doi: 10.13241/j.cnki.pmb.2021.22.002

丹酚酸 B 对肝癌荷瘤小鼠抑瘤作用及对肝纤维化的影响 *

肖珊珊[1] 张卓尔[2] 杨巧红[3] 李建婷[3] 季湍云[3]

（1 广州中医药大学第一附属医院病理科 广东 广州 510405；2 南方医科大学临床医学系 广东 广州 518056；
3 广州中医药大学基础医学院病理教研室 广东 广州 510006）

摘要 目的：探讨丹酚酸 B(salvianolic acid B，Sal B)对肝癌荷瘤小鼠抑瘤作用及对肝纤维化的影响。**方法：**将 HepG2 肝癌细胞株皮下注射于裸鼠左腋下成瘤，将荷瘤小鼠(n=42)随机平分为三组：模型组、Sal B 1 组与 Sal B 2 组。Sal B 1 组与 Sal B 2 组于造模成功当天开始分别给予 10 mL/kg/d 和 15 mL/kg/d 丹酚酸 B 进行灌胃，模型组给予等量生理盐水灌胃，每周 2 次，连续 4 周。**结果：**治疗第 2 周与第 4 周后，Sal B 1 组、Sal B 2 组的移植瘤重量均低于模型组(P<0.05)，抑瘤率高于模型组(P<0.05)，Sal B 1 组与 Sal B 2 组对比差异有统计学意义(P<0.05)。Sal B 1 组、Sal B 2 组肝脏系数与肝脏表面癌结节数目均低于模型组(P<0.05)，Sal B 2 组低于 Sal B 1 组(P<0.05)。Sal B 1 组、Sal B 2 组血清天门冬氨酸氨基转移酶(Aspartate transaminase，AST)、丙氨酸氨基转移酶(Alanine transaminase，ALT)含量均低于模型组(P<0.05)，Sal B 2 组低于 Sal B 1 组(P<0.05)。Sal B 1 组、Sal B 2 组肝组织转化生长因子 -β1(Transforming growth factor-beta 1，TGF-β1)、Smad3 蛋白相对表达水平均低于模型组 (P<0.05)，Sal B 2 组低于 Sal B 1 组(P<0.05)。**结论：**Sal B 在肝癌荷瘤小鼠中能发挥抑瘤作用，可抑制血清 ALT 与 AST 的释放，其可能是通过 TGF-β1/Smad3 信号发挥抗肝纤维化 - 肝癌作用。

关键词：丹酚酸 B；肝癌；肝纤维化；天门冬氨酸氨基转移酶；转化生长因子 -β1；肝脏系数

中图分类号：R-33；R735.7；R575.2 **文献标识码：**A **文章编号：**1673-6273(2021)22-4207-04

Salvianolic Acid B on Tumor-inhibiting Effect of Hepatocarcinoma-bearing Mice and Its Effect on Liver Fibrosis Expression*

XIAO Shan-shan[1], ZHANG Zhuo-er[2], YANG Qiao-hong[3], LI Jian-ting[3], JI Tuan-yun[3]

(1 Department of Pathology, First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Guangzhou, Guangdong, 510405, China; 2 Department of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, 518056, China; 3 Department of Pathology, School of Basic Medicine, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, 510006, China)

ABSTRACT Objective: To investigate the tumor-inhibiting effect of salvianolic acid B (Sal B) on liver cancer tumor-bearing mice and its influence on the expression of liver fibrosis. **Methods:** Mice bearing liver cancer (n=42) were randomly divided into three groups-model group, Sal B 1 group and Sal B 2 group. Sal B 1 group and Sal B 2 group were separately given 10 mL/kg/d and 15 mL/kg/d salvianolic acid B by gavage on the day of modeling, and the model group were given the same amount of normal saline by gavage twice a week for 4 consecutive weeks. **Results:** The weight of the transplanted tumors in the Sal B 1 group and Sal B 2 group were lower than that of the model group (P<0.05) in the 2nd and 4th weeks of treatment, and the tumor inhibition rate were higher than that of the model group(P<0.05), and compared the difference between the Sal B 1 group and the Sal B 2 group were also statistically significant (P<0.05). The liver coefficient and the number of liver surface cancer nodules in the Sal B 1 group and Sal B 2 group were lower than the model group (P<0.05) in the second and fourth weeks of treatment, and the Sal B 2 group were also lower than the Sal B 1 group (P<0.05). The serum aspartate transaminase (AST) and alanine transaminase (ALT) levels of the Sal B 1 group and Sal B 2 group were lower than the model in the 2nd and 4th weeks of treatment Group(P<0.05), Sal B 2 group were also lower than Sal B 1 group(P<0.05). The relative expression levels of transforming growth factor-β1 (TGF-β1) and Smad3 protein in liver tissues in the 2nd and 4th weeks of treatment in the Sal B 1 group and Sal B 2 group were lower than those in the model group(P<0.05), the Sal B 2 group were also lower than the Sal B 1 group (P<0.05). **Conclusion:** The application of salvianolic acid B in hepatocarcinoma-bearing mice can inhibit tumors and inhibit the release of serum ALT and AST, which may be through the TGF-β1/Smad3 signal to play anti-liver fibrosis-liver cancer effect.

Key words: Salvianolic acid B; Liver cancer; Liver fibrosis; Aspartate aminotransferase; Transforming growth factor-β1; Liver coefficient

Chinese Library Classification(CLC): R-33; R735.7; R575.2 Document code: A

Article ID: 1673-6273(2021)22-4207-04

* 基金项目：广东省中医药局科研项目(20211122)

作者简介：肖珊珊(1980-)，女，硕士，主治医师，研究方向：肿瘤病理诊断，电话：020-36591877，E-mail：xiaoshan801002@163.com

（收稿日期：2021-04-07 接受日期：2021-04-30）

前言

肝癌是人类主要的恶性肿瘤之一，其致死率高于其他多数肿瘤[1,2]。肝细胞癌占肝癌总数的 80.0%以上，其中 75%左右的肝细胞癌患者均存在肝硬化，而肝纤维化是各种肝病导致肝内结缔组织异常增生并发展为肝硬化的共同途径，因此抑制肝纤维化可能当前肝癌防治的重点[3,4]。研究显示：大部分肝癌患者确诊时已发生了淋巴结转移和局部浸润，失去了手术根治指征，导致 5 年生存率一直较低[5,6]。丹参始载于《神农本草经》，为唇形科植物丹参的干燥根及根茎，味苦，性微寒，具有通经止痛、凉血消痈、活血祛痕、清心除烦等多种功效[7,8]。Sal B 即紫草酸、丹参乙酸、丹参酚酸 B，是丹参水溶性有效成分丹酚酸中活性最强、含量最高的一种成分[9]。Sal B 具有抑制核苷转运活性，能够抑制胶原蛋白的沉积并改善体内纤维化水平，也可增强抗代谢药等化疗药物的抗肿瘤作用[10,11]。TGF-β1 为多种信号通路的调节因子，参与机体多种生命发生与发育的过程，也可参与肝纤维化向肝癌的发生发展过程[12]；Smad3 为其在细胞内信号转导的关键信号分子，可调控纤溶酶原激活物抑制剂 -1(Plasminogen activator inhibitor-1，PAI-1)及相关癌基因表达，从而促进肝纤维化 - 肝癌进程[13,14]。本文具体探讨了 Sal B 对肝癌荷瘤小鼠抑瘤作用及对肝纤维化的影响，以明确 Sal B 的作用效果与机制。现总结报道如下。

1 资料与方法

1.1 研究材料

SPF 级 BALB/c-nu 裸鼠(n=48)购于上海斯莱克实验动物有限责任公司(许可证号 20848221)，雌性，周龄 6-8w，体重(20.32± 1.62)g。

Sal B 购于成都普思生物科技股份有限公司(纯度≥ 99%)，AST、ALT 检测试剂盒购自宁波美康生物科技有限公司，抗 TGF-β1 抗体(稀释度 1:2000)与抗 Smad3 抗体(稀释度 1:2000)购自美国 CST 公司。

1.2 肝癌荷瘤小鼠模型的建立

收集对数生长期肝癌细胞株 HepG2，将细胞浓度调整为 1× 10^8 个 /mL，在每只裸鼠左腋下注射 0.2 mL HepG2 细胞，观察小鼠致瘤情况。建模成功标准：肿瘤大小≧0.1 cm^2。

1.3 实验分组与干预

共有 42 只建模成功的小鼠，将其随机平分为三组：模型组、Sal B 1 组与 Sal B 2 组。Sal B 1 组与 Sal B 2 组于造模成功当天开始分别给予 10 mL/kg/d 和 15 mL/kg/d Sal B 进行灌胃，模型组给予等量生理盐水灌胃，每周 2 次(周一、周四各 1 次)，连续 4 周。

1.4 观察指标

(1) 在实验过程中密切观察裸鼠的一般状况，包括精神状态、毛发、饮食、活动等。在治疗第 2 周与第 4 周，三组裸鼠分别腹主动脉取血、处死取肝组织及肿瘤组织。(2)分别于治疗第 2 周和第 4 周，每组各取 7 只小鼠，麻醉后断颈法处死，将移植瘤取出并称重，计算其移植瘤重量和抑瘤率【抑瘤率(%)=(对照组平均瘤重 - 处理组瘤重)/ 对照组瘤重× 100%)】。

(3)迅速取出小鼠肝脏后，冲洗干净吸去表面多余水分后，仔细观察肝脏外观，称重并计算肝脏系数(即肝脏重量与体重之比)，计数肝脏表面癌结节数目。同时取肝组织及结节固定于 4 %福尔马林溶液中，病理制片，HE 染色，镜下观察。(4)腹主动脉取血后，低温下 2000 rpm 离心 10 min，分离上层血清，采用全自动生化分析仪(海力孚 HF-240 型)测定血清 ALT、AST 含量。(5)另取部分新鲜肝组织，研磨后进行裂解，混匀离心，提取总蛋白，上样 SDS-PAGE 电泳，转膜后室温封闭 1 h，加入兔抗 TGF-β1 多克隆抗体、兔抗 Smad3 单克隆抗体、兔抗 β-actin 单克隆抗体，5℃孵育过夜，洗膜，加入二抗室温孵育 1 h，洗膜后进行曝光显影，以 β-actin 为内参蛋白，采用图像分析软件分析 TGF-β1、Smad3 蛋白相对表达水平。

1.5 统计学方法

采用 SPSS22.00 进行数据分析，计量数据采用均数± 标准差表示，对比行方差检验及 LSD-t 检验，检验水准为 α=0.05。

2 结果

2.1 一般状况与病理改变

一般状况：模型组：皮毛无光泽、饮食减少、活动量减少、精神萎靡；Sal B 1 组与 Sal B 2 组：精神状态、毛发、饮食、活动等表现均有明显改善。

病理改变：模型组：肝小叶结构完全被破坏，可见大片胞浆淡染的肿瘤区，肝细胞排列紊乱，细胞核深染、异型性明显增多。Sal B 1 组与 Sal B 2 组：肝小叶结构有所改善，细胞排列相对整齐，细胞核异型性明显减轻。

2.2 移植瘤重量和抑瘤率对比

治疗第 2 周与第 4 周后，Sal B 1 组、Sal B 2 组移植瘤重量均低于模型组(P<0.05)，抑瘤率高于模型组(P<0.05)，Sal B 1 组与 Sal B 2 组对比差异也有统计学意义(P<0.05)。见表 1。

表 1 三组移植瘤重量与抑瘤率对比

Table 1 Comparison of tumor weight and tumor suppressive rate three groups

Groups	n	2 weeks of treatment		4 weeks of treatment	
		Weight of transplanted tumor(g)	Tumor suppressor(%)	Weight of transplanted tumor(g)	Tumor suppressor(%)
Model group	7	6.23± 0.22	0.03± 0.01	7.23± 0.33	0.05± 0.01
Sal B 1 group	7	4.91± 0.15*	23.71± 3.22*	4.55± 0.13*	31.88± 2.18*
Sal B 2 group	7	4.01± 0.22*#	40.86± 6.31ab	3.67± 0.13*#	56.29± 5.29*#
F		13.492	342.103	18.921	456.103
P		0.000	0.000	0.000	0.000

Note: Compared with the model group, *P<0.05; Compared with the model group, #P<0.05.

2.3 肝脏系数与肝脏表面癌结节数目对比

治疗第 2 周与第 4 周后，Sal B 1 组、Sal B 2 组肝脏系数与肝脏表面癌结节数目均低于模型组（$P<0.05$），Sal B 2 组低于 Sal B 1 组（$P<0.05$）。见表 2。

表 2 三组肝脏系数与肝脏表面癌结节数目对比

Table 2 Comparison of Liver Coefficient and Nodules on Liver Surface Cancer in Three Groups

Groups	n	2 weeks of treatment		4 weeks of treatment	
		Liver coefficient(%)	Number of nodules on liver surface cancer(n)	Liver coefficient(%)	Number of nodules on liver surface cancer(n)
Model group	7	14.22± 1.83	73.29± 18.11	16.29± 2.44	58.17± 15.72
Sal B 1 group	7	10.22± 1.11*	56.29± 9.11*	13.09± 1.22*	49.99± 11.57*
Sal B 2 group	7	9.11± 0.98*#	43.02± 8.13*#	10.00± 2.17*#	30.98± 7.88*#
F		11.932	15.684	18.883	9.223
P		0.000	0.000	0.000	0.002

Note: Compared with the model group, *$P<0.05$; Compared with the model group, #$P<0.05$.

2.4 血清 ALT 与 AST 含量对比

Sal B 1 组与 Sal B 2 组治疗第 2 周与第 4 周后，血清 ALT 与 AST 含量均低于模型组（$P<0.05$），Sal B 2 组也低于 Sal B 1 组（$P<0.05$）。见表 3。

表 3 三组血清 ALT 与 AST 含量对比(U/L)

Table 3 Comparison of serum ALT and AST contents in three groups (U/L)

Groups	n	2 weeks of treatment		4 weeks of treatment	
		ALT	AST	ALT	AST
Model group	7	456.22± 54.19	733.28± 67.20	511.48± 78.10	801.47± 98.22
Sal B 1 group	7	293.81± 45.01*	388.82± 56.16*	311.47± 76.28*	413.87± 87.10*
Sal B 2 group	7	221.09± 41.76*#	267.99± 67.01*#	243.91± 50.28*#	281.65± 77.88*#
F		34.922	45.864	46.775	67.772
P		0.000	0.000	0.000	0.000

Note: Compared with the model group, *$P<0.05$; Compared with the model group, #$P<0.05$.

2.5 TGF-β1、Smad3 蛋白相对表达量对比

治疗第 2 周与第 4 周后，Sal B 1 组、Sal B 2 组肝组织 TGF-β1、Smad3 蛋白相对表达水平均低于模型组（$P<0.05$），Sal B 2 组也低于 Sal B 1 组（$P<0.05$）。见表 4。

表 4 三组肝组织 TGF-β1、Smad3 蛋白相对表达量对比

Table 4 Comparison of relative expression of TGF-β1, Smad3 proteins in three groups

Groups	n	2 weeks of treatment		4 weeks of treatment	
		TGF-β1	Smad3	TGF-β1	Smad3
Model group	7	5.33± 0.49	4.20± 0.11	6.13± 0.03	5.23± 0.31
Sal B 1 group	7	2.63± 0.10*	2.41± 0.26*	3.11± 0.41*	2.84± 0.24*
Sal B 2 group	7	1.49± 0.08*#	1.32± 0.22*#	1.74± 0.34*#	1.53± 0.22*#
F		29.013	19.222	38.924	27.736
P		0.000	0.000	0.000	0.000

Note: Compared with the model group, *$P<0.05$; Compared with the model group, #$P<0.05$.

3 讨论

当前肝癌的发生率逐年增加，虽然其诊断和治疗技术在进步，但是很多患者在就诊时已处于晚期，导致预后比较差[15,16]。肝癌是起源于肝脏上皮或间叶组织的恶性肿瘤，通常由慢性肝炎进展为肝纤维化，再由肝纤维化进展为肝硬化，最终演变成肝癌[17]。Sal B 属酚酸类化合物，是从丹参中提取的一种水溶性成分，具有凉血消痈的功效，主要用于脘腹胁痛、胸痹心痛、癥瘕积聚等疾病的治疗[18,19]。

本研究显示治疗第 2 周与第 4 周后 Sal B 1 组与 Sal B 2 组的移植瘤重量均低于模型组（$P<0.05$），抑瘤率高于模型组（$P<0.05$），Sal B 1 组与 Sal B 2 组对比差异也有统计学意义（$P<0.05$）；Sal B 1 组与 Sal B 2 组肝脏系数与肝脏表面癌结节数目均低于模型组（$P<0.05$），Sal B 2 组也低于 Sal B 1 组（$P<0.05$）。

提示 Sal B 不仅可减小原发肿瘤的大小，而且可减少转移瘤的数量，从而抑制肿瘤的生长，结合相关研究分析其原因在于：Sal B 的结构中含有多个酚羟基故具有还原性，具有抗氧化应激作用，可增强机体的抗肿瘤作用，也可逆转肿瘤细胞的多药抗药性[20]。同时 Sal B 对于心肌细胞与神经元也具有一定保护作用，拮抗低密度脂蛋白的氧化，可抑制成纤维细胞增殖以及细胞内胶原合成，从而可发挥抑制肝癌增殖的作用[21]。Xu J 等研究结果显示：Sal B 能够抑制恶性肿瘤的增殖，可以剂量依赖的方式抑制前列腺素 E2 的合成，促进恶性肿瘤细胞凋亡，从而抑制癌症发生，与本研究结果一致[22]。

Sal B 相对分子量为 718.59，由 3 分子丹参素与 1 分子咖啡酸聚合而成[23]。Sal B 的激发波谱范围在 380-430 nm 之间，发射波谱在 400-600 nm 之间。Sal B 有强烈的抗氧化和清除氧自由基的活性，有利于清除血液中的氧自由基，也可抑制体内的血小板聚集，从而保证心脑血管和神经免疫系统的正常功能[24]。Sal B 也能抑制肾脏系膜细胞 NF-κB 的活性，能够通过保护肝线粒体形态和功能，从而发挥对肝脏的保护作用[25]。本研究显示治疗第 2 周与第 4 周后，Sal B 1 组、Sal B 2 组的血清 ALT 与 AST 含量均低于模型组（P<0.05），Sal B 2 组也低于 Sal B 1 组（P<0.05），提示 Sal B 可抑制血清 ALT 与 AST 的释放，从而发挥保护肝脏的作用。

肝纤维化是各种慢性肝病发展的共同结果，也是肝癌发生的前兆[26,27]。病毒等致肝损伤因子反复刺激肝细胞导致肝脏炎症发生，继而产生肝纤维化，最终致肝细胞癌的发生[28]。在肝纤维化的过程中，TGF-β1 与膜上的受体结合后，活化Ⅰ型受体，使 Smad3 蛋白 C 末端磷酸化，形成复合体，转位入核，调节靶基因 p21，从而促进肝癌的形成[29,30]。本研究显示 Sal B 1 组、Sal B 2 组治疗第 2 周与第 4 周后肝组织中 TGF-β1、Smad3 蛋白的相对表达水平都低于模型组（P<0.05），Sal B 2 组也低于 Sal B 1 组（P<0.05）。相关研究[31,32]显示 Sal B 可以通过促进 Smad3 信号转换和影响其下游靶基因来促进癌细胞凋亡，从而发挥抗癌作用，支持了本研究上述结果。本研究也有一定的不足，Sal B 的作用通路比较复杂，对肝癌荷瘤小鼠的影响机制还不明确，且缺乏其他药物的应用对比方式，可能存在研究偏倚，将在后续研究中深入分析。

总之，Sal B 在肝癌荷瘤小鼠中能发挥抑瘤作用，可抑制血清 ALT 与 AST 的释放，其可能是通过 TGF-β1/Smad3 信号发挥抗肝纤维化 - 肝癌作用。

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