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中药单体抗乳腺癌作用机制进展

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【摘要】 乳腺癌是女性常见的恶性肿瘤,中药对其有较好的治疗作用。通过梳理相关文献,从化合物属性(黄酮类、萜类、生物碱类、其他)角度归纳整理中药单体抗乳腺癌的作用机制,以期为中医药治疗乳腺癌的研究工作及新药的研发提供参考。中药单体抗乳腺癌的主要机制涉及细胞毒性的直接杀伤作用,调节肿瘤免疫微环境,增强靶向药物治疗敏感性及辅助放射治疗、化学疗法等方面。部分中药单体的生物毒性、成药性等问题亟待解决,具有开发潜力的中药单体作用机制、衍生物开发、药代动力学、给药方式、用药安全性等研究数据亦有待补充。

【关键词】 乳腺癌;中药单体;中医药疗法;黄酮;生物碱;多糖;抗肿瘤

Research progress on mechanism of anti-breast cancer action of Chinese herbal monomers

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Abstract: Breast cancer is a common malignant tumor in women, and the therapeutic effects of traditional Chinese herbal medicines (TCHMs) are satisfactory. By reviewing relevant literature, we summarized the mechanism of action of Chinese herbal monomers against breast cancer in terms of compound properties (flavonoids, terpenoids, alkaloids and others), with the aim of providing a reference for the research on traditional Chinese medicine for breast cancer treatment and the development of new drugs. The main mechanisms of Chinese herbal monomers against breast cancer mainly involve direct cytotoxicity, regulation of the tumor immune microenvironment, increasing sensitivity to targeted drug therapy, and suppor radiotherapy and chemotherapy. Some issues, such as the biological toxicity and developability of certain Chinese herbal monomers, need to be addressed. Research data on the mechanisms of action, development of derivatives, pharmacokinetics, administration methods, and drug safety of Chinese herbal monomers with development potential also need to be supplemented.

Keywords: breast cancer; Chinese herbal monomer; traditional Chinese medicine therapy; flavonoids; alkaloids; polysaccharides; antitumor

根据肿瘤分子标志物的表达,在乳腺癌的诊断中将其分为雌激素受体/孕激素受体阳性乳腺癌(HR+)、人表皮生长因子受体2阳性乳腺癌(HER2+;HER又称ErbB)、三阴性乳腺癌3种亚型,且有充分证据表明相较于HR+和HER2+乳腺癌,三阴性乳腺癌的预后更差、总生存期更短[1]。在乳腺癌的临床治疗手段中(除手术治疗外),HR+的乳腺癌主要采用化学疗法(简称"化疗")及内分泌药物进行治疗;HER2+的乳腺癌在分子靶向治疗中取得了较大的成功,如以曲妥珠单抗为代表的单克隆抗体治疗以及小分子赖氨酸激酶抑制剂等;三阴性乳腺癌则依旧采取传统化疗的方式进行治疗。[1]在上述主流治疗策略的基础上,临床还常采用辅助治疗手段来增强治疗效果、减轻相应的毒副作用。

据统计,1981年至2019年美国食品药品监督管理局(FDA)批准的247种抗癌药物中,有18种来自天然产物,有44种为天然产物衍生物[2]。中药治疗疾病已有3 000多年的历史,中医学在2 000多年前就有关于肿瘤的记载。在如今的乳腺癌治疗中,中医药依旧发挥着重要作用。但中药的作用成分复杂,有些药物成分毒性尚不明确,临床又常采用多味药组合的形式,因此阻碍了现代中药的抗肿瘤机制研究。青蒿素的发现及研究为中药的现代研究提供了思路,因此近年来中药单体的抗肿瘤研究也日益丰富。我们通过梳理国内外相关文献,从化合物属性角度归纳整理中药单体抗乳腺癌的作用机制,以期为中医药治疗乳腺癌的研究

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工作及新药的研发提供参考。

1 黄酮类

黄酮类化合物是生物活性较为广泛的中药单体成分，具有抗炎、抗氧化、抗肿瘤等药理作用，常见的黄酮类单体有槲皮素、芹菜素、表没食子儿茶素没食子酸酯（EGCG）、木犀草素、刺芒柄花素、黄芩素等。黄酮类化合物具有低毒或无毒的特性，在常见的水果蔬菜中含量极为丰富，这为其应用提供了便利。

槲皮素可通过调节含半胱氨酸的天冬氨酸蛋白水解酶（Caspase）-3 诱导乳腺癌细胞凋亡，并有逆转乳腺癌细胞耐药（阿霉素）的作用[3-4]。芹菜素可通过直接抑制磷脂酰肌醇 3-激酶（PI3K）活性、阻止 P13K 与 HER2/人表皮生长因子受体 3（HER3）二聚体的分子对接而抑制蛋白激酶 B（AKT）的磷酸化，其对 HER2 自体磷酸化和转磷酸化亦有抑制作用[5]。绿茶中的黄酮类化合物 EGCG 不仅可以提高耐药后乳腺癌细胞的药物敏感性，还可以通过抑制 ErbB 家族蛋白的自身磷酸化作用，调节丝裂原活化蛋白激酶（MAPK）、AKT、哺乳动物雷帕霉素靶蛋白（mTOR）等信号通路，诱导细胞凋亡等途径抑制乳腺癌细胞生长[6]。木犀草素可以通过靶向多分子影响乳腺癌细胞的增殖、凋亡及细胞周期，从而起到化学预防和治疗作用，但其生物利用度较低[7]。

多种肿瘤组织和细胞中有芳香烃受体（AhR）的表达，AhR 介导了 *CYP1A1* 基因的转录激活，这可能与肿瘤的发生有关。槲皮素、山柰酚、黄酮醇、高良姜素等均可以阻断 AhR，进而影响 *CYP1A1* 的表达[8-9]。刺芒柄花素是一种天然植物类雌激素，与雌激素药物相比，其诱发乳腺癌的风险比较低，因此具有代替雌激素药物进行乳腺癌内分泌治疗的潜能[10]。乳腺癌细胞在传统放射治疗（简称“放疗”）、化疗后的耐药现象会严重影响治疗效果，有研究[11]认为肿瘤干细胞（CSC）的自我更新能力是导致药物治疗耐药和癌症复发的重要原因，中药单体黄芩素、小豆蔻明等具有抑制 CSC 富集的作用[12-13]。

黄酮类中药单体抗乳腺癌的效应及主要机制见表 1。

表 1 黄酮类中药单体抗乳腺癌的效应及主要机制

中药单体	来源	研究对象	效应	主要机制	参考文献
槲皮素	黄芪、紫花地丁等	MCF-7、MDA-MB-231	诱导 M 期、G2 期阻滞，诱导凋亡；逆转阿霉素耐药	Caspase-3/8/9 ↑、Bax/Bcl-2 ↑、AIF ↑；细胞周期蛋白 B1 ↑、Cdc2 ↑，p21CIP1/WAF1 ↑	[3-4, 14]
芹菜素	车前子、络石藤、洋甘菊等	HER2+细胞、MCF-7	抑制增殖、逆转抗雌激素药物耐药	HER2 蛋白 ↓、HER2 下游信号 ↓；ERα ↓、p38 ↓、PKA ↓，MAPK 和 AKT 通路信号 ↓	[5, 15]
鹰嘴豆芽素 A	红车轴草	MCF-7、SK-BR-3	在体内抑制 ER+乳腺癌肿瘤生长；抑制 HER2+细胞增殖	pHER2 ↓、ERK1/2 ↓、AKT ↓、mTOR ↓	[16-17]
白杨素	木蝴蝶种子	MDA-MB-231	抑制增殖、迁移	MMP10 ↓、EMT ↓，PI3K/AKT 通路信号 ↓	[18]
EGCG	绿茶	MDA-MB-231、BT474、MCF-7/BOS	增强化学疗法作用；增强曲妥珠单抗药物敏感性；对雌激素诱发的乳腺细胞的癌变有预防作用	NF-κB ↓、EGFR ↓、VEGF ↓、MAPK ↓、AKT ↓、β-catenin ↓	[6, 19-20]
非瑟酮	木蜡树	4T1、MCF7、MDA-MB-231	诱导 Caspase 依赖性凋亡、抑制细胞保护性自噬功能	Caspase-7/8/9 ↑、PARP 的裂解、p53 ↑；PI3K/ AKT/ mTOR 通路信号 ↓	[21-23]
橙皮素	枳壳	MCF-7、SK-BR-3、MDA-MB-231	诱导 G1 期阻滞，诱导凋亡；诱导细胞死亡	ROS ↑，ASK1/JNK 通路信号 ↑；HER2 酪氨酸激酶抑制剂；Caspase-9/3 ↑、Bax/Bcl-2 ↑	[24-26]
山柰酚	银杏叶、金钱草等	MDA-MB-231、MCF-7	抑制增殖，诱导细胞周期阻滞、凋亡、DNA 损伤；体内、外抑制肿瘤生长	γH2AX ↑、Caspase-3/9 ↑、p-ATM ↑；Cyclin D1/E ↑、组织蛋白酶 D ↑、p21 ↓、Bax ↓、pIRS-1 ↓、pAKT ↓、pMEK1/2 ↓	[27-28]
木犀草素	金银花、夏枯草等	MDA-MB-231、MCF-7	与顺铂发挥协同作用、增强紫衫醇诱导的细胞凋亡；诱导 G1 期的细胞周期阻滞、诱导凋亡	调控 Nrf2-ARE 信号，STAT3 信号 ↓；Notch 通路信号 ↓；死亡受体（如 DR5）↑、Caspase 家族蛋白 ↑、线粒体膜电位瓦解、细胞色素 c ↑，Bcl-2/Bax ↑	[29-32]
桑色素	桑叶、无花果等	MDA-MB-231	抑制高转移性、诱导周期阻滞	EMT ↓ 和 AKT 通路信号 ↓，ERK ↑、p21 ↑，FOXM1 通路信号 ↓	[33-34]
杨梅素	杨梅	MDA-MB-231	抑制转移；对细胞杀伤	MMPs ↓；胞外 H_2O_2 ↑，引发氧化应激，诱发胞内芬顿反应，ROS ↑	[35-36]
柚皮素	枳实	MCF-7、4T1/RFP	抑制细胞增殖、代谢	AKT 和 MAPK 通路信号 ↓，胰岛素刺激下的葡萄糖摄取 ↓；PKC ↓，阻止 TGF-β1 从反式高尔基网络运输，TGF-β1 ↓	[37-38]
柚皮苷	陈皮等	MDA-MB-231	促进凋亡、G1 期阻滞	p21 ↑、survivin ↓、β-catenin 通路信号 ↓	[39]

表1（续）

中药单体	来源	研究对象	效应	主要机制	参考文献
根皮素	苹果	MDA-MB-231、MCF-10A	诱导凋亡	2型葡萄糖转运体信号↓，对葡萄糖的摄取↓；JNK↑、p38↑、Caspase-3↑	［40-41］
水飞蓟素	水飞蓟	MDA-MB-468、MDA-MB-231、MCF-7	诱导G1期阻滞；诱导凋亡	Cip1/p21↓；MAPK通路信号↓	［42-43］
甘草查尔酮A	甘草	MDA-MB-231、MCF-7	诱导凋亡、促进自噬	ROS↓，MAPK/AKT通路信号↓；SP1↓；PI3K/AKT/mTOR通路信号↓	［44-46］
黄腐酚	啤酒花	MCF-7、4T1	恢复对阿霉素和放射治疗的敏感性；抑制肿瘤生长	BIG3-PHB2↓，ERα信号↓；肿瘤中心坏死，炎症细胞数↓，局灶增殖面积↓，凋亡细胞百分比↑，微血管密度↓；调控Th1/Th2的平衡；Notch通路信号↓	［47-51］
异鼠李素	沙棘	多种乳腺癌细胞	抑制增殖、迁移	AKT和MEK通路信号↓；MMP2/9↓	［52-53］
高良姜素	高良姜	MCF-7	诱导细胞凋亡	*CYP1A1*↓，芳香烃受体的激动剂/拮抗剂；PI3K/AKT通路信号↓，Caspase-3/8/9↑、p21/27/53↑、细胞周期蛋白D3/B1↑、CDK1/2/4↑	［9,54］
花青素类	多类水果、蔬菜、花卉	MCF-7荷瘤小鼠、HER2+细胞	抑制增殖、转移；原花青素逆转曲妥珠单抗耐药	pHER2↓；RAS/RAF/MAPK通路信号↓	［55-57］
刺芒柄花素	红车轴草	MCF-7、MDA-MB-231、4T1	诱导G0/G1期阻滞；与二甲双胍具有协同作用	IGF1/IGF1R-PI3K/AKT通路信号↓，细胞周期蛋白D1↓；PI3K/AKT通路信号↓，MMP2/9表达↓	［58-60］
鸢尾黄素	射干、鸢尾	MDA-MB-231、MCF-7	抑制细胞增殖、诱导Caspase依赖凋亡	AKT和MAPK通路信号↓，Caspase家族蛋白↑	［61］
槐黄烷酮G	苦参	MDA-MB-231	诱导线粒体途径凋亡、抑制增殖	MAPK通路信号↓；EGFR/P13K/AKT通路信号↓	［62-63］
木蝴蝶苷A	木蝴蝶	MDA-MB-231、MCF-7	诱导G2/M期阻滞、内质网应激介导的细胞衰老	ROS↑，内质网应激↑，*ATF4*和*GRP78*基因表达↑，p38↑	［64］
黄芩素	黄芩	MDA-MB-231	体内、外有诱导凋亡和自噬的作用；使耐药细胞恢复敏感性	MMP2/9表达↓、MAPK通路信号↓；*SATB1*↓、*vimentin*↓、*SNAIL*↓、*E-cadherin*↑、*Wnt/β-catenin*↓；P13K/AKT通路信号↓；IFIT2的表达↓、干细胞样特征↓	［12,65-67］
鱼藤素	西非灰毛豆	MDA-MB-231、SK-BR-3、MDA-MB-468、MCF-7	抑制增殖、诱导凋亡	调节Wnt通路信号；EGFR相关通路信号↓；survivin和XIAP的表达↓；IGF-1R↓、IGFBP-3↑	［68-71］
小豆蔻明	草豆蔻	MDA-MB-231、MCF-7、SUM190	抑制增殖、诱导G2/M阻滞和凋亡；选择性抑制化学疗法药物富集的乳腺耐药干细胞	mTOR/p70S6K通路信号↓，HIF-1α通路信号↓，葡萄糖代谢摄入↓；JNK-FOXO3a通路信号↑；IL-6↓、IL-8↓、MCP-1↓、NF-κB/IKBα↑、STAT3↑	［13,72-73］
染料木素	大豆	多种乳腺癌细胞	诱导G2/M期阻滞；抑制增殖；调控细胞内多种基因的甲基化	雌激素和生长因子刺激信号↓；AKT介导的NF-κB通路活性↓	［74-76］

注：MCF-7为雌激素受体阳性（ER+）人乳腺癌细胞系，MDA-MB-231、MDA-MB-468为三阴性乳腺癌细胞系，SK-BR-3为表皮生长因子受体2阳性（HER2+）人乳腺腺癌细胞系，4T1为小鼠乳腺癌细胞。EGCG为表没食子儿茶素没食子酸酯。Caspase为含半胱氨酸的天冬氨酸蛋白水解酶，Bax为B淋巴细胞瘤-2相关X蛋白，Bcl-2为B淋巴细胞瘤-2蛋白，AIF为细胞凋亡诱导因子，Cdc2为细胞分裂周期蛋白2，p21CIP1/WAF1是由肿瘤抑制因子p53调节的周期蛋白依赖性激酶（CDK）抑制剂，PKA为蛋白激酶A，MAPK为丝裂原活化蛋白激酶，AKT为蛋白激酶B，PI3K为磷脂酰肌醇3-激酶，ERK为细胞外调节蛋白激酶，MMP为金属基质蛋白酶，EMT为上皮间质转化，NF-κB为核因子-κB，EGFR（HER1）为表皮生长因子受体，VEGF为血管内皮生长因子，β-catenin为β-连环蛋白，PARP为聚腺苷二磷酸核糖聚合酶，ROS为活性氧，ASK1为细胞凋亡信号调节激酶1，JNK为c-Jun氨基末端激酶，γH2AX为H2A组蛋白家族成员X的蛋白磷酸化形式，ATM为一种丝氨酸/苏氨酸蛋白激酶，Cyclin D1/E为细胞周期蛋白D1/E，pIRS-1为磷酸化胰岛素受体-1，MEK1/2为丝裂原活化蛋白1/2，Nrf2为核因子NF-E2相关因子，ARE为抗氧化反应元件，STAT为信号转导和转录激活蛋白，Notch为神经源性位点缺口同源蛋白，FOXM1为叉头框蛋白M1，PKC为蛋白酶C，TGF-β1为转化生长因子-β1，survivin为存活蛋白，Cip1为周期素依赖激酶相互作用蛋白1，SP1为特异性蛋白1，BIG3为布雷菲尔丁A抑制鸟嘌呤核苷酸交换蛋白3，PHB2为抗增殖蛋白2，ERα为雌激素受体α，Th为辅助性T细胞，IGF为胰岛素样生长因子，IGFR为胰岛素样生长因子受体，IFIT2为干扰素诱导的三角形四肽重复蛋白2，XIAP为X连锁凋亡抑制蛋白，IGFBP为胰岛素样生长因子结合蛋白，p70S6K为p70核糖体蛋白S6激酶，IL为白介素，MCP-1为人巨噬细胞趋化蛋白-1，IKBα为核因子-κB抑制蛋白α。↑表示表达增加/激活，↓表示表达减少/抑制。多种乳腺癌细胞表示超过5种且3种类型乳腺癌细胞均包含。

2 萜类

萜类化合物是在中药中存在最多的化合物成分，可分为单萜、倍半萜、二萜、三萜、四萜、多萜等类型，具有抗炎、抗肿瘤、抗菌、抗病毒、抗疟、降血糖、防治心脑血管疾病等生物活性[77]，常见的萜类化合物有冬凌草甲素、青蒿素、桦木酸、雷公藤甲素、毛喉素等。

冬凌草中的冬凌草甲素具有抗前列腺癌、乳腺癌、

非小细胞型肺癌等肿瘤的作用[78-79]，其不仅可以诱导凋亡和自噬相关蛋白表达，抑制增殖和转移信号通路的激活[80]，还具有逆转氟维司群化疗耐药性的潜力[81]。

青蒿素可以延缓或预防口服致癌物7，12-二甲基苯蒽（DMBA）诱导大鼠乳腺癌的发生[82]，对组蛋白去乙酰化酶（HDACs）也有抑制作用[83]。桦木酸是一个非常有潜力的抗肿瘤中药单体，对乳腺癌细胞具有较强的细胞毒性，可调控基因及激酶的表达、调节免疫微环境，但其水溶性较差，因此桦木酸衍生物的开发研究具有一定的潜力[84-88]。

雷公藤与白花蛇舌草、半边莲配伍可用于治疗乳腺癌[89]。雷公藤甲素可以调控鼠双微粒体基因2（*MDM2*）或p53蛋白表达，进而在体内、外发挥抑制乳腺癌的作用，且对雌激素受体α阳性（ERα+）乳腺癌细胞更加敏感[90-91]。3′5′-环腺苷酸（cAMP）可通过蛋白激酶A（PKA）依赖或不依赖的方式影响细胞基因表达、增殖、分化、凋亡等功能，且与其他信号通路相互作用，如细胞外调节蛋白激酶通路[92]。研究[93]发现，毛喉素可以直接激活腺苷酸环化酶，使腺苷酸环化酶从ATP生成cAMP，从而提高细胞内cAMP水平，抑制ERK1/2信号通路，增加乳腺癌细胞对阿霉素的敏感性。

萜类中药单体抗乳腺癌的效应及主要机制见表2、表3、表4。

表2 萜类（单萜、倍半萜）中药单体抗乳腺癌的效应及主要机制

中药单体	来源	研究对象	效应	主要机制	参考文献
芍药苷	芍药	MDA-MB-231、MCF-7	增强他莫西芬敏感性；抑制增殖、迁移	Notch-1通路信号↓；FOXO1/Cyclin D1/β-catenin轴，microRNA-15b↓；PI3K/AKT通路信号↓，HIF-1α表达↓，EMT↓	[94-96]
青蒿素	青蒿	T41体内、外，MCF-7、BT474	提高免疫功能、降低肿瘤免疫逃逸；阻断细胞雌激素刺激；抑制增殖	Treg和MDSC细胞数量↓，T-bet↑、IFN-γ↑、*TNF-α* mRNA↑、*TGF-β* mRNA↓、$CD4^+$T细胞活化↑；ERα表达水平↓；HER2↓、survivin↓、c-MYC↓	[97-99]
莪术醇	莪术	MDA-MB-231、4T1	增强阿霉素敏感性；抑制迁移；诱导*p53*突变细胞凋亡	调控miR-181b-2-3p-ABCC3轴；JNK1/2↓AKT↓，NF-κB通路信号↓，MMP9↓；p73↑、PUMA↑；与eEF1A1表达有相关性	[100-103]

注：MCF-7为雌激素受体阳性（ER+）人乳腺癌细胞系，MDA-MB-231为三阴性乳腺癌细胞系，BT474为表皮生长因子受体2阳性（HER2+）人乳腺腺癌细胞系，4T1为小鼠乳腺癌细胞。Notch为神经源性位点缺口同源蛋白，FOXO1为叉头状转录因子O1，Cyclin D1为细胞周期蛋白D1，β-catenin为β-连环蛋白，microRNA-15b为微小核糖核酸15b，AKT为蛋白激酶B，PI3K为磷脂酰肌醇3-激酶，HIF-1α为缺氧诱导因子-1α，EMT为上皮间质转化，Treg为调节性T细胞，MDSC为髓源性抑制细胞，T-bet为T细胞特异性转录因子，IFN-γ为γ干扰素，TNF为肿瘤坏死因子，ERα为雌激素受体α，survivin为存活蛋白，c-MYC为c-髓细胞瘤原癌基因产物，ABCC3为ATP结合盒转运蛋白C3，JNK为c-Jun氨基末端激酶，NF-κB为核因子-κB，MMP为金属基质蛋白酶，PUMA为p53上调凋亡因子，eEF1A1为真核细胞延伸因子1A1。↑表示表达增加/激活，↓表示表达减少/抑制。

表3 萜类（二萜）中药单体抗乳腺癌的效应及主要机制

中药单体	来源	研究对象	效应	主要机制	参考文献
冬凌草甲素	冬凌草	MDA-MB-231、4T1、MCF-7	诱导自噬和凋亡；抑制增殖、肿瘤生长	ERK↓、JNK↑、p38↑；MMPs表达↓，整合素β1/FAK通路信号↓；Notch通路信号↓；EMT↓，HIF-1α/VEGF通路信号↓	[80，104-106]
蓝萼甲素	香茶菜	MCF-7、Hs578T、MDA-MB-231	诱导G2/M期阻滞、凋亡，抑制增殖	JNK通路信号↑，FasL↑；p53表达↑，调控组蛋白甲基化；PI3K/AKT通路信号↓	[107-109]
雷公藤甲素	雷公藤	MCF-7、BT-474、MDA-MB-231、MDA-MB-468	体内、外均有较强的细胞毒性作用；诱导自噬、凋亡	Wnt/β-catenin通路信号↓；与ERα相关，ERα和p53蛋白的表达有关；靶向HMGB1；干扰MDM2与REST的相互作用，AKT↓；p38/ERK/mTOR通路信号↓	[90-91，110-113]
穿心莲内酯	穿心莲	MDA-MB-231、MCF-7、T47D、MDA-MB-361、BT549	诱导凋亡；抑制肿瘤生长和血管生成；抑制增殖	p53↑、Bax/Bcl-2↑、Caspase-3↑；P300-HAT通路信号↓，COX-2表达↓，VEGF通路信号↓；HIF-1α↓，诱导P13K/AKT通路信号↓	[114-116]
毛萼乙素	毛萼香茶菜	MDA-MB-231、MCF-7、4T1	诱导自噬、凋亡	AKT/mTOR/p70S6K通路信号↓；与ATP结合位点的相互作用，VEGF↓，VEGFR-2及下游通路信号↓；NF-κB↓，p65↓、STAT3↓、Bax/Bcl-2↑、MMP↑、Caspase-3↑	[117-119]
毛喉素	毛猴鞘蕊花	MDA-MB-231	增强对阿霉素的敏感性	cAMP/PKA通路信号↓，ERK1/2↓	[93]
鼠尾草酚	迷迭香	MDA-MB-231	诱导细胞G2期阻滞、beclin1非依赖性自噬和凋亡	$p21^{WAF1}$↑，p27↓；靶向STAT3诱导ROS依赖性蛋白酶体降解，STAT3通路信号↓	[120-121]

表3（续）

中药单体	来源	研究对象	效应	主要机制	参考文献
鼠尾草酸	迷迭香	MCF-7、T47D、SK-BR-3、BT474	与姜黄素、莫昔芬、曲妥珠单抗有协同作用；诱导Caspase-3/TRAIL依赖凋亡	抗氧化基因、凋亡基因表达↑；细胞周期基因、转录抑制因子基因表达↓	［122-124］

注：MCF-7为雌激素受体阳性（ER+）人乳腺癌细胞系，MDA-MB-231、MDA-MB-468、BT549为三阴性乳腺癌细胞系，4T1为小鼠乳腺癌细胞，SK-BR-3为表皮生长因子受体2阳性（HER2+）人乳腺腺癌细胞系，T47D为人乳腺管癌细胞系。ERK为细胞外调节蛋白激酶，JNK为c-Jun氨基末端激酶，MMP为金属基质蛋白酶，FAK为局部粘着斑激酶，Notch为神经源性位点缺口同源蛋白，EMT为上皮间质转化，HIF-1α为缺氧诱导因子-1α，VEGF为血管内皮生长因子，VEGFR为血管内皮生长因子受体，FasL为凋亡相关因子（Fas）受体，AKT为蛋白激酶B，PI3K为磷脂酰肌醇3-激酶，Wnt/β-catenin为Wnt/β-连环蛋白，HMGB1为高迁移率族蛋白B1，MDM2为鼠双微粒体基因2，REST为抑制因子-1沉默转录因子，mTOR为哺乳动物雷帕霉素靶蛋白，Bax为B淋巴细胞瘤-2相关X蛋白，Bcl-2为B淋巴细胞瘤-2蛋白，Caspase为含半胱氨酸的天冬氨酸蛋白水解酶，P300为高度同源的腺病毒E1A相关的300 kDa蛋白，HAT为组蛋白乙酰转移酶，COX-2为环氧合酶-2，HIF-1α为缺氧诱导因子-1α，p70S6K为p70核糖体蛋白S6激酶，ATP为腺嘌呤核苷三磷酸，NF-κB为核因子-κB，STAT为信号转导和转录激活蛋白，cAMP为环腺苷酸，PKA为蛋白激酶A，$p21^{WAF1}$为细胞周期调控蛋白，ROS为活性氧。↑表示表达增加/激活，↓表示表达减少/抑制。

表4　萜类（三萜、四萜）中药单体抗乳腺癌的效应及主要机制

中药单体	来源	研究对象	效应	主要机制	参考文献
桦木酸	黄芪、白芍、桦树皮	MDA-MB-231、MCF-7、4T1、MCF-10A	诱导凋亡、与紫衫醇有协同作用；抑制增殖、迁移；抑制有氧糖酵解	调控microRNA-27a-ZBTB10-Sp轴，VEGFR↓；靶向GRP78；STAT3↓、FAK↓，MMPs↓及其抑制剂TIMP-2↑，免疫微环境中MDSCs数量↓；调控Cav-1/NF-κB/c-MYC通路	［84-87］
常青藤皂苷元	铁线莲、续断	MDA-MB-231、MCF-7	诱导凋亡	线粒体Apaf 1↓，细胞色素c蛋白↓；Caspase-3/9活性↑	［125］
柴胡皂苷	柴胡	MDA-MB-231、MCF-7	抑制增殖；抑制侵袭、迁移；逆转阿霉素耐药	CXCR4相关通路信号；调节Th1/Th2的平衡（柴胡皂苷A）；STAT3通路信号↓，VASP↓，MMP2/9↓（柴胡皂苷b2）；靶向β-catenin信号通路（柴胡皂苷D）	［126-130］
人参皂苷	人参	MDA-MB-231、MCF-7	诱导凋亡、自噬、抑制转移和血管生成、免疫调节、诱导周期阻滞、降低多药耐药、增强放射治疗和化学疗法敏感性、诱导遗传毒性	p21↑和Cyclin D1↑，E2F释放↓；诱导免疫应答和肿瘤发生相关基因的甲基化变化，增强免疫原性（人参皂苷Rh2）；结合和激活雌激素受体（人参皂苷Rb1）；NF-κB通路信号↓，Bax/Bcl-2↑、p53↑、ERK↓、AKT↓（人参皂苷Rg3）	［131-133］
熊果酸	女贞子、夏枯草等	MMTV-Wnt-1小鼠、DA-MB-231、MCF-7	抑制增殖；诱导线粒体途径凋亡，调节糖皮质激素受体和激活蛋白-1的能力	PI3K/AKT和MAPK细胞通路信号↓；FoxM1↓，调控CyclinD1/CDK4；Bcl-2↓、多聚（ADP-核糖）聚合酶裂解；Keap1/Nrf2通路信号↓，EGFR/Nrf2通路信号↓	［134-137］
羽扇豆醇	羽扇豆、鹅不食草等	MDA-MB-231、MCF-7	诱导凋亡；与阿霉素具有协同作用	Bcl-2↓、Bcl-xL↓；刺激转录因子诱导三阴性乳腺癌雌激素受体的表达↑	［138-140］
雷公藤红素	雷公藤	MDA-MB-231、MCF-7、SK-BR-3、BT-474 BT-20、MCF-10A	抑制迁移、诱导线粒体途径凋亡、诱导DNA损伤；与曲妥珠单抗和拉帕提尼具有较强的协同作用；降低炎症反应	NF-κB通路信号↓，介导MMP9↓；PI3K/AKT/mTOR、AKT/GSK3β和AKT/NF-κB通路信号↓；ErbB2及相关通路信号↓；IL-1β↓	［141-144］
泽泻醇	泽泻	MDA-MB-231	诱导自噬、G0/G1期阻滞、凋亡、增殖	NF-κB和PI3K/AKT/mTOR通路信号↓、MMP2/9↓（泽泻醇A）；Caspase蛋白↑、p38↑、p65↓，AKT/mTOR通路信号↓（泽泻醇B）	［145-146］
番茄红素	番茄、胡萝卜等	MDA-MB-468、MDA-MB-231、MCF-7	乳腺癌化学预防作用；细胞周期阻滞	调控启动子甲基化调控基因表达；ERK1/2↑、cyclin D1↓、P12↑，AKT-mTOR通路信号↓	［147-148］

注：MCF-7为雌激素受体阳性（ER+）人乳腺癌细胞系，MDA-MB-231、MDA-MB-468为三阴性乳腺癌细胞系，4T1为小鼠乳腺癌细胞，SK-BR-3、BT474为表皮生长因子受体2阳性（HER2+）人乳腺腺癌细胞系，MCF-10A为人正常乳腺上皮细胞，MMTV-Wnt-1小鼠为卵巢切除C57BL/6小鼠皮下移植来自同基因Wnt-1转基因小鼠的乳腺肿瘤细胞小鼠。microRNA-27a为微RNA-27a，ZBTB10为锌指蛋白，Sp为特异性蛋白，VEGFR为血管内皮生长因子受体，STAT为信号转导和转录激活蛋白，FAK为局部粘着斑激酶，MMP为金属基质蛋白酶，TIMP-2为血清组织金属蛋白酶抑制剂-2，MDSCs为为髓源性抑制细胞，Cav-1为小窝蛋白-1，NF-κB为核因子-κB，c-MYC为细胞髓细胞瘤，Apaf 1为凋亡蛋白酶活化因子1，Caspase为含半胱氨酸的天冬氨酸蛋白水解酶，CXCR4为趋化因子受体4，Th为辅助性T细胞，VASP为血管扩张刺激磷蛋白，β-catenin为β-连环蛋白，Cyclin D1为细胞周期蛋白D1，E2F为转录因子，ERK为细胞外调节蛋白激酶，AKT为蛋白激酶B，PI3K为磷脂酰肌醇3-激酶，MAPK为丝裂原活化蛋白激酶，FOXM1为叉头框蛋白M1，CDK为周期蛋白依赖性激酶，Keap1/Nrf2为Kelch样ECH相关蛋白1-核因子E2相关因子2，Bax为B淋巴细胞瘤-2相关X蛋白，Bcl-2为B淋巴细胞瘤-2蛋白，mTOR为哺乳动物雷帕霉素靶蛋白，GSK3β为糖原合成酶激酶3β，ErbB2为人表皮生长因子受体2，IL为白介素。↑表示表达增加/激活，↓表示表达减少/抑制。

3 生物碱类

生物碱类化合物是在中药提取物中发现的一类含氮碱性的有机化合物，其药理作用得到了广泛关注和研究，但此类化合物具有一定的生物毒性，因此其结构改造是药物研究中的重点。在恶性肿瘤的临床一线治疗药物中，生物碱类药物表现出良好的抗癌活性，如长春碱、长春新碱及其衍生物长春地辛、长春瑞滨，又如DNA拓扑异构酶抑制剂喜树碱类药物-羟基喜树碱、拓扑替康、伊立替康。

小檗碱又称黄连素，是从黄连属中药黄连、黄柏中提取的一种异喹啉生物碱，其抗乳腺癌的作用机制主要涉及调节活性氧水平影响乳腺癌细胞代谢、通过Caspase依赖和非依赖途径诱导凋亡及激活Fas受体、通过与DNA和mRNA直接结合形成复合物抑制细胞增殖、抑制HER2激活介导细胞信号通路的活性、抑制p53介导的细胞增殖活性、调控转录因子和基因转录调控因子的激活、靶向microRNAs影响mRNA的翻译等[149]。低剂量小檗碱在腺苷5'-单磷酸激活的蛋白激酶（AMPK）信号通路中依赖于缺氧诱导因子-1α（HIF-1α）发挥抑制作用，高剂量小檗碱则可以直接诱导AMPK介导的细胞凋亡[150]。

汉防己碱可以通过调控PI3K/AKT/mTOR通路抑制增殖、调节Caspase-3和B淋巴细胞瘤-2相关X蛋白/B淋巴细胞瘤-2蛋白（Bcl-2/Bax）表达比率诱导细胞凋亡、增加自噬受体蛋白1（p62/SQSTM1）表达诱导细胞自噬等途径对三阴性乳腺癌细胞起到抑制作用[151-152]，其与亚砷酸盐有协同作用[153-154]。一项晚期非小细胞肺癌的临床研究[155]结果显示，使用汉防己联合化疗的患者近期疗效明显，且不良反应较少，提示汉防己碱具有从临床前到临床研究及应用的潜力。

莒芰明宁碱有望成为信号转导和转录激活蛋白（STAT）3的天然抑制剂[156]，对3种乳腺癌亚型均有抑制作用。其可通过抑制PI3K/AKT/mTOR信号通路诱导细胞凋亡，增强多西他赛的细胞毒性作用和口服生物利用度，进而发挥抗肿瘤（三阴性乳腺癌）作用[157]；还可以通过调节活性氧（ROS）的累积，调控相关基因和蛋白的表达，进而起到诱导细胞凋亡、抑制细胞增殖的作用（HER2+和HR+乳腺癌）[158-160]。

生物碱类中药单体抗乳腺癌的效应及主要机制见表5。

表5 生物碱类中药单体抗乳腺癌的效应及主要机制

中药单体	来源	研究对象	效应	主要机制	参考文献
小檗碱	黄连、黄柏等	MDA-MB-231、MCF-7、SK-BR-3、BT474	诱导线粒体和Caspase依赖途径凋亡；增强紫衫醇、阿霉素和拉帕替尼的敏感性	MMP2/9↓，AKT通路信号↓；AMPK-HIF-1α-P-gp轴（低剂量），AMPK-p53通路（高剂量）；HER2/PI3K/AKT通路信号↓，ROS水平↑	[150，161-164]
川芎嗪	川芎	MDA-MB-231、MCF-7、T47D	诱导凋亡、降低黏附；增强蒽环类药物敏感性	Bcl-2/Bax↓；抑制JAK2/STAT3通路信号↓，FGG↓	[165-166]
胡椒碱	黑胡椒、莒芰	MDA-MB-231、MCF-7、SKBR3、BT-474	诱导G2期阻滞、Caspase依赖途径凋亡；增强紫衫醇敏感性	pAKT↓、MMP2/9↓；HER2↓、ERK1/2、p38 MAPK和AKT通路信号↓，EGF诱导的MMP9↓	[167-168]
苦豆碱	苦豆子	MDA-MB-231、MCF-7	诱导Caspase依赖途径凋亡、迁移	Ras通路信号↓，Bax/Bcl-2↑、Caspase-3/9↑、MMP2/9↓	[169]
苦参碱	苦参	MDA-MB-231、MCF-7	抑制增殖、诱导凋亡和周期阻滞	miR-21/PTEN/AKT通路信号↓、PI3K/AKT通路信号↓、AKT/mTOR通路信号↓；EGF/VEGF-VEGFR1-AKT-NF-κB通路信号↓	[170-173]
龙葵碱	龙葵	4T1、MCF-7	体内诱导凋亡、抑制血管生成和肿瘤生长	Bcl-2/Bax↓（α-龙葵碱）；FAK-PI3K/AKT通路信号↓，增强顺铂的化学疗法敏感性	[174-175]
粉防己碱	汉防己	MDA-MB-231、MCF-7、SUM-159	诱导自噬；诱导凋亡；与亚砷酸盐协同作用	PI3K/AKT/mTOR通路信号↓、p62/SQSTM1↑、*Beclin1*↓、LC3-Ⅰ/Ⅱ↓；Caspase-3↑、Bax/Bcl-2↑、Bid↑、survivin↓和PARP↓；靶向抑制炎症性和侵袭性乳腺癌起始细胞	[151-154，176]
莒芰明宁碱	莒芰	多种乳腺癌细胞	诱导Caspase依赖凋亡；抑制增殖	天然STAT3抑制剂；PI3K /AKT/mTOR通路信号↓；增强多西他赛的细胞毒性和口服生物利用度；ROS积累↓，IKKβ↓；ROS介导的HER家族受体的表达↓	[156-157，159-160，177]
青藤碱	青藤	MDA-MB-231、MCF-7、4T1	诱导细胞周期阻滞、凋亡；抑制细胞增殖；降低乳腺癌诱导的骨破坏	MAPK通路信号↑；EMT↓、CSC特性↓；调控miR-29/PDCD4轴、NF-κB激活的IL4/miR-324-5p/CUEDC2轴；缺氧条件下，PI3K/AKT/mTOR通路信号↓；IL-8/CXCR1和c-Fos/NFATc1通路信号↓	[178-183]

注：MCF-7为雌激素受体阳性（ER+）乳腺癌细胞系，MDA-MB-231为三阴性乳腺癌细胞系，4T1为小鼠乳腺癌细胞，SK-BR-3、BT474为人表皮生长因

子受体阳性(2HER2+)人乳腺腺癌细胞系,T47D 人乳腺管癌细胞系。MMP 为金属基质蛋白酶,AKT 为蛋白激酶 B,AMPK 为腺苷 5′-单磷酸激活的蛋白激酶,HIF-1α 为缺氧诱导因子-1α,PI3K 为磷脂酰肌醇 3-激酶,ROS 为活性氧,Bax 为 B 淋巴细胞瘤-2 相关 X 蛋白,Bcl-2 为 B 淋巴细胞瘤-2 蛋白,JAK2 为 Janus 激酶 2,STAT 为信号转导和转录激活蛋白,FGG 为纤维蛋白原 γ 链,ERK 为细胞外调节蛋白激酶,MAPK 为丝裂原活化蛋白激酶,EGF 为人表皮生长因子,Caspase 为含半胱氨酸的天冬氨酸蛋白水解酶,miR-21/29 为微小 RNA-21/29,PTEN 为张力蛋白同源物,mTOR 为哺乳动物雷帕霉素靶蛋白,VEGF 为血管内皮生长因子,VEGFR 为血管内皮生长因子受体,NF-κB 为核因子-κB,FAK 为局部粘着斑激酶,SQSTM1 为自噬受体蛋白 1,*Beclin1* 为卷曲螺旋肌球蛋白样 BCL2 结合蛋白/自噬基因,LC3-Ⅰ/Ⅱ为微管相关蛋白轻链Ⅰ/Ⅱ,Bid 为 BH3 相互作用域死亡激动剂,survivin 为存活蛋白,PARP 为聚腺苷二磷酸核糖聚合酶,IKKβ 为 IκB 激酶 β,CSC 为肿瘤干细胞,PDCD4 为程序性细胞死亡因子 4,CUEDC2 为 CUE 结构域蛋白 2,CXCR1 为 CXC 趋化因子受体 1,NFATc1 为活化 T 细胞 c1 核因子。↑表示表达增加/激活,↓表示表达减少/抑制。多种乳腺癌细胞表示超过 5 种且 3 种类型乳腺癌细胞均包含。

4 多糖类

中药多糖是由多个单糖组成的一类高分子化合物,其化学结构较其他中药单体更为复杂,但作为碳水化合物,多糖类化合物衍生物具有水溶性、生物利用率高、毒副作用小的优点,其抗肿瘤生物活性主要表现在细胞毒性的直接抑瘤作用和调节免疫微环境的间接杀伤肿瘤细胞作用。

黄芪多糖可以下调 Wnt/β-catenin 信号通路,阻碍上皮细胞间充质转化,从而抑制肿瘤细胞增殖和迁移侵袭[184];其可以通过下调 AKT 信号通路抑制乳腺癌细胞的增殖,这一过程与 p53 蛋白和 *PTEN* 基因的表达有关[185];在乳腺癌免疫微环境中,其可以激活巨噬细胞并释放一氧化氮(NO)和肿瘤坏死因子-α(TNF-α),从而杀伤乳腺癌细胞[186]。

研究[187-190]发现,灰树花多糖与乳腺癌患者的免疫功能具有相关性,其可以增强乳腺癌的化疗敏感性,并调节患者的免疫微环境,从而提高免疫细胞对肿瘤的杀伤作用。Li 等[191]在体外实验中发现,香菇多糖可以通过诱导自噬和 Caspase-7 介导的凋亡抑制人乳腺癌移植瘤的生长。Razali 等[192]研究发现,经龙葵多糖干预的乳腺癌模型小鼠肿瘤体积和肿瘤质量抑制率分别为 65% 和 40%,肿瘤组织中浸润性 T 细胞、自然杀伤细胞和巨噬细胞增加,血清中 TNF-α、γ 干扰素(IFN-γ)、白介素(IL)-4 水平升高,IL-6 水平降低。

多糖类中药单体抗乳腺癌的效应及主要机制见表 6。

表 6 多糖类中药单体抗乳腺癌的效应及主要机制

中药单体	来源	研究对象	效应	主要机制	参考文献
黄芪多糖	黄芪	MCF-7、MDA-MB-468、MDA-MB-231、4T1 荷瘤小鼠	诱导细胞凋亡;抑制肿瘤生长	激活巨噬细胞;Wnt/β - catenin 通路信号↓,EMT↓;pAKT↓,与 p53 和 PTEN 表达相关;EGFR↓、ANXA1↓	[184-186,193]
灰树花多糖	灰树花	BALBc 小鼠	抑制肿瘤生长	*SPARC* mRNA↓、VEGF↓	[194]
香菇多糖	香菇	MCF-7、4T1 荷瘤小鼠	诱导细胞凋亡、自噬;调节免疫、抑制肿瘤转移	Caspase-7↑、胞浆细胞色素 c↑、Bax/Bcl-2↑;IL-35↓、IFN-γ↑、p35↓、EBI3↓	[191,195]
枸杞多糖	枸杞	MCF-7、MDA-MB-231	诱导细胞铁死亡,抑制增殖;抑制 IGF-1 诱导的血管生成	x CT/GPX4 通路信号↓;ERK↓;PI3K/HIF-1α/VEGF 通路信号↓	[196-198]
红花多糖	红花	MDA-MB-435、MCF-7	诱导凋亡;诱导凋亡、抑制转移	PI3K/AKT/mTOR 通路信号↓;Bcl-2↓、Bax↑、MMP9↓、MMP1↑	[199-200]
灵芝多糖	灵芝	MDA-MB-231	诱导 G0/G1 期阻滞;诱导凋亡	AKT/NF-κB 通路信号↓,Cyclin D1↓、CDK4↓;细胞色素 c↑、Caspase3/9↑、PARP↑	[201-202]
党参多糖	党参	MCF-7	抑制增殖、诱导凋亡;	CCHE1↓	[203]
槐耳多糖	槐耳	MCF-7、4T1 小鼠荷瘤	诱导凋亡;抑制侵袭、迁移	MTDH↓、Bax/Bcl-2↑;EMT↓	[204-205]
人参多糖	人参	MDA-MB-231	抑制增殖、诱导凋亡	E-cadherin↑、vimentin↓,Caspase-3↑、p53↑、TNF-α↑、JNK↑、pAKT↑、pNF -κB↑、p65↑、p50↑、*IKZF1*↑	[206]

注:MCF-7 为雌激素受体阳性(ER+)乳腺癌细胞系,MDA-MB-231、MDA-MB-468 为三阴性乳腺癌细胞系,4T1 为小鼠乳腺癌细胞。Wnt/β-catenin 为 Wnt /β-连环蛋白,EMT 为上皮间质转化,AKT 为蛋白激酶 B,PTEN 为张力蛋白同源物,EGFR(HER1)为表皮生长因子受体,ANXA1 为膜联蛋白 A1,SPARC 为富含半胱氨酸的酸性分泌糖蛋白,VEGF 为血管内皮生长因子,Caspase 为含半胱氨酸的天冬氨酸蛋白水解酶,Bax 为 B 淋巴细胞瘤-2 相关 X 蛋白,Bcl-2 为 B 淋巴细胞瘤-2 蛋白,IL 为白介素,IFN-γ 为 γ 干扰素,EBI3 为 β 链 EB 病毒诱导基因 3 亚基,x CT(SLC7A11)为胱氨酸/谷氨酸反向转运体系统的轻链亚单位 Xc^-,GPX4 为谷胱甘肽过氧化物酶 4,HIF-1α 为缺氧诱导因子-1α,VEGF 为血管内皮生长因子,AKT 为蛋白激酶 B,PI3K 为磷脂酰肌醇 3-激酶,mTOR 为哺乳动物雷帕霉素靶蛋白,MMP 为金属基质蛋白酶,NF-κB 为核因子-κB,Cyclin D1 为细胞周期蛋白 D1,CDK 为周期蛋白依赖性激酶,PARP 为聚腺苷二磷酸核糖聚合酶,CCHE1 为子宫颈癌高表达长链非编码 RNA 1,MTDH 为异粘蛋白,E-cadherin 为上皮细胞钙黏蛋白,vimentin 为存活蛋白,TNF-α 为肿瘤坏死因子-α,JNK 为 c-Jun N 端激酶。↑表示表达增加/激活,↓表示表达减少/抑制。

5 其他

除上述中药单体外，丁香、肉桂、肉豆蔻等中药中提取出的酚类化合物丁香酚也表现出积极的抗乳腺癌作用。有研究者[207]用4种不同类型的乳腺癌细胞证明了丁香酚诱导乳腺癌细胞凋亡的作用，其对E2F1/存活蛋白（survivin）通路具有靶向性，且不依赖p53和ERα，对细胞周期素依赖性激酶抑制剂$p21^{WAF1}$的表达亦有抑制作用。丁香酚对三阴性乳腺癌和HER2+乳腺癌的抑制作用，可能是通过抑制金属基质蛋白酶（MMP）2/9、调控Caspase家族蛋白的表达，进而诱导细胞凋亡来实现的[208]。除此之外，丁香酚还可以抑制乙醛脱氢酶（ALDH）的活性、调控NF-κB信号通路，从而增加肿瘤细胞对顺铂的敏感性[209]。

姜黄素是从中药姜黄中分离出的一种多酚类化合物，目前已被用于肿瘤的治疗或辅助治疗。姜黄素可以通过抑制MMP2/9、上调血清组织金属蛋白酶抑制剂（*TIMP*）*1*、*TIMP4*基因表达抑制乳腺癌细胞转移[210]，且对不同类型乳腺癌细胞株均表现出诱导凋亡和G2/M期细胞周期阻滞的作用，这可能与降低Cdc25、dc2蛋白表达，升高p21蛋白表达，抑制AKT/mTOR磷酸化及线粒体凋亡通路有关[211]。姜黄素可以同时抑制HER2过表达乳腺癌细胞BT474和SK-BR-3的AKT、MAPK信号通路，以及BT474中NF-κB的表达[212]。姜黄素治疗转移性乳腺癌的I期临床试验[213]结果显示，姜黄素（推荐给药剂量为6 000 mg/d）与紫衫醇联用表现出良好的安全性和耐受性。Theracurmin®（高生物利用度姜黄素）的开发使姜黄素在小鼠体内的生物利用度提高了30倍，临床试验亦显示出较好的治疗作用和安全性[214-216]。

百里醌是黑草籽挥发油中的一种活性成分，可以通过激活过氧化物酶增殖物激活受体-γ（PPAR-γ）通路[217]、上调p53表达[218]、增加ROS引起的p38磷酸化等[219]途径诱导乳腺癌细胞凋亡，并能破坏趋化因子受体4（CXCR4）信号轴的信号转导，从而抑制乳腺癌细胞的骨转移、调节乳腺癌的肿瘤微环境[220-221]。此外，百里醌与现有的化疗药物（如紫衫醇、吉西他滨）具有明显的协同作用[222-225]。目前，百里醌治疗乳腺癌的临床前研究较为丰富，但其药代动力学、安全性等还需进一步评估。

6 总结与展望

综上，多种中药单体具有预防及治疗乳腺癌的作用，主要机制涉及细胞毒性的直接杀伤作用，调节肿瘤免疫微环境，增强靶向药物治疗敏感性及辅助放疗、化疗等方面。黄酮类、萜类等中药单体在乳腺癌的治疗中具有双向性，既可以选择性杀伤乳腺癌细胞，又能保护正常组织细胞免受药物毒性的伤害。生物碱类化合物的抗乳腺癌活性较强，但其自身较强的生物毒性是其进入临床研究前亟待解决的问题。根据现有的研究结果及目前已用于临床治疗的天然生物碱类药物的开发经验，对有抗肿瘤活性的中药生物碱类单体的分子结构进行改造，增效减毒，是促进生物碱类单体进入临床研究的有效方式。药代动力学研究发现，部分抗乳腺癌中药单体的水溶性较差、生物利用度较低，严重阻碍了成药性，因此有研究者利用纳米载药、脂质体载药等技术开发了中药单体衍生物。

具体来看，中药单体芹菜素、木犀草素、黄芩素、冬凌草甲素、小檗碱、雷公藤甲素、雷公藤红素、荜茇明宁碱、百里醌等均有开发成乳腺癌治疗或辅助治疗新药的潜力，EGCG、橙皮素、柚皮素、柚皮苷、根皮素、毛萼乙素、番茄红素、染料木素、鼠尾草酚、鼠尾草酸、花青素类、灰树花多糖等在乳腺癌的预防、乳腺癌预后、肿瘤营养学研究等方面具有一定的研究及发展价值，青蒿素、人参皂苷、姜黄素、黄芪多糖（伯恩）、槐耳颗粒等目前已用于临床的药物，希望可以为乳腺癌的临床“用药指南”提供参考。

中药单体在抗乳腺癌中的研究空间还很大，新的中药单体尚待发现，具有开发潜力的中药单体作用机制、衍生物开发、药代动力学、成药性、给药方式、用药安全性等研究数据亦有待补充。

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