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金银花活性成分诱导癌细胞凋亡的信号网络机制

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摘要 化疗、放疗及免疫抑制剂等常规疗法虽能遏制癌症的进展, 但常伴随严重的免疫损伤和感染风险。因此, 临床急切需要开发安全性高、疗效确切的替代方案。在癌症的机制研究中, 细胞凋亡被认为是评价抗癌药物疗效的关键指标。然而, 现有的细胞凋亡研究多聚焦于对PI3K/AKT、MAPK等单一信号通路的解析, 缺乏对信号通路上、下游级联调控网络及多通路交叉对话(cross-talk)的系统整合。中药金银花(Lonicerae japonicae Flos)具有“清热解毒”功效, 现代药理研究证实其富含的黄酮类及有机酸类活性成分在诱导癌细胞凋亡方面疗效显著, 但其分子机制尚未被系统阐明。该文重点综述金银花活性成分通过多维信号网络及多靶点协同调控干预癌细胞凋亡的研究现状, 旨在为中药小分子药物的临床转化及抗癌机制研究提供系统性的视角。

关键词 金银花; 活性成分; 细胞凋亡; 抗肿瘤

Research Progress on the Effects of the Active Components of Lonicerae Japonicae Flos on Cancer Cell Apoptosis

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Abstract Regular cancer therapies, such as chemotherapy, radiotherapy and immunosuppressants, often give rise to severe immunotoxicity and increased infection risks; hence, alternative therapeutic regimens with enhanced safety profiles and proven efficacy are urgently demanded. As apoptosis remains a critical mechanistic hallmark for evaluating anticancer drug effectiveness, current studies often focus on a few isolated signaling pathways, including PI3K/AKT (phosphatidylinositol 3-kinase/protein kinase B) and MAPK (mitogen-activated protein kinase). As a result, these evaluations usually fail to provide a multi-pathway crosstalk view for pharmacology. Since LJF (Lonicerae japonicae Flos) contains abundant bioactive flavonoids and organic acids with apoptosis induction capacity in various cancer cells, this article comprehensively summarizes recent progress regarding LJF active components in regulating cancer cell apoptosis via multi-dimensional signaling networks and multi-target synergistic interventions here. This work aims to provide a systematic perspective to support the clinical translation of LJF-derived small molecules and the further exploration of their anticancer mechanisms.

Keywords Lonicerae japonicae Flos; active component; apoptosis; anti-tumor

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据世界卫生组织(World Health Organization, WHO)统计, 癌症已成为危害人类健康的主要疾病, 全球约六分之一的人口死亡与恶性肿瘤相关[1]。化疗是目前临床癌症治疗的主要方式, 然而, 化疗药物的应用常导致患者产生耐药性, 或因免疫损伤而引发继发性感染等毒副作用。因此, 探寻并开发低毒、高效的天然植物药成为肿瘤临床研究的重要方向。传统中药凭借其安全性高、耐受性好以及药理活性确切的综合优势, 在临床转化与新药研发领域展现出显著的应用潜力。随着对传统中药癌症治疗机制的深入探究, 细胞凋亡(apoptosis)已被确定为基础研究中评价抗癌药效的核心指标之一[2]。

金银花(Lonicerae japonicae Flos)是由忍冬科植物忍冬(*Lonicera japonica* Thunb.)的花蕾或待初开的花干燥后制成, 主要产区在中国山东、河南、河北等地。作为传统“清热解毒”功效的经典药食同源的中药材, 金银花含有丰富的生物活性物质, 展现出潜在的抗癌活性。此外, 金银花还具有抗菌、消炎、抗病毒、抗氧化、抗糖尿病、保肝、保护心血管及神经系统、增强机体免疫功能和降血脂等药理作用[3]。因此, 本文通过在中国知网(China National Knowledge Infrastructure, CNKI)、万方、PubMed、Google Scholar、Web of Science等中英文数据库中查询自2016至2025年间发表的文献, 明确金银花中具有抗癌活性的代表性化学成分(图1), 并对其诱导癌细胞凋亡的分子机制相关的通路和分子, 如磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, AKT)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、信号转导与转录激活因子3(signal transducer and activator of transcription 3, STAT3)、核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)/Kelch样ECH关联蛋白1(Kelch-like ECH-associated protein 1, Keap1)、Ca^{2+}和microRNA等进行分析和归纳。

1 金银花提取物的抗癌研究

尽管现阶段金银花单味制剂的抗肿瘤基础研究与临床研究相对匮乏, 但基于其提取物和关键活性成分与抗肿瘤之间的谱效关联研究, 进一步开发新型制剂和构建协同疗法的策略在金银花肿瘤防治研究中展现出广阔的应用前景。例如, 金银花的“核心成分”绿原酸(chlorogenic acid)的抗肿瘤作用已在多种癌细胞模型中得到验证, 且具有独特的研发优势。LAS^{NB}(一种含绿原酸的中药复方)可同时阻断受体酪氨酸激酶(receptor tyrosine kinase, RTK)-丝裂原活化蛋白激酶激酶(MAPK/ERK kinase, MEK)-细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)和核因子-κB(nuclear factor-κB, NF-κB)信号通路, 抑制人结肠癌细胞HCT116、HCT15和小鼠结肠癌细胞CT26的增殖以阻滞结肠癌恶性进展, 表明绿原酸是金银花等中药发挥抗肿瘤活性的关键效应成分[4]。另外, 炮制药理学研究证实, 不同温度制备的金银花炮制品(药效核心物质仍以绿原酸为主)对非小细胞癌细胞A549和胃癌细胞MGC80-3的抑制作用显著高于肝癌细胞SMMC-7721, 提示绿原酸的抗肿瘤作用具有明显的选择特异性[5]。

相较于单一活性成分, 金银花总提取物依据其多成分协同作用的特点发挥广谱抗肿瘤效应。其中, 以芦丁(rutin)、木犀草苷(luteolin-7-*O*-glucoside)为代表的金银花黄酮类活性组分通过调控AKT/雷帕霉素靶蛋白(mechanistic target of rapamycin, mTOR)、ERK和Keap1/Nrf2/抗氧化反应元件(antioxidant response element, ARE)信号通路, 有效诱导肝癌细胞HepG2、SMMC-7721发生凋亡, 进而抑制肝癌细胞恶性增殖[6-7]。金银花多酚类提取物可下调AKT信号通路活性, 同时激活Caspase凋亡级联反应, 通过线粒体内源性凋亡通路介导A549非小细胞肺癌细胞凋亡[8]。而负载金银花水提物的家蚕丝素蛋白生物膜材料, 凭借自身良好的生物相容性、可降解性以及药物长效缓释的优势, 高效诱导HeLa宫颈癌细胞凋亡, 这为金银花活性成分与生物材料联合应用于肿瘤局部治疗提供了新思路[9]。此外, 金银花提取物还可与光动力治疗产生协同抗肿瘤效应, 二者协同激活PKCδ信号分子, 启动肺鳞癌细胞CH27线粒体凋亡通路[10]。

2 金银花活性成分的结构与含量比例

中药长久以来的用药经验显示, 除了部分通过肠道菌群调节发挥作用的物质外, 被吸收进入全身循环系统的成分最可能是该中药的生物活性成分。因此, 本文系统分析绿原酸、咖啡酸(caffeic acid)、木犀草苷、槲皮素(quercetin)、木犀草素(luteolin)和芦丁等金银花入血成分诱导癌细胞凋亡的分子

机制，各成分结构式见图1[11-12]。上述6种成分在金银花中的含量比例呈现显著梯度差异。其中，绿原酸为最主要成分以高效液相色谱法(high performance liquid chromatography, HPLC)、超高效液相色谱法(ultra performance liquid chromatography, UPLC)和液相色谱–质谱联用(liquid chromatography-mass spectrometry, LC-MS)测得的含量总体介于2.5%至3.0%之间[13-25]，远高于芦丁(0.039%~0.117%)[13-14,19,22-24,26-30]、木犀草苷(0.011%~0.088%)[13-14,17-19,21-29,31]、木犀草素(约0.011%~0.013%)[14,19,21,24,26,31-32]、咖啡酸(0.006 6%~0.016 6%)[21-22,24,28]和槲皮素(约0.004%)[19,31]的含量范围。因此，6种成分的含量排序为绿原酸>芦丁>木犀草苷≈木犀草素≈咖啡酸>槲皮素，各自结构式见图1。虽然不同检测方法所得数值略有波动，但各成分的相对丰度次序一致。由此可知，金银花以绿原酸为质量标志物，并辅以多种黄酮协同作用，为其药效物质基础研究提供了明确的量化依据，见表1。

3 细胞凋亡途径

细胞的凋亡途径可分为内源性(线粒体)凋亡和外源性(死亡受体)凋亡，由Caspases家族蛋白启动和执行。其中，Caspase-8和Caspase-9分别是外源性和内源性细胞凋亡的启动者，负责激活下游的Caspase-3和Caspase-7执行蛋白[33]。Caspase-3的活化是细胞凋亡发生的标志性事件。

3.1 内源性凋亡

内源性凋亡程序受Bcl-2家族蛋白精密调控，该家族依据功能可分为抗凋亡蛋白(Bcl-2、Bcl-xL、Mcl-1等)与促凋亡蛋白(Bax、Bak)两大类，此两类蛋白的活性平衡状态直接决定细胞凋亡命运[34]。

内源性凋亡起始于DNA损伤、氧化应激等刺激诱导的BH3-only蛋白(Bid、Bim、PUMA、NOXA等)

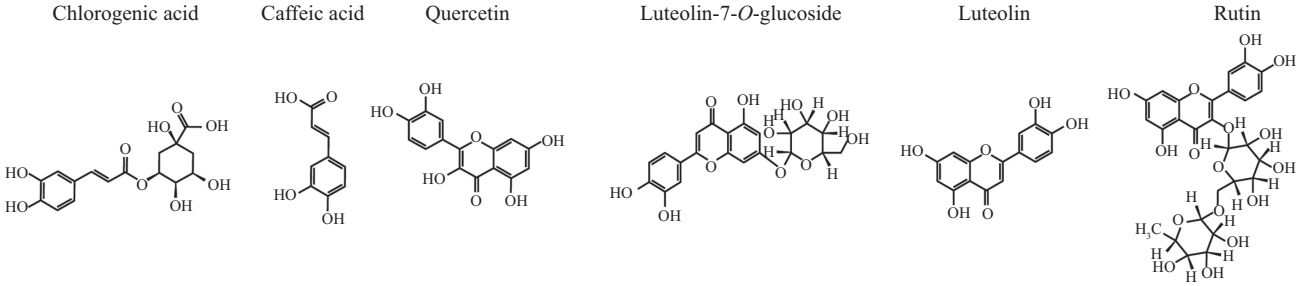


图1 金银花中6种活性成分基本结构

Fig.1 Basic structures of six active components in LJF

表1 6种活性成分在金银花中的含量比例

Table 1 Contents and proportions of six active components in LJF

成分 Component	含量比例/% Content /%			参考文献 References
	HPLC	UPLC	LC-MS	
Chlorogenic acid	2.917 6	3.040 7	2.521 7[a]	[13-25]
			4.528 6[b]	
Caffeic acid	0.009 4	0.016 6	0.006 6[a]	[21-22,24,28]
			0.029 1[b]	
Luteolin-7-*O*-glucoside	0.087 7	0.063 4	0.010 6[a]	[13-14,17-19,21-29,31]
			0.069 9[b]	
			0.051 7[c]	
Rutin	0.116 8	0.108 9	0.039 1[a]	[13-14,19,22-24,26-30]
			0.057 2[b]	
			0.061 7[c]	
Luteolin	0.011 2	—	0.013 3[b]	[14,19,21,24,26,31-32]
Quercetin	0.004 3	—	—	[19,31]

LC-MS数据涵盖UPLC-TSQ-MS[a]、UFLC-QTRAP-MS[b]及UPLC-MS/MS[c]三种技术平台。—: 未提及。

The LC-MS data were generated using three technical platforms, namely UPLC-TSQ-MS[a], UFLC-QTRAP-MS[b], and UPLC-MS/MS[c]. —: not mentioned.

表达上调, 其中Bim竞争性结合Bcl-2, 释放并激活Bax。活化的Bax嵌入线粒体外膜与Bak结合, 寡聚成孔, 引发线粒体外膜通透化(mitochondrial outer membrane permeabilization, MOMP)、线粒体膜电位(mitochondrial membrane potential, MMP)下降以及细胞色素C(cytochrome C, Cyto-C)与SMAC/DIABLO释放。其中, Cyto-C可同胞质中的Apaf1蛋白和dATP组装形成凋亡体, 进而激活凋亡启动蛋白Caspase-9; SMAC则拮抗凋亡抑制蛋白(inhibitor of apoptosis proteins, IAPs)家族——IAP1/2和XIAP, 解除其对Caspase-9的抑制, 活化的Caspase-9进一步切割激活Caspase-3和Caspase-7, 推动凋亡发生, 见图2[35]。

3.2 外源性凋亡途径

外源性凋亡程序主要由死亡配体(FasL、TNF-α、TRAIL等)结合细胞膜表面对应的死亡受体(Fas、TNFR、DR5等)启动, 随后受体招募连接蛋白FADD、cFLIPs进而与Pro-Caspase-8组装, 形成死亡诱导信号复合物。此复合物促使Caspase-8完成聚合、自切割和活化, 而活化的Caspase-8一方面直接激活Caspase-3和Caspase-7, 剪切聚(ADP-核糖)聚合酶[Poly (ADP-ribose) polymerase, PARP]使其失活, 阻碍DNA修复; 另一方面将Bid水解为tBid, 生成的tBid则转位至线粒体激活Bax, 以此交联外源性、内源性两条凋亡通路, 见图2[36]。

4 凋亡相关调控通路

IAPs是Caspases最直接的上游负调控因子。除此之外, 亦有多条信号通路或通过蛋白级联反应及相关转录因子的转录水平, 调控Bcl-2家族和Caspases活性来介导细胞凋亡[37]。而依据调控效应可将相关信号通路分为促凋亡和抗凋亡两类。其中, p53、MAPK[包括p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38 MAPK)和

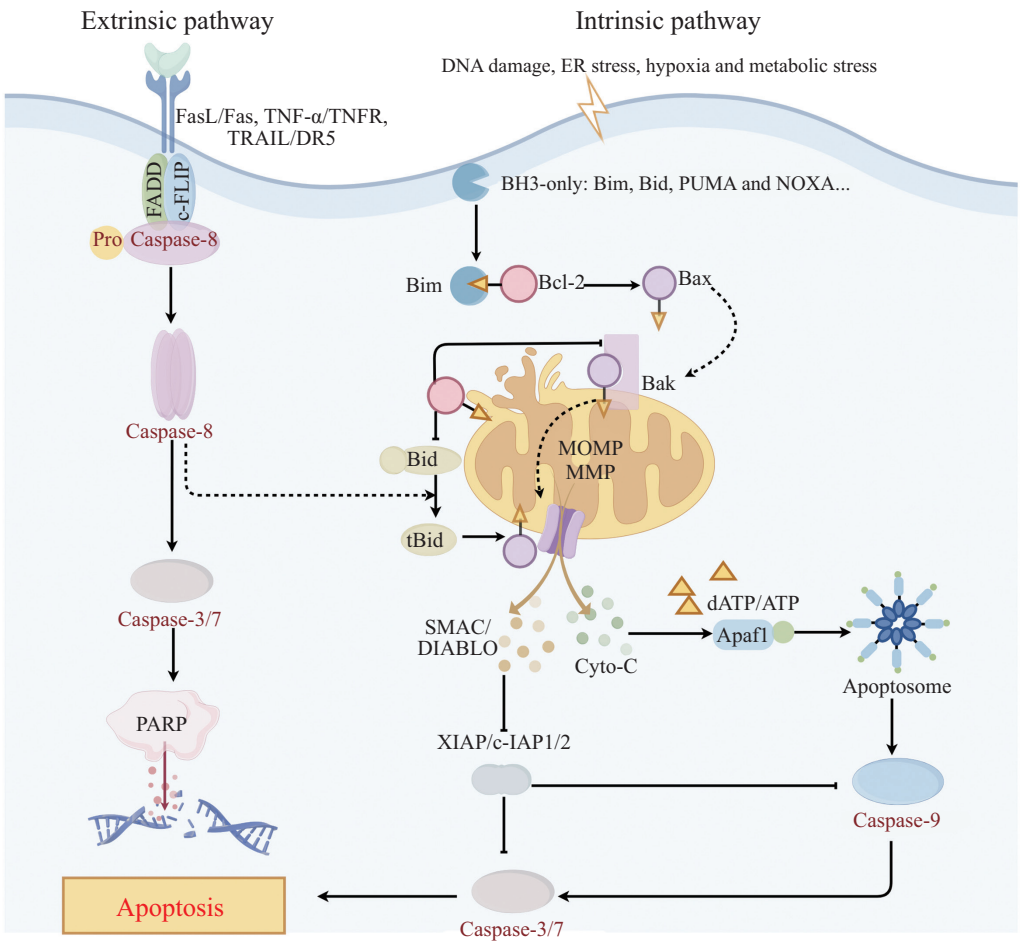


图2 由Caspase调控的内源性和外源性凋亡示意图

Fig.2 Schematic illustration of Caspase-mediated intrinsic and extrinsic apoptotic pathways

c-Jun氨基末端激酶1/2(c-Jun N-terminal kinase 1/2, JNK1/2)]、Ca^{2+}超载和microRNA表观遗传调控可上调Caspase或下调Bcl-2家族成员的表达, 进而促进细胞凋亡。而PI3K/AKT[包括叉头框蛋白O1(forkhead box protein O1, FOXO1)、NF-κB和mTOR]、STAT3和Nrf2/Keap1等信号通路可抑制Caspases表达、上调Bcl-2等抗凋蛋白的表达而拮抗细胞凋亡。其中ERK1/2具有双向调控特性, 在不同细胞背景下可分别发挥促凋亡或抑凋亡作用。

5 金银花来源的成分诱导癌细胞凋亡机制

本文在对金银花及其提取物抗癌研究的基础上, 系统性地梳理了其黄酮类与有机酸类的活性成分对细胞凋亡相关信号通路的调控规律, 揭示了其干预肿瘤的共性和特性机制。

金银花活性成分通过激活促凋亡信号通路和抑制抗凋亡信号通路, 在肝癌、胃癌、非小细胞肺癌、三阴性乳腺癌及多种生殖、骨骼系统恶性肿瘤细胞中展现出显著的促凋亡效应。其中, 木犀草素以激活p53、p38 MAPK和JNK通路为核心, 同时抑制NF-κB、FOXO1和STAT3信号通路形成促凋亡与抑制生存的双重调控; 槲皮素侧重激活JNK通路并辅以microRNA表观遗传调控, 同时协同抑制AKT和NF-κB通路; 芦丁主要依赖microRNA介导的表观遗传来调控凋亡程序; 木犀草苷通过激活p38 MAPK和JNK信号通路, 抑制mTOR信号以及直接激活死亡配体途径实现三重调控凋亡程序; 而有机酸成分绿原酸则通过激活p38 MAPK和p53通路, 抑制ERK1/2、AKT和NF-κB信号通路调控癌细胞凋亡; 咖啡酸主要通过调控胞内钙离子水平和特异性抑制Nrf2/Keap1通路, 降低细胞解毒能力而调控细胞凋亡, 详见表2[38-69]。

5.1 金银花活性成分促凋亡调控

5.1.1 p53信号通路 肿瘤抑制蛋白p53的主要功能在于持续监控细胞基因组完整性并对DNA损伤进行响应, 其失活或转录功能丧失与癌症发生密切相关。p53可依据DNA的损伤程度决定细胞命运: 对于可修复的DNA损伤, p53通过激活下游靶基因的转录以阻滞细胞周期, 促进DNA修复; 当损伤不可修复时, p53被激活并通过上调促凋亡基因转录和表达, 启动内源性凋亡程序以清除异常细胞[70]。此外, 在氧化应激状态下, p53可被ATM/ATR等激酶直接激活, 转位至线粒体与Bcl-2家族蛋白相互作用, 导致MOMP水平的升高和Cyto-C的释放, 从而激活内源性凋亡程序[71]。

在抗肝癌相关研究中, 木犀草素可通过激活肝癌细胞HepG2中p53通路, 使线粒体中Bax/Bcl-2蛋白比例失衡而激活内源性凋亡[38]。而在肝癌细胞Huh-7中, 木犀草素通过靶向抑制AKT1活性, 介导MDM2蛋白磷酸化失活, 稳定并激活p53蛋白, 使其转位至核内, 上调BH3-only家族*PMAIP1*、*BBC3*等基因表达[39]。而对于非小细胞肺癌, 木犀草素亦可通过上调A549细胞和移植H460细胞的小鼠模型中miR-34a-5p的表达, 抑制MDM4的活性, 从而解除其对*TP53*的转录抑制, 进而激活内源性凋亡途径[40]。除此之外, 槲皮素可嵌入DNA双螺旋结构, 直接激活*TP53*基因, 进而促进靶基因*BAX*转录和翻译, 诱导Swiss albino小鼠和Nalm6人急性淋巴细胞白血病细胞凋亡, 见图3[50]。

由上述内容可知, 金银花中的成分通过多靶点、多层次的分子交互, 精细调控p53介导的凋亡程序。金银花中的黄酮类成分主要通过三种途径激活p53介导的抗肿瘤效应: 首先, 通过抑制负反馈调节因子鼠双微体2(mouse double minute 2, MDM2)的活性, 解除其介导的p53蛋白泛素化降解, 提高p53蛋白的稳定性; 其次, 可竞争性阻断鼠MDM4与p53 TAD结构域的结合, 恢复*TP53*的转录功能; 此外, 部分活性成分可作为DNA损伤剂, 激活*TP53*基因调控的应激通路, 诱导癌细胞凋亡, 见图3。

5.1.2 MAPK信号通路 MAPK通路相关蛋白包含p38 MAPK、JNK和ERK等亚族, 其中p38 MAPK和JNK主要通过介导氧化应激诱导细胞凋亡, 而ERK则表现出环境依赖性的双向调控特征。肿瘤微环境中炎症因子等刺激诱导细胞产生的活性氧(reactive oxygen species, ROS), 可氧化激活MAP3Ks中的ASK1, 促使其从14-3-3蛋白的抑制性结合中解离。活化的ASK1则通过激活MAP2Ks中的MKK3/6和MKK4/7, 分别级联激活下游对应的p38 MAPK和JNK1/2[72-73]。上述两种激酶的激活可进一步诱导ROS产生, 形成正反馈环路以持续放大凋亡信号[74]。

金银花中的木犀草素、槲皮素、木犀草苷、绿原酸和咖啡酸等成分以及部分不同小分子西药和抑制剂联合治疗的方案已被证实可精准靶向p38 MAPK、JNK及ERK等关键靶点, 在多种恶性

表2 金银花活性成分调控癌细胞凋亡的分子机制

Table 2 Molecular mechanisms of active components from LJF in regulating apoptosis of cancer cells

成分 Component	癌症 Cancer type	模型 Model	作用机制 Mechanism of action	参考文献 Reference
Luteolin	Liver cancer	HepG2	Activates p53 pathway, upregulates Bax/Bcl-2 ratio	[38]
		Huh-7	Targeted inhibition of AKT1, dephosphorylation and inactivation of MDM2 to activate p53, upregulating NOXA and PUMA Targeted inhibition of AKT1, dephosphorylation and activation of FOXO1, upregulating TRAIL Targeted inhibition of AKT1, inhibition of IKKs/IκB, activation of NF-κB p65, upregulating Bcl-XL and Bcl-2 Targeted inhibition of Src/STAT3, downregulating Bcl-xL, Mcl-1, and Survivin	[39]
	NSCLC (non-small cell lung cancer)	A549, H460 H460 xenograft mice	Epigenetically regulates miR-34a-5p/MDM4/p53 pathway, upregulates Bax/Bcl-2 ratio	[40]
		NCI-H460, H1299 and BALB/c nude mice	Activates p38 MAPK pathway, downregulates Bcl-2, upregulates Caspase-3, -8, -9 protein expression	[41]
	Esophageal cancer	EC109, TE-1	Activates ASK1/MKK4/JNK pathway, upregulates Bax, Bcl-2, NOXA, Caspase-3 and Caspase-9 protein expression	[42]
	Gastric cancer	HGC27, SGC7901/DDP	Inhibits HSP90/STAT3/SHP-1 pathway, downregulates Mcl-1, Survivin, and Bcl-xL expression	[43]
Quercetin	Melanoma	A375SM nude mice	Activates JNK/p38 MAPK/ERK1/2 signaling pathway, upregulates Bax and downregulates Bcl-2	[44]
		SK-MEL-28, G-361	Downregulates GM3 and GD3 expression, inhibits FAK/paxillin/AKT signaling, upregulates Bax/Bcl-2 ratio	[45]
	Choriocarcinoma	JAR, JEG3	Inhibits PI3K/AKT/mTOR pathway, downregulates p-P70S6K and c-FLIP; activates p38 MAPK/JNK and ERK1/2 pathways, upregulates p-P90RSK and ROS levels	[46]
	Primary effusion lymphoma	BC3, CBL1, BC1	Inhibits JNK/STAT3 pathway, downregulates IL-6 and IL-10; inhibits PI3K/AKT/mTOR, downregulates c-FLIP	[47]
	Meningioma	HBL-52	Upregulates miR-197, inhibits *IGFBP5* transcription, disrupts Bax/Bcl-2 balance	[48]
	Gastric cancer	AGS-cyr61	Inhibits CYR61/NF-κB p65/MRP1 pathway, downregulates MRP1, upregulates Caspase-9, -7, -3	[49]
	Human acute lymphoblastic leukemia	Nalm6 Swiss albino mice	Activates p53 pathway, upregulates Bax expression	[50]
	Liver cancer	MHCC97H	Activates Cyto-C/Caspases pathway	[51]
Rutin	Pancreatic cancer	PANC-1, SW1990 and MIA PaCa-2	Upregulates miR-877-3p, inhibits *BCL2* mRNA, upregulates Caspase-3, -8, -9	[52]
	Cervical cancer	SiHa	Inhibits *COPS5* mRNA transcription and translation, upregulates Bax/Bcl-2 ratio, promotes Cyto-C, Caspase-9 and Caspase-3 expression	[53]
		HeLa, Caski	Activates Caspases pathway, upregulates ROS levels	[54-55]
Rutin-LCNs	Lung adenocarcinoma	A549	Mechanism not elucidated	[56]
Luteoloside	Cervical cancer	HeLa	Activates the p38 MAPK/JNK pathway, increases p53 protein level to upregulate Bax and Fas and downregulate Bcl-2; inhibits the PI3K/AKT/mTOR pathway	[57]
	Nasopharyngeal carcinoma	NPC-039, NPC-BM	Inhibits AKT signaling, upregulates Bax, DR5, Fas, and TNFR, downregulates Bcl-2 and Bcl-xL	[58]
Chlorogenic acid	NSCLC	A549	Activates p38 MAPK and JNK pathways, upregulates Bax	[59]

续表2

成分 Component	癌症 Cancer type	模型 Model	作用机制 Mechanism of action	参考文献 Reference
	Melanoma	U2OS, MG-63	Inhibits ERK1/2 signaling pathway	[60]
	TNBC (triple-negative breast cancer)	MDA-MB-231, MCF-7	Inhibits IKKs/IκBα/NF-κB p65 pathway, downregulates p-IκBα and suppresses the transcriptional activity of NF-κB p65	[61]
		BALB/c mice		[62]
		MDA-MB-231, MDA-MB-453 and 4T1		[63]
	Liver cancer	HepG2, Huh-7	Inhibits non-canonical NF-κB pathway, downregulates BIRC3/TRAF1 complex, suppresses the transcriptional activity of RelB/NF-κB2 p52, upregulates PUMA and Bax	[64]
CACNs	Thyroid cancer	BCPAP BALB/c nude mice	Upregulates ROS levels, inhibits KRAS/BRAF/MEK1/ERK pathway	[65]
Caffeic acid	Chronic myeloid leukemia	K562	Upregulates Ca^{2+} concentration, activates TG2	[66]
	Gastric cancer	SCM1	Activates GPCR/PLC/Ca^{2+} and PKC, leading to mitochondrial and cytosolic Ca^{2+} overload	[67]
	Ovarian cancer	A2780	Inhibits GST and GSR expression, upregulates Caspase-3	[68]
	Melanoma	SK-Mel-28	Upregulates Caspase-1, -3, -8 expression	[69]

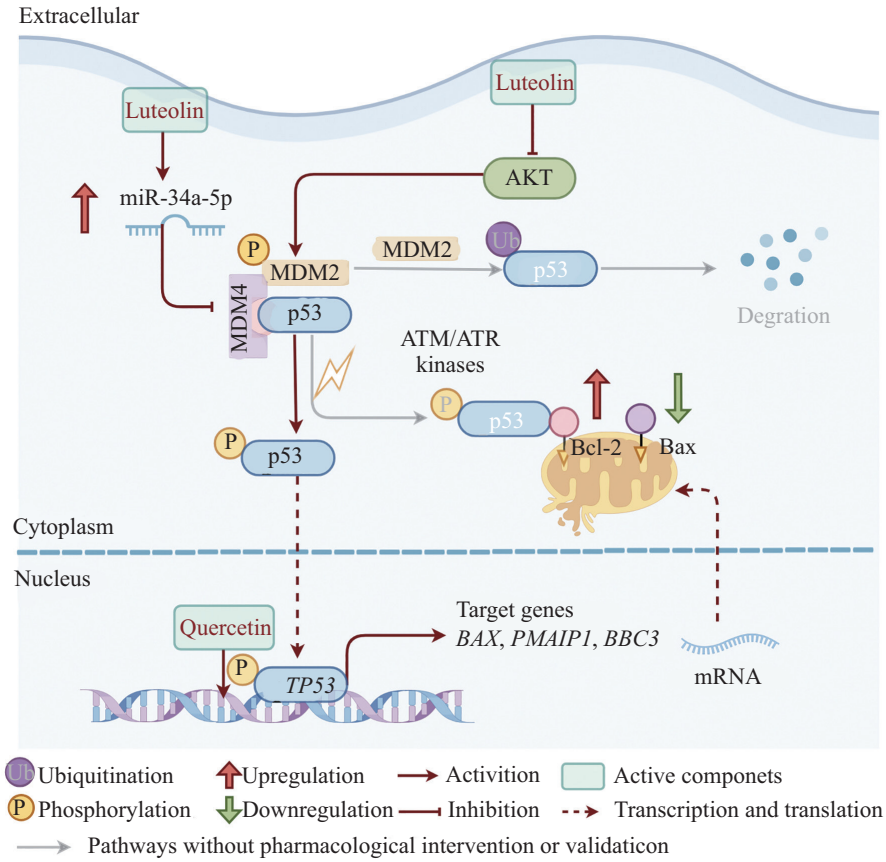


图3 木犀草素和槲皮素调控p53信号通路促凋亡分子机制图

Fig.3 Molecular mechanism of p53 pathway-mediated apoptosis induced by quercetin and luteolin

肿瘤模型中调控MAPK级联反应, 重塑肿瘤细胞内的信号平衡并诱导程序性死亡。例如, 在异种移植NCI-H460细胞的BALB/c裸鼠模型以及NCI-H460和H1299两种细胞的体外模型中, 木犀草素预处理联合电离辐射(ionizing radiation, IR)可磷酸化激活p38 MAPK信号通路, 显著上调ROS水平, 下调Bcl-2的表达, 进而触发Caspase-3/8/9的级联反应, 同时激活内源性和外源性两种凋亡途径[41]。而在EC109和TE-1食管癌细胞中, 木犀草素与低剂量紫杉醇(paclitaxel)协同激活ASK1/MKK4/JNK通路, 诱导ROS产生, 在蛋白层面上调Bax、NOXA、Caspase-3和Caspase-9的表达, 促进癌细胞凋亡[42]。

槲皮素通过诱导A375SM黑色素瘤细胞的氧化应激反应, 同时激活p38 MAPK、ERK1/2和MKK4/7/JNK信号通路。其中JNK经磷酸化激活后获得转录活性, 转位入核, 上调下游激活蛋白1(activator protein 1, AP-1)复合物(即c-Jun/c-Fos二聚体)的转录活性。该复合物促进Bax的表达, 而降低Bcl-2的表达水平, 最终激活内源性凋亡途径[44,75]。此外, 木犀草苷亦可同时激活宫颈癌细胞中的p38 MAPK和JNK信号通路, 活化后的p38 MAPK和JNK转录入核, 作为转录因子协同促进*TP53*的转录, 上调Bax和Fas的表达, 而Bcl-2的表达被抑制, 从而同时激活内源性和外源性凋亡途径[57]。

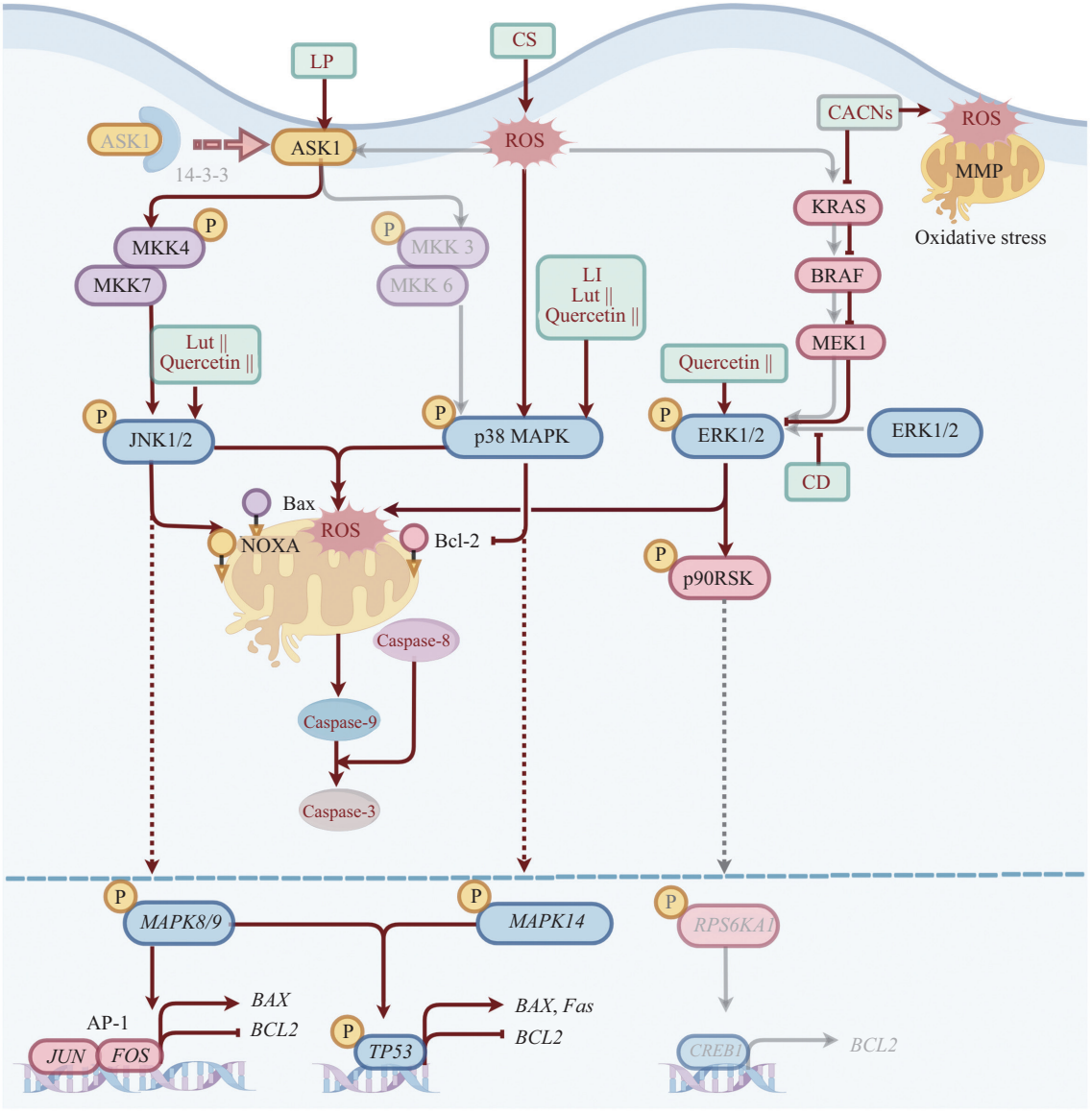
在MAPK信号网络中, 由ERK1/2和p38 MAPK/JNK调控的促生存与促凋亡信号之间的动态平衡决定细胞的命运。在生理状态下, ERK1/2被激活后可通过p90RSK/CREB轴促进*BCL2*转录, 上调Bcl-2等抗凋亡蛋白的表达来发挥促生存效应[76], 此外, ERK1/2本身可由上游Ras-Raf-MEK级联反应激活, 形成完整的信号传递链[77]。而在部分情况下, ERK1/2活性受到抑制或被过度激活会导致生存–凋亡平衡向促凋亡方向倾斜[78]。

在非小细胞肺癌A549细胞中, 绿原酸与SB203580等抑制剂联用, 亦可通过显著增加细胞内ROS积累来激活p38 MAPK和JNK信号通路, 进而上调*BAX*的基因转录表达而触发线粒体依赖性凋亡[59]。而在骨肉瘤细胞U2OS和MG-63中, 绿原酸与doxorubicin联用则通过抑制ERK1/2的磷酸化激活, 增强细胞凋亡的敏感性, 激活内源性凋亡途径[60]。由此可知, 绿原酸是通过促凋亡与阻生存双重机制协同放大肿瘤细胞凋亡效应的。

此外, 在JAR和JEG3绒毛膜癌细胞中, 槲皮素干预可同时激活p38 MAPK、JNK和ERK通路以及ERK下游的p90RSK激酶, 同时显著上调ROS水平, 从而导致细胞凋亡[46]。CACNs(包裹咖啡酸的碳纳米点)可通过上调BCPAP低分化甲状腺癌细胞系中的ROS水平, 诱导氧化应激, 进而破坏MMP而激活内源性凋亡途径; 同时下调KRAS/BRAF/MEK1/ERK1/2通路相关蛋白表达, 从而抑制细胞增殖并促进细胞凋亡, 见图4[65]。

5.1.3 钙离子稳态 钙离子(Ca^{2+})稳态对维持细胞存活和调控蛋白质折叠、ATP合成、囊泡分泌及细胞骨架重组等生理功能有至关重要的作用。细胞受到药物等外源性刺激导致细胞内外的Ca^{2+}平衡紊乱, 从而触发细胞凋亡的级联反应。

在钙信号调控线粒体凋亡机制方面, 咖啡酸可通过干扰肿瘤细胞内钙离子浓度的动态平衡诱导肿瘤细胞的凋亡。以胃癌细胞SCM1为例, 咖啡酸与细胞膜上的G蛋白偶联受体(G protein-coupled receptor, GPCR)结合, 激活下游磷脂酶C(phospholipase C, PLC), 生成三磷酸肌醇(inositol 1,4,5-trisphosphate, IP_3), 从而介导内质网–线粒体之间的Ca^{2+}转运, 导致线粒体内的Ca^{2+}超载。由此引发MMP崩溃, 线粒体通透性转换孔(mitochondrial permeability transition pore, mPTP)开放, 释放Cyto-C等促凋信号而触发内源性凋亡途径。内质网外膜上的IP_3R和线粒体外膜上的电压依赖性阴离子通道1(voltage-dependent anion channel 1, VDAC1)、葡萄糖调节蛋白75(glucose-regulated protein 75, GRP75)在内质网–线粒体结构偶联(mitochondria-associated membranes, MAMs)形成桥接复合物, 实现内质网与线粒体内膜间的Ca^{2+}传递, 随后Ca^{2+}经线粒体钙单向转运体(mitochondrial calcium uniporter, MCU)被转运至线粒体基质[79-80]。咖啡酸亦可通过激活钙离子感应受体(calcium-sensing receptor, CaSR), 使下游的蛋白激酶C(protein kinase C, PKC)发生磷酸化激活, 此时细胞膜上钙离子通道打开, Ca^{2+}内流增加, 进而引起胞质内钙超载; 同时, 活化的PKC可转位至线粒体, 诱导MMP下降而引起细胞死亡[67,81]。此外, 咖啡酸还可直接上调人慢性粒细胞白血病细胞中的Ca^{2+}浓度, 激活组织型转谷氨酰胺酶2(tissue transglutaminase type 2, TG2), 从而促进ROS的累积, 最终触发Caspase级联反应, 诱导细胞凋亡, 见图5[66]。



Lut: luteolin-7-*O*-glucoside　　CACNs: caffeic acid carbon nanodots　　LI: Lut+IR (γ-ionizing radiation)

LP: luteolin+paclitaxel　　CS: CGA+SB203580　　CD: CGA+doxorubicin

||: parallel activation of distinct molecular pathways

图4　木犀草素、槲皮素、木犀草苷、绿原酸和咖啡酸激活MAPK信号通路促凋亡分子机制

Fig.4　Molecular mechanism of pro-apoptotic effects mediated by luteolin, quercetin, luteolin-7-*O*-glucoside, chlorogenic acid and caffeic acid components via MAPK signaling pathway activation

5.1.4　表观遗传调控　　表观遗传修饰不仅能直接调控Bcl-2家族基因的转录水平，还可间接干预其蛋白功能，从而实现对细胞凋亡进程的精细调节[82]。目前，癌症研究聚焦于通过调控microRNA或mRNA水平介导癌细胞凋亡，例如促凋亡miR-34a-5p、miR-197和miR-877-3p等，以及和细胞凋亡相关的Jun活化域结合蛋白1(Jun activation domain-binding protein 1, Jab1，编码基因*COPS5*) mRNA[83]。

金银花中的木犀草素、槲皮素、芦丁等成分，在多种肿瘤模型中被证实可通过精准靶向特定的microRNA或mRNA表达，打破Bcl-2家族蛋白平衡来诱导癌细胞凋亡。研究表明，miR-34a可通过靶向*MDM4* mRNA外显子11开放阅读框(open reading frame, ORF)内的8-mer靶点，促进*MDM4* mRNA降解并降低其蛋白水平，进而解除*MDM4*对*TP53*的转录抑制，激活p53下游促凋亡通路[84]。例如，在非小细胞肺癌细胞模型和移植H460细胞的小鼠模型中，木犀草素可直接上调miR-34a-5p的表达，抑制MDM4

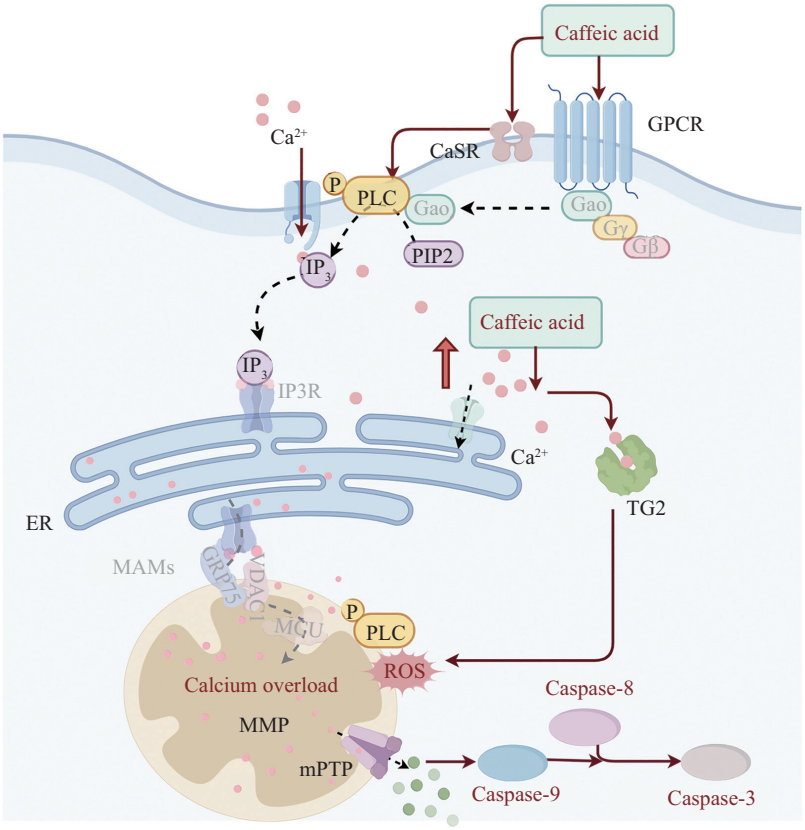


图5 咖啡酸调节Ca^{2+}稳态促凋亡分子机制

Fig.5 Molecular mechanism of caffeic acid in regulating Ca^{2+} homeostasis to promote apoptosis

的活性, 从而解除MDM4对*TP53*的转录抑制作用, 上调Bax/Bcl-2蛋白比例以激活内源性凋亡(机制见5.1.1部分)[40]。在脑膜瘤细胞HBL-52中, 槲皮素可上调miR-197的表达, 直接靶向抑制胰岛素样生长因子结合蛋白5(insulin-like growth factor-binding protein 5, *IGFBP5*)的转录和翻译, 进而激活线粒体凋亡途径[48]。此外, 研究证实在正常心肌细胞中过表达miR-877-3p, 可靶向抑制*BCL2*的转录和翻译, 从而诱导心肌细胞凋亡[85]。而芦丁在干预胰腺癌细胞PANC-1、SW1990和MIA PaCa-2时, 同样可上调miR-877-3p的表达, 后者直接靶向*BCL2* mRNA并抑制其翻译, 进而激活Caspase-8/3/9级联反应, 诱导细胞凋亡[52]。除此之外, Jab1在癌组织中的表达水平显著高于正常组织, 敲低*COPS5*可导致Bax表达上调, Bcl-2表达下调, 从而诱导细胞凋亡[86]。因此, 在SiHa子宫颈鳞癌细胞中, 芦丁可通过下调*COPS5* mRNA的转录水平, 使线粒体表面Bax/Bcl-2的蛋白比例上调, 从而启动Cyto-C/Caspase-9/3调控的细胞程序性凋亡, 见图6[53]。

5.2 金银花活性成分抑生存、促凋亡信号通路

5.2.1 PI3K/AKT信号通路 在正常条件下,PI3K/AKT通路的活化能够促进细胞生存, 抵抗细胞凋亡。磷脂酰肌醇4,5-二磷酸(phosphatidylinositol 4,5-bisphosphate, PIP2)在PI3K的作用下被催化生成磷脂酰肌醇3,4,5-三磷酸(phosphatidylinositol 3,4,5-trisphosphate, PIP3), 激活AKT以调节下游的FOXO1、NF-κB、mTOR等多种靶点来抑制细胞凋亡并维持细胞生存。此外, 神经节苷脂(gangliosides) GD3和GM3亦可从上游激活AKT。

5.2.2 FOXO1信号通路 FOXO1可被活化的AKT1蛋白磷酸化激活, 而14-3-3蛋白促使p-FOXO1发生泛素化降解, 降低其转录活性, 从而抑制细胞凋亡[87]。当PI3K/AKT信号通路被抑制或FOXO1维持在去磷酸化状态时, FOXO1可转位入核, 从而上调BH3-only蛋白Bim和死亡受体TRAIL及FasL等的表达, 启动细胞凋亡。研究表明, 木犀草素通过靶向抑制Huh-7细胞中AKT1的活性, 使下游的FOXO1发生去磷酸化, 进而促进其核转位并上调TRAIL的表达, 激活凋亡通路, 见图7[39]。

5.2.3 NF-κB信号通路 NF-κB的活化受PI3K/AKT/IKK/核因子κB抑制蛋白(inhibitor-κ binding protein, IκB)

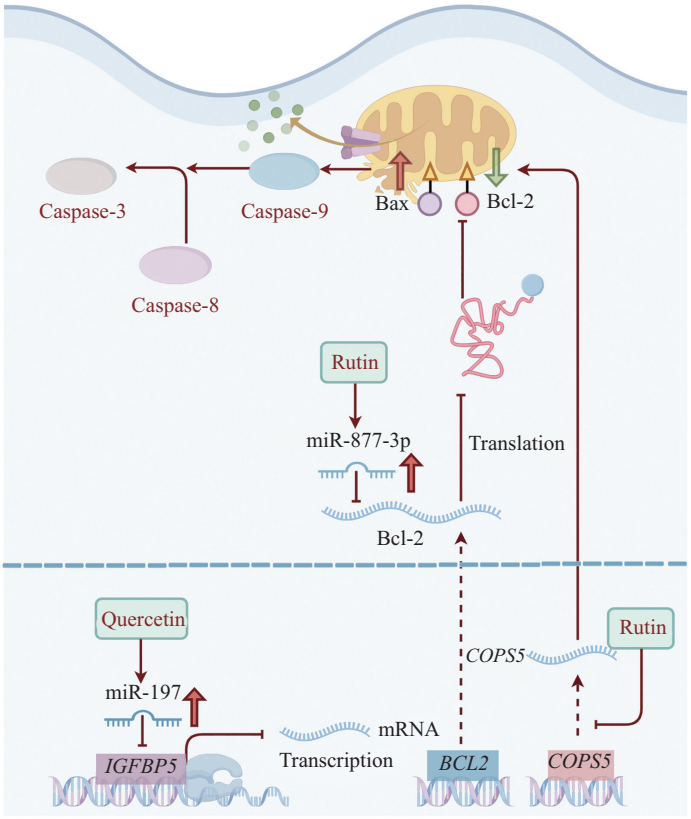


图6　槲皮素和芦丁调节表观遗传的促凋亡分子机制

Fig.6　Molecular mechanism of epigenetic pro-apoptotic regulation by quercetin and rutin

级联信号通路的调控[88]。IKK复合体经PI3K/AKT信号激活后，将IκB磷酸化，生成p-IκB。p-IκB被E3泛素连接酶泛素化标记而被降解。p-IκB降解后，NF-κB(p50/p65)从与IκB结合并受抑制的状态中释放出来并转位入核，从而上调*BCL2*、*BCL2L1*等基因转录。当PI3K/AKT活性被抑制或IKK的活化被阻断时，IκB对NF-κB的负调控持续存在而导致NF-κB的转录活性降低，细胞更趋向于凋亡[89]。

木犀草素通过抑制Huh-7细胞中的IKK活性，阻止IκB降解，从而抑制NF-κB p65的核转位，导致下游Bcl-2和Bcl-xL等的表达水平降低，从而削弱细胞的抗凋亡能力[39]。在半胱氨酸丰富血管生成诱导因子61(cysteine-rich angiogenic inducer 61, CYR61)过表达的AGS-*cyr61*胃癌耐药细胞系中，*CYR61*可与细胞膜上整合素结合而上调NF-κB p65转录活性，促进多药耐药相关蛋白1(multidrug resistance-associated protein 1, MRP1)的编码基因*ABCC1*的转录，赋予肿瘤细胞耐药性，并增强细胞抵抗凋亡的能力。槲皮素则通过抑制其CYR61/NF-κB p65通路，下调MRP1和NF-κB p65蛋白的表达，从而逆转CYR61介导的多药耐药性，激活Caspase-9/7/3级联反应的内源性凋亡途径[49]。

绿原酸则对不同种类癌细胞的NF-κB信号通路具有双重调控作用：一方面通过抑制IKK/IκBα/NF-κB p65经典通路，阻断MDA-mb-231、MDA-mb-453和4T1乳腺癌细胞中NF-κB p65的核转位，促进细胞凋亡[61-63]；另一方面则通过抑制HepG2和Huh-7细胞中细胞凋亡抑制蛋白2(cellular inhibitor of apoptosis protein 2, cIAP2)/肿瘤坏死因子受体相关因子1(TNF receptor-associated factor 1, TRAF1)复合物的表达，阻断NF-κB家族蛋白p52/RelB二聚体的核转位，上调*BBC3*和*BAX*基因的表达，从而诱导线粒体凋亡[64]。在非经典NF-κB信号通路中，细胞膜上的TNFR超家族受体被激活后，诱导膜上TRAF/cIAP2复合物降解，此时胞内的NF-κB诱导激酶(NF-κB-inducing kinase, NIK)稳定积累并被活化，激活下游的IKKα激酶，后者对p100/RelB前体进行磷酸化修饰，诱导p100泛素化切割，最终形成成熟的p52/RelB二聚体[49]。然而，上述机制尚未在绿原酸诱导肝癌细胞的相关研究中深入探讨。

5.2.4 mTOR信号通路 在肿瘤微环境中, PI3K/AKT通路的持续性激活可导致mTOR信号过度活化, 促进肿瘤细胞异常增殖。活化的mTOR(即p-mTOR)通过磷酸化激活核糖体蛋白S6激酶β-1(ribosomal protein S6 kinase β-1, S6K1, 又称p70S6K)和核糖体蛋白S6(ribosomal protein S6, RPS6), 使c-FLIP蛋白磷酸化而稳定存在于胞内, 避免其降解, 从而阻碍细胞凋亡, 维持细胞存活[90]。当mTOR/p70S6K/RPS6信号轴被抑制时, c-FLIP因失去磷酸化保护而加速降解, 细胞凋亡程序随之启动。

这一机制可在槲皮素干预的由卡波西肉瘤相关疱疹病毒(Kaposi's sarcoma-associated herpesvirus, KSHV)诱导的BC3、BCBL1和BC1原发性渗出性淋巴瘤(primary effusion lymphoma, PEL)细胞模型中体现[46-47]。而在JAR和JEG3绒毛膜癌细胞中, 槲皮素亦可通过抑制PI3K/AKT/mTOR信号通路, 阻断其下游p70S6K和RPS6的磷酸化激活, 诱导MMP降低和ROS水平升高, 从而激活内源性凋亡。木犀草苷也可通过降低mTOR磷酸化水平, 抑制PI3K/AKT/mTOR信号通路, 从而解除该通路对宫颈癌细胞的负调控作用, 见图7[57]。

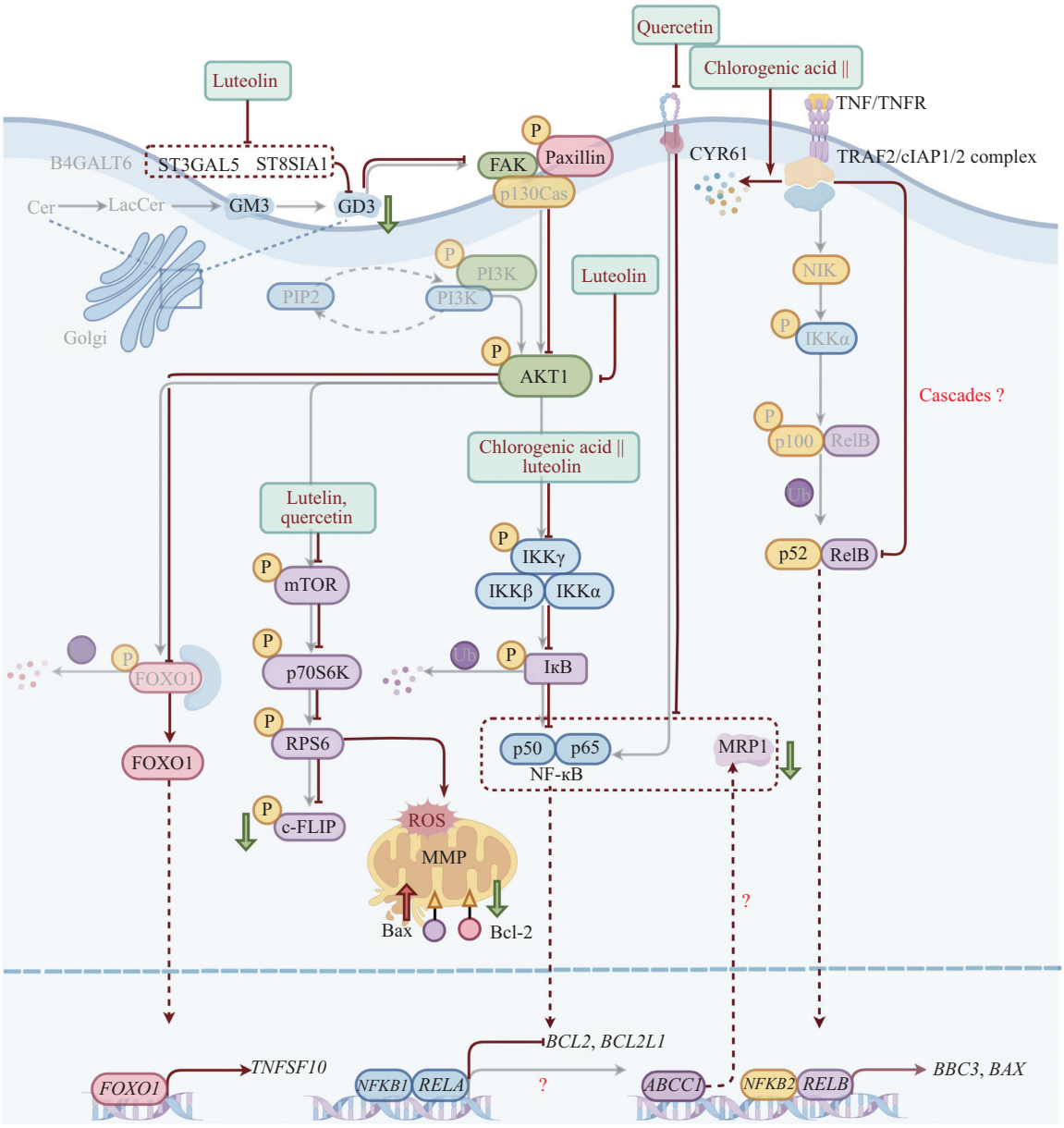
5.2.5 神经节苷脂 神经酰胺(ceramide, Cer)在高尔基体中经ST3GAL5和ST8SIA1合成酶催化产生双唾液酸GD3和单唾液酸GM3[91]。在黑色素瘤细胞中, GD3的高表达可促进黏着斑激酶(focal adhesion kinase, FAK)与p130Cas结合, 继而磷酸化激活Paxillin, 最终激活AKT抗凋亡通路, 阻断黑色素瘤细胞的凋亡进程[92]。槲皮素可通过降低ST3GAL5和ST8SIA1的活性, 减少恶性黑色素瘤细胞中GM3和GD3的表达量, 抑制FAK/Paxillin/AKT通路, 从而激活线粒体凋亡途径, 见图7[45]。

5.2.6 STAT3信号通路 STAT3可被细胞膜表面细胞因子/生长因子受体招募的Janus激酶(Janus kinase, JAK)和肉瘤酪氨酸激酶(sarcoma tyrosine kinase, Src)磷酸化激活。例如, 白细胞介素-6(interleukin-6, IL-6)与其相应受体结合, 诱导糖蛋白130(glycoprotein 130, gp130)形成同源二聚体, 其胞内段招募并磷酸化激活JAK, 随后由p-JAK磷酸化STAT3上Tyr705位点, 形成p-STAT3[93]。p-STAT3通过其Src同源2(Src homology 2, SH2)结构域识别并结合另一磷酸化STAT3单体上的Tyr705位点, 形成具有转录活性的二聚体[94-95]。此外, RTK受生长因子诱导后, 发生二聚化, 促使胞内段Tyr残基自磷酸化, 进而通过SH2结构域招募Src, Src聚集后经自身磷酸化激活, 亦可磷酸化STAT3的Tyr705位点[96]。

STAT3的持续激活可导致癌细胞异常增殖, 与多种恶性肿瘤进展和不良预后密切相关。因此, 靶向抑制STAT3的活化已成为抗癌治疗的热点。由金银花分离出的木犀草素和槲皮素可精准靶向STAT3上游的激活酶或伴侣蛋白, 有效阻断STAT3的持续活化。例如, 在PEL细胞中槲皮素通过抑制JAK2/STAT3信号, 阻止STAT3活化与核转位, 从而降低IL-6和IL-10等促生存信号的表达水平[47]。此外, 木犀草素可直接靶向抑制Src/STAT3信号通路, 下调Bcl-xL、Mcl-1和Survivin等蛋白的表达, 促进Huh-7细胞凋亡[39]。在胃癌耐药细胞系HGC27和SGC7901/DDP中, 木犀草素可直接结合STAT3的伴侣蛋白HSP90, 促使p-STAT3解离释放, 随后SHP-1与p-STAT3结合, 导致p-STAT3去磷酸化失活, 进而激活Caspase-3线粒体凋亡途径[43]。作为p-STAT3二聚体的伴侣蛋白, HSP90不仅能够稳定其构象, 还可促进其核转位; 而在细胞核内HSP90亦有增强p-STAT3转录活性的功能, 见图8[97]。

5.2.7 Keap1信号通路 Nrf2/Keap1信号通路是调控细胞氧化还原稳态与细胞药物毒性稳态的核心枢纽[98]。在生理状态下, Keap1可作为Cullin 3-E3泛素连接酶复合物的底物识别亚基, 通过结合Nrf2并介导其泛素化降解, 维持Nrf2的低表达状态[99]。而在氧化应激状态下, Keap1经氧化修饰后构象发生改变, 导致Nrf2解离, 后者在胞质中稳定存在, 随后转位至核内与小分子肌腱膜纤维肉瘤蛋白(small musculoaponeurotic fibrosarcoma protein, sMaf)结合形成二聚体, 此二聚体与ARE结合, 促进谷胱甘肽*S*-转移酶(glutathione *S*-transferase, GST)和谷胱甘肽还原酶(glutathione reductase, GSR)等基因家族的转录, 调控细胞抗氧化、解毒代谢和细胞存活等生理功能[100]。

咖啡酸在正常细胞中主要发挥抗氧化作用, 具体表现为咖啡酸可直接结合或经活性氧作用于Keap1蛋白的半胱氨酸残基(cysteine residue, Cys), 促使Keap1与Nrf2解离, 后者转位进入细胞核, 上调GSR、GST等蛋白表达, 从而增强细胞的抗氧化能力并降低其耐药性。而在癌细胞中咖啡酸则通过促氧化效应与增强细胞毒性, 诱导癌细胞凋亡[101]。顺



? The mechanism has not been confirmed in existing literature
||: parallel activation of distinct molecular pathways

图7 木犀草素、木犀草苷、槲皮素和绿原酸抑制PI3K/AKT生存信号通路并促进细胞凋亡的分子机制

Fig.7 Molecular mechanisms by which luteolin, luteolin-7-*O*-glucoside, quercetin and chlorogenic acid inhibit the PI3K/AKT survival signaling pathway and promote apoptosis

铂是临床癌症治疗中使用的广谱化疗药物，其可进入核内与DNA链间及链内的嘌呤碱基发生不可逆的共价交联，形成Pt-DNA加合物，导致DNA双螺旋结构扭曲损伤，最终诱导癌细胞凋亡[102]。然而，顺铂在临床应用过程中可诱发的氧化应激与炎症反应等，并产生肾毒性、耳毒性、神经毒性及骨髓抑制等副作用。咖啡酸及其衍生物(如咖啡酸苯乙酯)可降低顺铂引起的耳毒性和肾毒性等毒副作用，而保护正常细胞不受损伤[103]。

此外，咖啡酸亦可通过“氧化应激”与“解毒抑制”的双重效应诱导癌细胞凋亡。具体如下：一方面可通过调控氧化应激，直接诱导结肠癌细胞凋亡[104]；另一方面其与顺铂同时给药时，咖啡酸可迅速进入核内，并占据GST和GSR蛋白对应基因的活性位点，导致GST和GSR的表达下调，降低A2780卵巢癌细胞的抗氧化和解毒能力。由此，顺铂得以在胞内保留

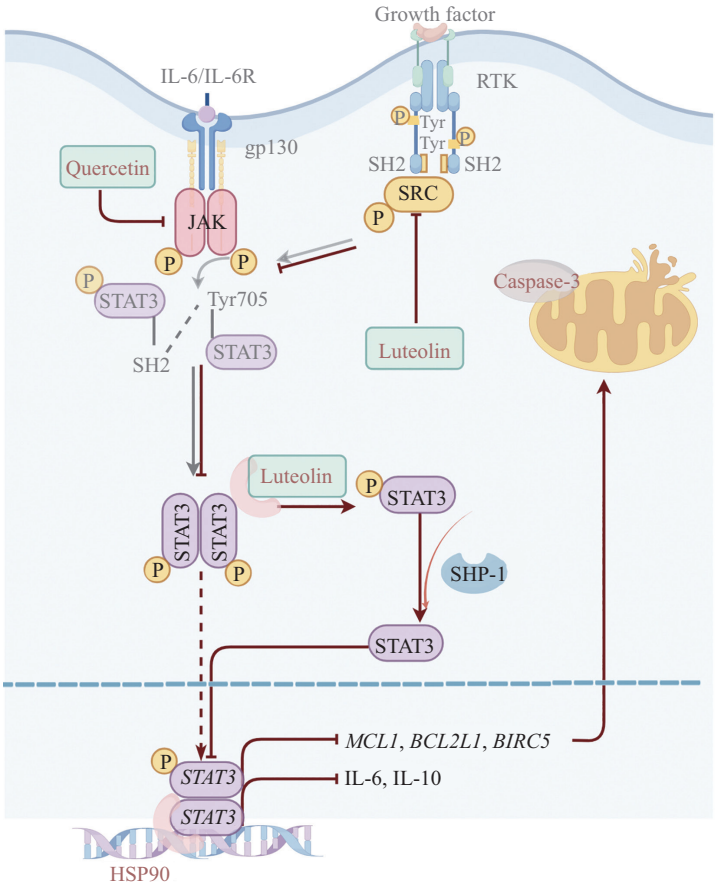


图8 木犀草素和槲皮素抑制STAT3信号通路促凋亡机制

Fig.8 Molecular mechanism of luteolin and quercetin inhibiting the STAT3 signaling pathway to suppress survival and promote apoptosis

并转位入核, 直接与DNA结合, 诱导DNA损伤, 从而激活Caspase-3依赖性凋亡途径。而咖啡酸先于顺铂给药, 则会诱导GST和GSR蛋白表达上调, 增强细胞的解毒能力, 进而降低顺铂的细胞毒性[68]。因此, 咖啡酸诱导细胞凋亡的机制依赖于联合用药的给药时机和顺序, 见图9。

5.3 金银花成分新剂型

除上述描述的经典通路外, 金银花活性成分的新型递送系统通过多种机制诱导不同癌细胞凋亡。例如, 在MHCC97H肝癌细胞中, 槲皮素纳米颗粒(quercetin nanoparticles, QNs)可激活Cyto-C/Caspases级联反应触发线粒体凋亡[51]。芦丁–褐藻糖胶复合物(rutin-fucoidan complex)复合物可显著上调HeLa和Caski宫颈癌细胞内ROS水平, 通过氧化应激降低线粒体膜电位, 进而诱导细胞凋亡[54]。而负载芦丁的液晶纳米颗粒(rutin-loaded liquid crystalline nanoparticles, rutin-LCNs)在改善芦丁溶解度和生物利用度的同时, 可直接进入肺腺癌细胞A549诱导其凋亡[56]。

6 总结与展望

金银花作为中医传统“清热解毒”药的典型代表, 兼具抗炎、抗病毒及显著的抗肿瘤药理活性。现代药理学研究证实, 金银花提取物及其核心活性组分可通过多靶点机制有效遏制恶性肿瘤的进展, 削弱癌细胞的生存能力, 从而展现出显著的抗肿瘤潜力。

本文通过系统梳理金银花来源的黄酮类(即芦丁、槲皮素、木犀草素和木犀草苷)及有机酸类(即绿原酸和咖啡酸)成分诱导癌细胞凋亡的相关文献, 得出以下结论。一是多维通路协同介导癌细胞凋亡级联。金银花活性成分通过精准调控p53、PI3K/AKT(FOXO1、mTOR、NF-κB)、MAPK(p38 MAPK、JNK和ERK)、STAT3和Nrf2等关键信号通路、调控胞内Ca^{2+}稳态平衡以及microRNA的表观调控等, 共同触发线粒体介导的内源性凋亡或死亡受体介导的外源性凋亡通路。二是核心信号轴的广谱调控特征。在以往的研究中, 金银花活性组分干

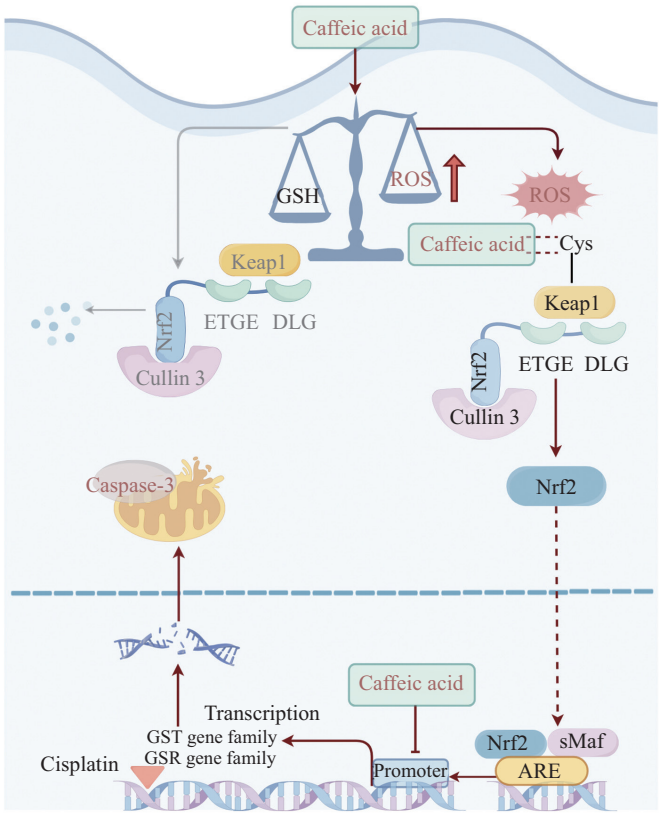


图9 咖啡酸激活Nrf2/Keap1信号通路促凋亡分子机制

Fig.9 Molecular mechanism of caffeic acid inhibiting the Nrf2/Keap1 signaling pathway to promote apoptosis

预在不同类型癌细胞时，其促凋亡机制均高度聚焦于MAPK和PI3K两大经典通路。这个现象提示在广谱抗肿瘤机制中，金银花药物对不同的恶性肿瘤干预可能存在高度保守的“共性靶点”调控模式。三是单一成分对复杂调控网络的系统干预。以木犀草素诱导肝癌凋亡为例，其通过同步激活p53与抑制AKT等非单一途径发挥作用。这表明单一中药小分子对肿瘤细胞的干预并非孤立的单点调节，而是通过“多通路–多靶点”的复杂网络调控实现生物学效应的。四是离子稳态失衡拓展了有机酸类成分的作用机制。咖啡酸等有机酸组分可通过激活钙调控蛋白诱导胞内Ca^{2+}稳态失衡，进而触发凋亡。该发现提示，有机酸类成分可能与钙离子通道或特异性调控蛋白结合。五是表观遗传调控在凋亡干预中的补充价值。芦丁等成分通过调节microRNA和相关基因的mRNA表达水平，从表观遗传维度精确调控凋亡进程。上述内容强调了在关注经典蛋白信号通路的同时，microRNA介导的表观调控亦是揭示中药抗癌机制不可忽视的重要领域。综上所述，本文通过对金银花活性成分诱导癌细胞凋亡机制的系统梳理，不仅阐明了其多靶点、多途径的药效学内涵，也为今后金银花及同类药材向临床抗肿瘤药物转化提供了明确的研究路径。

尽管金银花在离体实验与动物模型中展现出确切的抗癌潜力，但其从基础研究向临床应用的转化过程仍面临严峻挑战。目前研究的局限性主要体现在以下三个维度。首先，转化医学衔接不足。现有证据多局限于基础实验模型，缺乏高质量的临床循证医学支撑，导致其成药性评价与安全性验证尚不充分。其次，对于分子靶位解析深度有限。机制探讨多聚焦于蛋白与基因表达水平的调节，缺乏利用化学和生物学等手段对药物与靶蛋白真实结合位点的精确辨析。最后，整体观药理优势体现不强。现有研究模式多偏向单一活性成分的拆解，未能充分诠释中医药“多组分、多靶点、多途径”协同干预肿瘤信号网络的系统性优势。因此，未来研究应致力于构建“体内–体外–药代–毒理”的一体化评价体系，并在精准验证药靶互作位点的基础上，积极探索新型药物递送系统以提升活性成分的生物利用度与肿瘤靶向性。此外，深入挖掘金银花在

表观遗传修饰及基因组稳定性维度的调控机制，将是揭示其抗癌科学内涵的新增长点。唯有通过多学科交叉的深度探究，方能突破临床转化的瓶颈，开发出具有中医药特色的低毒、高效抗癌新药。

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