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Original Article

Sesamin reduces acute hepatic injury induced by lead coupled with lipopolysaccharide

Hsiu-Mei Chiang [a], Hsiang Chang [b], Pei-Wun Yao [c], Yuh-Shuen Chen [d], Kee-Ching Jeng [e], Jen-Shu Wang [f], Chien-Wei Hou [b,*]

[a] *Department of Cosmeceutics, China Medical University, Taichung, Taiwan, ROC*
[b] *Department of Biotechnology, Yuanpei University, Hsinchu, Taiwan, ROC*
[c] *Institute of Biotechnology, National TsingHua University, Hsinchu, Taiwan, ROC*
[d] *Department of Food Nutrition, Hungkuang University, Taichung, Taiwan, ROC*
[e] *Department of Medical Research, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan, ROC*
[f] *Department of Chinese Medicine, Taichung Tzuchi Hospital, Taichung, Taiwan, ROC*

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Abstract

Background: In this study, we investigated the potential anti-inflammatory and antioxidative effects of sesamin on acute liver injury. Lead (Pb) causes oxidative damage and enhances the effects of low-dose lipopolysaccharide (LPS), inducing acute hepatic injury in rats.
Methods: Male Sprague–Dawley rats were given intraperitoneal injections of Pb acetate (5 mg/kg) and LPS (50 μg/kg) to induce liver injury, and we tested the effects of oral administration of sesamin (10 mg/kg) on liver damage. To assess the extent of acute hepatic injury in the rats, we measured the anti-inflammatory and antioxidant markers and relevant signaling pathways: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), reactive oxygen species (ROS), tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, nitric oxide (NO), and cyclooxygenase-2 (COX-2), inducible NO synthase (iNOS) levels, mitogen-activated protein kinases (MAPKs), c-Fos, and GADD45β.
Results: Sesamin significantly decreased the serum AST, ALT, and CRP levels in the rat model. In the Pb and LPS-stressed rats, sesamin administration reduced the serum levels of TNF-α, IL-1, IL-6, NO, and ROS generation, and liver tissue expressions of c-Jun N-terminal kinase (JNK), p38 MAPK, GADD45β, COX-2, and iNOS.
Conclusion: Collectively, these results demonstrate that sesamin is associated with antioxidant and anti-inflammatory activity. The observed effect of scavenging of ROS and NO and inhibiting the production of proinflammatory cytokines may be achieved through the suppression of COX-2, iNOS, and MAPK pathways in the acute hepatic injury rats.

Keywords: cyclooxygenase-2; inducible nitric oxide synthase; kinases; mitogen-activated protein; sesamin

1. Introduction

Lead (Pb) is a persistent environment and industrial pollutant that is known to cause oxidative damage in living organisms.[1] The International Agency for Research on Cancer has upgraded Pb from a possible to a probable human carcinogen.[2] Low levels of Pb exposure may cause disorders of the circulatory, renal, and nervous systems.[3] Children are

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* Corresponding author. Dr. Chien-Wei Hou, Department of Biotechnology, Yuanpei University, 306, Yuanpei Street, Hsinchu 300, Taiwan, ROC.
E-mail address: rolis.hou@mail.ypu.edu.tw (C.-W. Hou).

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more susceptible to Pb toxicity because enzyme inhibition and damage caused by this metal are more severe in early development.[4,5] Additionally, coexposure to Pb and lipopolysaccharide (LPS) causes severe hepatic injury in rats and mice.[6–9]

Lead synergistically increases the LPS-stimulated expression of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-Iβ.[6–9] The Pb-augmented, LPS-stimulated TNF-α directly increases liver injury in mice, although evidence suggests that it is produced outside the liver *in vivo*.[10–12] Monocytes and macrophages are the cells primarily responsible for producing excess TNF-α through protein kinase C and the p42/44 mitogen-activated protein kinase (MAPK) pathway.[12,13] Lead increases LPS-induced liver damage through protein kinase C and p42/44 MAPK modulation of TNF-α, but modulation of TNF-α does not affect nitric oxide (NO) in rats.[10,13,14]

Sesame oil is a potential anti-inflammatory agent that is commonly used as an antioxidant with sesamin and sesamolin as two major lignans. Sesamin inhibits IL-6 and TNF-α productions from microglia under LPS stimulation.[15] We have demonstrated that inhibition of LPS-induced cytokine and iNOS mRNA/protein by sesamin is mainly through its antioxidative activity and suppression of the p38 MAPK signal pathway.[15,16] P38 MAPK is thought to mediate inflammatory responses in various cell types and mice through the activation of transcription factors that induce expression of inflammatory genes.[17,18] It has been shown that treatment with sesame oil can protect mice from acute hepatic injury from Pb plus LPS toxicity, and this protection can be attributed to the inhibition of proinflammatory cytokines and NO.[19] However, the precise mechanism of this model by its active component is unclear. We hypothesized that sesamin would inhibit the inflammatory cytokines and reactive oxygen species (ROS) or reactive nitrogen species (RNS) production by suppression of certain signaling pathways in the model of acute hepatic injury. Therefore, the aim of this study was to investigate the effect and mechanism of sesamin protection from acute hepatic injury in rats induced by Pb and LPS.

2. Methods

2.1. Reagents

Lead acetate was purchased from Merck Co. (Darmstadt, Germany). LPS (*Escherichia coli* 0111:B4) was obtained from Sigma-Aldrich (St. Louis, MO, USA), and sesamin was provided by Joben Bio-Medical Co. (Kaohsiung, Taiwan).

2.2. Animals and drug administration

Male Sprague–Dawley rats (300–400 g) obtained from the National Laboratory Animal Center (Taipei, Taiwan) were maintained in the Animal Center of the Chinese Medical University (Taichung, Taiwan). The animal studies were performed following the guidelines of the *Guidebook for the Care and Use of Laboratory Animals* (2002) published by the Chinese Society of Animal Science in Taiwan. The rats were

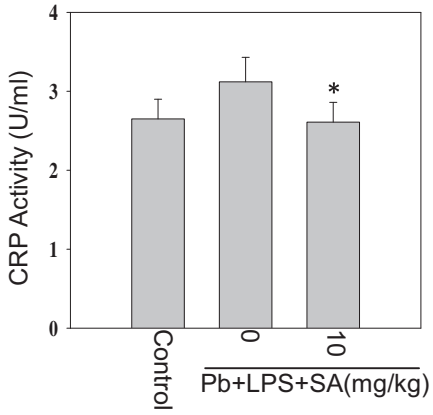

Fig. 1. The effect of sesamin on serum CRP levels in the acute hepatic injury model. Experimental rats (the PL group) were given IP injections of lead acetate (5 mg/kg) and LPS (50 μg/kg). The SA group was given oral sesamin (10 mg/rat) in addition to the IP injections. Serum CRP levels were measured after 4 hours of treatment. Data are expressed as the mean ± SD. *$p < 0.01$ as compared to the PL group. CRP = C-reactive protein; IP = intraperitoneal; LPS = lipopolysaccharide.

divided into five groups and were fasted for 12 hours prior to intraperitoneal drug administration. One control group was given saline (blank), and the experimental groups (PL) were given 5 mg/kg of Pb + 50 μg/kg of LPS. The sesamin (SA)

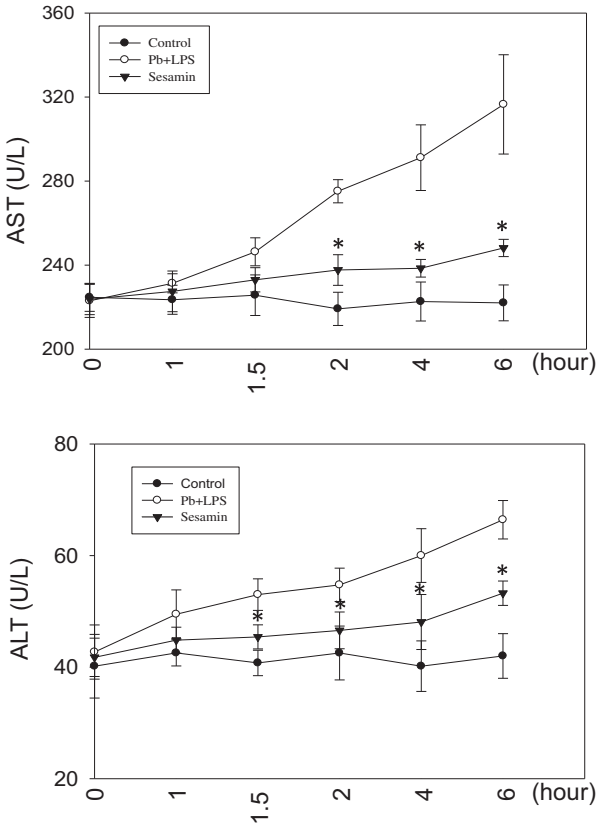

Fig. 2. Serum AST and ALT concentrations in response to Pb and LPS stress and sesamin treatment. Serum AST and ALT were determined at 0 hours, 1 hour, 1.5 hours, 2 hours, 4 hours, and 6 hours after treatment. Data are presented as the mean ± SD. *$p < 0.01$ as compared to the PL group. ALT = alanine aminotransferase; AST = aspartate aminotransferase; LPS = lipopolysaccharide; Pb = lead.