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褐藻寡糖对LPS诱导家兔肺脏损伤的保护作用

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[摘 要] 【目的】探究褐藻寡糖(AOS)对脂多糖(LPS)诱导家兔肺脏损伤的保护作用。【方法】选用40只35日龄健康家兔,随机分为4组(每组10只):对照组、LPS组、AOS低剂量(100 mg/kg AOS)组和AOS高剂量(200 mg/kg AOS)组。预试期7 d,正试期28 d。正试期第25~28天,LPS组及AOS组腹腔注射0.25 mg/(kg·d) LPS,对照组注射等体积PBS。试验结束,每组随机处死6只家兔,采集肺组织备用。采用HE染色观察肺脏组织形态学变化;采用ELISA试剂盒测定肺脏组织中TNF-α、IL-1β、IL-6、MDA和SP-C含量以及GSH-Px、SOD活性;免疫荧光检测肺泡上皮细胞SP-C蛋白表达水平。【结果】HE染色显示,LPS组家兔肺脏组织出现出血、炎性细胞浸润及蛋白沉积;AOS低剂量和高剂量组家兔肺脏损伤均减轻。LPS组家兔肺脏组织中TNF-α、IL-1β、IL-6含量较对照组显著升高($P<0.05$),2个AOS组上述因子含量较LPS组显著降低($P<0.05$)。LPS组家兔肺脏MDA含量较对照组显著升高,GSH-Px及SOD活性显著降低($P<0.05$);AOS低剂量和高剂量组家兔肺脏MDA较LPS组显著降低($P<0.05$),GSH-Px和SOD活性显著升高($P<0.05$),且AOS高剂量组SOD显著高于AOS低剂量组($P<0.05$)。ELISA检测结果显示,LPS组家兔肺脏SP-C蛋白质量浓度较对照组显著降低($P<0.05$);AOS低剂量和高剂量组家兔肺脏SP-C蛋白质量浓度较LPS组分别显著升高了21.59%和25.10%($P<0.05$)。免疫荧光检测结果显示,LPS组家兔肺脏SP-C蛋白表达水平较对照组显著降低($P<0.05$),AOS低剂量组SP-C蛋白表达水平较LPS组显著上调($P<0.05$),且低剂量组高于高剂量组($P<0.05$)。【结论】饲料添加AOS可显著缓解LPS诱导的家兔肺脏损伤,保护肺脏功能。

[关键词] 褐藻寡糖;LPS诱导;肺脏损伤;抗炎保护作用;氧化应激
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Protective effects of alginate oligosaccharides on LPS-induced lung injury in rabbits

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Abstract:【Objective】This study aims to investigate the protective effects of alginate oligosaccharides (AOS) on lipopolysaccharide (LPS)-induced lung injury in rabbits.【Method】Forty healthy 35-day-old rabbits were randomly divided into four groups with 10 rabbits in each group: a control group, an LPS group, a low-dose AOS group (100 mg/kg AOS), and a high-dose AOS group (200 mg/kg AOS). The pretrial period lasted 7 days, followed by a 28-day experimental period. From days 25 to 28 of the experimental period, rabbits in the LPS and AOS groups were intraperitoneally injected with LPS at 0.25 mg/(kg·d), while those in the control group received an equal volume of phosphate-buffered saline (PBS). At the end of the experiment, six rabbits from each group were randomly euthanized, and their lung tissues were collected for subsequent analysis.

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Histomorphological changes in lung tissues were observed using hematoxylin and eosin (HE) staining. The contents of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), malondialdehyde (MDA), and surfactant protein C (SP-C), as well as the activities of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), were measured using enzyme-linked immunosorbent assay (ELISA) kits. The expression of SP-C in alveolar epithelial cells was detected by immunofluorescence. 【Result】 HE staining revealed that lung tissues in the LPS group exhibited hemorrhage, inflammatory cell infiltration, and protein deposition, whereas these pathological changes were markedly alleviated in both the low- and high-dose AOS groups. Compared with the control group, the contents of TNF-α, IL-1β, and IL-6 in lung tissues were significantly increased in the LPS group ($P<0.05$), while these indicators were significantly decreased in the two AOS groups ($P<0.05$). Compared with the control group, the LPS group exhibited significantly higher MDA content and lower activities of GSH-Px and SOD ($P<0.05$). Compared with the LPS group, both the low-and high-dose AOS groups showed significantly decreased MDA contents and increased GSH-Px and SOD activities ($P<0.05$), with the high-dose AOS group exhibiting significantly higher SOD activity than that in the low-dose AOS group ($P<0.05$). ELISA results demonstrated that the concentration of SP-C was significantly lower in the LPS group than in the control group ($P<0.05$), but was markedly increased by 21.59% and 25.10% in the low-dose and high-dose AOS groups, respectively ($P<0.05$). Immunofluorescence analysis showed that SP-C protein expression level was significantly lower in the LPS group than in the control group ($P<0.05$). Compared with the LPS group, both the low-and high-dose AOS groups showed markedly increased SP-C expression ($P<0.05$), with the increase being higher in the low-dose AOS group than that in the high-dose AOS group ($P<0.05$). 【Conclusion】 Dietary supplementation with AOS significantly alleviates LPS-induced lung injury and protects pulmonary function in rabbits.

Key words: alginate oligosaccharides; LPS induction; lung injury; anti-inflammatory protection; oxidative stress

我国家兔养殖业作为畜牧业的重要组成部分，正加速向规模化、标准化和产业化方向发展，家兔凭借生产性能高、肉质优良和市场前景广阔而备受关注[1]。然而，呼吸系统疾病仍是家兔养殖业持续健康发展的主要影响因素[2]。此类疾病多由革兰氏阴性菌感染引起，在高密度、集约化养殖条件下发病率明显升高，常表现为呼吸急促、肺水肿及免疫功能紊乱等[3]，严重影响家兔群体的健康与生产性能，进而造成严重的经济损失。

褐藻寡糖(alginate oligosaccharides，AOS)是由褐藻胶(源自海带、马尾藻等褐藻的天然无毒多糖)经酸水解、酶解或氧化等方式降解所得的寡糖。AOS由1,4-β-*D*-甘露糖醛酸(M)与1,4-α-*L*-古洛糖醛酸(G)单体通过糖苷键随机排列组成，聚合度为2～25，具有优异的水溶性、生物利用度及生物相容性[4-6]。作为一种低聚糖类益生元[7]，AOS来源丰富且安全性高，在动物营养与饲料领域具有广阔的应用前景。研究表明，AOS可显著改善水产动物的生长性能与健康状况，邓婉珍[8]研究发现，饲料中添加AOS可显著提高大菱鲆的生长性能、免疫力、增重率及饲料转化率；YANG等[9]研究指出，AOS能促进草鱼肝脏发育，调节脂肪代谢并增强其抗氧化应激能力。

尽管AOS在水产及畜禽领域的生物活性研究成果丰富，但其在家兔疾病防治中的作用尚缺乏系统研究。为此，本研究采用脂多糖(lipopolysaccharide，LPS)腹腔注射法建立家兔急性肺损伤模型[10]，系统探究不同浓度AOS对肺损伤的保护作用，为AOS作为绿色饲料添加剂的应用提供理论依据，并为家兔养殖业呼吸系统疾病防控提供新的思路与策略。

1 材料与方法

1.1 试验材料

试验所用AOS由山东洁晶集团股份有限公司提供。试验肉兔为伊普吕肉兔，由济源阳光兔业科技有限公司提供。试验所有试剂盒均购自南京建成生物工程研究所。

1.2 试验设计与饲养管理

试验选取40只体质量相近的35日龄家兔，经过7 d的预试期后进行为期28 d的试验。将家兔按照体质量相近的原则随机分为对照组(control group，CON)、LPS组及AOS低剂量组(low-dose

AOS，LD_{AOS}）和高剂量组（high-dose AOS，HD_{AOS}），每组10只。CON和LPS组家兔饲喂基础日粮，LD_{AOS}、HD_{AOS}组家兔分别饲喂在基础日粮中添加100和200 mg/kg AOS的试验日粮。在正试期第25～28天，LPS、LD_{AOS}、HD_{AOS}组家兔连续腹腔注射0.25 mg/（kg·d）LPS，对照组家兔腹腔注射等量PBS溶液。试验期内家兔自由饮水、采食。

1.3　样品的采集和处理

饲养试验结束后，将所有家兔禁食24 h后空腹称体质量，随后将家兔处死并迅速开胸取出双侧肺脏。参照肺损伤系统化取样原则[11-12]进行统一取样，取相同解剖位置的组织块，部分置于40 g/L多聚甲醛中固定，用于组织病理学观察；另取对应组织，液氮速冻后置于－80 ℃冰箱保存，用于后续分子生物学检测。

1.4　测定指标及方法

1.4.1　肺脏组织病理学观察　取多聚甲醛固定后的肺脏组织，修剪后放入固定盒，脱水，透明。将透明后的肺脏组织置于液体石蜡中进行包埋，获得包埋石蜡块后进行冷冻处理，采用石蜡切片机进行连续切片，切片厚度控制在4～5 μm。将切片进行HE染色后，于光学显微镜下观察组织病理结构变化，同步采集显微图像。最后通过CaseViewer 2.4.0软件进行图像分析。对肺脏病理损伤进行评分，依据肺泡水肿、炎性细胞浸润、出血及肺泡壁增厚情况进行评定，总分0～4分。

1.4.2　家兔肺脏组织中炎性因子、氧化应激指标检测　采用酶联免疫吸附试验（ELISA）测定家兔肺脏组织中炎症因子白介素-1β（interleukin-1β，IL-1β）、白介素-6（interleukin-6，IL-6）、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）及丙二醛（malondialdehyde，MDA）含量，并检测谷胱甘肽过氧化物酶（glutathione peroxidase，GSH-Px）和超氧化物歧化酶（superoxide dismutase，SOD）活性。各指标具体测定方法均按试剂盒说明书进行。

1.4.3　家兔肺脏组织中肺表面活性蛋白C（surfactant protein C，SP-C）质量浓度的测定　采用ELISA法测定家兔肺脏组织中SP-C蛋白的质量浓度。

1.4.4　家兔肺脏组织中SP-C蛋白表达水平的免疫荧光检测　制备的石蜡切片经脱蜡、抗原修复、封闭后，依次进行自发荧光淬灭、一抗与二抗孵育、4′，6-二脒基-2-苯基吲哚（4′，6-diamidino-2-phenylindole，DAPI）细胞核复染，最终封片并于4 ℃避光保存。使用荧光显微镜采集图像，并使用ImageJ软件对肺组织中SP-C蛋白的表达水平进行定量分析（以肺泡SP-C阳性面积占比表示）。

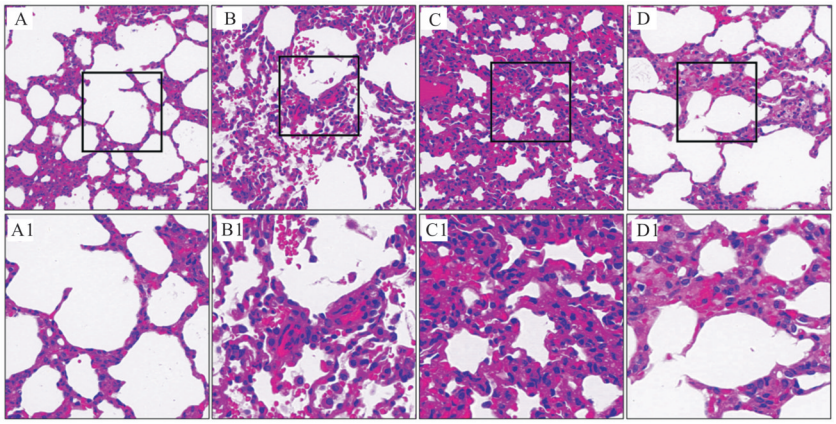
1.5　数据统计分析

试验数据采用SPSS 25.0软件进行分析，采用单因素方差分析（one-way ANOVA）比较组间差异显著性，运用Duncan's法进行多重比较；采用GraphPad Prism 8.0进行图表绘制。

2　结果与分析

2.1　AOS对LPS诱导家兔损伤肺脏的组织病理学影响

试验家兔肺脏组织HE染色结果见图1。



A. 对照组；B. LPS组；C. LD_{AOS}组；D. HD_{AOS}组。A～D为肺组织HE染色代表性图像，放大倍数为200×；A1～D1分别为A～D图中方框区域的局部放大图，放大倍数为400×。

A. Control group; B. LPS group; C. LD_{AOS} group; D. HD_{AOS} group. Representative HE-stained lung tissue sections are shown at 200× magnification (A－D). Higher-magnification views (400×) of the boxed areas in panels A－D are presented in panels A1－D1.

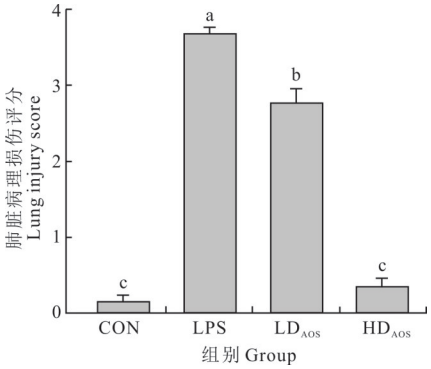
图1　AOS改善LPS诱导家兔损伤肺脏的组织病理学观察

Fig. 1　Histopathological observation of AOS in ameliorating LPS-induced lung injury in rabbits

由图1可知,CON组家兔肺组织形态清晰,肺泡结构正常,无明显破裂,呼吸性细支气管和肺泡囊完整,间质无明显炎性细胞浸润。与CON组相比,LPS组家兔肺脏出现细支气管内红细胞蓄积,肺泡壁大量破裂,肺泡及肺泡囊不完整,且肺间质出血并伴有炎性细胞浸润。与LPS组相比,LD_{AOS}、HD_{AOS}组家兔肺间质出血减少,炎性细胞浸润明显减轻,肺泡囊有所恢复。病理损伤评分结果(图2)显示,与CON组相比,LPS组肺损伤评分由0.17显著升高至3.70($P<0.05$);与LPS组相比,LD_{AOS}、HD_{AOS}组肺脏损伤评分分别显著降低至2.80和0.37($P<0.05$),其中HD_{AOS}组的改善效果更为明显。

2.2 AOS对LPS诱导家兔损伤肺脏中炎症因子的影响

由图3可知,与CON组相比,LPS组家兔肺脏组织中的TNF-α、IL-1β、IL-6含量显著升高($P<0.05$);与LPS组相比,LD_{AOS}、HD_{AOS}组家兔肺脏组织中TNF-α、IL-1β、IL-6含量均显著下调($P<0.05$),但LD_{AOS}与HD_{AOS}组间无显著性差异。



图柱上标不同小写字母表示组间差异显著($P<0.05$)。下图同。
Different lowercase letters indicate significant differences among groups ($P<0.05$). The same below.

图2 AOS对LPS诱导家兔肺脏病理损伤评分的影响
Fig. 2 Effects of AOS on lung injury scores in LPS-induced rabbits

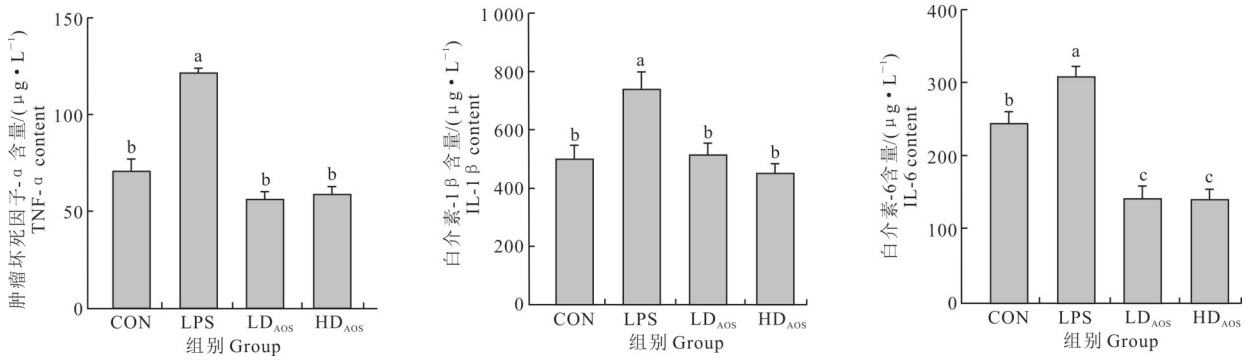


图3 AOS对LPS诱导家兔损伤肺脏中炎症因子的调节作用
Fig. 3 Regulatory effects of AOS on inflammatory factors in LPS-induced lung injury in rabbits

2.3 AOS对LPS诱导家兔损伤肺脏中氧化应激指标的影响

由图4可知,与CON组相比,LPS组家兔肺脏组织中MDA含量显著升高,而GSH-Px和SOD活性显著降低($P<0.05$)。与LPS组相比,LD_{AOS}、HD_{AOS}组的MDA含量显著降低($P<0.05$),LD_{AOS}、HD_{AOS}组间无显著差异,且LD_{AOS}组与对照组无差异。LD_{AOS}、HD_{AOS}组的GSH-Px活性无显著差异,但均显著高于LPS组($P<0.05$);LD_{AOS}、HD_{AOS}组SOD活性均显著高于LPS组($P<0.05$),且HD_{AOS}组的SOD活性显著高于LD_{AOS}组($P<0.05$)。

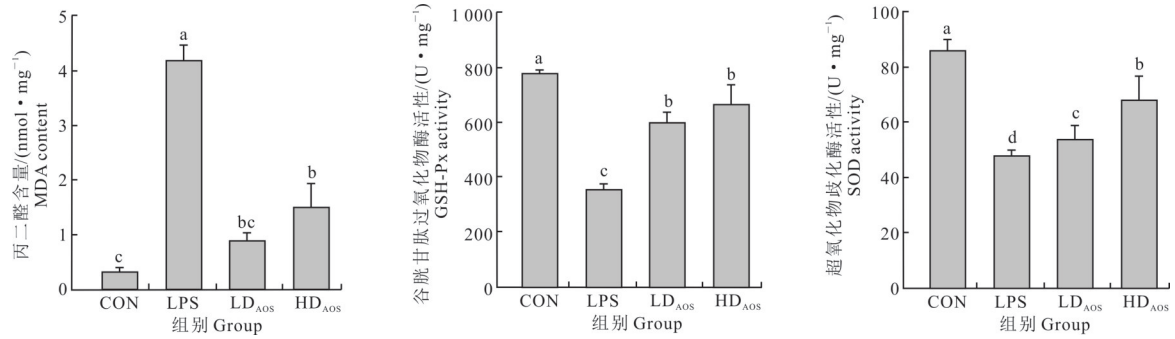


图4 AOS对LPS诱导家兔损伤肺脏中氧化应激指标的调节作用
Fig. 4 Regulatory effects of AOS on oxidative stress markers in LPS-induced lung injury in rabbits

2.4　AOS对LPS诱导家兔损伤肺脏中SP-C蛋白质量浓度的影响

如图5所示，与CON组相比，LPS组家兔肺脏组织中SP-C蛋白质量浓度显著降低（$P<0.05$）；LD_{AOS}、HD_{AOS}组SP-C蛋白质量浓度（9.01和9.28 μg/L）显著高于LPS组（7.41 μg/L）（$P<0.05$），分别较LPS组提高了21.59%和25.10%。

2.5　AOS对LPS诱导家兔损伤肺脏中SP-C蛋白表达水平的影响

由图6可知，与CON组相比，LPS组家兔肺泡SP-C阳性面积占比由6.58%显著降低至3.34%（$P<0.05$）。与LPS组相比，LD_{AOS}组SP-C阳性面积占比显著升高至4.68%（$P<0.05$），而HD_{AOS}组为3.39%，与LPS组差异不显著（$P>0.05$），且LD_{AOS}组显著高于HD_{AOS}组（$P<0.05$）。

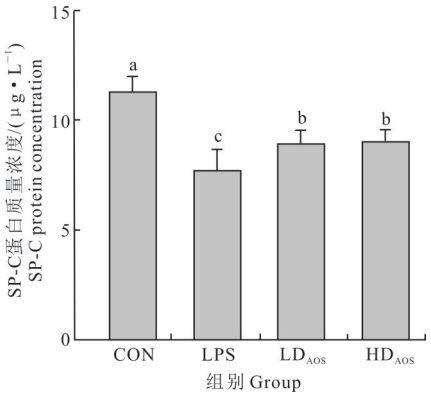
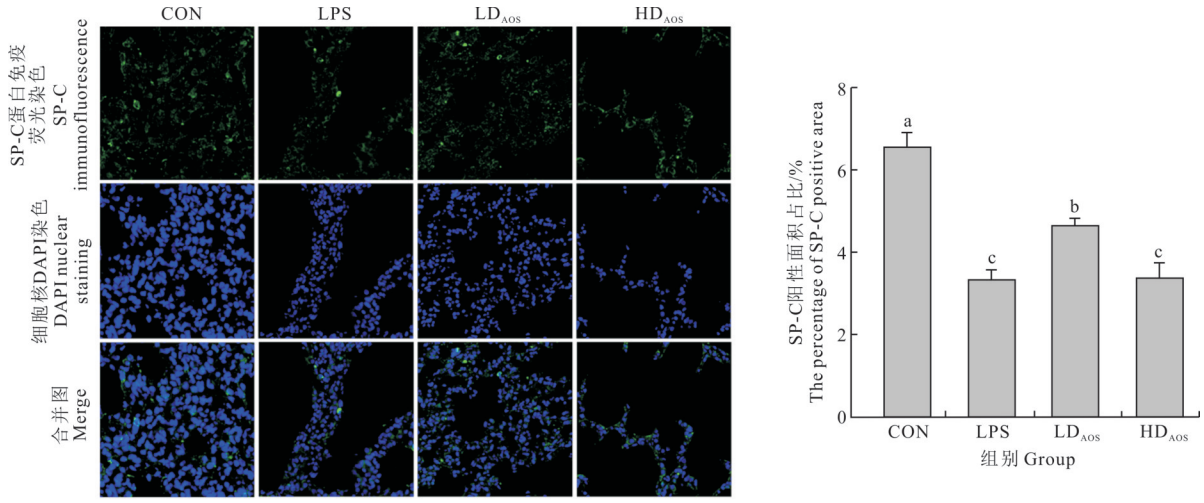


图5　AOS对LPS诱导家兔损伤肺脏中SP-C蛋白质量浓度的影响

Fig. 5　Effects of AOS on SP-C protein concentration in LPS-induced lung injury in rabbits



所有图片原始放大倍数为200×。

All images were captured at original magnification 200×.

图6　AOS对LPS诱导家兔损伤肺脏中SP-C蛋白表达水平的影响

Fig. 6　Effects of AOS on SP-C protein expression in LPS-induced lung injury in rabbits

3　讨　论

频发且难以防控的呼吸系统疾病严重威胁着家兔的健康与生产性能，其病原以兔源支气管败血波氏杆菌和肺炎克雷伯菌最为常见[13-14]。抗生素是防控细菌感染的常用药物，但随着人们食品安全意识的提升和国家禁抗政策的实施，开发安全高效的抗生素替代品以防治家兔呼吸系统疾病已成为迫切需求。

肺脏损伤通常由炎症反应和氧化应激引起[15-16]。LPS作为革兰氏阴性菌细胞壁的重要组成成分，已被广泛用于急性肺损伤动物模型的建立[17]。LPS可激活TLR4/NF-κB通路，促进TNF-α、IL-1β和IL-6等促炎因子释放，诱导活性氧（reactive oxygen species，ROS）生成，从而加重肺泡上皮损伤和组织坏死[18]。MDA是脂质过氧化的终末产物，可反映氧化损伤程度；GSH-Px与SOD为关键抗氧化酶，其活性下降会削弱机体的抗氧化防御能力，进一步放大炎症反应[19-20]。已有研究表明，多种植物提取物可通过调节炎症与氧化应激缓解肺损伤。牛凯琳等[21]研究发现，藏药仁青郎波能减轻LPS诱导的小鼠肺泡增生与炎症浸润。AOS是一类来源于褐藻的低聚糖，具有显著的抗炎[22]和免疫调节作用[23]。邓雄[24]、史旭阳[25]和熊燕飞[26]的研究均证实，AOS可降低机体炎性因子水平，抑制炎症反应。另有研究证实，AOS可缓解小鼠沙门氏菌氧化损伤[27]、卵巢早衰[28]及大鼠肺动脉高血压氧化[29]，其作用机制可能与激活Nrf2通路、清除ROS

并协同抑制NF-κB介导的炎症反应有关。本研究中,LPS组家兔肺泡壁破裂、炎性细胞浸润和毛细血管淤血,且肺脏中TNF-α、IL-1β和IL-6含量显著升高,与既往采用LPS建立炎症相关肺损伤模型的研究结果一致,表明腹腔注射LPS能够有效模拟炎症介导的急性肺损伤状态[10,19],肺脏损伤模型构建成功。本试验结果表明,饲料中添加AOS可明显缓解上述病理变化,降低炎性因子水平,表现出显著的抗炎作用。同时,LPS可显著增强氧化应激反应,导致MDA含量升高、GSH-Px和SOD活性下降,而AOS可逆转此变化,显著降低MDA水平并提升抗氧化酶活性,且高剂量组效果更为显著,提示AOS的抗氧化作用可能具有剂量依赖性。

肺泡表面活性蛋白SP-C由Ⅱ型肺泡上皮细胞合成,是维持肺泡稳定性的重要疏水性蛋白。肺脏损伤时,Ⅱ型肺泡上皮细胞受损导致SP-C表达下降,影响肺泡表面活性物质功能并降低肺顺应性[30]。SONG等[31]发现,LPS可增强Ⅱ型肺泡上皮细胞自噬并诱导细胞异常凋亡,从而降低SP-C水平;褚璨灿等[32]的研究表明,肺泡上皮细胞的增殖会提高肺泡SP-C蛋白的表达水平。本研究结果显示,LPS可显著降低家兔肺脏组织SP-C表达,而AOS能显著恢复其水平,提示AOS可维持Ⅱ型肺泡上皮细胞功能,保护肺泡屏障稳定性,但AOS高剂量组的SP-C蛋白表达水平与低剂量组无明显差异,说明AOS的作用可能存在剂量阈值。

综上,AOS能通过抑制炎症反应和氧化应激、维持SP-C蛋白稳定表达,有效缓解LPS诱导的家兔肺脏损伤。本研究为AOS在家兔养殖业中的应用提供了理论依据,但其分子机制及在生产中的推广应用仍需进一步研究。

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