DOI：10.12287/j.issn.2096-8965.20210408

柴胡皂苷A的药理活性和作用机制研究现状及进展

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【摘要】柴胡皂苷A（Saikosaponin A, SSA）在中华人民共和国药典（国家药典委员会2020年版）中被规定为评价柴胡质量的标记化合物之一。目前对于柴胡及其方剂的临床应用已经比较广泛，但是对于其主要活性成分SSA的药理活性和作用机制的研究仍处于探索阶段。研究显示SSA在体内外均具有生物活性，尤其是在抗炎、抗肿瘤、免疫调节、神经调节与抗病毒等方面。本文旨在结合文献资料深入探讨SSA的体内外药理活性及作用机制，为其今后的进一步开发与临床应用提供参考。

【关键词】柴胡皂苷A；药理活性；作用机制

中图分类号：R966，R-1　文献标识码：A　文章编号：2096-8965(2021)04-0060-07

Advances on the pharmacological activity and mechanism of saikosaponin A

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【**Abstract**】Saikosaponin A (SSA) is specified as one of the labeled compounds for evaluating the quality of Bupleurum in the Pharmacopoeia of the People's Republic of China (the 2020 edition of the Chinese Pharmacopoeia Commission). Since its discovery, SSA has been found to play an important role in treating diverse diseases via a variety of mechanisms. This review summarizes the current research status and prospects of activities of SSA, providing novel insights into the limitations of current studies. In addition, it discusses whether SSA can be applied in clinical therapy and the possible mechanisms by which SSA may facilitate therapy. The research is significant to understand the potentials of SSA in the development of SSA-based therapeutic strategies and clinical practice.

【**Keywords**】Saikosaponin A; Pharmacological activity; Mechanism of action

SSA（$C_{42}H_{68}O_{13}$）（见图1）是柴胡和银柴胡的主要活性成分之一，属于皂苷衍生物，其结构骨架为五环三萜类齐墩果烷型[1]，相对分子质量780.99 g/mol。SSA对于炎性疾病[2]、肿瘤[3]、免疫系统疾病[4]、神经系统疾病[5]、病毒感染性疾病[6]等皆具有药理活性。目前，SSA在用于过敏性鼻炎、子宫内膜炎、肺炎、胰腺炎、胰腺纤维化、心肌纤维化、肝纤维化、脑损伤、肾损伤、肝损伤、缺血再灌注损伤、银屑病、肥胖症、乳腺癌、过敏性哮喘、假性过敏反应、抑郁、焦虑、癫痫疾病的作用机制研究相对多，为未来可能的临床转化研究奠定了基础。

基金项目：甘肃省科技计划项目（21JR1RA144）；兰州大学第二医院“萃英科技创新”计划项目（CY2020-MS10）

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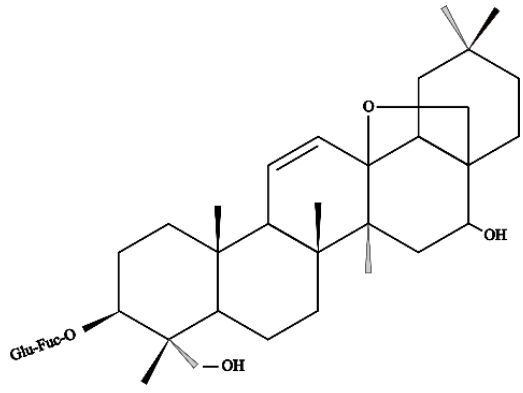

图1 SSA的化学结构

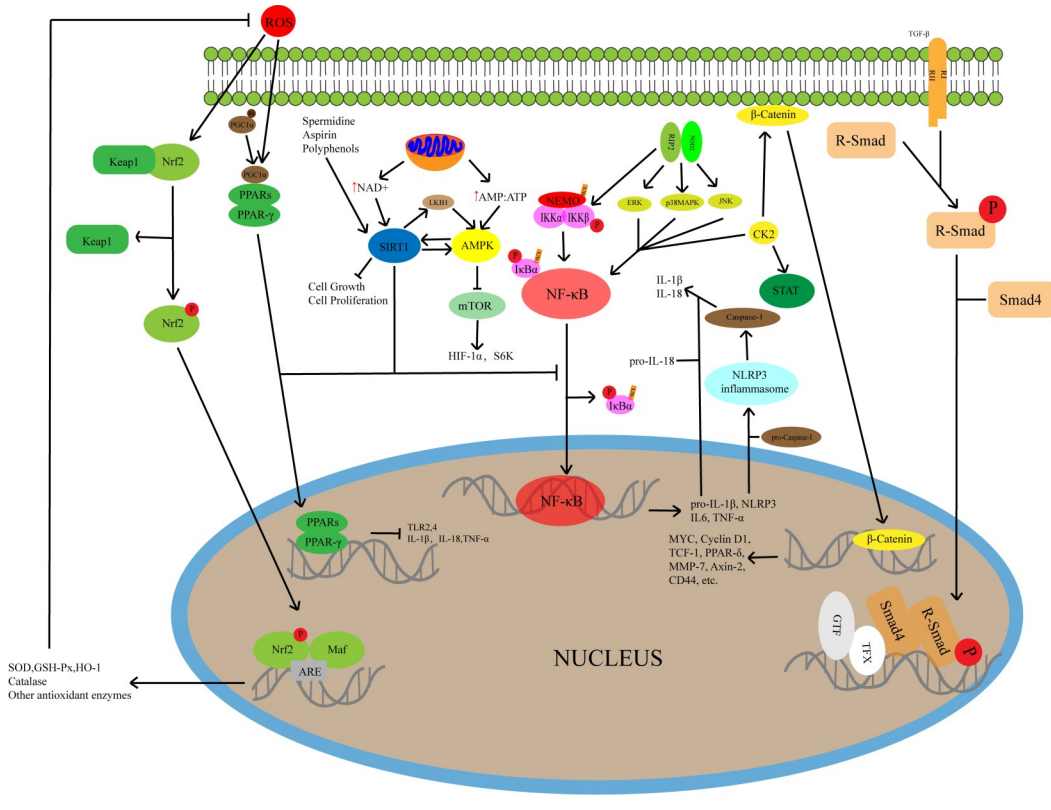

图2 SSA的抗炎机制

1 抗炎活性

炎症反应存在于诸多疾病中，药物的抗炎活性研究颇为重要。研究显示SSA的抗炎活性在柴胡皂苷中最强，针对其抗炎活性的研究也最多，其抗炎核心机制（见图2）可以总结为SSA通过减弱IκBα的磷酸化和p65 NF-κB由胞质入核来抑制NF-κB信号通路的激活[7]。相关研究团队对SSA的抗炎活性的研究各有侧重，详细研究内容见表1。

2 抗肿瘤活性

SSA作为一种中药提取物，在多种疾病的抗炎过程中具有重要作用，同样对机体免疫系统也具有调节作用，而炎症、免疫和肿瘤发生发展具有较多交互作用，同时由于SSA具有低毒特性，因此在抗肿瘤研究中引起了较多关注（见图3）。Zhao等[26]研究发现，SSA可以通过IL-12/STAT4途径使Th1/Th2平衡向Th1移动来缓解乳腺癌；而Wang等[3]发现，SSA可通过CXCR4/SDF-1、Akt/mTOR、PI3K/Akt途径缓解三阴性乳腺癌的发生发展。随着临床化疗药物大剂量、长时程应用的增加，化疗药物敏感性降低和多药耐药问题日趋明显，有研究显示SSA通过细胞凋亡途径可以增敏顺铂[27]，并可以通过下调Wnt/β-catenin信号通路逆转肺癌细胞A549对顺铂的耐药性[28]，改善包括阿霉素、长春新碱、紫杉醇在内的化疗药物的多药耐药性[29]。虽然化疗能够有

表1 SSA的抗炎活性

疾病/模型	动物品系/细胞系	刺激因素	药物剂量	给药时间	信号通路	参考文献
肾脏损伤	鲤鱼肾脏	铅			Nrf2/NF-κB	[2]
脑缺血缺氧损伤	新生大鼠中分离的原代海马神经细胞	氧-葡萄糖剥夺/复氧	2.5、5、10 mol/L	24 h	Nrf2/HO-1	[8]
过敏性鼻炎	6周龄自交雄性BALB/c小鼠	卵清蛋白	2、10 mg/kg	10 d	IL-6/ROR-γt/STAT3/ IL-17/NF-κB	[9]
缺血再灌注损伤	（180~220）g雄性Sprague-Dawley大鼠		0.001%、0.01%、0.1%食物重量	7 d	抑制核内HMGB1释放入血	[10]
胰腺纤维化	胰腺星形细胞		1、10、20、30、40、50 μg/mL	24 h	AMPK/mTOR	[11, 12]
高脂血症性胰腺炎	八周龄（200~230）g雄性Sprague-Dawley大鼠	高脂饮食两周，牛磺胆酸钠	10、20 mg/kg	13 h	PPAR-γ/NF-κB	[13]
急性重症胰腺炎	八周龄（220~240）g雄性Sprague-Dawley大鼠	牛磺胆酸钠	10、20、40 mg/kg	7 d	Keap1/Nrf2-ARE	[14]
银屑病	HERα细胞		5、10 、20 μM	24 h	凋亡，NF-κB	[15]
	八周龄（20~25）g雌性BALB/c小鼠	咪喹莫特	37.5、75 mg/kg	8 d		
子宫内膜炎	C57BL/6小鼠	LPS	5、10、20 mg/kg	25 h	Nrf2/NF-κB	[16]
急性肺损伤	雄性BALB /c小鼠	LPS	5、10、20 mg/kg	11 h	NLRP3/NF-κB	[17]
肺部炎症	六周龄（20~25）g雄性C57BL/6小鼠	香烟烟雾	5、10、20 mg/kg	5 d	NF-κB	[18]
心肌纤维化	新生大鼠心肌细胞、成年小鼠心脏成纤维细胞、小鼠心脏内皮细胞	AngⅡ、TGFβ	1、3、10 、30 μM	12 h	TGFβ/smad Wnt/β-catenin	[19]
	八至十周龄雄性C57BL/6小鼠	主动脉绑扎手术	5、40 mg/kg	28 d		
肝纤维化	HSC-T6、LX-2细胞				固有线粒体依赖性途径	[20]
动脉粥样硬化	HUVECs细胞	ox-LDL	10、20、40 μM（SSs）	24 h、48 h	ERK1/2/p38MAPK JNK/p38MAPK	[21]
外伤性脑损伤	成年（295~325）g雄性Sprague-Dawley大鼠	皮层撞击	20 mg/kg	24 h、48 h 7 d	MAPK	[22]
急性炎性小鼠足肿胀	（18~22）g雄性昆明小鼠	福尔马林	0.52、1.56、4.68 g/kg	3 d	SIRT1/NF-κB	[23]
肝损伤	（180~200）g雄性Wistar大鼠	CCl	1.0、2.5、5.0 mg/kg	1h、2h、4h 6h、8 h	NOD2/NF-κB	[24]
肥胖症	3T3-L1细胞		100 nM	24 h	ERK/NF-κB	[25]

效抑制肿瘤，但是化疗后患者容易出现骨髓抑制导致的中性粒细胞减少，最新研究表明，SSA可以通过CBL-ERK1/2通路明显逆转环磷酰胺诱导的中性粒细胞减少[30]。对SSA的结构进行更深入的研究后发现，SSA的C-16、C-23位α构型羟基可促进其细胞毒性作用，有效杀伤人肝癌细胞系HepG2及Hep3B、人乳腺癌细胞系Bcap-37及MCF-7和人肺腺癌细胞系A549[31]。目前关于SSA的抗肿瘤活性仅在乳腺癌中有较深入的机制研究，SSA对其他肿瘤的抗肿瘤活性的作用机制仍不清楚，有待继续深入探索。

3 免疫调节活性

SSA的免疫调节活性与T细胞密切相关。SSA可直接抑制T细胞的增殖和活化，导致细胞周期停滞在G0/G1期，并通过线粒体途径诱导凋亡，从而在Sprague-Dawley大鼠中显示其免疫调节作用[32]；也可通过抑制NF-κB通路间接减少Th2和Th17细胞因子的产生，从而改善卵清蛋白诱导的小鼠过敏性鼻炎[8]和大鼠过敏性哮喘[33]。

除T细胞外，SSA还可通过Mas相关基因Mrgprx2途径减少钙离子内流和人肥大细胞LAD2脱颗粒来抑制化合物诱导的不依赖于IgE的假过敏反应[4]；通过Wnt/β-catenin通路促进骨髓基质细胞的成骨分化，间接调节造血干细胞形成[34]，进而影响免疫系统。由此可见，针对SSA免疫调节活性的研究较少（见图3），可供参考的机制尚不全面。

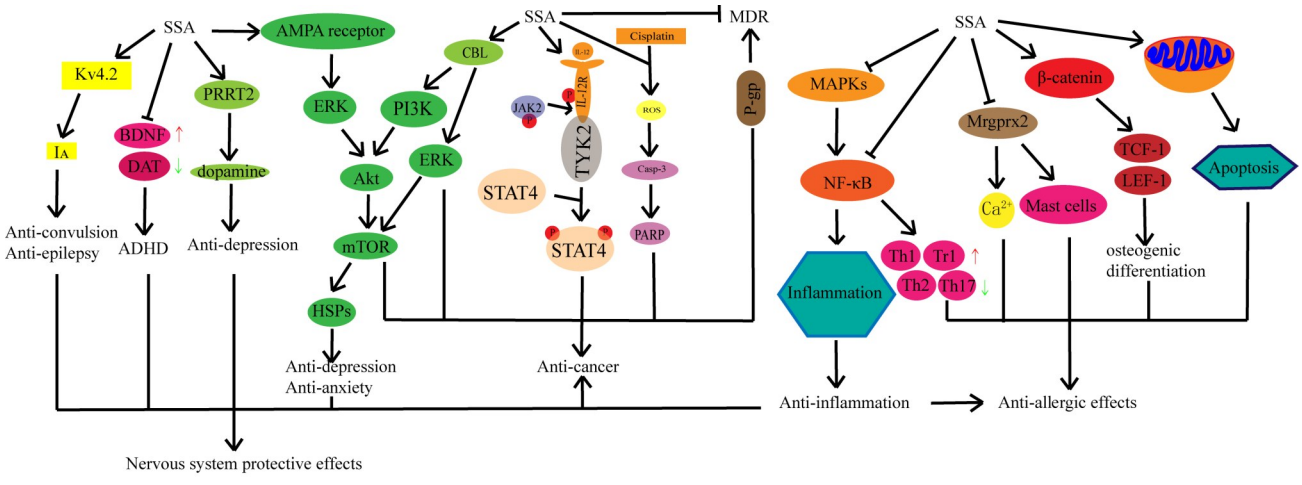

图3 SSA的抗肿瘤、免疫调节、神经调节机制

4 神经调节活性

最新研究表明，SSA通过p-CREB/BDNF通路改善脑缺血后抑郁样行为并抑制海马神经元凋亡[5]。此前也有诸多研究表明，SSA可通过改善下丘脑-垂体-肾上腺轴的失调以减少神经炎症并促进脑源性神经营养因子表达[35]、上调PRRT2的表达水平和海马中多巴胺的含量[36]，以及通过mTOR信号通路[37]改善各种原因所致的抑郁症状。抑郁和焦虑可谓一体两面，通过mTOR信号通路亦可缓解慢性皮质激素导致的焦虑作用[37]。

除了在抗焦虑和抗抑郁方面发挥作用，还有研究发现，SSA可通过减弱海马神经元的自发性癫痫样放电并上调电压门控型钾通道介导的A型电压门控钾电流来缓解癫痫症状[38]，还通过下调多巴胺转运蛋白和增强自发性高血压大鼠的脑源性神经营养因子表达减轻多动障碍的症状[39]。Maccioni等[40]先后发现，SSA可通过激活γ-氨基丁酸B受体降低大鼠对酒精的自我摄取，并通过5-羟色胺2C受体降低暴饮暴食大鼠对黄油或巧克力饼干的进食[41]。SSA由于其显著的药理活性和低毒高效的作用机制，有望成为治疗神经系统疾病的新药物（见图3）。

5 抗病毒活性

新型冠状病毒肺炎发生后，Yan等[6]应用分子对接研究发现，SSA与SARS-CoV-2 ACE Ⅱ受体具有高亲和力，并可抑制M蛋白酶以发挥抗2019-nCoV作用。当然，Cheng等[42]也证明SSA可通过减弱病毒的附着和侵入以显著抑制HCoV-229E病毒感染。受新冠肺炎的影响，近两年对于冠状病毒的研究众多，遗憾的是，尚未发现显著有效的治疗药物。

6 总结及展望

SSA是柴胡皂苷A~D中一种结构明确、研究最

深入的小分子植物提取物，尤其在抗炎、抗肿瘤、免疫调节、神经调节和抗病毒等相关研究中对其作用机制进行了深入细致的探索。截止目前，在SSA抗炎方面的研究成果最为丰富，例如通过Nrf2/NF-κB分别改善铅诱导的肾损伤和LPS诱导的子宫内膜炎，以及通过Nrf2/HO-1可改善氧-葡萄糖剥夺/复氧刺激的脑缺血缺氧损伤和通过Keap1/Nrf2-ARE可改善牛黄胆酸钠诱导的急性重症胰腺炎；还可通过IL-6/ROR-γt/STAT3/IL-17/NF-κB诸多通路缓解卵清蛋白诱发的过敏性鼻炎，通过PPAR-γ/NF-κB改善高脂饮食和牛黄胆酸钠诱导的高脂血症性胰腺炎，通过NLRP3/NF-κB改善LPS诱导的急性肺损伤，通过SIRT1/NF-κB改善福尔马林诱导的急性炎性小鼠足肿胀，通过NOD2/NF-κB缓解CCl_4诱导的肝损伤，通过ERK/NF-κB改善肥胖症，通过NF-κB通路也可治疗咪喹莫特诱导的银屑病和香烟烟雾导致的肺炎。此外，SSA亦可通过抑制核内HMGB1释放入血改善缺血再灌注损伤，通过AMPK/mTOR减缓胰腺纤维化，通过TGFβ/smad和Wnt/β-catenin减缓心肌纤维化、通过固有线粒体途径缓解肝纤维化，通过ERK1/2/p38MAPK和JNK/p38MAPK改善动脉粥样硬化，通过MAPK缓解外伤性脑损伤。同时，由于SSA具有低毒副作用，其抗炎研究在临床转化中也被广泛关注，尤其是韩国在2014年就对SSA治疗胃病进行了多药物联合实验，获得良好的研究成果并申报了发明专利。纵观现有研究，SSA针对各类疾病均有较好的疗效，且相应的分子机制也较为明确，但是这些研究目前仍停留在细胞和细胞系异种移植模型（Cell line Derived Xenograft，CDX）水平，需要更好的临床前类器官模型和人源性肿瘤异种移植模型（Patient Derived Xenograft，PDX）进行验证。SSA具有的抗炎、抗肿瘤、免疫调节、神经调节和抗病毒活性，为治疗包括肿瘤在内的诸多疾病提供了新的方案。期望在未来的研究中能够将SSA的基础研究向临床研究转化，使其真正成为造福患者的良药，体现天然产物的重要价值。

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［收稿日期］2021-06-08

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[收稿日期] 2021-10-26