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不同剂量朱砂七总蒽醌对 H22 荷瘤小鼠免疫功能及抗氧化能力的影响 *

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摘要 目的：探讨不同剂量朱砂七总蒽醌对 H22 荷瘤小鼠免疫功能及抗氧化能力的影响。**方法：**选取清洁级昆明小鼠 60 只，按照随机数字表法分为正常对照组、H22 荷瘤组、环磷酰胺组、低剂量组、中剂量组、高剂量组，每组各 10 只。除正常对照组外，其余 5 组小鼠建立 H22 荷瘤小鼠模型。低剂量组、中剂量组、高剂量组分别给予 0.3 g/kg、0.6 g/kg、1.2 g/kg 的朱砂七总蒽醌悬浊液干预，环磷酰胺组给予 0.02 g/kg 的环磷酰胺干预，正常对照组和 H22 荷瘤组给予等剂量的 1%的羧甲基纤维素钠干预。比较各组小鼠的肿瘤体质量、抑瘤率、T 淋巴细胞亚群以及血清超氧化歧化酶（SOD）、谷胱甘肽过氧化物酶（GSH-Px）、丙二醛（MDA）、乳酸脱氢酶（LDH）水平。**结果：**环磷酰胺组、高剂量组的肿瘤体质量低于低剂量组，抑瘤率高于低剂量组，差异具有统计学意义（P<0.05）。高剂量组的 $CD4^+$、$CD4^+/CD8^+$ 均高于环磷酰胺组、低剂量组、中剂量组，$CD8^+$ 低于环磷酰胺组、低剂量组、中剂量组，差异均有统计学意义（P<0.05）。高剂量组血清 SOD、GSH-Px 水平高于其他 5 组，MDA、LDH 水平低于 H22 荷瘤组、低剂量组、中剂量组，差异均有统计学意义（P<0.05）。**结论：**朱砂七总蒽醌具有明显的抗肿瘤作用，可增强小鼠的免疫功能和抗氧化能力，且具有剂量效应。

关键词：朱砂七总蒽醌；H22 荷瘤小鼠；免疫功能；抗氧化

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Effects of Different Doses of Total Anthraquinone From Zhushaqi on Immune Function and Antioxidant Capacity in H22 Tumor Bearing Mice*

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ABSTRACT Objective: To investigate the effects of different doses of total anthraquinone from Zhushaqi on immune function and antioxidant capacity in H22 tumor bearing mice. **Methods:** 60 clean grade Kunming mice were selected, and the mice were divided into normal control group, H22 tumor bearing group, cyclophosphamide group, low dose group, medium dose group and high dose group according to random number table method, with 10 mice in each group. In addition to the normal control group, the mice in other 5 groups were established H22 tumor bearing mice model. Low dose group, middle dose group and high dose group were given 0.3 g/kg, 0.6 g/kg, 1.2 g/kg total anthraquinone from Zhushaqi suspension intervention, respectively, cyclophosphamide group was given 0.02 g/kg cyclophosphamide intervention, normal control group and H22 tumor bearing group were given equal dose of 1% sodium carboxymethyl cellulose intervention. Tumor mass, tumor inhibition rate, T lymphocyte subsets, levels of serum superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), malondialdehyde (MDA) and lactate dehydrogenase (LDH) were compared between the mice in each group. **Results:** The tumor mass in cyclophosphamide group and high-dose group was lower than that in low dose group, the tumor inhibition rate was higher than that of low dose group, and the difference was statistically significant (P<0.05). The $CD4^+$ and $CD4^+/CD8^+$ of high dose group were higher than those of cyclophosphamide group, low dose group and middle dose group, and $CD8^+$ was lower than that of cyclophosphamide group, low dose group and middle dose group, the difference was statistically significant (P<0.05). The levels of serum SOD and GSH-Px in the high dose group were higher than those in the other 5 groups, and the levels of MDA and LDH were lower than those in the H22 tumor bearing group, low dose group and medium dose group (P<0.05). **Conclusion:** Total Anthraquinone from Zhushaqi has obvious anti-tumor effect, it can enhance the immune function and antioxidant capacity of mice, and it has dose effect.

Key words: Total anthraquinone from Zhushaqi; H22 tumor bearing mice; Immune function; Antioxidation

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前言

朱砂七又被称作朱砂莲、黄药子，其味苦、性凉，是寥科植物金线草的块根，我国的朱砂七多产于陕西、河南、甘肃等地

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[1]。朱砂七具有较高的药用价值,在古代便用于治疗急性胃痛、胃肠炎、扁桃体炎、菌痢、跌打损伤、尿路感染及风湿腰痛等,具有清热解毒、止血止泻、活血凉血 、祛风湿等功效,被列为太白七药之列[2,3]。蒽醌类物质是朱砂七的主要成分,近年来有研究发现[4],朱砂七总蒽醌具有抗肿瘤的作用,可抑制肿瘤细胞增殖,并能够诱导肿瘤细胞凋亡,这为恶性肿瘤的治疗提供了新的思路。机体的免疫功能及抗氧化能力与肿瘤具有重要的联系,当机体存在免疫缺陷或免疫功能低下时,各种肿瘤的发病率会明显上升,同时恶性肿瘤患者的免疫功能低下也是普遍现象,由此可见机体的免疫功能与肿瘤的发生、发展密切相关[5-7]。恶性肿瘤患者的抗氧化能力明显下降,导致氧化与抗氧化作用失衡,对机体造成氧化损伤,且抗氧化能力可导致自由基增多,过量的自由基可对 DNA 造成多级损伤, 而 DNA 损伤正是引发肿瘤的基础条件[8-10]。本研究通过建立动物对照实验,分析不同剂量的朱砂七总蒽醌对 H22 荷瘤小鼠免疫功能及抗氧化能力的影响,以进一步探讨朱砂七总蒽醌的抗肿瘤机制,现将研究结果整理报道如下。

1 材料与方法

1.1 实验动物与瘤株

清洁级昆明小鼠 60 只,雌雄各半,体重 20.62 g-25.71 g,平均体重(22.34± 1.26)g。饲养温度保持在 20℃-25℃范围内,环境湿度控制在 55%左右,每天 12 h 光照,避免噪音,保持通风,分笼喂养,每笼 6 只,适应性喂养 1 周,期间所有小鼠均自由饮食、活动。实验小鼠购于北京华阜康生物科技股份有限公司,许可证号:SCXK(京)2009-0004。H22 肝癌瘤株购于天津赛尔生物技术有限公司。本实验经动物实验伦理委员会审查批准。

1.2 方法

适应性喂养 1 周后将所有小鼠按照随机数字表法分为正常对照组、H22 荷瘤组、环磷酰胺组、低剂量组、中剂量组、高剂量组,每组各 10 只。选取出接种 H22 肝癌瘤株 7 d 并且生长良好的小鼠,在无菌条件下取其腹水,用生理盐水按照 1:4 的比例进行稀释,将肿瘤细胞数调整为 2.5× 10^7 个 /mL,除正常对照组外, 其余 5 组小鼠均于右侧腋窝皮下接种 0.2 mL 稀释好的肿瘤细胞。建模成功后(接种 24 h 后),低剂量组、中剂量组、高剂量组均给予朱砂七总蒽醌悬浊液 (用 1%的羧甲基纤维素钠与朱砂七总蒽醌配成 10%的混悬液)干预,灌胃给药,剂量分别为 0.3 g/kg、0.6 g/kg、1.2 g/kg,1 次 /d; 正常对照组和 H22 荷瘤组给予等剂量的 1%的羧甲基纤维素钠干预,灌胃给药,1 次 /d;环磷酰胺组给予环磷酰胺(江苏盛迪医药有限公司,国药准字 H32020856,规格:0.1 g)干预,腹腔注射,剂量为 0.02 g/kg,1 次 /2 d。每组小鼠均连续干预 10 d。

1.3 小鼠 T 淋巴细胞亚群检测

末次给药后 2 h,采用摘眼球法取血,将血液标本分为两部分。取其中一份血液标本, 加入 1%的肝素钠抗凝, 取抗凝血 200 μL,加入 20 μL 抗体(FITC anti-mouse $CD3^+$、PE anti-mouse $CD4^+$、PE anti-mouse $CD8^+$, 均购于上海恪敏生物科技有限公司),充分震荡混匀,室温下避光孵育 20 min,加入 600 μL 红细胞裂解液,震荡混匀,室温下避光孵育 10 min,以 1500 r/min 的离心速度进行 5 min 的离心运动,弃上清,加入 PBS 缓冲液 1 mL,以 1500 r/min 的离心速度进行 5 min 的离心运动,弃上清;加入 1%多聚甲醛 300 μL 固定,采用流式细胞仪(美国 BD 公司, 型号:LSR II) 检测 T 淋巴细胞亚群 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$。

1.4 小鼠抗氧化能力相关指标检测

取另一份未处理的血液标本,以 3000 r/min 的离心速度进行 10 min 的离心运动,提取上层血清,置于 -20℃的环境下保存待测。黄嘌呤氧化酶法测定超氧化歧化酶 (superoxide dismutase, SOD)的水平,二硫代二硝基苯甲酸法检测谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)的水平,硫代巴比妥比色法检测丙二醛(malondialdehyde, MDA)水平,2,4- 二硝基苯肼显色法检测乳酸脱氢酶 (lactate dehydrogenase, LDH)水平,上述试剂盒均购于上海恒远生物科技有限公司,所有操作步骤均严格遵循相关试剂盒的说明书进行。

1.5 小鼠肿瘤体质量和抑瘤率的检测

颈椎脱臼法处死小鼠,剥除肿瘤体,测定肿瘤体质量,计算干预组小鼠(包括环磷酰胺组、低剂量组、中剂量组、高剂量组)的抑瘤率,计算公式如下:抑瘤率 =(H22 荷瘤组小鼠肿瘤体质量 - 干预组小鼠肿瘤体质量)/H22 荷瘤组小鼠肿瘤体质量× 100%。

1.6 统计学方法

所有数据均用 SPSS19.0 进行统计分析, 计数资料以率(%)的形式表示,采用 x^2 检验,计量资料以($\bar{x}$± s)的形式表示,采用单因素方差分析,组间比较采用 t 检验。以 P<0.05 为差异有统计学意义。

2 结果

2.1 各组小鼠肿瘤体质量和抑瘤率比较

各组小鼠的肿瘤体质量和抑瘤率的整体比较均存在统计学差异(P<0.05);环磷酰胺组、高剂量组的肿瘤体质量低于低剂量组,抑瘤率高于低剂量组,差异具有统计学意义(P<0.05)。见表 1。

2.2 各组小鼠 T 淋巴细胞亚群比较

各组小鼠的 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 整体比较均存在统计学差异(P<0.05);高剂量组的 $CD4^+$、$CD4^+/CD8^+$ 均高于环磷酰胺组、低剂量组、中剂量组,$CD8^+$ 低于环磷酰胺组、低剂量组、中剂量组,差异均有统计学意义(P<0.05)。见表 2。

2.3 各组小鼠血清 SOD、GSH-Px、MDA、LDH 水平比较

各组小鼠血清 SOD、GSH-Px、MDA、LDH 水平整体比较均存在统计学差异(P<0.05);高剂量组血清 SOD、GSH-Px 水平高于其他五组,MDA、LDH 水平低于 H22 荷瘤组、 低剂量组、中剂量组,差异均有统计学意义(P<0.05)。见表 3。

3 讨论

朱砂七总蒽醌具有抗炎、抗病毒等多种作用,近年来其抗肿瘤的作用逐渐被发现,赵勤等[11]人对 S180、H22 荷瘤小鼠进行朱砂七总蒽醌干预,并用 MTT 法和 Giemsa 染色法检测朱砂七总蒽醌对 HL-60 细胞增殖和凋亡的影响,结果发现朱砂七总蒽醌可显著抑制 S180、H22 荷瘤小鼠肿瘤体的生长,且体外实验结果显示, 朱砂七总蒽醌能抑制 HL-60 细胞增殖、诱导

HL-60 细胞凋亡。肿瘤的发生、发展与机体的免疫功能存在紧密的联系，虽然肿瘤细胞也有免疫原性，也会激发机体免疫系统的免疫应答，但肿瘤细胞的免疫原性较弱，难于激发较强的免疫应答，且近年来研究发现，调控免疫系统可有效提高恶性肿瘤的治疗效果[12-14]。自由基是正常代谢过程中产生的高活性分子，参与了生物体内正常的生理生化过程，相关研究显示[15-17]，恶性肿瘤患者体内的自由基呈现异常表达，过表达的自由基可攻击 DNA 链，导致 DNA 发生突变，使得细胞分裂、增殖失去控制，利于肿瘤的发生、发展，因此抗氧化清除多余的自由基对肿瘤的防治具有重要的意义。

表 1 各组小鼠肿瘤体质量和抑瘤率比较($\bar{x}\pm s$)

Table 1 Tumor mass and tumor inhibition rate in each group of mice ($\bar{x}\pm s$)

Groups	n	Tumor mass(g)	Tumor inhibition rate(%)
H22 tumor bearing group	10	3.34± 0.58	-
Cyclophosphamide group	10	1.53± 0.33^{ab}	54.19^{b}
Low dose group	10	1.96± 0.53^{a}	41.32
Medium dose group	10	1.72± 0.41^{a}	48.50
High dose group	10	1.51± 0.45^{ab}	54.79^{b}
F/x^2		57.684	21.364
P		0.000	0.000

Note: compared with H22 tumor bearing group, $^{a}P<0.05$, compared with low dose group, $^{b}P<0.05$.

表 2 各组小鼠 T 淋巴细胞亚群比较($\bar{x}\pm s$)

Table 2 Comparison of T lymphocyte subsets in each group ($\bar{x}\pm s$)

Groups	n	$CD3^+$(%)	$CD4^+$(%)	$CD8^+$(%)	CD4+/CD8+
Normal control group	10	30.56± 0.47	21.65± 0.36	16.74± 0.87	1.29± 0.21
H22 tumor bearing group	10	10.02± 0.52^{a}	11.32± 0.65^{a}	16.54± 1.46	0.68± 0.23^{a}
Cyclophosphamide group	10	13.63± 0.81^{ab}	15.12± 0.78^{ab}	17.23± 1.65	0.88± 0.15^{ab}
Low dose group	10	13.45± 0.62^{ab}	14.87± 0.72^{ab}	16.32± 1.21	0.91± 0.14^{ab}
Medium dose group	10	14.35± 0.73^{ab}	15.21± 0.88^{ab}	15.87± 1.33^{ac}	0.96± 0.17^{ab}
High dose group	10	14.62± 0.65^{ab}	16.89± 0.73^{abcde}	14.36± 1.24^{abcde}	1.18± 0.13^{abcde}
F		169.356	107.362	31.025	136.354
P		0.000	0.000	0.000	0.000

Note: compared with the normal control group, $^{a}P<0.05$; compared with H22 tumor bearing group, $^{b}P<0.05$; compared with cyclophosphamide group, $^{c}P<0.05$; compared with low dose group, $^{d}P<0.05$; compared with medium dose group, $^{e}P<0.05$.

表 3 各组小鼠血清 SOD、GSH-Px、MDA、LDH 水平比较($\bar{x}\pm s$)

Table 3 Comparison of levels of serum SOD, GSH-Px, MDA and LDH in each group ($\bar{x}\pm s$)

Groups	n	SOD(U/mL)	GSH-Px(μmol/L)	MDA(nmol/mL)	LDH(U/mL)
Normal control group	10	186.36± 32.15	286.32± 12.36	5.26± 0.33	3.61± 1.11
H22 tumor bearing group	10	141.36± 28.64^{a}	121.33± 9.98^{a}	7.54± 1.28^{a}	7.88± 1.20^{a}
Cyclophosphamide group	10	145.37± 31.26^{a}	123.12± 11.23^{a}	5.28± 0.86b	7.76± 1.02^{a}
Low dose group	10	170.32± 33.65^{abc}	289.65± 21.36^{bc}	7.39± 0.93^{ac}	7.15± 0.88^{a}
Medium dose group	10	186.64± 31.87^{bcd}	507.33± 25.97^{abcd}	6.37± 0.73^{abcd}	6.74± 0.93^{ab}
High dose group	10	215.32± 34.69^{abcde}	812.65± 41.24^{abcde}	5.24± 0.78^{bde}	5.62± 1.03^{abcde}
F		143.68	269.36	63.254	53.624
P		0.000	0.000	0.000	0.000

Note: compared with the normal control group, $^{a}P<0.05$; compared with H22 tumor bearing group, $^{b}P<0.05$; compared with cyclophosphamide group, $^{c}P<0.05$; compared with low dose group, $^{d}P<0.05$; compared with medium dose group, $^{e}P<0.05$.

在本次研究中，环磷酰胺组、高剂量组的肿瘤体质量低于低剂量组，抑瘤率高于低剂量组($P<0.05$)。这说明环磷酰胺与高剂量的朱砂七总蒽醌均能有效抑制肿瘤生长，降低肿瘤体质量，这验证了朱砂七总蒽醌的抗肿瘤作用，且提示在抗肿瘤中朱砂七总蒽醌具有剂量效应。T 淋巴细胞来源于骨髓，在胸腺激素的诱导下分化成熟，在体液免疫和细胞免疫中均有重要的作用[18,19]。$CD3^+$ 亚群是成熟的 T 淋巴细胞，其比值大小与细胞免疫功能的强弱呈正相关，水平降低后机体易发生感染；$CD4^+$

为辅助/诱导功能细胞，对机体免疫功有重要的调节作用；$CD8^+$为抑制/杀伤功能细胞，是免疫反应中的直接杀伤性细胞，其比值升高可引发免疫缺陷；$CD4^+/CD8^+$比值是临床上评估机体免疫功能是否紊乱的常用指标，其比值降低说明机体处于免疫抑制状态[20,21]。在本次研究中，高剂量组的$CD4^+$、$CD4^+/CD8^+$均高于环磷酰胺组、低剂量组、中剂量组，$CD8^+$低于环磷酰胺组、低剂量组、中剂量组（$P<0.05$）。这说明朱砂七总蒽醌具有免疫调节作用，并且高剂量的朱砂七总蒽醌效果最佳，可显著增加$CD4^+$、$CD4^+/CD8^+$比值，降低$CD8^+$比值。SOD是体内重要的氧自由基清除剂，能促使过氧化物游离基转化成过氧化氢和氧，具有强大的抗炎作用[22]；GSH-Px是机体内分布广泛的一种过氧化物分解酶，能将过氧化物还原成羟基化合物，避免细胞膜的结构及功能受到过氧化物的干扰[23]；MDA是膜脂过氧化最重要的产物之一，它的产生还能加剧膜的损伤，并能和自由基结合使DNA发生交联或单链断裂[24]；LDH是糖无氧酵解过程中的重要的酶，肿瘤细胞的无氧代谢可增加LDH的水平，LDH可催化丙酮酸与L-乳酸之间的还原与氧化反应[25]。在研究结果显示，高剂量组血清SOD、GSH-Px水平高于其他五组，MDA、LDH水平低于H22荷瘤组、低剂量组、中剂量组（$P<0.05$）。这说明在肿瘤小鼠血清中SOD、GSH-Px降低，MDA、LDH水平升高，抗氧化能力显著减弱，而朱砂七总蒽醌能增加SOD、GSH-Px水平，降低MDA、LDH水平，增加抗氧化能力，且高剂量的朱砂七总蒽醌效果最明显，这可能是朱砂七总蒽醌的抗肿瘤机制之一。

综上所述，高剂量朱砂七总蒽醌可抑制H22荷瘤小鼠的肿瘤体生长，具有较高的抑瘤率，提高免疫功能，改善抗氧化能力，但其具体的作用机制还有待进一步研究。

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