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Hans汉斯

白藜芦醇对乳腺癌分子机制的研究进展

李　平[1*]，李景兴[2]，邹　青[1]，吕　圆[1]，徐克前[3]，杜振芳[1#]

[1]湖南环境生物职业技术学院医药技术学院，湖南　衡阳
[2]衡阳市中心医院儿童康复科，湖南　衡阳
[3]中南大学湘雅医学院，湖南　长沙

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摘　要

白藜芦醇(Resveratrol)是一种天然存在于葡萄、浆果和花生中的多酚化合物，因其显著的抗氧化、抗炎和抗癌特性，近年来在乳腺癌研究中备受关注。文章综述了白藜芦醇在乳腺癌细胞中的分子机制及其在抗肿瘤过程中的作用。白藜芦醇通过靶向多种信号分子，抑制乳腺癌细胞的增殖，诱导细胞凋亡和自噬，抑制细胞迁移和侵袭，并重组细胞代谢。此外，白藜芦醇与化疗和放疗药物具有协同作用的潜力。尽管临床前研究结果令人鼓舞，但白藜芦醇的生物利用度和稳定性问题仍需解决。未来的研究应聚焦于优化白藜芦醇的递送系统，深入揭示其分子作用机制，并评估其长期使用的安全性和有效性，为乳腺癌患者提供更有效的治疗选择。

关键词

白藜芦醇，乳腺癌，分子机制，耐药性

Research Progress on the Molecular Mechanisms of Resveratrol in Breast Cancer

Ping Li[1*], Jingxing Li[2], Qing Zou[1], Yuan Lv[1], Keqian Xu[3], Zhenfang Du[1#]

[1]School of Medical Technology, Hunan Polytechnic of Environment and Biology, Hengyang Hunan
[2]Pediatric Rehabilitation Department, Hengyang Central Hospital, Hengyang Hunan
[3]Xiangya School of Medicine, Central South University, Changsha Hunan

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[*]第一作者。
[#]通讯作者。

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Abstract

Resveratrol, a polyphenolic compound naturally found in grapes, berries, and peanuts, has attracted significant attention in recent years due to its potent antioxidant, anti-inflammatory, and anti-cancer properties. This review summarizes the molecular mechanisms of resveratrol in breast cancer cells and its role in tumor suppression. Resveratrol exerts its effects by targeting multiple signaling molecules, thereby inhibiting the proliferation of breast cancer cells, inducing apoptosis and autophagy, suppressing cell migration and invasion, and reprogramming cellular metabolism. Additionally, resveratrol shows potential synergistic effects when combined with chemotherapeutic and radiotherapeutic agents. Despite promising preclinical results, issues related to the bioavailability and stability of resveratrol remain to be addressed. Future research should focus on optimizing resveratrol delivery systems, deeply elucidating its molecular mechanisms, and evaluating the safety and efficacy of long-term use, with the ultimate goal of providing more effective treatment options for breast cancer patients.

Keywords

Resveratrol, Breast Cancer, Molecular Mechanisms, Drug Resistance

1. 引言

乳腺癌是全球女性最常见的恶性肿瘤之一，其发病率和死亡率居高不下。据世界卫生组织(WHO)统计，乳腺癌每年约占全球新发癌症病例的 24.5%，并且是女性癌症死亡的主要原因之一[1]。尽管乳腺癌在早期诊断和治疗方面取得了显著进展，如手术、放疗、化疗和靶向治疗等多种方法的综合应用[2] [3]，使得生存率显著提高，但仍面临巨大挑战。例如，传统的化疗和放疗常伴随严重的副作用，会引起脱发、神经毒性、胃肠道不适等症状[4]。此外，耐药性是乳腺癌治疗中的另一大难题[5] [6]。因此，寻找新的治疗方法和药物，以提高治疗效果、降低副作用和克服耐药性，成为当前乳腺癌研究的重点。

在探索新型抗癌药物的过程中，天然化合物因其多样的生物活性和较低的毒副作用等优势，备受关注[7] [8]。白藜芦醇(Resveratrol)是一种天然的多酚类化合物，广泛存在于葡萄、花生、蓝莓、黑莓和一些药用植物中[9]。它具有反式和顺式两种结构，其中反式结构可以跨越细胞膜，并与多种细胞内靶点相互作用，在体内发挥多种生物效应[10]。研究表明，白藜芦醇具有多种生物学活性，包括抗肿瘤[11]、抗氧化[12]、抗炎[13]、抗衰老[14]、心血管保护[15]等。近年来，越来越多的研究集中在白藜芦醇的抗癌潜力上，特别是在乳腺癌领域，其独特的作用机制和多靶点特性，使其成为一种备受瞩目的候选抗癌药物。

本文综述了近年来白藜芦醇抗乳腺癌分子机制的最新研究进展，详细探讨其在细胞增殖、凋亡、迁移、自噬及细胞代谢等方面的作用及其潜在的临床应用，为白藜芦醇在乳腺癌的应用提供参考价值。

2. 白藜芦醇对乳腺癌分子机制

2.1. 抑制细胞增殖

细胞周期的严格调控对正常细胞增殖至关重要。而癌细胞通常通过扰乱这一调控机制实现无限增殖。

研究表明，白藜芦醇将细胞周期阻滞在 S 期，抑制 4T1 细胞的增殖[16]。白藜芦醇通过抑制细胞周期蛋白依赖性激酶(CDK)2、CDK4 和 CDK6，使 MCF-7 细胞停留在 G1 期[17]。白藜芦醇介导 p53 和 p21 途径，抑制 MCF-7 和 MDA-MB-231 细胞的增殖[18]。Giménе 等研究进一步表明白藜芦醇介导 p53/p21Cip1/Waf1 通路，阻滞细胞在 G2/M 期，抑制其增殖[19]。可见，白藜芦醇通过抑制细胞周期相关的蛋白及信号通路来抑制乳腺癌细胞增殖。

白藜芦醇能调控多种信号通路，抑制乳腺癌细胞的增殖[20]。PI3K/AKT 信号通路异常激活在乳腺癌等多种癌症中普遍存在。白藜芦醇通过抑制 PI3K/Akt/mTOR 通路，抑制多种乳腺癌细胞的增殖[21]-[24]。白藜芦醇还能调节丝裂原活化蛋白激酶家族成员(MAPK)的信号通路，通过级联反应调节细胞增殖。主要是通过抑制细胞外信号调节激酶 1 和 2(ERK1/2) [18] [25] [26]和 p38MAPK [18]的活性，阻止乳腺癌细胞的增殖。然而，有研究表明，白藜芦醇能上调 SK-BR-3 细胞 ERK1/2 的活性，抑制细胞凋亡[27]。此外，白藜芦醇还可通过核因子 κB(NF-κB) [28]、信号转导与转录激活因子 3 (STAT3) [29]、Notch [30]等信号通路抑制乳腺癌细胞的增殖。

2.2. 诱导细胞凋亡

诱导细胞凋亡在癌症治疗中起着重要的作用。多项研究表明，白藜芦醇可通过降低线粒体膜电位[31] [32]、诱导半胱氨酸天冬氨酸蛋白水解酶(Caspase)家族级联反应[33] [34]、以及调节 Bcl-2 家族蛋白[33] [35]等机制，诱导乳腺癌细胞凋亡。白藜芦醇能联合辐射上调促凋亡蛋白 Bax、caspase-3 和 caspase-8 的表达，下调抗凋亡蛋白 Bcl-2，诱导 MCF-7 细胞凋亡[32]。白藜芦醇以剂量依赖的方式降低 DNA 聚合酶催化亚基 1 (POLD1)的 mRNA 和蛋白质表达，抑制增殖细胞核抗原(PCNA)和抗凋亡蛋白 Bcl-2 的表达，促进多腺苷二磷酸核糖聚合酶(PARP)和 caspase-3 的活化，促进三阴性乳腺癌(TNBC)细胞的凋亡[33]。

白藜芦醇还通过调控相关的信号分子诱导乳腺癌细胞凋亡。白藜芦醇依赖 p53 途径诱导野生型 p53 系 MCF-7 细胞凋亡[20]。进一步研究发现，白藜芦醇可与 MCF-7 细胞的 p53 核心结构域(p53C)存在相互作用，但能减少含有突变型 p53 的肿瘤细胞系(MDA-MB-231 和 HCC-70) p53C 蛋白的聚集[36]。这一发现为白藜芦醇通过调节 p53 对抗癌症提供了直接证据。Paula 等研究表明，白藜芦醇通过抑制酪蛋白激酶 2 (CK2)的表达，增强细胞内活性氧(ROS)的生成，显著降低线粒体膜电位，诱导细胞凋亡[37]。MicroRNAs (miRNAs)是一类非编码 RNA，参与癌症相关的生物学过程的调控。白藜芦醇通过调节 miRNA-122-5p 的表达，提高乳腺癌细胞对阿霉素的化学敏感性，诱导细胞凋亡[17]。此外，白藜芦醇也可调控 NF-κB [28]、MAPK [38]、STAT3 [39]、PI3K/AKT/mTOR [27]等信号通路诱导乳腺癌细胞凋亡。

2.3. 诱导细胞自噬

自噬是维持内稳态和细胞生存重要机制。在癌细胞中，自噬具有双重功能：既可以保护癌细胞免于凋亡，促进肿瘤细胞转移，又能抑制肿瘤细胞增殖，增加化疗的敏感性[40] [41]。白藜芦醇通过激活沉默信息调节蛋白 3 (SIRT3)/磷酸化 AMP 活化蛋白激酶(AMPK)信号通路诱导细胞自噬，从而抑制 4T1 细胞侵袭和转移，以及异种移植小鼠肿瘤的生长[42]。白藜芦醇也可与其他药物联合诱导细胞自噬。白藜芦醇调节乳腺癌细胞自噬受肿瘤微环境、细胞类型等因素的影响。白藜芦醇可抑制细胞自噬，阻碍 PARP 抑制剂 talazoparib 对 MCF-7 细胞的增殖[43]。然而白藜芦醇联合二甲双胍也可促进细胞自噬，增强 MCF-7 细胞凋亡[44]。这表明，白藜芦醇介导自噬既可抑制肿瘤细胞的凋亡，又可促进肿瘤细胞的凋亡，提示自噬和凋亡在肿瘤细胞中存在复杂的相互作用。

2.4. 抑制细胞迁移和侵袭

上皮间充质转化(EMT)是癌细胞获得迁移和侵袭能力的关键过程。EMT 表型的特征，主要是上皮标

记物的表达减少和间充质标记物的表达增加。E-cadherin 是上皮细胞之间的重要黏附分子，其表达的丧失是 EMT 的重要标志。白藜芦醇通过增加组蛋白乙酰化，上调 E-cadherin 和 p21 的表达，阻止癌细胞迁移[24]。转化生长因子 β (TGF-β)是诱导 EMT 的重要信号通路[45]。研究表明，白藜芦醇通过抑制 TGF-β1 介导的 EMT 来抑制乳腺癌的迁移和侵袭[42] [46]。同时，白藜芦醇会下调 N-cadherin，β-catenin，vimentin，snail 和 slug 等间质细胞标志物抑制乳腺癌细胞迁移[46] [47]。某些基质金属蛋白酶(MMPs)是一类能够降解细胞外基质(ECM)的酶，在癌细胞迁移和侵袭过程中发挥重要作用。白藜芦醇主要通过抑制 MMP-2 和 MMP-9 的表达和活性，阻止乳腺癌细胞的迁移和侵袭[46] [48]。此外，白藜芦醇通过 PI3K/AKT 和 Wnt/β-catenin 信号通路抑制 MCF-7 细胞的侵袭和迁移[49]。白藜芦醇也可非竞争性地抑制 Na^+依赖的 Pi 转运体，以抑制 MDA-MB-231 细胞的迁移[50]。由此可见，白藜芦醇通过调节相关信号通路，抑制 EMT 转化和某些金属蛋白酶的表达，来抑制乳腺癌细胞迁移和侵袭。

2.5. 重组细胞代谢

癌细胞与正常细胞之间存在显著的新陈代谢差异。癌细胞更倾向利用糖酵解途径来满足增殖和生长需求。白藜芦醇通过抑制 6-磷酸果糖-1-激酶(PFK)，降低 MCF-7 细胞的活力、葡萄糖消耗和 ATP 含量[51]。白藜芦醇也可调节转录因子 c-Myc，进而抑制 PI3K/AKT 通路降低途径磷酸甘油酸激酶 1 (PGK1)的表达，抑制 BT-549 细胞中糖酵解途径[52]。脂质代谢异常也是癌症代谢的另一个显著特征。白藜芦醇能降低 MCF-7 和 MDA-MB-231 细胞中的磷脂，增加脂肪酸，并调控脂质代谢相关的酶类物质，从而抑制癌细胞的增殖[22] [53]。可见，白藜芦醇通过调节糖代谢和脂质代谢途径，对抗乳腺癌细胞的恶性生物学行为。

3. 逆转药物耐药性，增强药物敏感性，联合药物协同治疗

3.1. 逆转化疗药物耐药性

乳腺癌的化疗药物，如顺铂和阿霉素往往会导致乳腺癌产生耐药性，影响治疗效果。研究表明，白藜芦醇与顺铂联合使用对乳腺癌细胞具有协同抑制作用。具体而言，白藜芦醇通过调控 PI3K/AKT、Smad、NF-κB、JNK 和 ERK 途径抑制 EMT，从而抑制 MDA-MB-231 细胞的迁移和侵袭，降低乳腺癌细胞对顺铂耐药性[54]。此外，白藜芦醇通过调节与阿霉素耐药相关的基因表达(如 CCND1、CDH1、ESR1、PTPN11、HSP90、HSP70 和 MAPK3)，增强阿霉素在乳腺癌中的长期毒性[55]。联合他莫昔芬，白藜芦醇可上调 p53 和 caspase-8 的表达，诱导 MCF-7 和 CAL-51 细胞凋亡[56]。

3.2. 增强放疗药物敏感性

放疗对乳腺癌治疗常会导致耐药性及产生副作用。白藜芦醇提高乳腺癌细胞对放疗的敏感性。10 μmol/L 白藜芦醇和 3 Gy 电离辐射联合使用，通过降低 Bax/Bcl-2 比值，激活 caspase 8，诱导 MCF-7 细胞凋亡，并且通过增加 p53 表达和阻滞细胞周期来抑制细胞增殖[57]。

3.3. 联合药物协同治疗

白藜芦醇与传统化疗药物联合使用，显示出协同抗癌作用。索拉非尼是 ERK1/2 通路的组成部分，是一种多激酶抑制剂。白藜芦醇协同低剂量的索拉非尼能够通过上调 ROS 水平，p53，caspase-9、caspase-3 和 Bax/Bcl2 表达，增加 PARP 的裂解，促进细胞凋亡[58]。白藜芦醇与化疗药物 FL118 联合使用还能抑制 EMT，抑制迁移和侵袭[47]。此外，白藜芦醇可以与其他天然化合物联合使用，协同治疗乳腺癌。例如，白藜芦醇和原花青素联合作用可通过上调 Bax 表达和下调 Bcl-2 表达，促进 MDA-MB-231 细胞的

凋亡，降低 DNA 甲基转移酶活性和组蛋白去乙酰化酶(HDAC)活性，调节 DNA 甲基化和组蛋白修饰，抑制乳腺癌细胞[59]。

白藜芦醇对乳腺癌作用的靶点及机制总结见表 1。

Table 1. Mechanisms of action of resveratrol on breast cancer
表 1. 白藜芦醇对乳腺癌的作用机制

细胞类型	白藜芦醇剂量	分子机制和效果	参考文献
4T1	50~250 μmol/L	增加 S 期细胞数量增加，减少 G1/G0 细胞中的细胞数量，抑制细胞周期，诱导细胞凋亡。	[16]
MCF-7	100、200、300 μmol/L	增强 miRNA-122-5p 的表达，降低 Bcl-2、CDK2、CDK4 和 CDK6 的表达，诱导细胞凋亡和细胞周期阻滞。	[17]
MCF-7、MCF-10A MDA-MB-231	0.5、1、10 μmol/L	依赖 ABC 转运体，通过 p53/p21Cip1/Waf1 通路，阻滞细胞 G2/M 期，抑制细胞生长。	[19]
MDA-MB-231、HCC-70、MCF-7	0.005~5 μmol/L	减少含有突变型 p53 的肿瘤细胞系中 p53 的聚集，抑制细胞增殖。	[36]
MCF-7、T47D	0、10、20、40、80 μmol/L	抑制 ERK1/2/EZH2 通路，抑制细胞的增殖。	[26]
MCF-7	50~500 μmol/L	降低乙二醛酶 1(GLO1)的表达，降低线粒体膜电位，诱导线粒体功能障碍，对细胞产生毒性。	[31]
MCF-7、MDA-MB-231	10、25、50 μmol/L	增加 SIRT1 表达，增强细胞毒性，诱导癌症干细胞分化。	[60]
MCF-10A-Tr	5~100 μmol/L	提高 p21 的表达，降低抗凋亡蛋白质(PI3K、AKT、NF-κB)的表达，降低细胞周期调节蛋白(Cyclins, CDC-2, CDC-6)和碱基切除修复蛋白，诱导细胞凋亡。	[23]
MDA-MB-231、MCF-10A	100、200 μmol/L	下调 POLD1 的 mRNA 和蛋白质表达，抑制 PCNA 和 Bcl-2 的表达，促进 PARP 的活化和 caspase-3 的裂解，促进细胞凋亡。	[33]
MCF-7	50~400 μmol/L	通过抑制酪蛋白激酶 2 (CK2)的表达，增强 ROS 的生成，显著降低线粒体膜电位，诱导细胞凋亡。	[37]
MDA-MB-231	0、10、20、40、80、160 μmol/L	调控 Notch 通路的 Notch1、Dll4 和 Hes-5 的 mRNA 和蛋白质，抑制乳腺癌细胞的生长和增殖。	[30]
MDA-MB-231	0~80 μg/mL	在低氧环境中，低浓度白藜芦醇(0~10 μg/mL)激活 JAK3/STAT3 信号通路促进细胞增殖和迁移，高浓度白藜芦醇(20~80 μg/mL)通过 MAPK 信号通路抑制细胞增殖，诱导自噬和凋亡。	[38]
BT-549	2、4、8、16、32、64、128 μg/mL	通过调节 c-Myc/PI3K/AKT，降低细胞中 PGK1 的表达，阻断细胞糖酵解途径，抑制细胞增殖。	[52]
MCF-7、MDA-MB-231	10、25、50、100 μmol/L	抑制细胞周期蛋白 D1、c-Myc、MMP-2 和 MMP-9 表达，抑制 CAF-CM 诱导的乳腺癌细胞的迁移和侵袭。	[61]
MDA-MB-231、MDA-MB-453、MDA-MB-436、BT-549 无胸腺裸鼠	0、12.5、25、50、100 μmol/L 40 mg/kg	上调 E-cadherin，降低 MMP-2、MMP-9、fibronectin、α-SMA、P-PI3K、P-AKT、Smad2、Smad3、P-Smad2、P-Smad3、vimentin、snail1 和 slug 的表达，逆转 TGF-β1 诱导的 EMT 来抑制细胞的迁移，并抑制小鼠模型的肺转移。	[46]

续表

MDA-MB-231	10mM	抑制 Na 依赖的 Pi 转运体，抑制粘附或迁移。	[50]
4T1、 异种移植小鼠	12.5、25、50 μmol/L 40 mg/Kg	通过激活 SIRT3/AMPK/自噬途径，抑制 TGF-β1 介导的 MMP-9、EMT 相关标记物的表达，抑制乳腺癌细胞的迁移和侵袭以及异种移植小鼠肿瘤的生长。	[42]
MCF10A、MCF-7	1~25 μmol/L	增加 GLI2 和 WNT4 增强子内的 DNA 甲基化，下调 Hedgehog 和 Wnt 信号下游基因，通过在表观遗传方面的改变降低致癌信号通路。	[62]
小鼠肿瘤模型	12.5、25 mg/kg	通过抑制 PD-1 的表达，促进 CD8 + T 和 Th1 细胞的免疫反应，增加 IFN-γ 和 IL-2 的数量，增强抗肿瘤免疫，防止乳腺癌细胞的肺转移。	[63]
MCF-7	10~50 μmol/L	通过上调 Rad9 作为肿瘤抑制因子，降低 EMT 标志物的表达水平，下调 Slug，抑制细胞增殖，抑制细胞侵袭和迁移。	[64]
SK-BR-3、MCF-7、MDA-MB-231、T47D	10、15、20、25 μmol/L	联合通过抑制 HER-2、AKT，MAPK 途径，增强多西紫杉醇诱导细胞凋亡，提高多西紫杉醇的化疗疗效。	[27]
MCF-7、MDA-MB-231	10、20、50、100、200 mg/L	抑制 PI3K/AKT/mTOR 信号通路，上调促凋亡蛋白 caspase-3 的表达，抑制对阿奇霉素耐药的乳腺癌细胞的增殖和转移，促进细胞凋亡。	[65]
MCF-7	10 μmol/L	与 3 Gy 电离辐射联合使用，降低 Bax/Bcl-2 比值，激活 caspase 8，诱导细胞凋亡，增加 S 期细胞数量，上调 p53 表达，抑制细胞增殖。	[57]
BT-549、Cal51	0、20、50、100 μmol/L	协同 piceatannol 药物通过介导 NF-κB 程序性细胞死亡配体 1 (PD-L1)，上调 DNA 损伤指标 γH2AX，caspase 3 的活化，下调 p38-MAPK 和 c-Myc，诱导 G1/S 细胞周期阻滞，降低细胞存活。	[66]
MCF-7	10、30、60、120 μmol/L	调节与阿霉素治疗耐药的基因 CCND1、CDH1、ESR1、PTPN11、HSP901、HSPAA1 和 MAPK3 的表达，增加阿霉素在乳腺癌中的长期毒性。	[55]
MCF-7	25~1000 μmol/L	联合辐射和热疗上调 Bax，激活 caspase-3，下调 Bcl-2，降低细胞活力，诱导细胞凋亡，增强辐射和热疗对 MCF-7 细胞的影响。	[32]
MDA-MB-231	12.5~250 μmol/L	与顺铂联合作用，通过 PI3K/AKT、Smad、NF-κB、JNK 和 ERK 途径调控 EMT，抑制细胞的迁移和侵袭。	[54]
MDA-MB-436、MDA-MB-468	1~200 μmol/L	联合 FL118 药物，激活 Caspase-3/7 水平，细胞周期停留在 G1 期，下调 N-cadherin、β-catenin、vimentin、snail 和 slug 的表达，上调 E-cadherin 的表达，逆转 EMT，诱导细胞凋亡，抑制细胞侵袭和迁移。	[47]
MDA-MB-231、T-47D、THP-1	25 μmol/L	联合顺铂，通过促进 M1/M2 巨噬细胞极化率，抑制 IL-6/pSTAT3 通路，抑制乳腺癌细胞增殖。	[67]
MCF-7、T47D	0~30 μmol/L	和奥拉帕尼联合治疗，引起过度的 DNA 损伤，并同时抑制同源重组修复途径(HR 通路)，增强乳腺癌细胞的死亡。	[68]

续表

MCF-7、MCF-10A、MDA-MB-231、免疫缺陷的雌性SCID 小鼠	0、12.5、25、50、100 μmol/L 50 mg/kg	通过双重抑制 AKT 磷酸化和自噬通量，增强 talazoparib 药物对乳腺癌敏感性，并减少 SCID-小鼠模型中肿瘤体积。	[43]
MCF-7	70、144、287、383、575 μmol/L	和二甲双胍联合作用，降低 ROS，增加 G0/G1 细胞数量，上调 LC3-II，诱导细胞周期阻滞，诱导细胞自噬和凋亡。	[44]

4. 结论与展望

综上所述，白藜芦醇在多种乳腺癌细胞类型均表现出显著的抗肿瘤活性。白藜芦醇通过调节 PI3K/AKT、p53、MAPK 等信号通路及细胞周期相关蛋白，抑制癌细胞增殖；通过调节相关信号分子，激活 Caspase 级联反应，调节 Bcl-2 家族蛋白，诱导细胞凋亡；通过调节自噬信号分子，调控细胞自噬(诱导和抑制)；通过调控 MMP、EMT 和相关分子通路(TGF-β、STAT3、NF-κB)，减少乳腺癌细胞的转移和侵袭；通过调节糖酵解和脂质代谢，重组细胞代谢；通过影响化疗和靶向药物的信号分子，增强药物敏感性。

尽管白藜芦醇在乳腺癌抗癌机制方面表现出显著效果，但其临床应用仍面临诸多挑战。白藜芦醇由于其疏水性和化学不稳定性等特性导致在体内的生物利用度较低，限制其抗癌效果。近年来，利用脂质纳米颗粒[69]、环糊精纳米海绵[70]和聚合物载体[71]等纳米技术，实现药物的靶向传送，显著提高白藜芦醇的治疗效率。此外，关于白藜芦醇细胞作用机制的研究仍处于早期阶段，其在乳腺癌中的作用机制复杂多样，缺乏完善的系统网络途径。新技术和新方法的出现，将有助于更全面地揭示白藜芦醇抗乳腺癌的分子机制，为未来的临床应用提供更多可信的理论支持。

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