doi:10.11659/jjssx.09E020093

·基础研究·

芦荟凝胶多糖对急性放射性皮肤损伤模型的修复作用及机制研究

刘太阳[1],刘卓卓[2],朱 玉[1],李 博[1] (1.重庆市涪陵中心医院烧伤整形科,重庆 408000;2.重庆市涪陵区妇幼保健院妇科,重庆 408000)

[摘 要] **目的** 研究芦荟凝胶多糖基于磷脂酰肌醇3-激酶(PI3K)-蛋白激酶B(Akt)-雷帕霉素靶蛋白(mTOR)信号通路对急性放射性皮肤损伤模型的修复作用。**方法** 选取40只雄性Wistar大鼠,10只为正常组(等体积生理盐水),其余30只建立急性放射性皮肤损伤模型,随机分为模型组、低剂量组、高剂量组,每组10只。模型组和正常组均给予等体积生理盐水干预,低剂量组、高剂量组分别以单层纱布浸润0.4 mg/mL、0.8 mg/mL的芦荟凝胶多糖外敷干预。记录创面愈合时间、放射性皮肤损伤评级,检测创面微血管密度、血管内皮生长因子(VEGF)含量,病理学观察创面组织细胞形态,Western blot检测PI3K-Akt-mTOR信号通路相关蛋白表达。**结果** 低剂量组和高剂量组创面愈合时间均短于模型组,且高剂量组创面愈合时间显著短于低剂量组($P<0.05$);与模型组相比,正常组大鼠0级较多,Ⅳ级较少;低剂量组和高剂量组大鼠Ⅳ级较少($P<0.05$)。模型组、低剂量组、高剂量组创面微血管密度、VEGF、PI3K、Akt蛋白表达量低于正常组,mTOR蛋白表达量高于正常组;低剂量组、高剂量组创面微血管密度、VEGF、PI3K、Akt蛋白表达量高于模型组,mTOR蛋白表达量低于模型组;高剂量组创面微血管密度、VEGF、PI3K、Akt蛋白表达量高于低剂量组,mTOR蛋白表达量低于低剂量组。**结论** 高剂量芦荟凝胶多糖可通过调控PI3K-Akt-mTOR信号通路促进急性放射性皮肤损伤模型创面新生血管形成,加快创面修复。

[关键词] 芦荟凝胶多糖;急性放射性皮肤损伤;创面愈合;磷脂酰肌醇3-激酶;蛋白激酶B;雷帕霉素靶蛋白

[中图分类号] R758.1 [文献标识码] A [收稿日期] 2020-09-21

Repair effect and mechanism of polysaccharide isolated from aloe vera gel on acute radiation-introduced skin damage model

LIU Tai-yang[1], LIU Zhuo-zhuo[2], ZHU Yu[1], LI Bo[1] (1. Department of Burn and Plastic Surgery, Fuling Central Hospital of Chongqing, Chongqing 408000, China; 2. Department of Gynecology, Fuling District Maternal and Child Health Care Hospital of Chongqing, Chongqing 408000, China)

Abstract: Objective To study the repair effect of polysaccharide isolated from aloe vera gel on acute radiation-introduced skin damage models through phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt)-mammalian target of rapamycin (mTOR) signaling pathway. **Methods** A total of 40 male Wistar rats were selected, 10 rats of them were included into the normal group (equal volume of normal saline), and the remaining 30 rats were randommizedly divided into the model group, the low dose group, and the high dose group, with 10 rats in each group for the establishment of acute radiation-introduced skin damage models. Rats in the normal group and the model group were given equal volume of normal saline for intervention, and those in the low dose group and the high dose group were given single layer of gauze infiltrated with 0.4 mg/mL and 0.8 mg/mL polysaccharide isolated from aloe vera gel for intervention. The wound healing time, radiation-induced skin damage rating were recorded, wound microvessel density, vascular endothelial growth factor (VEGF) content were detected, wound cell morphology was observed by HE staining, expression levels of PI3K-Akt-mTOR signaling pathway related proteins were detected by Western blot. **Results** The wound healing time of the low dose group and the high dose group was shorter than that of the model group, and the wound healing time of the high dose group was significantly shorter than that of the low dose group ($P<0.05$). Compared with the model group, there were more rats of grade 0 and less rats of grade Ⅳ in the normal group; and there were less rats of grade Ⅳ in the low dose group and the high dose group ($P<0.05$). The wound microvessel density expression levels of VEGF, PI3K and Akt proteins in the model group, the low dose group and the high dose group were lower than those in the normal group, and the expression level of mTOR protein was higher than that of the normal group. The wound microvessel density, expression levels of VEGF, PI3K and Akt proteins in the low dose group and the high dose group were higher than those in the model group, and the expression level of mTOR protein was lower than that of the model group. The wound microvessel density, expression levels of VEGF, PI3K and Akt proteins in the high dose group were higher than those in the low dose group, and the expression level of mTOR protein was lower than that of the low dose group. **Conclusion** High dose of polysaccharide isolated from aloe vera gel can promote angiogenesis and accelerate wound healing in acute radiation-introduced skin damage models through regulating PI3K-Akt-mTOR signaling pathway.

Keywords: polysaccharide isolated from aloe vera gel; acute radiation-introduced skin damage; wound healing; phosphatidylinositol 3-kinase; protein kinase B; mammalian target of rapamycin

[基金项目] 重庆市科卫联合医学科研项目(2019QNXM045)

[通信作者] 李 博,E-mail:244988753@qq.com

放射治疗简称放疗,是临床上治疗恶性肿瘤的常用手段,放射线在杀死肿瘤细胞的过程中也会损伤患者周围正常组织、器官,其中放射性皮肤损伤是放射治疗的主要并发症[1]。目前主要通过外敷乳膏、喷剂等治疗放射性皮肤损伤,例如细胞因子类、三乙醇胺乳膏以及糖皮质激素软膏等药物,也有少数通过静脉注射放射防护药物,但治疗效果均不显著[2-3]。芦荟凝胶多糖是芦荟中重要的生物活性物质,研究显示,其生理活性较强,在免疫调节方面具有广谱性,同时在抗辐射、抗肿瘤方面效果显著,还具有抗溃疡、美容护肤等功效[4-5]。目前芦荟凝胶多糖对急性放射性皮肤损伤的研究较少。本研究通过探讨芦荟凝胶多糖对急性放射性皮肤损伤模型的修复作用及相关机制,以期为其临床应用提供参考。

1 材料与方法

1.1 材料与主要试剂

选取40 只雄性Wistar 大鼠,体质量为160 ~220 g,均由华阜康生物科技股份有限公司提供[动物生产许可证号为 SCXK:(京)2019-0017]。所有大鼠均单笼饲养,自由饮水、进食,室温 18 ~25 ℃。库拉索芦荟购自海南南洋芦荟生物工程有限公司,酶联免疫试剂盒及其分析纯购自美国 GIBCO 公司,苏木精—伊红试剂购自上海慧颖生物科技有限公司,VEGF 抗体及 PI3K、Akt、mTOR 一抗和二抗购自武汉艾德思科技文化有限公司,BCA 试剂盒及其试剂购自上海晶抗生物工程有限公司。

1.2 方法

1.2.1 急性放射性皮肤损伤模型建立 40 只大鼠中选取 10 只为正常组,其余 30 只参考文献[6]建立急性放射性皮肤损伤模型:将大鼠固定后,采用脱毛试剂(饱和硫化钠 + 等量滑石粉)在大鼠左后肢均匀涂抹,20 min 后用纱布去除试剂并进行脱毛处理;0.1% 戊巴比妥钠腹腔麻醉,大鼠在摆位床中呈环形,保证左后肢在射线照射范围内;使用铅板对非照射部位进行遮挡。采用6 MeV电子线照射大鼠左后肢脱毛部位的皮肤,剂量率为 400 cGy/min,一次性照射剂量为 40 Gy。正常组仅做脱毛处理。

1.2.2 芦荟凝胶多糖制备及分组 摘取新鲜芦荟叶,清洗干净后,经过剪刺、去皮,将凝胶打浆,取 100 g 采用超声波协同复合酶法[7]浸提,真空抽滤,减压浓缩至 20 mL,加 4 倍体积无水乙醇沉淀,于 4 ℃静置过夜。经过沉淀、过滤后,分别添加无水乙醇、丙酮、乙醚洗涤,最后冷冻、干燥,得到白色粉末。采用硫酸—蒽酮法测定多糖含量,其范围在 5 ~40 μg/mL。30 只模型大鼠随机分为低剂量组、高剂量组、模型组各 10 只。低剂量组、高剂量组分别以单层纱布浸润 0.4 mg/mL、0.8 mg/mL 的芦荟凝胶多糖外敷干预;模型组和正常组的单层纱布浸润的等体积生理盐水外敷,各组大鼠均连续干预 1 个月。

1.2.3 创面愈合时间、放射性皮肤损伤评级 记录各组大鼠创面愈合时间。参考急性放射性皮肤损伤评级标准[8]对模型大鼠皮肤损伤状况进行评估:0 级,大鼠皮肤无任何变化;Ⅰ级,大鼠皮肤表现为点状红斑,脱毛,呈干性脱皮;Ⅱ级,大鼠皮肤红斑明显,伴有斑状湿性脱皮,中度水肿;Ⅲ级,大鼠产生融合性湿性脱皮,凹陷水肿;Ⅳ级,大鼠皮肤出现溃疡、出血、坏死等。

1.2.4 创面微血管密度、VEGF 含量检测 抽取大鼠腹部静脉血 3 mL,以 3 000 r/min 离心 10 min,分离上层血清。采用酶联免疫法检测 VEGF 含量:将提前稀释好的标准品 100 μL 加入相应的微孔板反应孔中,第1 孔只加样品稀释液为零孔。盖上模板混合均匀,在37 ℃下反应 90 min,甩去孔内液体,吸干水分;将准备好的 0.1 mL VEGF 抗体加入到每孔中,在 37 ℃下反应 60 min,空白孔不加底物四甲基联苯胺(tetramethylbenzidine,TMS);甩去孔内液体,每孔加满 0.01 mol/L PBS,浸泡 1 ~2 min,甩去孔内液体,吸干水分;每孔加入 90 μL TMS,避光处理 15 ~20 min;每孔加入 90 μL TMS 终止液,即蓝色变为黄色。在波长 450 mm 处分析 VEGF 水平。制作常规石蜡切片,选择 10 个连续不重叠的切片于高倍镜下观察微血管数量。

1.2.5 病理学观察 处死大鼠,解剖后快速提取左后肢皮肤组织制作标本,4% 多聚甲醛固定,制作常规石蜡切片;0.5% 苏木精—伊红染色 10 min,自来水冲洗 1 次;乙醇梯度脱水,中性树胶封片,显微镜下观察染色结果。

1.2.6 PI3K-Akt-mTOR 信号通路相关蛋白表达检测 采用 Western blot 检测,将采集到的血液标本以 3 000 r/min离心处理 10 min,取上清液,采用 BCA 法进行蛋白定量测定,在 2 × SDS 凝胶缓冲液中加入蛋白 50 μg,于 100 ℃下加热 5 min 进行蛋白变性。凝胶电泳,转膜,取膜,于 4 ℃在 5% 脱脂牛奶中固定、封闭处理 1 h,使用 0.05% ~0.1% TBST 稀释一抗(PI3K、Akt、mTOR,1∶1 000),于 4 ℃孵育过夜保存,之后使用 0.05% ~0.1% TBST 洗膜 3 次,每次 5 min。0.05% ~0.1% TBST 稀释二抗(1∶10 000),摇动孵育 1 h,再次用 TBST 连续洗膜 3 次,每次 5 min。DAB 显色,定量分析蛋白表达情况。以 GAPDH 为内参。

1.3 统计学处理

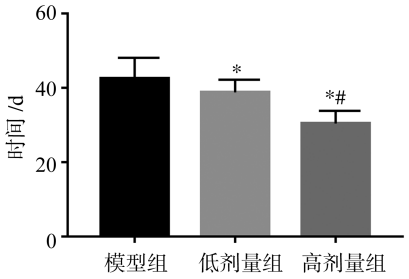
采用 SPSS 17.0 软件行统计分析,所有数据以均

数±标准差($\bar{x}\pm s$)表示,多组间比较采用方差分析,两组间比较采用t检验;计数资料及构成比以率(%)表示,组间比较采用χ^2检验。$P<0.05$为差异有统计学意义,$P<0.01$为差异有极显著性统计学意义。

2 结果

2.1 创面愈合时间比较

低剂量组和高剂量组创面愈合时间均短于模型组,且高剂量组短于低剂量组,差异有统计学意义($P<0.05$),见图1。



*:与模型组比较,$P<0.05$;#:与低剂量组比较,$P<0.05$

图1 创面愈合时间比较

2.2 放射性皮肤损伤评级比较

与模型组相比,正常组大鼠0级较多,Ⅳ级较少;与模型组比较,低剂量组和高剂量组大鼠Ⅳ级较少,差异有极显著性统计学意义($P<0.01$),见表1。

表1 放射性皮肤损伤评级比较($n=10$,只)

组别	0级	Ⅰ级	Ⅱ级	Ⅲ级	Ⅳ级
正常组	10*	0	0	0	0*
模型组	0	0	1	3	6
低剂量组	0	2	3	4	1*
高剂量组	2	4	3	1	0*

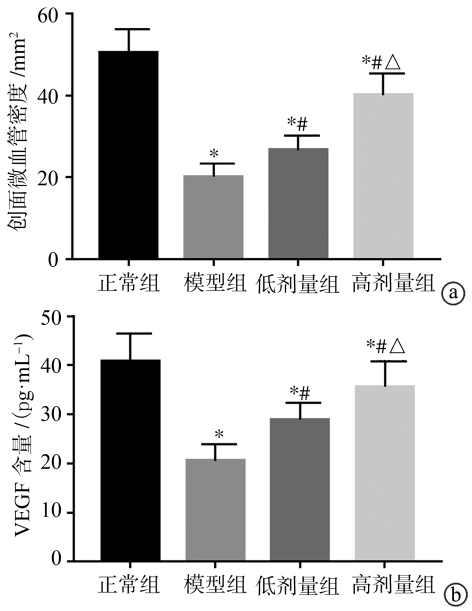
*:与模型组比较,$P<0.01$

2.3 创面微血管密度、VEGF含量比较

模型组、低剂量组和高剂量组创面微血管密度、VEGF含量均低于正常组($P<0.01$);低剂量组和高剂量组创面微血管密度、VEGF含量高于模型组($P<0.01$);高剂量组创面微血管密度、VEGF含量高于低剂量组,差异有极显著性统计学意义($P<0.01$),见图2。

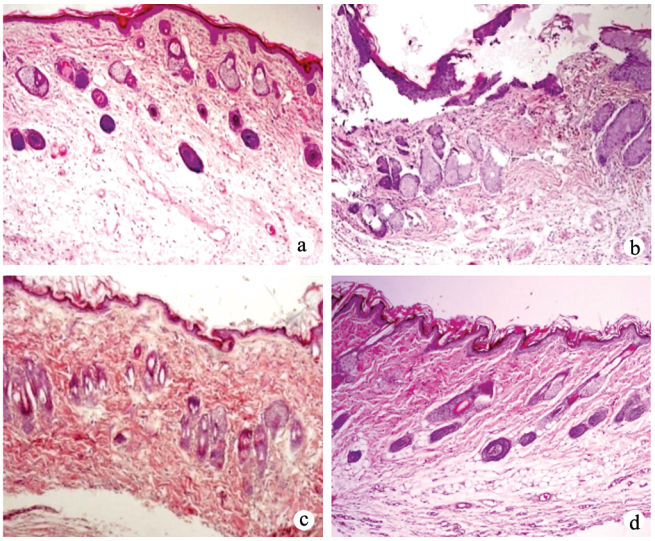
2.4 病理学观察

在显微镜下观察发现,正常组表皮细胞较为平整,棘细胞、成纤维细胞排列整齐,未发现狭窄、增宽等,皮脂腺、毛囊、汗腺等正常,肌纤维结构正常,无炎症细胞浸润;模型组细胞表皮呈波浪状,不整齐,无棘细胞排列,胶原纤维、毛囊、汗腺被破坏,真皮层内有大量炎症细胞浸润,新生血管较为少见;低剂量组和高剂量组溃疡表面有新生皮肤、肉芽形成,新生血管明显增加,炎症细胞浸润程度降低,其中高剂量组皮脂腺、毛囊、汗腺结构正常,胶原纤维、纤维母细胞数量增加,排列整齐(图3)。



a:创面微血管密度;b:VEGF含量 *:与正常组比较,$P<0.01$;#:与模型组比较,$P<0.01$;△:与低剂量组比较,$P<0.01$

图2 创面微血管密度、VEGF含量比较



a:正常组;b:模型组;c:低剂量组;d:高剂量组

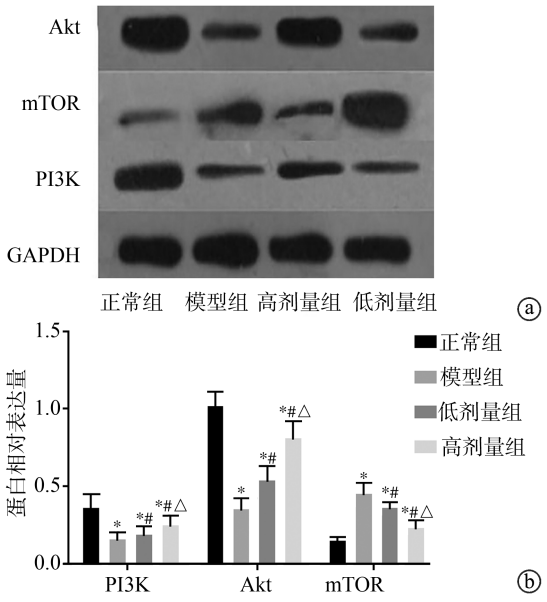
图3 病理学观察(HE ×200)

2.5 PI3K-Akt-mTOR信号通路相关蛋白表达

模型组、低剂量组和高剂量组PI3K、Akt蛋白表达量均低于正常组,mTOR蛋白表达量高于正常组($P<0.05$);低剂量组和高剂量组PI3K、Akt蛋白表达量高于模型组,mTOR蛋白表达量低于模型组($P<0.05$);高剂量组PI3K、Akt蛋白表达量高于低剂量组,mTOR蛋白表达量低于低剂量组($P<0.05$),见图4。

3 讨论

临床上将放射性皮肤损伤分为慢性放射性皮肤损伤、急性放射性皮肤损伤以及放射性皮肤癌[9]。放射性皮肤损伤患者临床表现主要为局部皮肤瘙痒,严重



*:与正常组比较,$P<0.05$;#:与模型组比较,$P<0.05$;△:与低剂量组比较,$P<0.05$

图4 PI3K-Akt-mTOR 信号通路相关蛋白表达

者会发生脱皮、疼痛、溃疡等,造成局部感染;病情严重的患者皮肤会变薄,产生瘢痕、挛缩[10-11]。研究证实,放射性皮肤损伤会降低患者生存质量,进而大大降低患者对放射治疗的依从性[9],导致患者中断放疗,甚至是放弃治疗,致使肿瘤得不到控制,生存率降低[12]。Yee 等[13]的研究指出,在不降低放射治疗效果的情况下,尽量减少放射治疗对患者周围正常皮肤组织产生的伤害,能明显减轻患者痛苦,提高患者生活质量,增加放射治疗的依从性。

临床研究显示,芦荟具有免疫调节、抗炎、抗病毒、抗真菌感染、抗辐射、促进伤口愈合等多种功效,在治疗烧伤、创伤方面效果显著[14]。芦荟的化学成分相对复杂,有 160 多种成分,主要是以糖类、醌类化合物为主,还包括大量的有机酸、氨基酸等,维生素、酶类物质也相对丰富,其中芦荟多糖是芦荟凝胶中最主要的活性物质[15-16]。目前,芦荟多糖在烫伤、烧伤方面的研究较多,但是其在放射性皮肤损伤中的应用相对较少。目前,放射性皮肤损伤发病机制尚未明确,有学者认为放射线会导致机体中 p53 和 Bax 蛋白表达升高,使局部组织中的血管内皮细胞、成纤维细胞以及表皮细胞发生坏死和凋亡,新生血管减少,创面收缩,进而导致表皮化发生[17]。也有研究指出,放射线会破坏活性氧、自由基结构及机体上皮细胞基底层,导致放射性皮肤损伤发生[18]。

本研究中,大鼠创面经过不同浓度的芦荟凝胶多糖干预后,创面愈合时间有不同程度的缩短,其中高剂量组创面愈合时间最短,说明芦荟凝胶多糖能促进放射性皮肤损伤创面愈合,且更高剂量的芦荟凝胶多糖对促进愈合的效果更好。放射性皮肤损伤大鼠皮肤损伤评级越高,皮肤损伤越严重[19]。本研究中,模型组大鼠皮肤损伤评级Ⅳ级的数量较多,主要表现为表皮厚度增加,脱皮、水肿、溃疡严重。低剂量组和高剂量组大鼠皮肤损伤为Ⅳ级的数量较模型组少,说明低剂量和高剂量芦荟凝胶多糖均能改善放射性皮肤损伤大鼠皮肤损伤状况。

创面微血管发生栓塞会导致组织缺血缺氧,这也是创面坏死的主要原因,创面微血管数量与组织中血流、氧供的修复有关,若创面有丰富的新生血管形成,创面组织能够获得足够的营养物质以及氧,则可加快创面愈合速度[20-21]。VEGF 是内皮细胞中重要的趋化因子,主要通过角质、巨噬细胞分泌合成,VEGF 会增加内皮细胞纤溶酶原激活剂、胶原酶含量,促进毛细血管融合,形成大血管,在血管内皮细胞的迁移、增殖过程中发挥着重要作用,可促进新生血管形成[22-23]。本研究结果显示,大鼠创面经不同浓度芦荟凝胶多糖干预后,创面微血管密度、VEGF 含量均有不同程度的提高,其中高剂量组效果最为显著,说明芦荟凝胶多糖能促进 VEGF 合成和释放,促进放射性皮肤损伤模型创面新生血管形成,进一步加快大鼠创面愈合,且具有剂量依赖性。

PI3K 是一种磷脂酰肌醇激酶,主要存在于细胞中,其活性主要体现在丝氨酸/苏氨酸激酶方面,通过激活下游信号分子,在多种细胞活动中发挥着重要的作用[24]。Akt 在磷酸化作用下,会激活 mTOR,参与生物学活动[25]。PI3K/Akt 信号通路在细胞凋亡过程中具有重要作用[26]。在创面早期,自噬是细胞保护机制之一,mTOR 参与信号转录以及蛋白合成过程,并且 mTOR 在自噬信号转换中发挥着关键性的作用,可诱导细胞自噬[27-28]。本研究结果表明,经不同浓度芦荟凝胶多糖干预后,大鼠 PI3K、Akt 蛋白表达量升高,mTOR 蛋白表达量降低,说明芦荟凝胶多糖可能通过调控 PI3K-Akt-mTOR 信号通路相关蛋白,促进大鼠创面愈合。在创面早期,由于炎症反应导致创面缺血、缺氧,营养不足,mTOR 通路将细胞中的坏死物质清除,有助于保持细胞结构的稳定,抵抗病原体入侵,减轻炎症反应,加快创面愈合速度[29-30]。

综上所述,高剂量芦荟凝胶多糖能促进急性放射性皮肤损伤大鼠模型创面新生血管形成,加快创面修复,其作用机制可能与 PI3K-Akt-mTOR 信号通路有关。

[参考文献]

[1] Borab Z, Mirmanesh MD, Gantz M, et al. Systematic review of hyperbaric oxygen therapy for the treatment of radiation-induced skin necrosis[J]. J Plast Reconstr Aesthet Surg, 2017, 70(4): 529 - 538. doi: 10.1016/

j. bjps. 2016. 11. 024.

[2] Jang H, Myung H, Lee J, et al. Impaired skin barrier due to sebaceous gland atrophy in the latent stage of radiation-induced skin injury: application of non-invasive diagnostic methods[J]. Int J Mol Sci, 2018, 19(1):185. doi:10.3390/ijms19010185.

[3] Kawashima S, Funakoshi T, Sato Y, et al. Protective effect of pre- and post-vitamin C treatments on UVB-irradiation-induced skin damage[J]. Sci Rep, 2018, 8(1):16199. doi:10.1038/s41598-018-34530-4.

[4] Burusapat C, Supawan M, Pruksapong C, et al. Topical Aloe vera gel for accelerated wound healing of split-thickness skin graft donor sites: a double-blind, randomized, controlled trial and systematic review[J]. Plast Reconstr Surg, 2018, 142(1):217-226. doi:10.1097/PRS.0000000000004515.

[5] Farzadinia P, Jofreh N, Khatamsaz S, et al. Anti-inflammatory and wound healing activities of Aloe vera, honey and milk ointment on second-degree burns in rats[J]. Int J Low Extrem Wounds, 2016, 15(3):241-247. doi:10.1177/1534734616645031.

[6] Cao J, Zhu W, Yu D, et al. The involvement of SDF-1α/CXCR4 Axis in radiation-induced acute injury and fibrosis of skin[J]. Radiat Res, 2019, 192(4):410-421. doi:10.1667/RR15384.1.

[7] Zhang MX, You YM, Guo Y. Optimization of ultrasonic combined enzymatic extraction of aloe gel polysaccharides[J]. Food Research and Development, 2019, 40(18):133-140. doi:10.12161/j.issn.1005-6521.2019.18.023.

[8] Xue J, Yu C, Sheng W, et al. The Nrf2/GCH1/BH4 axis ameliorates radiation-induced skin injury by modulating the ROS cascade[J]. J Invest Dermatol, 2017, 137(10):2059-2068. doi:10.1016/j.jid.2017.05.019.

[9] Yoo H, Kang JW, Lee DW, et al. Pyruvate metabolism: a therapeutic opportunity in radiation-induced skin injury[J]. Biochem Biophys Res Commun, 2015, 460(3):504-510. doi:10.1016/j.bbrc.2015.03.060.

[10] Kumar Soni S, Basu M, Agrawal P, et al. Evaluation of gamma radiation-induced biochemical changes in skin for dose assesment: a study on small experimental animals[J]. Disaster Med Public Health Prep, 2019, 13(2):197-202. doi:10.1017/dmp.2018.16.

[11] Adams TG, Yeddanapudi N, Clay M, et al. Modeling cutaneous radiation injury from fallout[J]. Disaster Med Public Health Prep, 2019, 13(3):463-469. doi:10.1017/dmp.2018.74.

[12] Lin KT, Chang TC, Lai FY, et al. Rhodiola crenulata attenuates γ-ray induced cellular injury via modulation of oxidative stress in human skin cells[J]. Am J Chin Med, 2018, 46(1):175-190. doi:10.1142/S0192415X18500106.

[13] Yee C, Wang K, Asthana R, et al. Radiation-induced skin toxicity in breast cancer patients: a systematic review of randomized trials[J]. Clin Breast Cancer, 2018, 18(5):e825-e840. doi:10.1016/j.clbc.2018.06.015.

[14] Oryan A, Alemzadeh E, Mohammadi AA, et al. Healing potential of injectable Aloe vera hydrogel loaded by adipose-derived stem cell in skin tissue-engineering in a rat burn wound model[J]. Cell Tissue Res, 2019, 377(2):215-227. doi:10.1007/s00441-019-03015-9.

[15] Barkat MA, Harshita, Pottoo FH, et al. Therapeutic intervention of Aloe gel containing nano-sized and micron-sized silver sulfadiazine gel on second-degree burn: a comparative study[J]. Int J Low Extrem Wounds, 2018, 17(3):176-183. doi:10.1177/1534734618791860.

[16] Minjares-Fuentes R, Femenia A, Comas-Serra F, et al. Compositional and structural features of the main bioactive polysaccharides present in the Aloe vera plant[J]. J AOAC Int, 2018, 101(6):1711-1719. doi:10.5740/jaoacint.18-0119.

[17] Song J, Zhang H, Wang Z, et al. The Role of FABP5 in radiation-induced human skin fibrosis[J]. Radiat Res, 2018, 189(2):177-186. doi:10.1667/RR14901.1.

[18] Singh M, Alavi A, Wong R, et al. Radiodermatitis: a review of our current understanding[J]. Am J Clin Dermatol, 2016, 17(3):277-292. doi:10.1007/s40257-016-0186-4.

[19] Rong X, Li J, Yang Y, et al. Human fetal skin-derived stem cell secretome enhances radiation-induced skin injury therapeutic effects by promoting angiogenesis[J]. Stem Cell Res Ther, 2019, 10(1):383. doi:10.1186/s13287-019-1456-x.

[20] Kumagai M, Guo X, Wang KY, et al. Depletion of WNT10A prevents tumor growth by suppressing microvessels and collagen expression[J]. Int J Med Sci, 2019, 16(3):416-423. doi:10.7150/ijms.26997.

[21] Chong DC, Yu Z, Brighton HE, et al. Tortuous microvessels contribute to wound healing via sprouting angiogenesis[J]. Arterioscler Thromb Vasc Biol, 2017, 37(10):1903-1912. doi:10.1161/ATVBAHA.117.309993.

[22] Wang N, Wu Y, Zeng N, et al. E2F1 hinders skin wound healing by repressing vascular endothelial growth factor (VEGF) expression, neovascularization, and macrophage recruitment[J]. PLoS One, 2016, 11(8):e0160411. doi:10.1371/journal.pone.0160411.

[23] Dohan Ehrenfest DM, Pinto NR, Pereda A, et al. The impact of the centrifuge characteristics and centrifugation protocols on the cells, growth factors, and fibrin architecture of a leukocyte- and platelet-rich fibrin (L-PRF) clot and membrane[J]. Platelets, 2018, 29(2):171-184. doi:10.1080/09537104.2017.1293812.

[24] Chamcheu JC, Roy T, Uddin MB, et al. Role and therapeutic targeting of the PI3K/Akt/mTOR signaling pathway in skin cancer: a review of current status and future trends on natural and synthetic agents therapy[J]. Cells, 2019, 8(8):803. doi:10.3390/cells8080803.

[25] Zhang Y, Yan H, Xu Z, et al. Molecular basis for class side effects associated with PI3K/AKT/mTOR pathway inhibitors[J]. Expert Opin Drug Metab Toxicol, 2019, 15(9):767-774. doi:10.1080/17425255.2019.1663169.

[26] Lee JJ, Loh K, Yap YS. PI3K/Akt/mTOR inhibitors in breast cancer[J]. Cancer Biol Med, 2015, 12(4):342-354. doi:10.7497/j.issn.2095-3941.2015.0089.

[27] Liu Y, Qin X, Lu X, et al. Effects of inhibiting the PI3K/Akt/mTOR signaling pathway on the pain of sciatic endometriosis in a rat model[J]. Can J Physiol Pharmacol, 2019, 97(10):963-970. doi:10.1139/cjpp-2019-0156.

[28] Hou Y, Wang K, Wan W, et al. Resveratrol provides neuroprotection by regulating the JAK2/STAT3/PI3K/AKT/mTOR pathway after stroke in rats[J]. Genes Dis, 2018, 5(3):245-255. doi:10.1016/j.gendis.2018.06.001.

[29] Xiao W, Tang H, Wu M, et al. Ozone oil promotes wound healing by increasing the migration of fibroblasts via PI3K/Akt/mTOR signaling pathway[J]. Biosci Rep, 2017, 37(6):BSR20170658. doi:10.1042/BSR20170658.

[30] Jin H, Zhang Z, Wang C, et al. Melatonin protects endothelial progenitor cells against AGE-induced apoptosis via autophagy flux stimulation and promotes wound healing in diabetic mice[J]. Exp Mol Med, 2018, 50(11):1-15. doi:10.1038/s12276-018-0177-z.

(编辑:龙小芬)