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Dietary Cannabis Seed Supplementation Attenuates Inflammation and Pancreatic Injury in a Cerulein-Induced Acute Pancreatitis Mouse Model

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Abstract

Cannabis seed (CS), also known as hemp seed, is a nutrient-dense plant-derived food material rich in polyunsaturated fatty acids and bioactive components with reported anti-inflammatory properties. However, potential nutritional effects of CS on acute pancreatitis (AP), an inflammation-driven disease with limited dietary management strategies, have not yet been investigated. In this study, we examined the effects of dietary CS extract in a cerulein-induced AP mouse model. CS extract (5, 10, or 50 mg/kg) or vehicle (dimethyl sulfoxide) was orally administered 1 h prior to cerulein injection, and mice were euthanized 6 h after the final challenge. Oral supplementation with CS significantly attenuated AP severity, indicated by reducing pancreatic weight-to-body weight ratio, serum amylase and lipase activities, histopathological pancreatic injury, and pancreatic myeloperoxidase activity. CS administration alleviated AP-associated acute lung injury; markedly suppressing pancreatic mRNA expression of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α. High-performance liquid chromatography analysis identified α-linolenic acid, an omega-3 polyunsaturated fatty acid, as a major nutritional component of CS extract. Collectively, these findings suggest that CS supplementation may contribute to nutritional modulation of inflammatory responses and systemic organ injury in experimental AP, supporting its potential as a functional food ingredient in inflammation-associated pancreatic disorders.

Keywords: cannabis seed; acute pancreatitis; α-linolenic acid; functional food; nutritional intervention

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1. Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the exocrine pancreas characterized by premature activation of digestive enzymes, acinar cell injury, and excessive inflammatory responses that may progress to systemic organ dysfunction and multi-organ

failure [1–3]. Despite its increasing global incidence and substantial disease burden, clinical management of AP remains largely supportive, with no established pharmacological or nutritional strategies capable of preventing disease progression or systemic complications [2,4]. In this context, increasing attention has been directed toward nutrition-based interventions and bioactive dietary components as potential modulators of inflammation-associated pancreatic injury.

Cannabis seed (CS), also known as hemp seed, is a plant-derived food material widely consumed for its nutritional value. It is rich in polyunsaturated fatty acids, high-quality proteins, phytochemicals, and phenolic compounds, and has been reported to exert antioxidant and anti-inflammatory effects in various experimental settings [5–7]. In particular, hemp seed is a notable dietary source of omega-3 polyunsaturated fatty acids, including α-linolenic acid, which has been shown to regulate inflammatory signaling pathways and suppress proinflammatory cytokine production [8–10]. These nutritional properties suggest that CS may function as a bioactive food component with potential relevance in inflammation-driven diseases.

Inflammation is a central determinant of AP pathogenesis and severity. The early phase of AP is characterized by acinar cell damage, neutrophil infiltration, increased myeloperoxidase (MPO) activity, and excessive production of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α [11–13]. These mediators not only exacerbate local pancreatic injury but also promote systemic inflammatory responses, leading to complications such as acute lung injury and multiple organ dysfunction [14–16]. Given this inflammatory cascade, nutritional modulation of immune cell activation and cytokine expression has emerged as an important area of investigation; however, evidence supporting specific dietary interventions in AP remains limited.

Although CS has been extensively studied as a nutritional and functional food source [6,7], its effects on AP have not yet been explored. To date, no studies have evaluated whether CS supplementation can attenuate pancreatic inflammation, digestive enzyme leakage, or AP-associated systemic organ injury in experimental models. Therefore, the present study aimed to investigate the effects of CS extract in a cerulein-induced AP mouse model, with a focus on inflammatory responses, pancreatic injury, and extra-pancreatic complications. In addition, the major nutritional component of the extract was characterized by ultra-performance liquid chromatography/mass spectrometry (UPLC/MS) to support the nutritional basis of its biological effects.

2. Materials and Methods

2.1. Plant Materials and Extraction

CS was obtained from Human Herb (Daegu, Republic of Korea); 100 g of crushed CS was reflux-extracted with 50% ethanol at 75 °C for 2 h. The extract was then filtered under reduced pressure and freeze-dried to obtain powder, with a final yield of 3.890%. Powdered CS extract was dissolved in dimethyl sulfoxide (DMSO) at a concentration of 50 mg/mL to obtain a stock solution.

2.2. Animals

All experiments were performed according to the protocols approved by the Animal Care Committee of Wonkwang University (approval no. WKU25-80; Iksan, Republic of Korea). C57BL/6 mice (6–8 weeks old, female, weighing 15–20 g), were purchased from Samtako Biokorea Co. Ltd. All animals were bred and housed in standard shoebox cages in a climate-controlled room with an ambient temperature of 23 ± 2 °C under a 12 h light/dark cycle for seven days. Animals were fed standard laboratory chow and water ad libitum. Mice were randomly assigned to control and experimental groups. Isoflurane

(induction, 4.5%; maintenance, 1.5%) in 95% O_2 and 5% CO_2 was used for anesthesia. CO_2 inhalation was used for euthanasia with a flow rate that displaced 50% of the cage vol/min, followed by cervical dislocation to ensure death post-CO_2 asphyxiation.

2.3. Experimental Design

Mice were intraperitoneally injected with 50 μg/kg cerulein (cat. no. H-3220; Bachem AG) six times/day at 1 h intervals. Prior to administration, CS stock solution was diluted to a final DMSO concentration of 10% for each dosage group. Mice were orally administered 100 μL of CS (5, 10, or 50 mg/kg) or vehicle (10% DMSO) 1 h before the first cerulein injection (Figure 1A). Mice were sacrificed 6 h after the last cerulein injection. The pancreas and lungs were immediately removed and stored at −80 °C for further analysis.

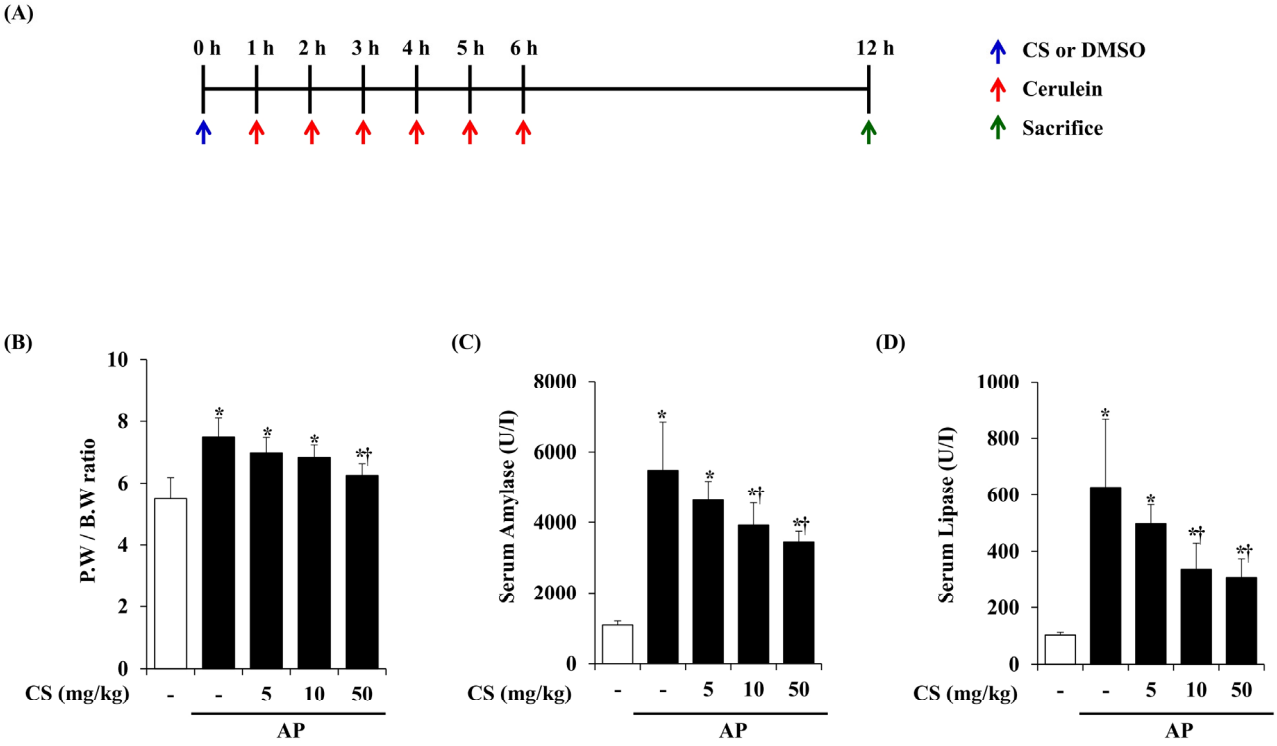

Figure 1. Effects of cannabis seed (CS) on the severity of cerulein-induced acute pancreatitis (AP). (**A**) Schematic illustration of the cerulein-induced AP mouse model for evaluating the effects of CS supplementation. Mice were orally administered CS extract (5, 10, or 50 mg/kg) or vehicle (dimethyl sulfoxide) 1 h prior to the first cerulein injection (50 μg/kg, intraperitoneal). Cerulein was administered at hourly intervals for six doses, and mice were sacrificed 6 h after the last injection. (**B**) Pancreatic weight-to-body weight ratio. (**C**) Serum amylase activity. (**D**) Serum lipase activity. Data are presented as mean ± standard deviation (SD) (n = 9 per group). Results are representative of three independent experiments. * $p < 0.05$ vs. vehicle control; † $p < 0.05$ vs. cerulein-induced AP.

2.4. Measurement of Serum Amylase and Lipase Levels

Blood samples for the determination of serum amylase and lipase levels were obtained 6 h after the last injection of cerulein. Mice were sacrificed via CO_2 asphyxiation followed by cervical dislocation; blood samples were withdrawn from the heart. Amylase and lipase activities were determined using the LabOPSECT 008AS analyzer (SG medical, Seoul, Republic of Korea).

2.5. Histological Analysis

Histological damage to the pancreas and lungs was assessed in a blinded manner using semi-quantitative scoring system. The tissues were fixed in 10% neutral-buffered-

formalin solution (HT-501128; Sigma-Aldrich Chemical Co., St. Louis, MO, USA) at room temperature for overnight. Next, dehydrated and paraffin-embedded tissues were cut into 4 μm-thick sections, stained with hematoxylin for 8 min and eosin for 2 min. Samples were examined under a light microscope. The pancreas sections were scored on a scale of 0–3 (0 corresponding to normal appearance and 3 corresponding to severe disease), based on the presence of interstitial edema and influx of immune cells. Lung tissue sections were also evaluated for wall thickening and immune cell influx in the same manner.

2.6. MPO Assay

Pancreatic neutrophil sequestration was assessed by measuring MPO activity. Tissue samples were weighed and homogenized in 50 mM phosphate buffer (pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide (HTAB). The samples were centrifuged at 10,000× *g* for 5 min at 4 °C, and the supernatants were obtained. Equal volumes of 0.5% HTAB solution, O-dianisidine (0.68 mg/mL), and 0.003% hydrogen peroxide were mixed with 50 μL of the supernatant from each sample. Following incubation at 37 °C, absorbance was detected at 450 nm using SpectraMax® ABS Plus microplate reader (San Jose, CA, USA).

2.7. Real-Time RT-PCR

RNA was isolated from the pancreas using the Easy-Blue™ RNA extraction kit (17061; iNtRON Biotechnology, Sungnam, Republic of Korea), and the purity of the RNA was measured using the Gene Quant Pro RNA calculator (Biochrom, Inc., Cambridge, UK). cDNA synthesis was performed using the ReverTra Ace™ qPCR RT Kit (TOYOBO, Osaka, Japan). Subsequently, cDNA was amplified using a SYBR Premix kit (4367659; Applied Biosystems, Carlsbad, CA, USA) on StepOne Plus Real-Time PCR system (Applied Biosystems, Foster City, CA, USA). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as a housekeeping gene for normalization. The $2^{-\Delta\Delta Ct}$ method was used to analyze relative gene expression.

2.8. UPLC/MS Analysis of CS Extract

To prepare an extract sample, 10 mg of CS extract was dissolved in 1 mL of methanol. The reference compound, α-linolenic acid, was purchased from Sigma-Aldrich Chemical Co. and dissolved in methanol to prepare standard solutions at concentrations of 1, 5, 10, 25, 50, and 100 μg/mL for quantitative analysis. UPLC analysis was performed using Waters ACQUITY UPLC instrument (Waters, Milford, MA, USA). Chromatographic separation was achieved using an ACQUITY UPLC BEH Shield C18 column (130Å, 1.7 μm, 2.1 mm × 100 mm). CS extract sample (3 μL, 10 mg/mL) and α-linolenic acid standard solution (3 μL) were injected in triplicate. The mobile phase consisted of 0.1% formic acid in water (A) and acetonitrile (B), with gradient elution as follows: 0–5 min, linear gradient from 70% B to 75% B; 5–10 min, linear gradient from 75% B to 100% B; 10–12 min, held at 100% B; and finally returned to initial conditions (70% B) for re-equilibration. Flow rate was set at 0.3 mL/min. The eluents were monitored using a UV detector at 195 nm. MS analysis was performed using an electrospray ionization source in negative ion mode with the following optimized parameters: capillary voltage, 4.00 kV; cone voltage, −30 V; extractor voltage, −2 V; RF lens, −0.2 V; source temperature, 120 °C; and desolvation temperature, 400 °C. The flow rates for desolvation and cone gas were set at 600 L/h and 100 L/h, respectively.

2.9. Statistical Analysis

Data were analyzed using GraphPad Prism software (version 8). Results are presented as the mean ± standard deviation (SD). Significance was evaluated using a one-way

analysis of variance (ANOVA) followed by post hoc Tukey's tests for multiple comparisons among groups. $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. CS Attenuated the Severity of Cerulein-Induced AP

To evaluate the efficacy of CS in cerulein-induced AP, CS at concentration of 5, 10, or 50 mg/kg or DMSO was administered orally 1 h before cerulein injection. Cerulein (50 μg/kg) was injected intraperitoneally to mice at 1 h intervals for six times/day, and mice were sacrificed 6 h after the last cerulein injection (Figure 1A). The severity of cerulein-induced AP was assessed by measuring the pancreas weight-to-body weight ratio (P.W./B.W.) and serum amylase and lipase levels. The P.W./B.W. ratio was significantly increased in the cerulein-induced AP group compared with the control group; however, CS treatment decreased the ratio in a dose-dependent manner (Figure 1B). In addition, while cerulein injection caused a significant increase in serum amylase and lipase levels, CS administration reduced these markers in a dose-dependent manner (Figure 1C).

3.2. CS Ameliorated Pancreatic Injury in Cerulein-Induced AP

To measure pancreatic edema, acinar cell death, and immune cell infiltration, we conducted H&E staining of the pancreatic tissue. Normal pancreatic structure was observed in the control group; however, the cerulein-induced AP group presented pancreatic edema, immune cell infiltration, and acinar cell death. CS treatment dose-dependently ameliorated these histological injuries (Figure 2). Moreover, compared with the normal group, the cerulein-induced AP group exhibited alveolar wall thickening and immune cell infiltration in the lungs. However, CS treatment dose-dependently attenuated AP-associated lung injury.

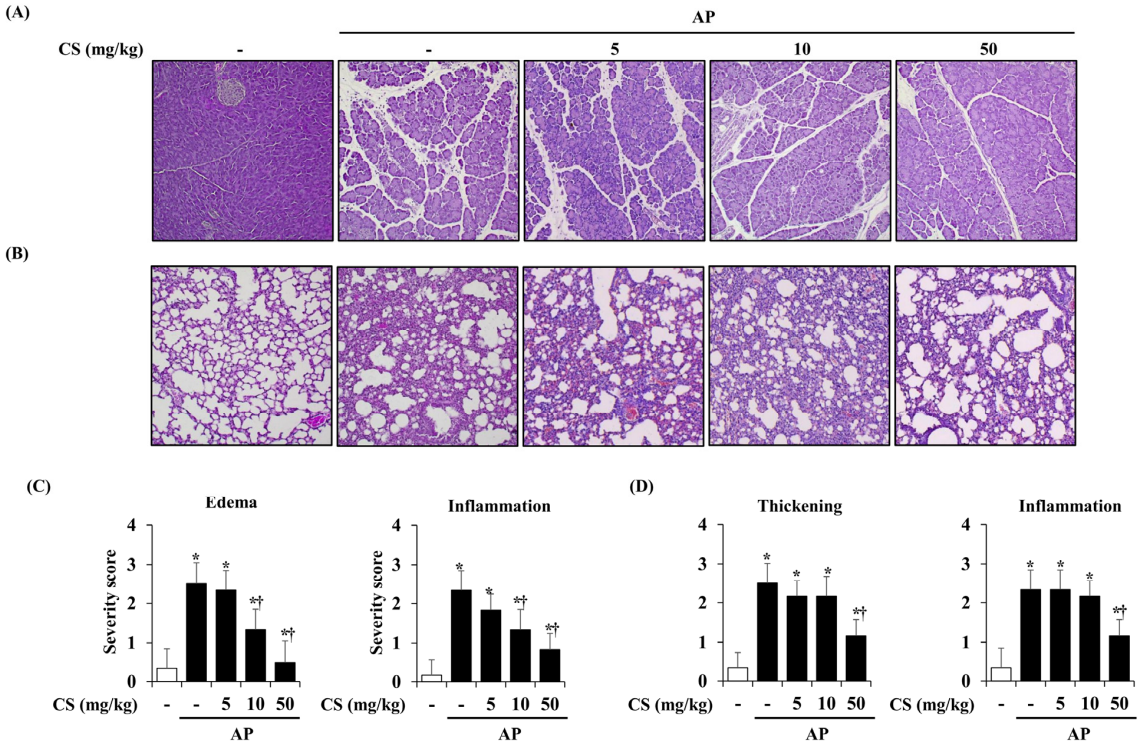

Figure 2. Effects of CS on pancreatic and pulmonary histopathological alterations in cerulein-induced AP. (**A**) Representative hematoxylin and eosin (H&E)-stained sections of pancreatic tissue. (**B**) Representative H&E-stained sections of lung tissue. (**C**) Histological scores for pancreatic edema

and inflammatory cell infiltration. (**D**) Histological scores for alveolar wall thickening and pulmonary inflammation. Mice were sacrificed 6 h after the last cerulein injection. Data are presented as mean ± SD (n = 9 per group). Results are representative of three independent experiments. * $p < 0.05$ vs. vehicle control; † $p < 0.05$ vs. cerulein-induced AP.

3.3. CS Inhibited the Accumulation of Polymorphonuclear Neutrophils (PMNs) in Cerulein-Induced AP

We assessed the degree of infiltration of PMNs into the pancreas by measuring the activity of MPO. As shown in Figure 3, cerulein significantly increased MPO activity in the AP group compared with the control group. However, CS treatment reduced MPO activity in a dose-dependent manner.

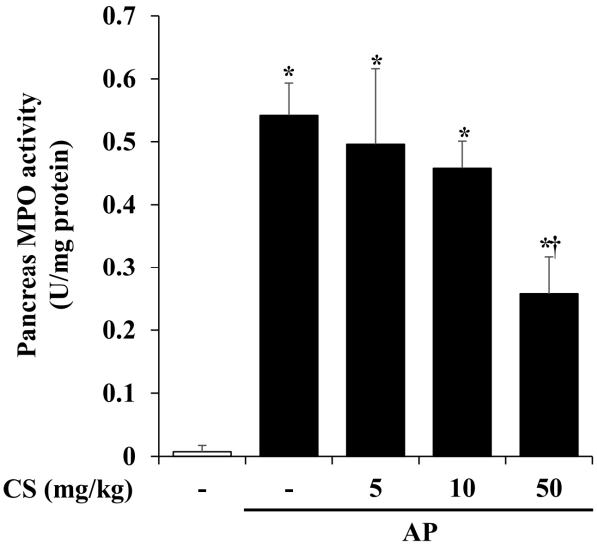

Figure 3. Effects of CS on pancreatic myeloperoxidase (MPO) activity in cerulein-induced AP. Pancreatic MPO activity was measured 6 h after the last cerulein injection as an index of neutrophil infiltration. Data are presented as mean ± SD (n = 9 per group). Results are representative of three independent experiments. * $p < 0.05$ vs. vehicle control; † $p < 0.05$ vs. cerulein-induced AP.

3.4. CS Inhibited the Production of Inflammatory Cytokines in Cerulein-Induced AP

We evaluated the changes in mRNA expression of proinflammatory cytokines using real-time PCR. In the cerulein-induced AP group, mRNA levels of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, were increased, but CS treatment significantly suppressed their expression (Figure 4).

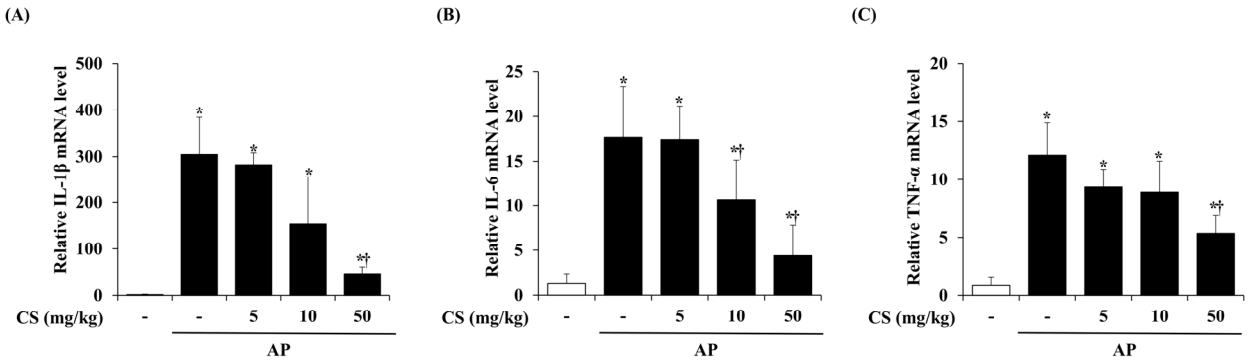

Figure 4. Effects of CS on pancreatic mRNA expression of proinflammatory cytokines in cerulein-induced AP. Pancreatic mRNA expression levels of (**A**) interleukin (IL)-1β, (**B**) IL-6, and (**C**) tumor

necrosis factor-α (TNF-α) were quantified by reverse transcription–quantitative polymerase chain reaction. Data are presented as mean ± SD (n = 9 per group). Results are representative of three independent experiments. * $p < 0.05$ vs. vehicle control; † $p < 0.05$ vs. cerulein-induced AP.

3.5. UPLC/MS Analysis of CS Extract

In this study, UPLC/MS analysis was performed to identify the major physiologically active components of the CS extract. Figure 5 illustrates the UPLC chromatograms of the CS extract and the standard compound. Comparison of the retention times of the major peaks with those of the reference compound confirmed the presence of α-linolenic acid, with a content of 5.87 ± 0.09 mg/g.

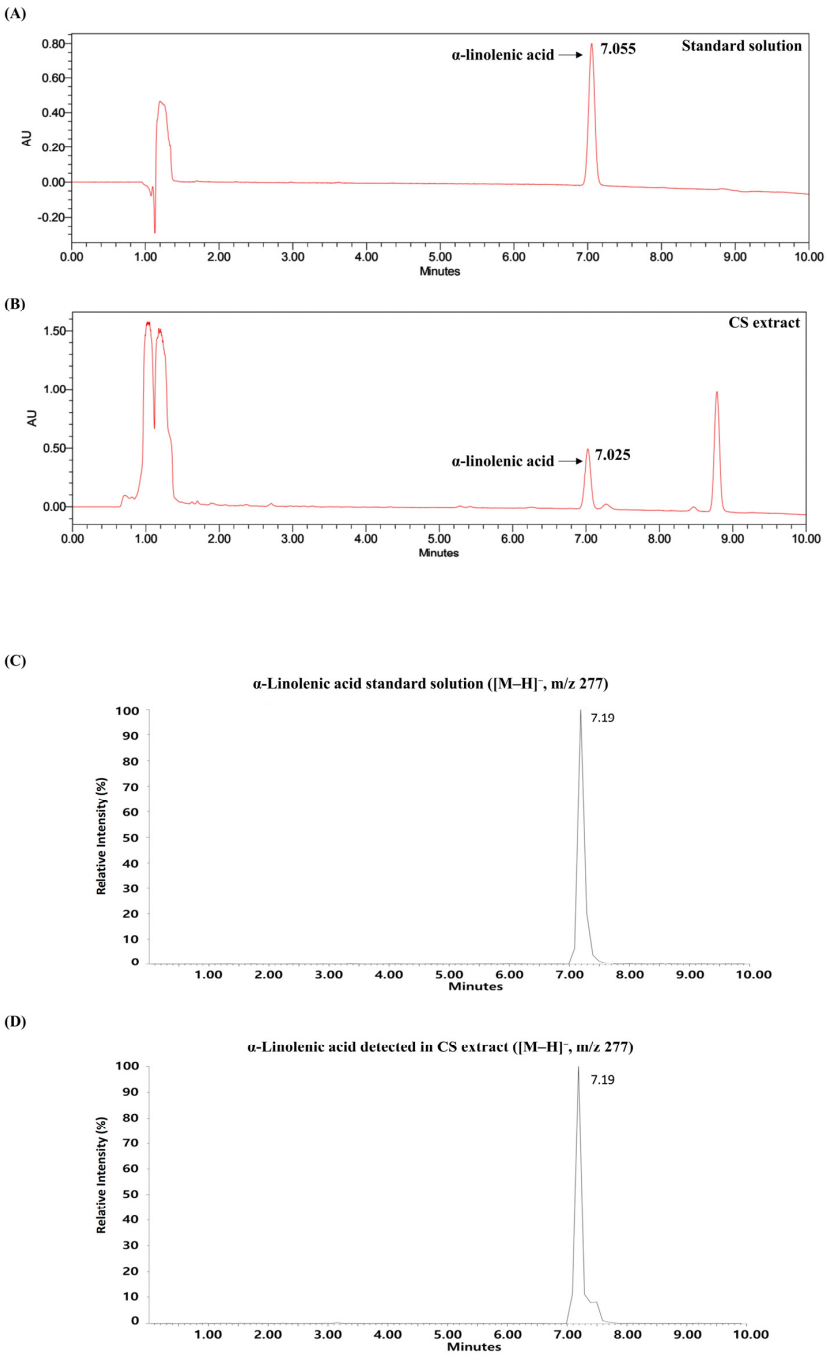

Figure 5. Ultra-performance liquid chromatography/mass spectrometry (UPLC/MS) analysis of CS extract. Representative UPLC chromatograms of (**A**) α-linolenic acid standard solution and (**B**) CS

extract. Representative mass spectra of (**C**) α-linolenic acid standard solution and (**D**) CS extract showing α-linolenic acid detected as the deprotonated molecular ion ($[M–H]^-$, m/z 277) in negative electrospray ionization mode.

4. Discussion

AP is an inflammation-driven pancreatic disorder characterized by acinar cell injury, premature activation of digestive enzymes, and excessive local and systemic inflammatory responses [1–3]. Despite advances in supportive care, effective preventive or adjunctive strategies—particularly from a nutritional standpoint—remain limited [2,4]. In the present study, we demonstrated that oral supplementation with CS extract significantly attenuated the severity of cerulein-induced AP, as evidenced by improvements in pancreatic edema, digestive enzyme leakage, histological damage, inflammatory cell infiltration, and AP-associated acute lung injury.

One of the earliest pathological features of AP is inflammatory mediators-induced increased vascular permeability, leading to pancreatic edema [17]. The pancreatic weight-to-body weight ratio is therefore widely used as an objective indicator of pancreatic inflammation and tissue swelling [18]. In this study, CS supplementation markedly reduced the elevated pancreatic weight-to-body weight ratio induced by cerulein, suggesting attenuation of inflammatory edema. Consistent with this finding, serum amylase and lipase levels—key biomarkers reflecting acinar cell injury and misdirected exocytosis of digestive enzymes—were significantly decreased following CS administration [4,19–21]. These results indicate that CS supplementation preserves pancreatic acinar cell integrity and limits enzyme leakage during the early inflammatory phase of AP.

Histological analysis further supported the protective effects of CS against pancreatic injury. Cerulein-induced AP is characterized by acinar cell degeneration, inflammatory cell infiltration, and interstitial edema, which collectively disrupt the pancreatic architecture [22–24]. CS treatment dose-dependently alleviated these histopathological alterations, suggesting that dietary CS supplementation can mitigate structural damage associated with acute pancreatic inflammation. Importantly, AP is not confined to the pancreas but often progresses to systemic inflammatory responses that affect distant organs, particularly the lungs. Acute lung injury is a major determinant of morbidity and mortality in severe AP [14,15]. In the present study, CS administration significantly reduced alveolar wall thickening and inflammatory cell infiltration in the lung tissues, indicating that its anti-inflammatory effects extend beyond the pancreas to extra-pancreatic organs [16].

Neutrophil infiltration plays a pivotal role in amplifying pancreatic inflammation during AP. Activated neutrophils release reactive oxygen species and proteolytic enzymes, including MPO, which exacerbate tissue injury and oxidative stress [25–27]. The observed reduction in pancreatic MPO activity following CS supplementation indicates suppression of neutrophil accumulation and activation within the pancreatic tissues. This finding suggests that CS may limit neutrophil-driven inflammatory amplification, thereby contributing to attenuation of pancreatic and systemic injury [28,29].

Proinflammatory cytokines are central mediators of AP progression and systemic complications. Cytokines such as IL-1β, IL-6, and tumor necrosis factor-α are rapidly upregulated during early stages of AP, promoting leukocyte recruitment, vascular permeability, and acinar cell death [11–13]. Sustained elevation of these cytokines is closely associated with disease severity, systemic inflammatory response syndrome, and multiple organ failure [30–32]. In this study, CS supplementation significantly suppressed pancreatic mRNA expression of IL-1β, IL-6, and tumor necrosis factor-α, indicating modulation of inflammatory responses at the transcriptional level.

From a nutritional perspective, the biological effects observed in this study may be partially explained by the composition of CS, which is a nutrient-dense food material rich in polyunsaturated fatty acids and bioactive compounds [6,7]. UPLC/MS analysis identified α-linolenic acid as a major nutritional component of CS extract. α-Linolenic acid is a plant-derived omega-3 polyunsaturated fatty acid that has been reported to exert anti-inflammatory effects through regulation of nuclear factor-κB signaling and downstream cytokine production [8–10]. Previous studies have demonstrated that omega-3 fatty acids, including α-linolenic acid, can attenuate inflammatory responses and cellular injury in pancreatic acinar cells and related inflammatory models [33]. However, it should be noted that the findings of the current study results suggest a correlation, rather than a definitive causal relationship, between the presence of α-linolenic acid and the protective effects of CS. To establish a direct causal relationship, further studies using purified α-linolenic acid or biologically active fractions are required.

Since the clinical management of AP is currently limited to symptomatic supportive care without curative drugs, identifying safe nutritional strategies has become a priority [1]. Therefore, safe nutritional interventions with minimal side effects are urgently needed. The CS extract identified in this study possesses a distinct advantage over single-target drugs in that it simultaneously controls multiple pathological pathways, including suppression of inflammatory mediators and modulation of neutrophil activity. This combined effect may effectively block the complex inflammatory cascade of acute pancreatitis, contributing to alleviating disease severity. Therefore, CS has high clinical value as an initial nutritional therapy for patients with acute pancreatitis or as a preventive adjuvant therapy to prevent recurrence. In conclusion, this study suggests that CS may be a promising multi-target nutritional therapy strategy that complements the limitations of existing treatments.

Several limitations of this study should be acknowledged. First, cerulein-induced AP model used in this study is widely used to investigate early inflammatory responses. However, because it represents relatively mild and reversible condition, it may not fully reflect the pathological complexity of necrotic and severe forms of human AP or progression to chronic pancreatic disease [34]. Therefore, further studies of CS in severe AP experimental models are needed. Second, although α-linolenic acid was identified as a major component of CS extract, the contribution of other bioactive compounds and potential synergistic interactions was not directly assessed [5,6]. Third, this study focused on short-term outcomes following CS supplementation; therefore, the effects of long-term dietary intake and post-onset intervention remain to be investigated.

In conclusion, the present study demonstrates that dietary supplementation with CS extract attenuates pancreatic inflammation, digestive enzyme leakage, and systemic organ injury in experimental AP. By modulating inflammatory responses and neutrophil-mediated tissue damage, CS shows potential as a functional food ingredient for nutritional management of inflammation-associated pancreatic injury. Further studies are warranted to elucidate the contributions of individual bioactive nutrients, optimize dietary dosing strategies, and evaluate the translational relevance of CS supplementation in clinically relevant models of pancreatic disease.

Author Contributions: Conceptualization, D.-G.K. and G.-S.B.; Methodology, D.-G.K. and G.-S.B.; Validation, D.-K.K.; Formal Analysis, D.-K.K.; Investigation, D.-U.K. and B.K.; Resources, D.-G.K.; Data Curation, D.-G.K.; Writing—Original Draft Preparation, D.-U.K. and B.K.; Writing—Review and Editing, D.-G.K. and G.-S.B.; Supervision, D.-G.K. and G.-S.B.; Project Administration, D.-G.K. and G.-S.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: All experiments were carried out in accordance with the animal care regulations set forth and approved by the Wonkwang University Animal Ethics Committee (protocol code WKU25-80 and date of approval December 3, 2025).

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

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