可能是莪术油发挥抗肿瘤作用的主要物质基础。

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莪术油具有难溶于水、稳定性差、生物利用度低等缺点,使其临床应用受限。目前,临床上使用的莪术油剂型以注射液为主,但远不能满足临床用药需求,且不良反应发生率较高^[5]。近年来,随着脂质体、微球、微囊等制剂新技术的出现,莪术油的溶解性、稳定性得以改善,刺激性有所降低,这将有助于减少莪术油的不良反应,并促进其在抗肿瘤方面的临床应用。基于此,本文从莪术油化学成分、抗肿瘤作用及制剂研究3个方面出发,对国内外近年来相关文献进行综述,以期对莪术油在抗肿瘤方面的应用及制剂研发提供理论依据。

1 莪术油的化学成分

莪术油是一种淡黄色至棕色、具有特殊芳香气味的挥发油,相对密度为0.987 0,折光率为1.509,比旋度为+24.146 8^[6]。莪术油的提取方法主要包括水蒸气蒸馏提取法(steam distillation method, SD)、CO₂超临界流体萃取法(CO₂ supercritical fluid extraction, SFE-CO₂)、索氏提取法、压榨提取法、微波提取法等。其中,SD法、SFE-CO₂法为常用的提取方法,但SD法受热温度高,可能会导致莪术油中的某些化学成分发生分解;SFE-CO₂法可保证莪术油化学成分的完整性,相比于SD法提取能力更强、效率更高,莪术油得率为2.99%~3.08%^[7-8]。

莪术油中主要含有萜类化合物,包括单萜及倍半萜类,其中单萜类成分有 α -蒎烯、 β -蒎烯、 α -松油烯、 β -罗勒烯等,倍半萜类成分有 β -榄香烯、莪术醇、莪术二酮、呋喃二烯、吉马酮等;现代研究发现,倍半萜类成分具有显著的抗肿瘤药理作用^[2,4,9-10]。相关研究发现,莪术油中的化学成分与莪术基原存在一定关联,如温郁金挥发油中莪术二酮的含量比其他基原中莪术二酮的含量高;蓬莪术挥发油中不含莪术二酮;桂莪术挥发油中 β -榄香烯含量较高,而莪术酮和莪术醇含量甚微^[7,11]。莪术油中萜类成分常含有双键、环等不饱和结构,可在光照、氧气、温度等环境因素的影响下,发生氧化、分解、异构化、光环加成反应,从而导致莪术油理化性质、有效成分种类及含量发生变化,进而降低莪术油药效作用,甚至引发毒副作用^[12-13]。因此,应在贮存、运输及使用过程中通过避光、控制环境含氧量和温度等方式提高莪术油的稳定性。

2 莪术油的抗肿瘤作用

莪术油对卵巢癌、宫颈癌、结直肠癌、肺癌、肝癌等多种恶性肿瘤均具有较好的治疗作用,主要通过调控血管内皮生长因子(vascular endothelial growth factor, VEGF)、核因子 κ B(nuclear factor κ B, NF- κ B)、信号转导及转录激活因子3(signal transducer and activator of transcription 3, STAT-3)等信号通路发挥抗肿瘤作用。

2.1 卵巢癌

卵巢癌的主要治疗手段为手术治疗联合铂类药物化疗,其中化疗耐药是影响卵巢癌患者治疗效果的主要原因之一^[14]。研究发现,莪术油可通过抑制卵巢癌SKOV3细胞荷瘤小鼠肿瘤组织中VEGF-A、STAT-3、雷帕霉素靶蛋白的表达来抑制卵巢癌细胞增殖,从而改善卵巢癌细胞的药物敏感性^[15]。同时,莪术油可通过减少肿瘤生长相关因子肿瘤转移抑制基因NM23、增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)及炎症相关因子NF- κ B p65、肿瘤坏死因子 α 的表达来抑制肿瘤细胞的增殖及转移,从而提高机体免疫力并降低细胞耐药性^[16]。此外,莪术油与紫杉醇联合应用,可通过将细胞阻滞于G₂/M期、上调胱天蛋白酶3(caspase-3)表达诱导细胞凋亡,增加卵巢癌细胞对紫杉醇的敏感性,从而发挥减毒增效、协同抗肿瘤的作用^[17]。

2.2 宫颈癌

宫颈癌是常见的生殖系统恶性肿瘤。相关研究发现,莪术油可将宫颈癌HeLa细胞阻滞在G₁期而抑制其增殖^[18],还可将宫颈癌CASKI细胞阻滞于G₂/M期而抑制其增殖^[19]。莪术油作用机制主要包括抑制蛋白酪氨酸磷酸酶/磷脂酰肌醇3-激酶/蛋白激酶B(protein kinase B, AKT)/NF- κ B信号通路活性^[20],从而诱导肿瘤细胞凋亡,以及上调人类白细胞抗原I、抗原肽转运蛋白1等表达,增强宫颈癌细胞表面的抗原呈递作用,从而阻止肿瘤细胞免疫逃逸^[21]。

2.3 结直肠癌

现代研究表明,莪术油的抗结直肠癌作用可能与诱导结直肠癌细胞凋亡^[22]、抑制肿瘤血管生成^[23]有关。体外研究表明,莪术油可显著抑制人结肠癌HCT 116细胞增殖,其作用机制可能与促进细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)磷酸化,上调ERK下游核内磷酸化蛋白p53、细胞周期依赖性蛋白激酶抑制因子2A(cyclin-dependent kinase inhibitor 2A, CDKN2A)、CDKN1A表达有关^[24]。莪术油对直肠癌SW1463细胞也具有较好的增殖抑制作用,其半数抑制浓度(IC₅₀)达120.04 mg/L,可通过上调caspase-3表达、降低抑凋亡蛋白B细胞淋巴瘤2(B-cell lymphoma-2, Bcl-2)与促凋亡蛋白Bcl-2相关X蛋白(Bcl-2-associated X protein, Bax)比例,从而诱导SW1463细胞凋亡^[25]。此外,莪术油还可通过上调直肠癌SW1463细胞中CXC趋化因子受体3(CXC chemokine receptor 3, CXCR-3)蛋白表达、下调白细胞介素8和CXCR-2蛋白表达,从而抑制肿瘤血管形成,进而抑制直肠癌细胞增殖^[26]。

2.4 肺癌

肺癌的治疗手段有化疗、放疗、手术治疗、免疫治疗、生物治疗等,但这些治疗存在不良反应明显、耐药性普遍等问题^[27]。动物实验研究表明,莪术油可明显降低Lewis肺癌荷瘤小鼠的瘤体质量,其作用效果与阳性对照药5-氟尿嘧啶相当,具体作用机制与降低细胞PCNA指数、升高视网膜母细胞瘤蛋白标记指数有关^[28]。莪术油对非小细胞肺癌细胞系H1299、A549、H23的生长具有抑制作用,IC₅₀分别为80.0、80.0、185.0 μg/mL,其主要通过抑制ERK1/2磷酸化,促进c-Jun氨基末端激酶1/2、p38丝裂原活化蛋白激酶表达,抑制AKT/NF-κB信号通路活性,诱导肺癌细胞凋亡^[29]。此外,相关研究发现,莪术油(100 μg/mL)可抑制肺腺癌A549细胞的增殖、迁移,阻滞细胞周期,且作用效果与卡铂注射液(25 μg/mL)相当^[27]。

2.5 肝癌

肝癌在我国肿瘤类疾病中发病率居第4位,但其死亡率居全国第2位^[30]。临床研究表明,莪术油肝动脉灌注栓塞治疗可明显延长原发性肝癌患者的平均生存期、中位生存期,提高其1年生存率^[31],对继发性肝癌也有效且毒性较低^[32]。动物实验证实,莪术油明胶微球对移植性肝癌模型大鼠的平均肿瘤生长抑制率为94.5%,且其可明显延长大鼠生存时间^[33-34]。体外研究表明,莪术油可将肝癌HepG2细胞阻滞于G₂期,并抑制其增殖^[35],其作用机制与抑制肝癌细胞中腺苷三磷酸合成酶活性和纤维蛋白原基因表达有关^[36]。

2.6 其他

除上述几种恶性肿瘤外,莪术油还对子宫内膜癌、胃腺癌、骨肉瘤具有显著的药理活性,其可通过上调Bax蛋白表达,下调Bcl-2蛋白表达,诱导胃腺癌和子宫内膜癌细胞凋亡^[37-38];可通过下调胰岛素样生长因子1及其下游AKT、Bcl-2蛋白表达,抑制骨肉瘤细胞增殖^[39]。

3 莪术油制剂的研究进展

目前,临床莪术油制剂以注射液为主。近年来,随着研究者对莪术油抗肿瘤作用的广泛关注,莪术油脂质体、微球、微乳/纳米乳等新剂型在肿瘤方面的应用研究也日渐深入。

3.1 脂质体

脂质体是以脂质双分子层包裹药物的新型药物递送系统,具有高生物相容性、低毒性,可延缓药物释放及降解,实现药物靶向递送^[40]。有研究者以环糊精包合技术结合脂质体技术制得莪术油包合物复合磷脂脂质体,其包封率为58.57%,平均粒径为212.6 nm,抑瘤率为59.42%(远高于同剂量莪术油的抑瘤率17.90%),表明莪

术油包合物复合磷脂脂质体可显著提高药物的抗肿瘤效果^[41]。

3.2 微乳/纳米乳

莪术油可以通过制备成微乳、纳米乳来增加其分散性,从而提高其溶解度、稳定性,降低刺激性,增强抗肿瘤作用。有研究采用相转换法制备以4.0%吐温-80与甘油为乳化剂的莪术油纳米乳液,所得乳液的含油量为1.2%,平均粒径为65.64 nm, Zeta电位为13.8 mV,具有良好的物理稳定性^[42]。王华华等^[43]采用星点设计-效应面法优化莪术油纳米乳的处方工艺,结果以最优工艺制得的莪术油纳米乳载药量为(7.99 ± 0.01)%、包封率为(98.48 ± 0.06)%、平均粒径为29.21 nm、平均Zeta电位为-0.447 mV;该纳米乳澄清透明、稳定性好,对肝癌细胞SMMC-7721的增殖抑制作用较同浓度的莪术油更强,且具有浓度和时间依赖性。

3.3 微球

微球是以天然或合成高分子材料包载药物的实心球体。相较于常规的莪术油自乳化制剂,微球具有提高挥发油生物利用率、延缓挥发油体内释放等优点^[44]。目前,莪术油微球的制备方法主要为溶剂蒸发法^[45]。邓嵘等^[46]制备了莪术油明胶微球,该微球的粒径范围为40~160 μm, Zeta电位为-27.36 mV,载药量为(2.13 ± 1.56)%、包封率为(19.36 ± 1.78)%、稳定性良好,且对肝癌细胞具有明显的抑制作用。另有研究采用溶剂蒸发法制备了莪术油壳聚糖微球,其粒径范围为62~135 μm, Zeta电位为(-25.6 ± 0.7) mV,包封率为(88.6 ± 5.4)%、载药量为(15.1 ± 1.8)%、可显著抑制肝肿瘤组织生长,延长荷瘤小鼠存活时间,且作用效果较同剂量莪术油注射液更佳^[47]。有研究团队通过乳化交联法制备了平均载药量为9.45%、包封率为32.34%的莪术油明胶微球,并在此基础上加入丝裂霉素制备成复方莪术油微球;进一步研究发现,该复方莪术油微球可通过下调肝肿瘤组织中PCNA表达、上调caspase-3表达,抑制肝癌细胞增殖,促进肝癌细胞凋亡^[48]。

3.4 注射液

莪术油目前已被开发成莪术油注射液,该注射液常被用于辅助治疗早期卵巢癌患者,可减轻常规化疗所产生的不良反应^[49]。如莪术油注射液联合顺铂+多西他赛可提高晚期非小细胞肺癌患者的治疗总有效率,延长患者生存期,且不增加不良反应^[50]。相关研究发现,莪术油注射液联用CAP化疗方案治疗早期高危子宫内膜癌有助于提高近期疗效,改善患者生活质量^[51]。值得注意的是,临床上莪术油注射液偶尔会引发以过敏性反应为主的皮肤泛红、呼吸困难、心悸、恶心等不良反应,发生

率为0.2%~0.3%,这些不良反应的发生可能与该制剂易受环境影响发生氧化分解、增溶剂吐温-80本身的致敏性、联用其他药物出现“破乳”现象等有关^[52-53],因此,应从制剂、储存、临床应用等多个环节严格把关莪术油注射液的质量,以减少不良反应的发生。

3.5 栓剂

栓剂在临床上常用于治疗妇科疾病,其给药方便且可避免肝脏首过效应,提高药物生物利用度,具有保护药效成分、减轻药物刺激性等优点^[54]。有研究表明,莪术油栓可通过减少宫颈癌患者体内细胞周期调节蛋白p16、肿瘤抑制蛋白p53、增殖细胞核抗原蛋白Ki67表达,抑制宫颈癌细胞活性,从而发挥治疗作用^[55]。

4 结语

莪术油对卵巢癌、宫颈癌、结直肠癌、肝癌、肺癌、子宫内膜癌等多种恶性肿瘤均具有较好的治疗作用,其抗肿瘤物质基础主要为 β -榄香烯、莪术醇、莪术二酮、呋喃二烯、吉马酮等倍半萜类成分,发挥抗肿瘤的作用机制主要通过调节VEGF、STAT-3、NF- κ B等信号通路,发挥抑制肿瘤血管生成、抑制肿瘤细胞增殖、诱导肿瘤细胞凋亡、阻滞细胞周期等作用。

目前市面上常见的莪术油制剂主要为注射液、栓剂等,其中注射液起效快,栓剂携带方便还可避免首过效应。现代制剂研究采用新技术将莪术油制备成脂质体、微乳/纳米乳、微球等,改善了莪术油的溶解性和稳定性,但是这些制剂目前尚处于实验室研究阶段,载油量不高、制备工艺较为复杂。未来研究者可从提高莪术油载油量、简化制备工艺方面进行深入研究,开发出新型莪术油抗肿瘤制剂,以期抗肿瘤制剂的开发提供参考。

参考文献

[1] 韩拓,冯嘉润,周彦婷,等. 基于数据挖掘的中药药对抗肿瘤成方规律分析[J]. 食品与药品, 2023, 25(2): 132-138.
HAN T, FENG J R, ZHOU Y T, et al. Analysis of prescription regularity of herb pairs for anti-tumor treatment based on data mining[J]. Food Drug, 2023, 25 (2) : 132-138.

[2] JIANG Z Y, JACOB J A, LOGANATHACHETTI D S, et al. β -elemene: mechanistic studies on cancer cell interaction and its chemosensitization effect[J]. Front Pharmacol, 2017, 8: 105.

[3] ZHANG J D, SU G, TANG Z W, et al. Curcumol exerts anticancer effect in cholangiocarcinoma cells via down-regulating CDKL3[J]. Front Physiol, 2018, 9: 234.

[4] 李冰,周平,靳义. 吉马酮对人非小细胞肺癌NCI-H1770细胞增殖、凋亡、侵袭和迁移的调节作用[J]. 中国免疫学

杂志, 2019, 35(7): 819-823.

LI B, ZHOU P, JIN Y. Effects of germacrone on proliferation, apoptosis, invasion and migration of human non-small cell lung cancer NCI-H1770 cells[J]. Chin J Immunol, 2019, 35(7): 819-823.

[5] 常虹,吴世福,李玉基,等. 737例莪术油注射液不良反应分析及文献回顾[J]. 中国药物警戒, 2017, 14(6): 359-363.
CHANG H, WU S F, LI Y J, et al. Analysis of 737 reports of adverse drug reactions induced by zedoray turmeric oil injection and literature review[J]. Chin J Pharmacovigil, 2017, 14(6): 359-363.

[6] 廖彬汛,唐超,于晓亮,等. 黔产莪术油的品质分析[J]. 广西植物, 2018, 38(4): 475-481.
LIAO B X, TANG C, YU X L, et al. Quality analysis on Guizhou zedoary turmeric oil[J]. Guihaia, 2018, 38 (4) : 475-481.

[7] 史克莉. 不同品种莪术挥发油成分GC-MS分析[J]. 湖北中医学院学报, 2009, 11(4): 29-31.
SHI K L. GC-MS analysis on ingredients in volatile oil in Rhizoma Curcumae of different varieties[J]. J Hubei Univ Chin Med, 2009, 11(4): 29-31.

[8] 邓丽梅,史克莉. 温莪术挥发油的最佳提取工艺研究[J]. 湖北中医药大学学报, 2011, 13(2): 37-39.
DENG L M, SHI K L. Optimizing extraction process of essential oil from *Curcuma aromatica* salisb[J]. J Hubei Univ Chin Med, 2011, 13(2): 37-39.

[9] TANG Q L, GUO J Q, WANG Q Y, et al. Curcumol induces apoptosis in SPC-A-1 human lung adenocarcinoma cells and displays anti-neoplastic effects in tumor bearing mice[J]. Asian Pac J Cancer Prev, 2015, 16 (6) : 2307-2312.

[10] 孙学然,杨克,吕玲玲,等. 莪术二酮对乳腺癌HCC1937细胞迁移和侵袭的影响及机制[J]. 中国实验方剂学杂志, 2019, 25(3): 66-73.
SUN X R, YANG K, LYU L L, et al. Effect and mechanism of curdione on migration and invasion of breast cancer HCC1937 cells[J]. Chin J Exp Tradit Med Formulae, 2019, 25(3): 66-73.

[11] 袁文娟,高文分,田颂九,等. 不同产地莪术挥发油气相色谱-质谱联用分析[J]. 中国药师, 2011, 14(11): 1578-1581.
YUAN W J, GAO W F, TIAN S J, et al. Comparison analysis of volatile oil in Rhizome Curcumae from different habitats by GC-MS[J]. China Pharm, 2011, 14(11): 1578-1581.

[12] ZUO Z J, WERADUWAGE S M, LANTZ A T, et al. Iso-

- prene acts as a signaling molecule in gene networks important for stress responses and plant growth[J]. *Plant Physiol*, 2019, 180(1):124-152.
- [13] 吴意, 万娜, 刘阳, 等. 中药挥发油稳定性影响因素、变化机制及保护策略[J]. *中草药*, 2022, 53(21):6900-6908.
WU Y, WAN N, LIU Y, et al. Influencing factors, changing mechanisms and protection strategies of volatile oil from traditional Chinese medicine[J]. *Chin Tradit Herb Drugs*, 2022, 53(21):6900-6908.
- [14] 唐茂艳, 丁丹妮, 解娅娅, 等. 中药抑制卵巢癌血管生成的作用机制研究进展[J]. *中国中药杂志*, 2023, 48(24):6572-6581.
TANG M Y, DING D N, XIE Y Y, et al. Advances in mechanism of traditional Chinese medicine in inhibiting angiogenesis in ovarian cancer[J]. *China J Chin Mater Med*, 2023, 48(24):6572-6581.
- [15] 曹知勇, 陈静芹, 吕挺, 等. 莪术油对卵巢癌 VEGFA, STAT3, mTOR 的调控机制[J]. *中国实验方剂学杂志*, 2021, 27(14):70-80.
CAO Z Y, CHEN J Q, LYU T, et al. Regulatory mechanism of zedoary turmeric oil on VEGFA, STAT3 and mTOR in ovarian cancer[J]. *Chin J Exp Tradit Med Formulae*, 2021, 27(14):70-80.
- [16] 陈仲波, 邢洁, 朱笕青, 等. 莪术油对卵巢癌裸鼠移植瘤的抑制作用及其联合顺铂的协同作用研究[J]. *中国现代应用药学*, 2019, 36(12):1462-1467.
CHEN Z B, XING J, ZHU J Q, et al. Antitumor effect and synergistic effect with cisplatin of zedoary turmeric oil on nude mice bearing ovarian cancer[J]. *Chin J Mod Appl Pharm*, 2019, 36(12):1462-1467.
- [17] ZHOU Y X, SHEN J, XIA L Q, et al. *Curcuma zedoaria* (Berg.) Rosc. essential oil and paclitaxel synergistically enhance the apoptosis of SKOV3 cells[J]. *Mol Med Rep*, 2015, 12(1):1253-1257.
- [18] 马培志, 李虎, 闫静静, 等. 莪术油注射液对宫颈癌细胞株 Hela 增殖及 Wnt/ β -catenin 信号通路的影响[J]. *中国医院药学杂志*, 2019, 39(6):577-579, 640.
MA P Z, LI H, YAN J J, et al. Effect of zedoary turmeric oil injection on the proliferation of cervical cancer cell line Hela and Wnt/ β -catenin signaling[J]. *Chin J Hosp Pharm*, 2019, 39(6):577-579, 640.
- [19] LIU Y, CHE L F, ZHAO G Z, et al. Effect of Rhizoma *Curcumae* oil on proliferation of human cervical carcinoma CASKI cells[J]. *Biomed Res Tokyo*, 2015, 26:807-810.
- [20] LIM C B, KY N, NG H M, et al. *Curcuma wenyujin* extract induces apoptosis and inhibits proliferation of human cervical cancer cells *in vitro* and *in vivo*[J]. *Integr Cancer Ther*, 2010, 9(1):36-49.
- [21] 贾静, 李云波, 王群. 莪术油影响宫颈癌细胞 MHC- I 类抗原呈递相关基因表达水平的实验研究[J]. *中国中西医结合杂志*, 2018, 38(11):1344-1349.
JIA J, LI Y B, WANG Q. Effect of zedoary turmeric oil on the expressions of MHC- I antigen presentation pathway associated genes in cervical cancer cells[J]. *Chin J Integr Tradit West Med*, 2018, 38(11):1344-1349.
- [22] 许政旭, 朱诗国, 潘年松, 等. 黔产莪术油对直肠癌 SW1463 细胞株分泌 Toll 样受体及相关免疫因子的影响[J]. *中国实验方剂学杂志*, 2018, 24(5):137-141.
XU Z X, ZHU S G, PAN N S, et al. Effect of Guizhou zedoary oil on toll like receptor and related immune factors in SW1463 cell line[J]. *Chin J Exp Tradit Med Formulae*, 2018, 24(5):137-141.
- [23] FENG Y W, DENG L, GUO H R, et al. The anti-colon cancer effects of essential oil of *Curcuma phaeocaulis* through tumour vessel normalisation[J]. *Front Oncol*, 2021, 11:728464.
- [24] SU M Q, ZHOU Y R, LI C Q, et al. Zedoary turmeric oil induces senescence and apoptosis in human colon cancer HCT116 cells[J]. *Nat Prod Commun*, 2018, 13(7):1934578X1801300.
- [25] 廖彬汛, 唐超, 潘年松, 等. 莪术油对直肠癌 SW1463 细胞株增殖、凋亡及 caspase-3、Bax、Bcl-2 蛋白表达的影响[J]. *药物评价研究*, 2017, 40(7):897-903.
LIAO B X, TANG C, PAN N S, et al. Effects of zedoary turmeric oil on cell proliferation and apoptosis and caspase-3, Bax, Bcl-2 protein expression in rectal carcinoma cell line SW1463[J]. *Drug Eval Res*, 2017, 40(7):897-903.
- [26] 朱诗国, 许政旭, 罗俊, 等. 黔产莪术油对人直肠癌细胞血管生成因子表达的影响[J]. *中国实验方剂学杂志*, 2017, 23(4):152-158.
ZHU S G, XU Z X, LUO J, et al. Effect of zedoary turmeric oil from Guizhou on expression of angiogenesis factors in human colorectal cancer SW1463 cells[J]. *Chin J Exp Tradit Med Formulae*, 2017, 23(4):152-158.
- [27] 袁文珺, 赵小梅, 杨志军, 等. 莪术油对人肺腺癌 A549 细胞增殖、迁移及细胞周期的影响[J]. *中药新药与临床药理*, 2020, 31(11):1312-1317.
YUAN W J, ZHAO X M, YANG Z J, et al. Effect of doary turmeric oil on the proliferation, migration and cell cycle of human lung adenocarcinoma A549 cells *in vitro* [J]. *Tradit Chin Drug Res Clin Pharmacol*, 2020, 31(11):1312-1317.

- [28] 汪伟民,汪波,刘荣玉,等. 中药莪术油对小鼠 Lewis 肺癌抑制作用的实验研究[J]. 中国中医药科技, 2003, 10(6):353-354.
WANG W M, WANG B, LIU R Y, et al. Experimental study on the inhibitory effect of zedoary turmeric oil on Lewis lung cancer in mice[J]. Chin J Tradit Med Sci Technol, 2003, 10(6):353-354.
- [29] CHEN C C, CHEN Y, HSI Y T, et al. Chemical constituents and anticancer activity of *Curcuma zedoaria* Roscoe essential oil against non-small cell lung carcinoma cells *in vitro* and *in vivo*[J]. J Agric Food Chem, 2013, 61(47):11418-11427.
- [30] ZHENG R S, QU C F, ZHANG S W, et al. Liver cancer incidence and mortality in China: temporal trends and projections to 2030[J]. Chung Kuo Yen Cheng Yen Chiu, 2018, 30(6):571-579.
- [31] 程剑华,常纲,吴万垠,等. 莪术油和化疗药对照肝动脉灌注栓塞治疗原发性肝癌的临床研究[J]. 中国中西医结合杂志, 2001, 21(3):165-167.
CHENG J H, CHANG G, WU W Y, et al. A controlled clinical study between hepatic arterial infusion with embolized *Curcuma* aromatic oil and chemical drugs in treating primary liver cancer[J]. Chin J Integr Tradit West Med, 2001, 21(3):165-167.
- [32] 陈春永,徐凯,朱迪盈,等. 莪术油肝动脉灌注栓塞治疗继发性肝癌 28 例疗效观察[J]. 新中医, 2003, 35(3):23-24.
CHEN C Y, XU K, ZHU D Y, et al. Treatment of secondary hepatocarcinoma by hepatic artery perfusion embolism of oleum curcumae: a clinical observation of 28 cases [J]. N J Tradit Chin Med, 2003, 35(3):23-24.
- [33] 邓嵘,陈济民,吴万垠. 肝动脉灌注莪术油明胶微球对荷瘤大鼠的抗癌活性[J]. 沈阳药科大学学报, 2000, 17(3):197-199.
DENG R, CHEN J M, WU W Y. The anti-tumor activity of zedoary turmeric oil gelatin microspheres for hepatic arterial embolization[J]. J Shenyang Pharm Univ, 2000, 17(3):197-199.
- [34] 吴万垠,邓嵘,区勇全,等. 经肝动脉灌注莪术油微球对大鼠移植性肝癌的治疗作用[J]. 中华肝脏病杂志, 2000, 8(1):24-26.
WU W Y, DENG R, OU Y Q, et al. Therapeutic efficacy of microsphere-entrapped *Curcuma aromatica* oil infused via hepatic artery against transplanted hepatoma in rats[J]. Chin J Hepatol, 2000, 8(1):24-26.
- [35] 王佳丽,王秀,夏泉,等. 莪术油中 3 种倍半萜类化合物对肝癌 HepG2 细胞增殖抑制作用的研究[J]. 中成药, 2014, 36(7):1535-1539.
WANG J L, WANG X, XIA Q, et al. Inhibitory effect of three sesquiterpenes in zedoary turmeric oil on the proliferation of hepatocellular carcinoma HepG2 cells[J]. Chin Tradit Pat Med, 2014, 36(7):1535-1539.
- [36] 王顺启,陈力,倪虹,等. 莪术油对肝癌细胞 SMMC-7721 基因表达的影响[J]. 食品科学, 2009, 30(19):240-243.
WANG S Q, CHEN L, NI H, et al. Effects of Turmeric Rhizome naphtha on gene expression of hepatocarcinoma cell SMMC-7721[J]. Food Sci, 2009, 30(19):240-243.
- [37] 李玲玲,邵淑丽,孙宏岩,等. 莪术油诱导人胃腺癌 SGC-7901 细胞凋亡的研究[J]. 中国细胞生物学学报, 2015, 37(9):1235-1241.
LI L L, SHAO S L, SUN H Y, et al. Research of zedoary turmeric oil induced apoptosis of human gastric carcinoma SGC-7901 cells[J]. Chin J Cell Biol, 2015, 37(9):1235-1241.
- [38] 李伟宏,田莉,刘俊保. 莪术油对子宫内腺癌 HEC-1-B 细胞增殖、凋亡及 Caspase-3、Bax、Bcl-2 蛋白表达的影响[J]. 河南中医, 2021, 41(3):384-387.
LI W H, TIAN L, LIU J B. The effects of zedoary turmeric oil on proliferation and apoptosis and expressions of Caspase-3 and Bax and Bcl-2 in HEC-1-B[J]. Henan Tradit Chin Med, 2021, 41(3):384-387.
- [39] 朱福良,刘金洋,黄凤香. 莪术油对骨肉瘤 saos-2 细胞 IGF-1R、Akt 及 Bcl-2 表达的影响[J]. 中国实验方剂学杂志, 2015, 21(17):126-128.
ZHU F L, LIU J Y, HUANG F X. Inhibition of IGF-1R, Akt and Bcl-2 by Curcumae Rhizoma oil on human osteosarcoma saos-2 cells[J]. Chin J Exp Tradit Med Formulae, 2015, 21(17):126-128.
- [40] LIU P, CHEN G L, ZHANG J C. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives[J]. Molecules, 2022, 27(4):1372.
- [41] 杨希雄,顾薇,万芳,等. 不同磷脂组成莪术油包合物脂质体的抗肿瘤作用比较[J]. 中国医院药学杂志, 2013, 33(5):362-365.
YANG X X, GU W, WAN F, et al. Comparison of antitumor activities of zedoary turmeric oil cyclodextrin complex liposomes with different lipid composition[J]. Chin J Hosp Pharm, 2013, 33(5):362-365.
- [42] WANG X W, GU Y X, HE Y P, et al. Preparation and optimization formulation of zedoary turmeric oil nanoemulsion based thermo-sensitive gel for improved application in ophthalmology[J]. J Drug Deliv Sci Technol, 2021, 65:102682.

- [43] 王华华,陈家琦,直炜炜,等. 星点设计-效应面法优化莪术油纳米乳的处方工艺及其体外抗肿瘤活性研究[J]. 中国药师,2022,25(4):566-572.
WANG H H, CHEN J Q, ZHI W W, et al. Preparation technology optimization of zedoary turmeric oil nano-emulsion by central composite design-response surface methodology and its antitumor activity *in vitro*[J]. China Pharm,2022,25(4):566-572.
- [44] YOU J, CUI F D, HAN X, et al. Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion-solvent-diffusion method and evaluation of the self-emulsification and bioavailability of the oil[J]. Colloids Surf B Biointerfaces, 2006, 48(1): 35-41.
- [45] SONG T, SUN R Y. Pharmacodynamics study of zedoary turmeric oil chitosan microspheres administered via arterial embolization[J]. Artif Cells Nanomed Biotechnol, 2016,44(8):1958-1963.
- [46] 邓嵘,陈济民,姚崇舜,等. 莪术油明胶微球用于肝动脉栓塞[J]. 药学学报,2000,35(7):539-543.
DENG R, CHEN J M, YAO C S, et al. Zedoary turmeric oil gelatin microspheres for hepatic arterial embolization [J]. Acta Pharm Sin,2000,35(7):539-543.
- [47] 张兴德,郁红礼,周玲玲,等. 正交法筛选莪术油微球制备工艺[J]. 南京中医药大学学报,2007,23(5):304-306.
ZHANG X D, YU H L, ZHOU L L, et al. Orthogonal method for screening preparation technique for oleum curcumae wenchowensis microballoon[J]. J Nanjing Univ Tradit Chin Med,2007,23(5):304-306.
- [48] 周玲玲,袁冬平,张兴德,等. 复方莪术油微球肝动脉栓塞治疗大鼠移植性肝癌的机制[J]. 中国老年学杂志, 2014,34(16):4575-4576.
ZHOU L L, YUAN D P, ZHANG X D, et al. Mechanism of hepatic artery embolization with compound zedoary turmeric oil microspheres in the treatment of transplanted liver cancer in rats[J]. Chin J Gerontol, 2014, 34(16): 4575-4576.
- [49] 梁丹,杨美春,林忠,等. 莪术油注射液配合常规化疗对早期卵巢癌患者生活质量的影响[J]. 疑难病杂志,2014, 13(5):448-450.
LIANG D, YANG M C, LIN Z, et al. The effects of zedoary turmeric oil injection combined with conventional chemotherapy on life quality of the patients with early stage ovarian cancer[J]. Chin J Difficult Complicat Cases,2014, 13(5):448-450.
- [50] 李平球,柯怀. 莪术油联合顺铂与多西他赛治疗晚期非小细胞肺癌的效果分析[J]. 中国社区医师,2023,39(11):77-79.
LI P Q, KE H. Effect analysis of zedoary turmeric oil combined with cisplatin and docetaxel in treatment of advanced non-small cell lung cancer[J]. Chin Community Dr,2023,39(11):77-79.
- [51] 赵卫群. 早期高危子宫内膜癌行CAP化疗方案联合莪术油注射液治疗的近期疗效及对患者生活质量的影响[J]. 吉林医学,2019,40(9):2020-2021.
ZHAO W Q. Short-term efficacy and quality of life of patients with early high-risk endometrial cancer treated with CAP chemotherapy combined with zedoary turmeric oil injection[J]. Jilin Med J,2019,40(9):2020-2021.
- [52] 王云庭,李春英,易艳,等. 注射用与药用聚氧乙烯脱水山梨醇单油酸酯(吐温-80)类过敏反应比较研究[J]. 中国中药杂志,2012,37(13):1890-1893.
WANG Y T, LI C Y, YI Y, et al. Comparative study on pseudoanaphylactoid reactions induced by medicinal tween 80 and injectable tween 80[J]. China J Chin Mater Med,2012,37(13):1890-1893.
- [53] 李心怡,武玉卓,杨基举,等. 基于真实世界数据的莪术油注射液临床用药特征分析[J]. 中国新药杂志,2023,32(5):547-552.
LI X Y, WU Y Z, YANG J J, et al. Analysis of clinical medication characteristics of zedoary turmeric oil injection based on real world data[J]. Chin J N Drugs,2023,32(5):547-552.
- [54] MELNYK G, YARNYKH T, HERASYMOVA I. Analytical review of the modern range of suppository bases[J]. Syst Rev Pharm,2020,11(4):503-508.
- [55] 辛德梅,何艳舫,夏凤艳,等. 莪术油对CIN组织中Ki67、P16、P53蛋白表达的影响[J]. 中国妇幼保健, 2013,28(24):4043-4044.
XIN D M, HE Y F, XIA F Y, et al. Effect of zedoary oil on immunity-related transcription factor in CIN tissue[J]. Matern Child Health Care China, 2013, 28(24): 4043-4044.

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