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# 天然活性成分抗乳腺癌的研究进展

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## 摘 要

**放眼全球，乳腺癌(Breast Cancer, BC)是最常见和反复发作的疾病之一，也是女性死亡的第二大原因。乳腺癌对女性不仅身体上造成伤害，还给精神和经济上带来沉重的负担。尽管有预防、诊断和治疗选择，如放疗和化疗，但发病率每年都在增加。目前应用的化学疗法仍然存在问题，如癌细胞的异质性、对正常组织的严重毒性、快速产生耐药性和疾病复发，以及癌症干细胞的聚集和无法阻止病情进展至侵入性/转移性阶段。因此，需要开发针对不同亚型乳腺癌的新型治疗药物。在可用于治疗乳腺癌的药物中，天然产物如植物衍生化合物显示出抗乳腺癌特性。这些物质属于不同的化学类别，如黄酮类、皂苷类、萜类和生物碱类等。它们通过不同的机制对乳腺癌细胞进行体内外的细胞毒性活性，包括抑制外源性和内源性凋亡途径、阻碍细胞周期和激活自噬。此外，它们还表现出抗血管生成和抑制侵袭的作用。本综述的目的是整理具有抗肿瘤活性的天然生物活性化合物对乳腺癌的作用机制，为天然活性成分抗乳腺癌的临床应用提供科学依据。**

## 关键词

**乳腺癌，天然活性成分，研究进展**

# Research Progress of Natural Active Ingredients against Breast Cancer

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## Abstract

**Globally, breast cancer (BC) is one of the most common and recurrent diseases and the second leading cause of death among women. Breast cancer not only takes a physical toll on women, but also places a heavy emotional and financial burden. Despite the availability of preventive, diagnostic and therapeutic options, such as radiotherapy and chemotherapy, the incidence is increasing every year. Currently applied chemotherapies still have problems such as heterogeneity of cancer cells, severe toxicity to normal tissues, rapid development of drug resistance and disease recurrence, as well as aggregation of cancer stem cells and inability to prevent progression to invasive/metastatic stages. Therefore, there is a need to develop novel therapeutic agents that target different subtypes of breast cancer. Among the drugs available for the treatment of breast cancer, natural products such as plant-derived compounds show anti-breast cancer properties. These substances belong to different chemical classes such as flavonoids, saponins, terpenoids and alkaloids. They exert cytotoxic activity against breast cancer cells ex vivo and in vivo through different mechanisms, including inhibition of exogenous and endogenous apoptotic pathways, obstruction of the cell cycle and activation of autophagy. In addition, they exhibit anti-angiogenic and inhibitory effects on invasion. The aim of this review is to organize the mechanisms of action of natural bioactive compounds with antitumor activity against breast cancer and to provide a scientific basis for the clinical application of natural active ingredients against breast cancer.**

## Keywords

**Breast Cancer, Natural Active Ingredients, Research Progress**



## 1. 乳腺癌

截至 2023 年，乳腺癌(Breast cancer, BC)仍是女性癌症发病率最高的癌症类型[1]。是国家肿瘤防治的重点。BC 不同亚型根据雌激素受体(ER)、孕激素受体(PR)、人表皮生长因子受体 2 (HER2)和 Ki67 四种分子生物标志物的状态进行分类[2]。乳腺癌的治疗方法主要有手术、放疗、化疗、免疫疗法等。由于化疗药物的副作用、手术的后遗症及心理疾病等暴露了这些治疗方式的缺点。来自天然来源的替代抗癌剂的需求正在增加[3]。在这种对更安全、更有用和更广泛适用的药物的迫切需求中，天然产物活性成分萜类、生物碱、皂苷、黄酮和多糖等以其独特的优势被越来越多的用于乳腺癌的治疗。研究发现其通过抑制乳腺癌细胞迁移，或促进乳腺癌细胞凋亡，或诱导乳腺癌细胞周期阻滞等达到发挥抗乳腺癌作用。

## 2. 黄酮类

黄酮类是一类广泛存在的植物多酚，具有 15 个碳的基本骨架，可表示为 C6-C3-C6，由两个苯环(C6)和线性三碳链(C3)连接而成[4]。有多种其他活性，包括抗炎[5]、舒张血管[6]、抗凝[7]、抗糖尿病[8]、神经保护[9]、和抗抑郁[10]等。黄酮类化合物通过调节活性氧(ROS)清除酶活性、参与细胞周期阻滞、诱导细胞凋亡和自噬、抑制癌细胞增殖和侵袭[11]。核因子-κB (NF-κB)是一种 B 细胞特异性转录因子，是促进细胞增殖、抑制细胞凋亡、加速细胞迁移和侵袭、刺激转移和血管生成的关键调节因子[12] [13]。活化

的 NF-κB 可以通过上皮间质转化(EMT)直接诱导转移扩散，并促进肿瘤细胞逃离原发肿瘤，从而导致癌细胞通过血管或淋巴管向远处器官(包括肺、骨、脑和淋巴结)转移[9]。为了探讨黄酮类在乳腺癌中的作用及其相关分子机制，Song [14]等发现淫羊藿苷(一种黄酮醇苷)通过 ROS 介导的线粒体途径和 SIRT6/NF-κB/EMT 途径参与乳腺癌细胞凋亡和迁移。此外，它可以显著下调细胞程序性死亡-配体 1 的表达水平、增加浸润的 CD4+/CD8+T 细胞的比例以及减少肿瘤中骨髓源性抑制细胞的丰度来改善肿瘤免疫抑制微环境。在小鼠乳腺癌(4T1)细胞的肿瘤小鼠模型中淫羊藿苷也表现出显着的肿瘤生长抑制作用。雷帕霉素(mTOR)信号通路参与细胞外和细胞内信号整合，进而负责增殖、生长、细胞代谢以及最终细胞存活的调节[15]。通过分子对接技术发现黄酮类可能是乳腺癌 mTOR 的有效抑制剂[16]。三阴性乳腺癌(TNBC)是具有 ER-/PR-/HER2-生物标志物的 BC 亚型，临床研究中预后最差[17] [18]。Li [19]等用槲皮素处理 MCF-7 细胞(TNBC 细胞系)后，表现出 G1 期阻滞，并阐明机制是通过抑制 PI3K/AKT/mTOR 信号通路。此外，其它类型的黄酮类化合物被报道在乳腺癌细胞中抑制 mTOR 通路从而发挥抗乳腺癌活性[20] [21] [22] [23]；同时，有研究报道 mTOR 抑制剂已用于临床试验(如表 1 所示)。因此，黄酮类可能是日后治疗乳腺癌的潜力候选物。

**Table 1.** Clinical trials of mTOR inhibitors for the treatment of different breast cancers
**表 1.** mTOR 抑制剂用于治疗不同乳腺癌的临床试验

| 药物 | 研究阶段 | 乳腺癌 |
|---|---|---|
| Exemestane + everolimus | Phase III (randomized trial) | Advanced breast cancer (hormone-receptor-positive) [24] |
| Temsirolimus | Phase II | Metastatic breast cancer [25] |
| Tamoxifen + everolimus | Phase II (randomized trial) | Metastatic breast cancer [26] |
| Plustrastuzumab + vinorelbine + everolimus | Phase III | HER2-positivebreast cancer [27] |
| Trastuzumab + ridaforolimus | Phase IIb | Trastuzumab-refractory metastatic breast cancer (human epidermal growth factor receptor 2-positive) [28] |
| Paclitaxel + trastuzumab + everolimus | Phase II | Advanced breast cancer (HER-2 positive) [29] |

## 3. 皂苷类

皂苷是许多植物物种中结构多样的一组特殊植物萜类化合物，由与寡糖部分连接的甾体或萜苷元组成，按照结构分为三萜皂苷与甾体皂苷[30] [31]。皂苷多种肿瘤类型中发挥显着的细胞毒性[32] [33]。为了探讨皂苷在 BC 中的抗肿瘤作用和潜在机制，Zhang [34]等发现用 Deltonin (一种从薯蓣中分离出来的甾体皂苷)处理 MDA-MB-231 细胞(TNBC 细胞系)导致半胱天冬酶-3 (caspase-3)和 caspase-8 活化。众所周知，凋亡过程中 caspase-3 的激活导致 poly (ADPribose)聚合酶(PARP)的裂解，Deltonin 以剂量依赖性方式增加切割的 PARP 水平，这与 Deltonin 诱导的 MDA-MB-231 细胞凋亡一致；此外，Deltonin 还下调 phospo-AKT 与 phospo-ERK1/2 的表达，而 AKT 与 ERK 信号通路是与介导细胞生长、存活和死亡相关的重要通路[35] [36]。因此，Deltonin 可能是治疗 BC 的有效治疗剂。Hippo 信号通路在监测器官大小、组织稳态、细胞增殖和死亡以及干细胞自我更新方面发挥着重要作用[37]。Hippo 通路在多种人类癌症中失调，包括乳腺癌、结直肠癌、肺癌、卵巢癌、胃癌和肝癌，通常与不良预后相关[38] [39] [40]。然而，针对 BC 中 Hippo 通路的研究和药物发现仍然很少，迫切需要发现用于 BC 治疗的新激活剂。Xiang [41]等发现中药重楼的一种甾体皂苷 PSVII 浓度依赖性地抑制 BC 细胞的增殖并抑制它们的集落形成。PSVII 降低了 Yes 相关蛋

白(YAP)的表达和核转位，YAP 是 Hippo 信号通路中的下游转录因子；YAP 的过度表达显着减弱 PSVII 诱导的自噬 PSVII 诱导的 YAP 介导的自噬与 YAP 上游效应子 LATS1 活性形式的增加相关。LATS1 的激活涉及多种蛋白(包括 MST2、MOB1 和 LATS 本身)参与 MST2 依赖性顺序激活级联。此外，PSVII 促进 LATS1 与 MST2 和 MOB1 的结合，并在 BC 细胞系中激活 LATS1。分子对接显示 PSVII 直接与 MST2-MOB1-LATS1 三元复合物结合。微尺度热泳分析和药物亲和力响应靶向稳定性测定证实了这种三元复合物之间的高亲和力。这项研究表明 PSVII 是一种新型的直接 Hippo 激活剂，在治疗 BC 方面具有巨大潜力。此外，皂苷也具有周期阻滞，抑制血管生成、调节肿瘤微环境、抗 BC 的转移、侵袭、耐药(如表 2 所示)。但是，由于皂苷存在溶血性，口服生物利用度低、组织刺激性强、溶解度小这大大限制了其临床应用。为了解决这一难题，Wang [42]等提出了一种低毒且高效的皂苷递送方法，即将薯蓣皂苷(Dio，类固醇皂苷)-Chonanofibers (NFs)和七叶皂苷 Ia (EIa, triterpenesaponin)-Cho 纳米颗粒(NPs)两种皂苷-胆固醇(Cho)纳米复合物，结果显示抗肿瘤(4T1 小鼠模型)功效，肿瘤抑制率为 61%；同时，它不会像游离 Dio 对小鼠那样引起极度刺激和疼痛。此外，与游离药物相比，制备的纳米复合物可以显著降低溶血和器官毒性，并降低了皂苷的毒性，同时保留了其抗肿瘤活性，这为皂苷在体内的递送方式提供了新的策略，以期用于临床治疗。

**Table 2.** The action way and mechanism of saponin against breast cancer
**表 2.** 皂苷抗乳腺癌的作用途径及机制

| 作用途径 | 皂苷化合物 | 机制 |
|---|---|---|
| 周期阻滞 | 绞股蓝皂苷 | 阻滞 G1 期[43] |
| 抑制血管生成 | 白头翁皂苷 | 靶向 TLR4/NF-$\kappa$ 诱导 M1 巨噬细胞极化[44] |
| 调节肿瘤微环境 | 三七皂苷 | 减少巨噬细胞数量，降低 IL-6、IL-10 和 TNF-$\alpha$ 的表达，血管迁移粘附相关蛋白在体内的表达[45] |
| 抗转移、侵袭 | 三七皂苷 | 促进 E-cadherin 表达，抑制 vimentin 表达[46] |
| 逆转耐药性 | 巴黎皂苷 VI | 抑制 MDR、P-糖蛋白的表达[47] |

## 4. 生物碱类

生物碱是一类主要源自氨基酸的低分子量含氮化合物[48]。生物碱存在生物活性，如抗癫痫[49]、镇痛[50]、抗病毒[51]等等。此外，生物碱类化合物也被报道存在抗肿瘤活性(如表 3 所示)。为了研究生物碱是否有抗乳腺癌作用，Chen [52]等研究了两种天然喹啉生物碱通过抑制 STAT3 激活协同诱导 MCF-7 细胞凋亡，采用细胞活力、流式细胞术和 Western blot 法评估两种生物碱单独或联合使用的抑制效果。数据显示，这两种生物碱在较低剂量下协同抑制癌细胞增殖，并阐明作用机制是通过抑制 STAT3 磷酸化并调节下游分子以诱导细胞凋亡，而在正常乳腺细胞中仅观察到微弱的杀伤作用。Grabarska [53]等从小檗根中分离出一种天然异喹啉生物碱巴马汀(PLT)，并使用 MCF-7 细胞在体外单独和与多柔比星(DOX)联合使用来研究其细胞毒性和抗增殖作用。结果表明 PLT 治疗以剂量依赖性方式抑制 MCF-7 细胞活力和增殖能力；并且 PLT 增加了 MCF-7 对 DOX 敏感性，说明生物碱还具有潜在的增敏作用。Liu [54]等证明用一种孕烷生物碱衍生物(Z)-3$\beta$-乙氨基-pregn-17(20)-en(1)治疗可导致 HIF-1$\alpha$/VEGF/VEGFR2 通路下调，抑制下游分子 AKT、mTOR、FAK 的磷酸化，并在细胞实验及动物实验发现能抑制 TNBC 转移和血管生成。此外，生物碱也是临床治疗癌症的常用药，例如长春碱是从夹竹桃科常见观赏植物长春花中提取的，临床用于治疗恶性淋巴瘤及小儿急性淋巴白血病[55]。喜树碱是从喜树中分离出来的喹啉生物碱，临床用于治疗胃肠道和头颈部肿瘤[56]，说明对生物碱的结构修饰以及活性筛选以期得到更安全有效的药物用来

在临床治疗乳腺癌是一个重要方向。

**Table 3.** Alkaloidal antitumor activity
**表 3.** 生物碱抗肿瘤活性

| 生物碱类化合物 | 癌细胞 | 作用机制 |
|---|---|---|
| 三萜类生物碱 | 结肠癌 | 诱导癌细胞 G2/M 细胞周期阻滞和凋亡[57] |
| 苦参碱 | 胰腺癌 | 调节 ROS/NF-KB/MMPs 通路引起细胞凋亡[58] |
| 苦参碱衍生物 | 非小细胞癌 | 激活 NLRP3/caspase-1/GSDMD 信号通路诱导细胞焦亡[59] |
| 吲哚生物碱 | 人神经胶质瘤 | 诱导癌细胞的自噬抑制细胞增殖[60] |
| 二聚吲哚生物碱 | 白血病 | 周期阻滞及提高 ROS 水平从而诱导癌细胞凋亡[61] |

## 5. 萜类

萜类化合物由异戊二烯单元$(C_5H_8)_n$组成，并且通常根据连接单体的数量进行分组，分为单萜类、倍半萜类、二萜类、三萜类和四萜类。截至目前，已经获得了超过 40,000 种不同的萜类化合物，它们分别来自植物，动物及微生物中[62]。在过去，一些研究报道了具有抗 BC 活性的萜类化合物[63] [64] [65] [66] (如表 4 所示)，证明了萜类化合物在预防和治疗乳腺癌方面的潜力。在肿瘤细胞中，新形成的肿瘤血管不成熟、不规则、扭曲、窦状壁薄、无连续的内皮细胞，这些异常的形态形成了具有高渗透性的血管，使肿瘤细胞能够进入血流并更容易扩散到其他组织[67] [68]。在 BC 中，较高的微血管密度预示着较高的转移风险和较差的临床预后[69]。因此，抑制肿瘤血管生成是抑制 BC 转移、实现长期有效控制的一条有意义的途径。二氢青蒿素(DHA)属于倍半萜，是青蒿素的第一代衍生物，通过将青蒿素的 C-10 羰基还原所生成的。Rao [70]等报道 DHA 显着减弱 MDAMB-231 细胞诱导的新血管形成。当暴露于 DHA 处理的细胞培养基时，它还能抑制 HUVEC 细胞的血管萌芽和管形成。此外，DHA 下调血管内皮生长因子 VEGF、基质金属蛋白酶(MMP-2)和 MMP-9 蛋白的表达。这为 DHA 作为新型抗肿瘤血管生成药物提供了实验基础。BC 骨转移会导致严重的并发症，包括慢性疼痛和病理性骨折，严重降低生活质量，继发于 BC 的骨转移与不良预后相关[71]。目前治疗转移和骨溶解的疗法远不能令人满意。因此，有必要开发新的替代疗法，以提高疗效和减少副作用。Zhai [72]等报道穿心莲内酯(二萜内酯)通过下调 MMP-9 蛋白表达水平以浓度依赖性方式抑制佛波醇 12-肉豆蔻酸酯 13-乙酸酯(PMA)诱导的 MDA-MB-231 细胞迁移和侵袭，并通过抑制 NF-κB 受体激活剂(RANK)配体(RANKL)介导的和 MDA-MB-231 细胞介导的人乳腺癌诱导的骨丢失；在体内，经穿心莲内酯治疗后，通过抑制 NF-κB 及 ERK/MAPK 信号传导，抑制植入骨的乳腺肿瘤(癌症骨转移)的生长和 MDA-MB-231 乳腺癌诱导的骨丢失。同时，Rabi 和 Bishayee [73]等发现萜类化合物(包括 d-柠檬烯、紫苏醇、视黄醇、反式维甲酸、齐墩果酸、熊果酸、胡萝卜素和番茄红素)作为乳腺上皮癌发生的化学预防剂的生物学效应，以及中间生物标志物作为癌前病变指标的效用。几项流行病学研究和

**Table 4.** Terpenoids with anti-breast cancer activity
**表 4.** 具有抗乳腺癌活性的萜类化合物

| BC 细胞系 | 萜类化合物 | 类型 |
|---|---|---|
| MCF-7 | 人参皂苷 | 四环二萜 |
| MCF-7 | 香叶醇 | 单萜醇 |
| Bcap-37、MDA-MB-231 | 葫芦素 E | 四环三萜 |
| MDA-MB-468、MDA-MB-436 | 熊果酸 | 五环三萜 |

随机临床试验表明，摄入番茄红素与各种癌症类型(包括前列腺癌、乳腺癌、肺癌、肝癌和结肠癌)的风险呈负相关[74] [75] [76]。这表明萜内化合物可能是治疗或预防 BC 的有潜力的候选药物。

## 6. 展望

近年来，由于目前化疗药物在癌症治疗中的缺点和特性，天然化合物获得了相当大的关注。目前，许多从中草药中提取的先导化合物已用于治疗多种临床肿瘤。对于提高癌症患者的免疫功能、缓解临床症状、延缓肿瘤进展、预防复发和转移等具有一定的疗效，并改善患者的生活质量[77]。因此，从中草药中发现天然活性先导化合物仍然是开发新的抗肿瘤药物的重要来源。然而，尚未生产出用于人类药物的天然活性先导化合物。由于体内癌症的发病机制复杂，现有的单一先导化合物仍然无效。大多数单药疗效较小且容易产生耐药性，毒副作用也不容小觑。这些天然产物还存在药效弱、毒性大等一些类药特性的缺陷，不能直接用于医药。因此，需要建立一种有效的方法来设计兼顾活性和毒性的药物分子结构，以有效地探索具有强抗肿瘤功效和对正常细胞和组织低毒性的先导化合物。本文讨论了一些重要的天然化合物抗乳腺癌的作用及其作用机制，未来以天然抗乳腺癌药物为重点的研究可以为乳腺癌治疗开辟新的视野，这将对提高乳腺癌患者的生存率及生活质量起到很大的作用。

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