



Research article

DHA-enriched phosphatidylserine alleviates bisphenol A-induced liver injury through regulating glycerophospholipid metabolism and the SIRT1-AMPK pathway

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ARTICLE INFO

Keywords:

Bisphenol A

DHA-PS

Liver injury

Lipidomics

Glycerophospholipid metabolism

SIRT1-AMPK pathway

ABSTRACT

To investigate the alleviating effect and mechanism of the docosahexaenoic acid-enriched phosphatidylserine (DHA-PS) on bisphenol A (BPA)-induced liver injury in mice, the murine liver injury model was established by gavage of BPA (5 mg/kg) or co-administration of BPA and DHA-PS (50 mg/kg or 100 mg/kg) for 6 weeks. The results showed that after administration of 100 mg/kg DHA-PS, the liver index, serum levels of AST, ALT, TC, TG, NEFA, and LDL-C in mice were significantly decreased, while HDL-C was significantly increased. The LPS, IL-6, IL-1 β , TNF- α , and MDA levels in liver tissues were effectively down-regulated, and IL-10, SOD, GSH-Px, and CAT levels were effectively up-regulated. The H&E and Oil Red O staining results showed that liver damage was notably repaired and lipid deposition was notably reduced after DHA-PS administration. Furthermore, metabolomics and immunohistochemical studies revealed that DHA-PS mainly regulates glycerophospholipid metabolism and the SIRT1-AMPK pathway to improve metabolic disorders of the liver caused by BPA. Therefore, DHA-PS could potentially alleviate BPA-induced murine liver injury through suppressing inflammation and oxidative stress, and modulating lipid metabolism disorders.

1. Introduction

Bisphenol A (BPA), a prevalent environmental endocrine disruptor, is frequently used as a monomer in the manufacturing of polycarbonate plastics and epoxy resins [1,2]. These materials are frequently used in manufacturing food packaging and protective coatings for containers [3,4]. Research has shown that BPA can enter the human body via inhalation, ingestion, and skin contact, leading to its accumulation in various tissues and organs [5–8]. This accumulation can cause disorders affecting the endocrine system, reproductive health, neurological functions, and digestive diseases. The liver, being the largest gland in the digestive system and a critical organ in metabolism, is particularly vulnerable to BPA [9]. Prolonged exposure to BPA has been linked to liver damage and associated metabolic disorders [10]. Therefore, the detrimental effects of BPA on human health and the strategies for mitigating its

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<https://doi.org/10.1016/j.heliyon.2024.e34835>

Received 25 May 2024; Received in revised form 10 July 2024; Accepted 17 July 2024

Available online 18 July 2024

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damage have raised significant concerns.

Docosahexaenoic acid-phosphatidylserine (DHA-PS) is a unique marine glycerophospholipid enriched with DHA [11]. It is characterized by a structure that includes a DHA-based polyunsaturated fatty acid at the sn-2 position and phosphatidylserine at the sn-3 position. This structure has demonstrated effective biological activities such as enhancing brain health, protecting kidneys, anti-cancer properties, and improving gut microbiota [12–15]. Additionally, Lin et al. [16] showed that DHA-PS could regulate lipid metabolism by inhibiting SREBP-1c-mediated lipogenesis and activating PPAR α -mediated fatty acid β -oxidation in the liver. Our prior research has found that DHA-PS could improve high-fat diet (HFD)-induced liver injury by inhibiting lipid accumulation, reducing oxidative stress and inflammation, and regulating gut microbiota [17]. However, the potential benefits of DHA-PS in alleviating BPA-induced liver injury and the underlying mechanisms remain unexplored.

Lipidomics offers extensive insights into the differences in lipids in the metabolic spectrum between groups, aiding in the identification of disease biomarkers and metabolic pathways [18,19]. Currently, metabolomics techniques have been widely applied in the research of tumors, cardiovascular diseases, and metabolic diseases [20,21]. Therefore, our study developed a murine model of liver damage induced by BPA to assess the protective effects of DHA-PS. We measured biochemical markers and conducted liver histopathology examinations. Additionally, immunohistochemistry and lipidomics were employed to investigate the mechanism by which DHA-PS alleviates liver damage.

2. Materials and methods

2.1. Materials and reagents

DHA-PS was prepared by enzymatic reaction of DHA-PC from *Clupea harengus* roes in our laboratory (PS content was 60.51%) [17]. The male C57BL/6J mice (15–17 g) were purchased from Hangzhou Hans Biotechnology Co., Ltd. BPA (purity > 99%) was purchased from Aladdin Biochemical (Shanghai, China). The assay kits for aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), non-esterified fatty acids (NEFA), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) were provided Jiancheng (Nanjing, China). ELISA assay kits for interleukin (IL)-1 β , IL-6, IL-10, and tumor necrosis factor (TNF)- α were supplied by Elabscience Biotechnology (Wuhan, China), or Solarbio (Beijing, China).

2.2. Animal experiment

Mice were raised in the specific pathogen-free animal room (SPF) with a 12 h light/dark cycle. During this period, mice had free access to food and water. After 7 days of adaptation, the mice were randomly divided into four groups ($n = 6$ /group): control group (CON), model group (MOD), 50 mg/kg DHA-PS group, and 100 mg/kg DHA-PS group [4]. Before administration, DHA-PS and BPA were ultrasonically pulverized for 30 min and dissolved in distilled water. The MOD and DHA-PS groups were orally administered with 5 mg/kg BPA, followed by an equal volume of ultrapure water or DHA-PS (50 mg/kg or 100 mg/kg) after 30 min [4,22], while the control group received an equal volume of ultrapure water daily for 6 weeks. After the final administration, mice fasted for 12 h, blood was collected via *retro*-orbital bleeding, and centrifuged (6000 rpm, 5 min, 4 °C) to obtain serum. Mice were euthanized by cervical dislocation, and the liver was dissected, weighed, and recorded for subsequent biochemical and pathological experiments.

2.3. Liver index measurement

The liver index provides an initial assessment of the overall functioning of the liver, which in turn indirectly reflects the effects produced by the drug on the liver tissue of mice. Therefore, the body weight and liver weight were recorded, and the liver index was calculated.

2.4. Determination of biochemical indicators

Serum levels of AST, ALT, TC, TG, NEFA, HDL-C, and LDL-C were determined using the related kits, especially. The collected livers were homogenized with normal saline and centrifuged (12000 rpm, 5 min, 4 °C) to obtain supernatants, and the levels of LPS, IL-1 β , IL-6, IL-10, TNF- α , MDA, SOD, CAT, and GSH-Px were determined in the supernatants.

2.5. Histopathological analysis of the liver

The liver was fixed in 4% paraformaldehyde solution, dehydrated, embedded in paraffin, and then cut into 5 μ m thick sections. The sections were stained with H&E and Oil Red O according to previous methods [4] and the instructions of the kits. Tissue sections were observed using a CX 31 optical microscope (Olympus, Tokyo, Japan).

2.6. Lipidomics analysis in liver

The lipidomics of liver tissue (50 mg) were processed by Majorbio (Shanghai, China). Metabolites were identified and analyzed using the Human Metabolome Database (HMDB) and Metlin database. OPLS-DA and permutation tests were performed on the

Majorbio cloud platform to evaluate model stability. With $VIP > 1$, $P < 0.05$ as the criteria to screen different groups of the metabolites. Metabolic enrichment and selection of key metabolic pathways were performed using the KEGG.

2.7. Immunohistochemical analysis

Following the method described by Tian et al. [23], paraffin-embedded liver tissue sections were deparaffinized and rehydrated. The sections were incubated with diluted primary antibodies (AMPK α 1, PPAR α , SIRT1, and SREBP-1c) with secondary antibodies, respectively. Finally, DAB staining was conducted, counterstained with hematoxylin to stain the cell nuclei, and mounted with neutral resin. Images were captured using a CX 31 electron microscope, and the results were analyzed using Image J.

2.8. Statistical analysis

SPSS 27.0 statistical software was used to analyze the data. The results were expressed as mean $\pm$ standard deviation ($\bar{x} \pm SD$). Differences between groups were compared by one-way analysis of variance (ANOVA) and LSD post-hoc tests and were considered statistically significant at $P < 0.05$.

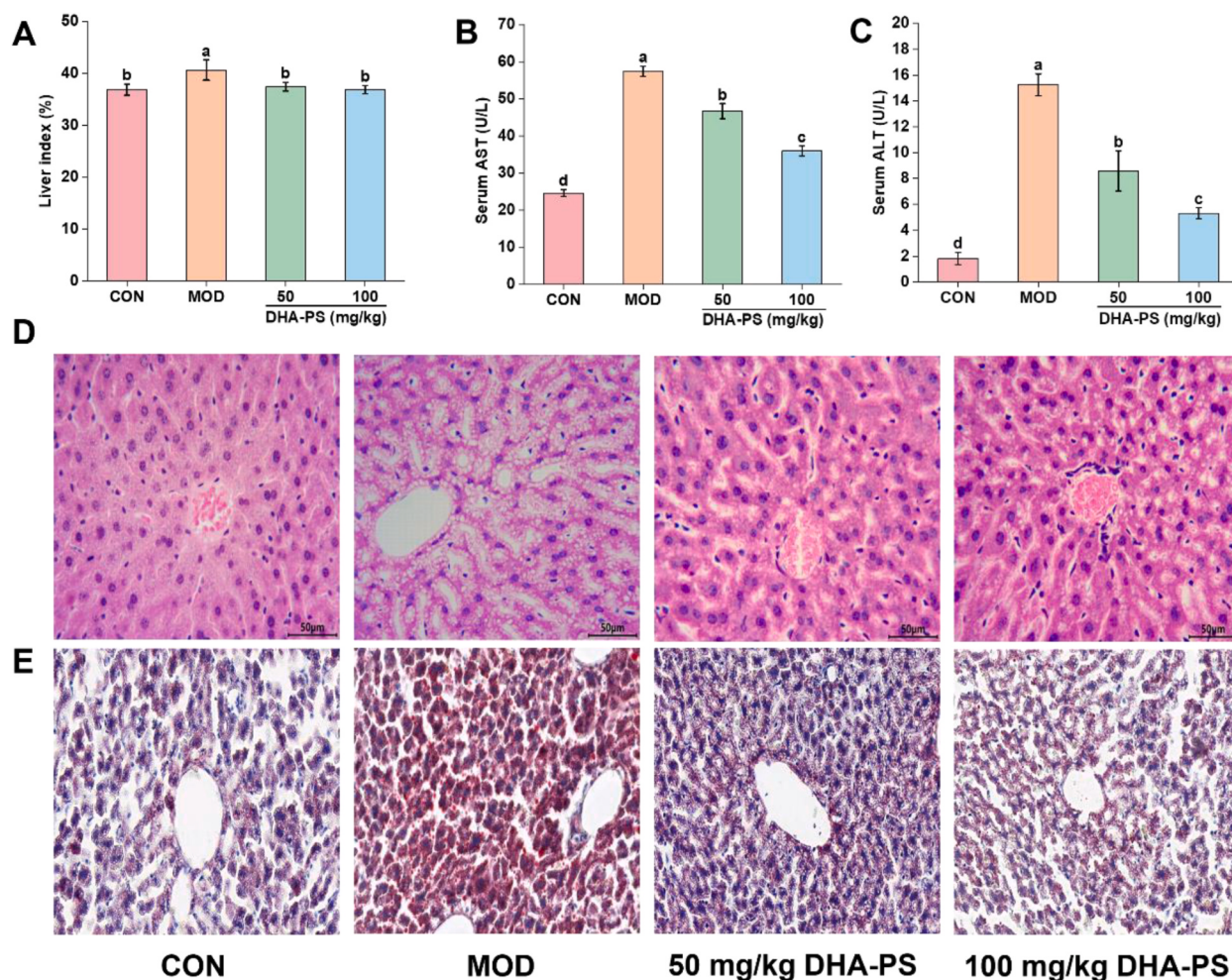


Fig. 1. Effect of DHA-PS on the indicators of BPA-induced liver injury ($n = 6$). (A) Liver index; (B) AST; (C) ALT; (D) H&E staining (400 $\times$); (E) Oil Red O staining (400 $\times$). Different letters indicate statistical significance between the two groups ($P < 0.05$), the same as below. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Results

3.1. DHA-PS alleviates liver injury induced by BPA

Compared with the CON group (Fig. 1A–C), the liver index of the MOD group notably increased by 3.80% ($P < 0.01$), and the AST and ALT levels increased by 32.87 ± 0.40 U/L and 13.43 ± 0.36 U/L, respectively ($P < 0.05$). This indicates that long-term exposure to BPA can cause abnormalities in the liver index and AST and ALT levels, leading to liver damage. After administration of DHA-PS, the liver index, AST, and ALT levels in the DHA-PS group decreased significantly compared to the MOD group ($P < 0.01$).

By observing liver tissue sections (Fig. 1D–E), the hepatocytes in the CON group were neatly arranged, with normal liver cords and no lipid accumulation. After 6 weeks of BPA feeding, large lipid vacuoles appeared between the hepatocytes of the mouse liver, and the liver cord disappeared. In addition, Oil Red O staining revealed an extensive presence of lipid droplets in the liver, indicating severe liver damage caused by BPA. After DHA-PS treatment, the liver tissue lesions improved significantly, and the deposition of lipids in the liver tissue decreased significantly.

3.2. DHA-PS alleviates BPA-induced lipid metabolism abnormalities

The contents of TC, TG, NEFA, LDL-C, and HDL-C in serum were determined to check the lipid-lowering effect of DHA-PS. In the MOD group, the levels of TC, TG, NEFA, and LDL-C (Fig. 2A–D) were notably higher than those in the CON group ($P < 0.05$), while the HDL-C (Fig. 2E) level was notably lower ($P < 0.01$). This indicates that BPA can lead to lipid metabolism disorders in mice. However, DHA-PS treatment reversed this trend, with corresponding levels of blood lipid indicators significantly increased or decreased ($P < 0.05$). This suggests that DHA-PS can improve lipid metabolism abnormalities caused by BPA.

3.3. DHA-PS alleviates liver inflammation and oxidative stress

Compared to the CON group, the IL-10 level was notably down-regulated (Fig. 3A, $P < 0.01$), while the levels of IL-6, IL-1 β , TNF- α , and LPS in the MOD group were notably up-regulated (Fig. 3B–E, $P < 0.05$), suggesting that BPA stimulated the occurrence of liver inflammation. After supplementation with DHA-PS (100 mg/kg DHA-PS), the levels of IL-6, IL-1 β , TNF- α , and LPS in liver tissue decreased by 27.57%, 17.07%, 52.63%, and 52.56%, respectively ($P < 0.01$), and the IL-10 level increased but without significant difference.

In addition, the levels of MDA, SOD, GSH-Px, and CAT in the liver were further analyzed. The content of MDA in the MOD group notably increased ($P < 0.01$), whereas its content in the DHA-PS group significantly decreased (Fig. 3F, $P < 0.05$). The antioxidant enzyme activities in liver tissues were significantly reduced after BPA intervention (Fig. 3G–I, $P < 0.05$), indicating that BPA caused

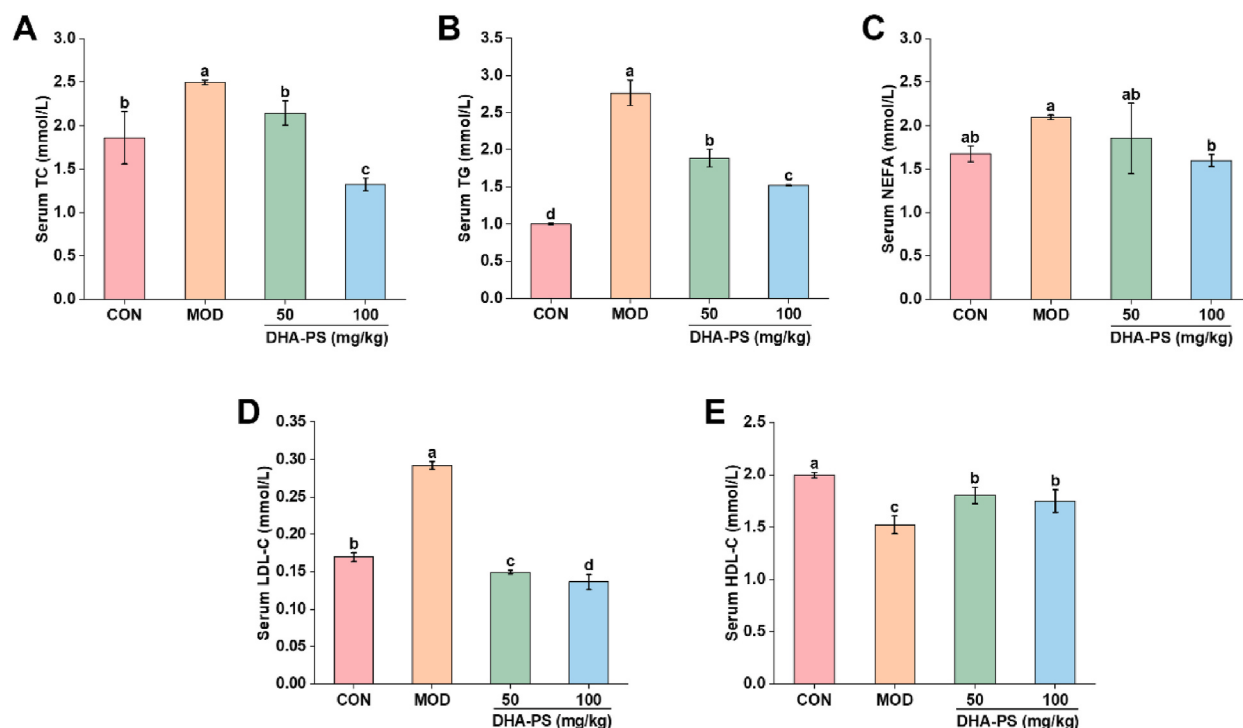


Fig. 2. Effect of DHA-PS on BPA-induced disorders of lipid metabolism ($n = 6$). (A) TC; (B) TG; (C) NEFA; (D) LDL-C; (E) HDL-C.

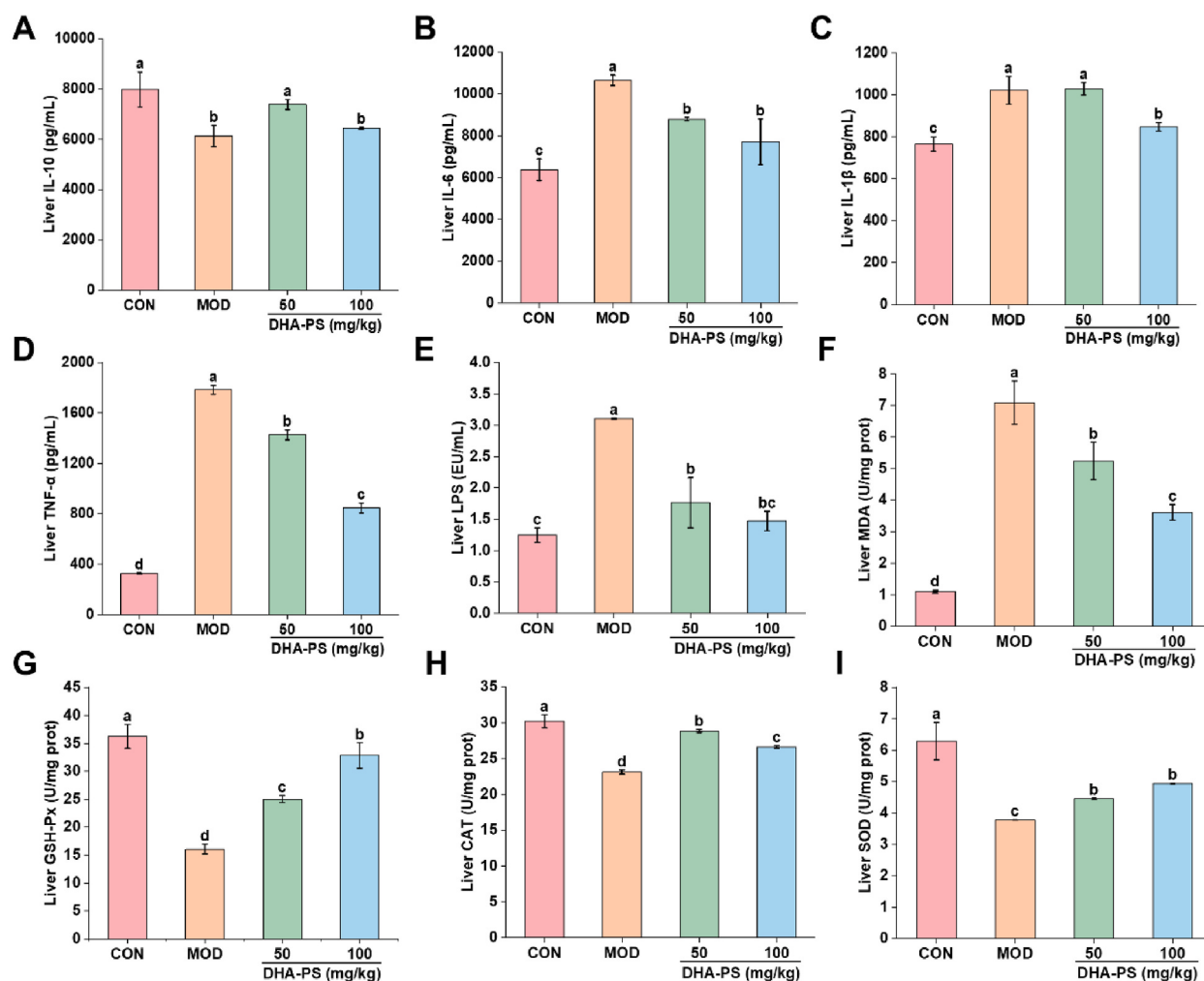


Fig. 3. Effect of DHA-PS on BPA-induced inflammatory factor levels and antioxidant activity in the liver ($n = 6$). (A) IL-10; (B) IL-6; (C) IL-1 β ; (D) TNF- α ; (E) LPS; (F) MDA; (G) GSH-Px; (H) CAT; (I) SOD.

oxidative stress in mouse liver. However, 100 mg/kg DHA-PS significantly changed the above phenomenon, with CAT, SOD, and GSH-Px activities increasing by 15.25%, 30.62%, and 104.29%, respectively ($P < 0.01$). The above results indicate that DHA-PS can effectively alleviate liver inflammation and oxidative stress induced by BPA.

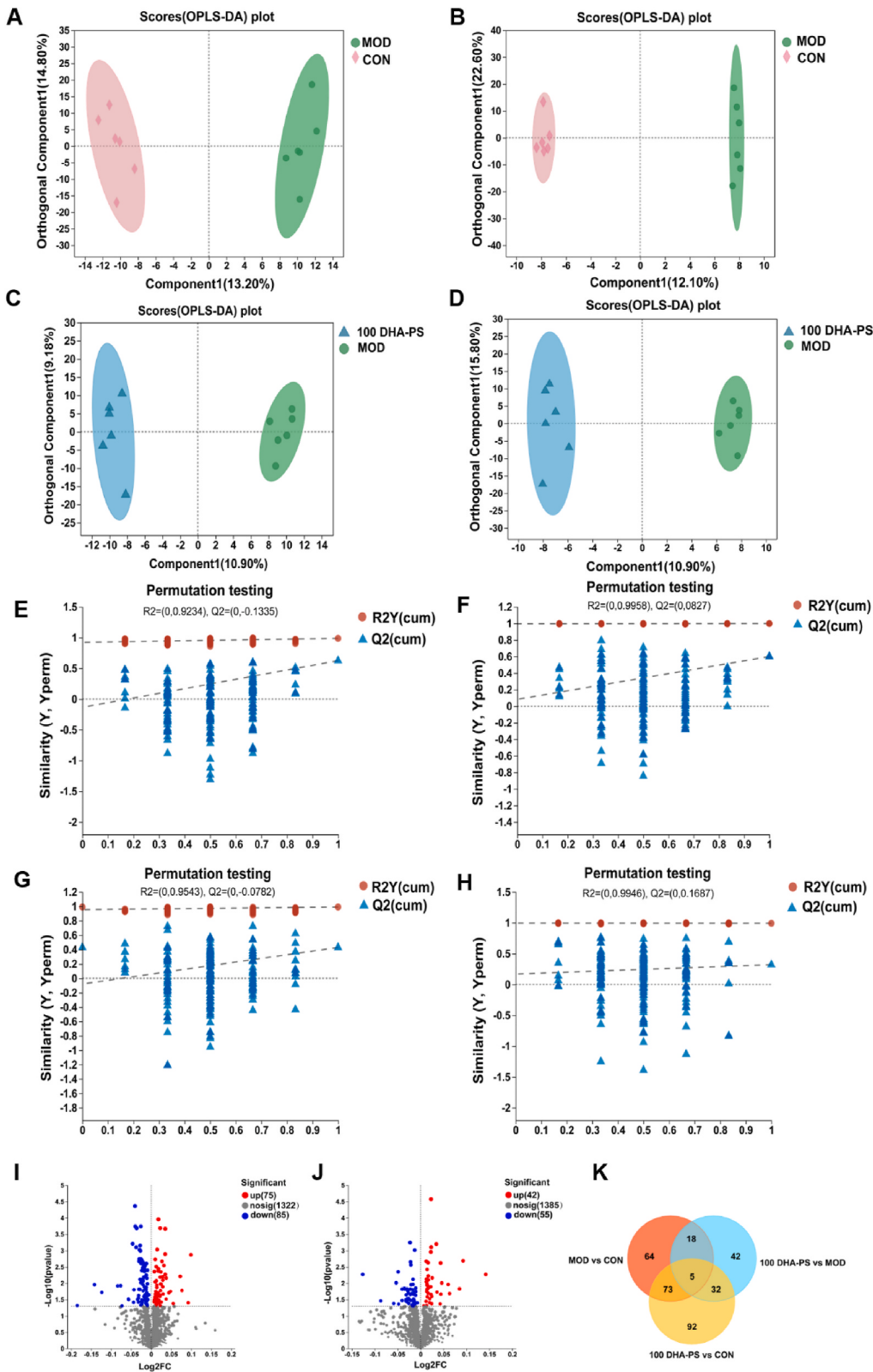
3.4. DHA-PS regulates liver metabolism in mice

To investigate the mechanism of DHA-PS in alleviating BPA-induced liver damage, lipidomics analysis was used to analyze the metabolic spectrum differences in liver tissue. As shown by the results of OPLS-DA, in the dual ion state, samples were significantly separated between the CON and MOD (Fig. 4A–B), as well as between the MOD group and the 100 mg/kg DHA-PS group (Fig. 4C–D). This indicated that BPA disrupts the liver metabolism in mice, while DHA-PS shows certain therapeutic effects. Moreover, the results of 200 permutation tests (Fig. 4E–H) show that the OPLS-DA model is reliable and effective, with no over-fitting phenomenon.

Venn diagrams (Venn) and volcano plots under the double ion mode were drawn according to the screening criteria ($P < 0.05$ and $VIP > 1$). The results (Fig. 4I–K) intuitively showed that there were 160 different metabolites in the MOD and CON groups, among which 75 were up-regulated and 85 were down-regulated. Of the 97 different metabolites screened in the DHA-PS and MOD groups, 42 were notably up-regulated and 55 were notably down-regulated.

Metabolites with VIP scores in the top 30 were visualized through cluster heatmaps. Compared to the CON group, lipids such as TG (20:4e/18:1/20:1), phosphatidylcholine PC (16:1/14:0), and PC (18:0e/18:1) were down-regulated in the MOD group (Fig. 5A), while in the treatment group (Fig. 5B), sphingomyelin SM (d18:1/24:2), SM (d20:0/24:2), and phosphatidylethanolamine PE (18:0/16:0) were up-regulated.

KEGG pathway enrichment analysis was conducted based on the differential metabolites in the liver. BPA and DHA-PS affected different metabolic pathways (Fig. 5C–D), with glycerophospholipid metabolism and glycosylphosphatidylinositol (GPI)-anchor



(caption on next page)

Fig. 4. Effect of DHA-PS on differential metabolites in mouse liver ($n = 6$). (A–B) The OPLS-DA score plots of CON vs MOD in cationic and anionic states; (C–D) The OPLS-DA score plots of MOD vs 100 DHA-PS in cationic and anionic states; (E–F) Permutation test chart of CON vs MOD under positive and negative; (G–H) Permutation test chart of MOD vs 100 DHA-PS under positive and negative; (I–J) Volcanic plots of differential metabolites in the CON vs MOD and MOD vs 100 DHA-PS; (K) Venn diagrams of shared and unique metabolites in different groups.

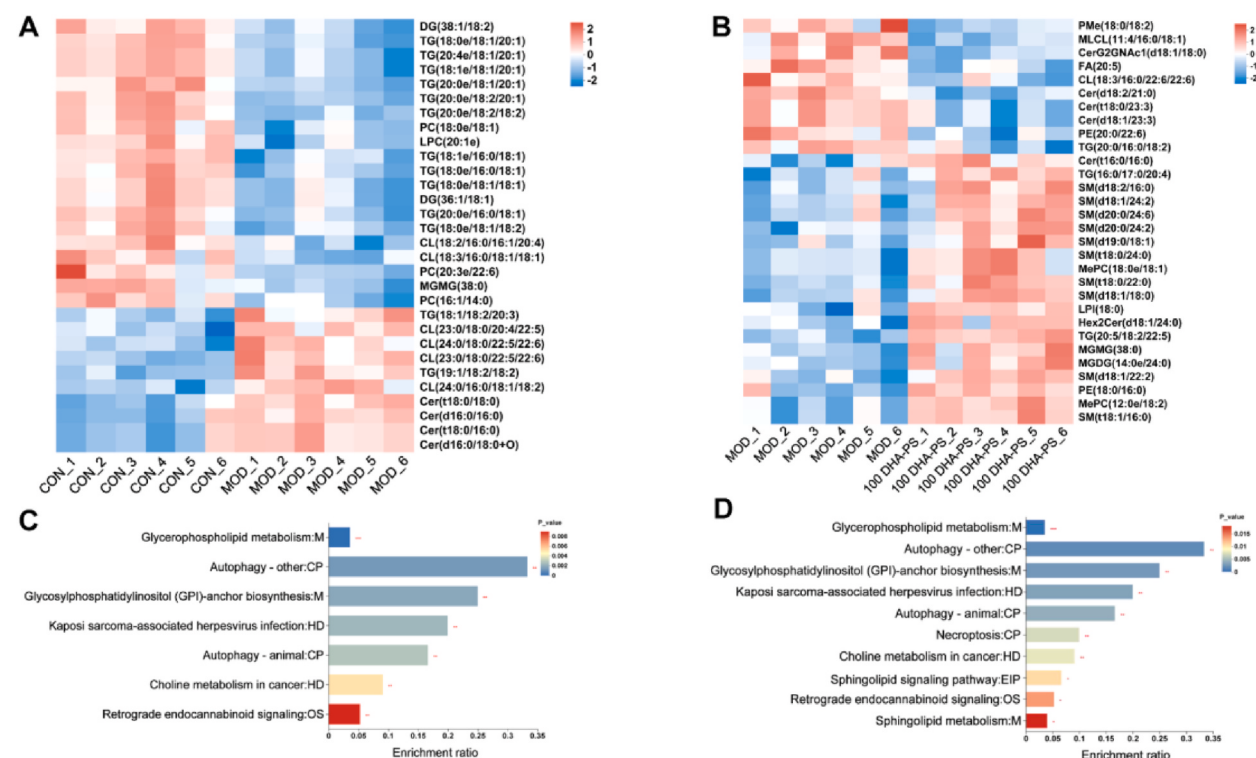


Fig. 5. Effects of DHA-PS on differential metabolites and metabolic pathways. (A–B) Heatmap of top 30 metabolite clustering in the CON vs MOD and MOD vs 100 DHA-PS; (C–D) KEGG enrichment analysis plots for CON vs MOD and MOD vs 100 DHA-PS.

biosynthesis being common pathways. From these results, it can be inferred that DHA-PS improves liver lipid metabolism disorder induced by BPA by affecting glycerophospholipid, GPI-anchor, and sphingolipid metabolism.

3.5. Effect of DHA-PS on the SIRT1-AMPK pathway

As shown in Fig. 6, BPA exposure resulted in a notable decrease ($P < 0.05$) in the expression levels of AMPK α 1, SIRT1, and PPAR α , while the lipid synthesis factor SREBP-1c showed a significant increase ($P < 0.05$) compared to the CON group. After supplementing with DHA-PS, the expression of the above proteins returned to their respective levels, indicating that DHA-PS could stimulate the SIRT1-AMPK pathway, thereby regulating the expression of proteins involved in lipid degradation and synthesis, mitigating the abnormalities in liver lipid metabolism triggered by BPA exposure.

3.6. Correlation analysis of liver metabolites with biochemical indices

The Spearman correlation algorithm was used to analyze the correlation between metabolites and serum or liver biochemical parameters. As shown in Fig. 7, PC (19:0/22:5), Cer (d17:1/22:0), and Cer (t17:0/22:0) were positively correlated with AST, ALT, lipid metabolism indicators (TG and NEFA), and pro-inflammatory factors (IL-6, IL-1 β , and TNF- α), while they were negatively correlated with liver oxidative stress indicators (CAT, SOD, and GSH-Px), PPAR α , and SIRT1 proteins. In addition, AMPK α 1 and PPAR α were significantly positively correlated with PE (18:1e/20:5), SM (d18:2/16:0), SM (t18:0/22:0), MePC (18:0e/18:1), and SM (t18:0/24:0), while serum TC, NEFA, and LDL-C were negatively correlated with them.

4. Discussion

BPA is extensively found in the environment and carries significant implications for human health, and exposure to BPA may result in oxidative damage and metabolic dysfunctions in the liver [24,25]. The liver is a critical site for biotransformation and metabolism,

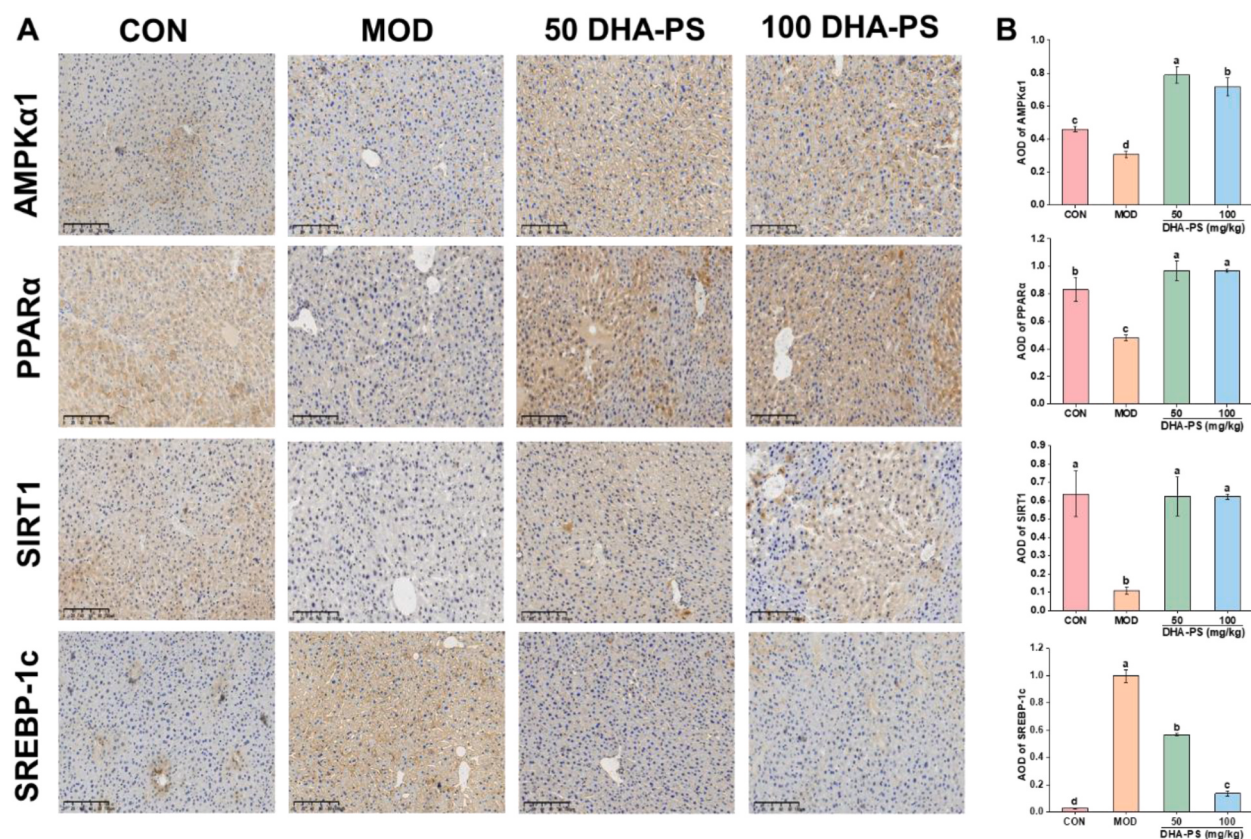


Fig. 6. Effect of DHA-PS on the SIRT1-AMPK pathway ($n = 3$). (A) Immunohistochemical analysis ($200 \times$); (B) Average optical density (AOD) values of AMPK α 1, PPAR α , SIRT1, and SREBP-1c in the liver.

playing an important role in maintaining normal physiological activities. Consequently, it is essential to investigate safe and effective agents to alleviate or prevent liver damage resulting from BPA exposure. DHA-PS has been shown to alleviate liver damage induced by an HFD [12]. Thus, this study established a BPA-induced murine liver injury model to evaluate the amelioration of DHA-PS and its related mechanisms.

After BPA treatment, the liver index of the MOD group increased significantly, and the liver exhibited obvious injury characteristics, such as irregular hepatocyte morphology, disordered liver sinusoid arrangement, and accompanied by vacuolar degeneration. Liver enzymes are sensitive markers of liver injury, especially AST and ALT. When hepatocytes are damaged, aminotransferases are released from the cells into the bloodstream, resulting in increased enzyme activity in the blood [26]. The results of this experiment exhibited that the serum levels of AST and ALT in the MOD group were notably higher than those in the CON group, which initially indicated that BPA could cause liver injury in mice. In addition, Liao et al. [1] found that BPA could cause lipid metabolism disorders, inducing murine hepatic fat accumulation and degeneration. By measuring serum lipid indicators, it was shown that after exposure to BPA, the concentrations of TC, TG, NEFA, and LDL-C in the serum significantly increased ($P < 0.05$), while the concentration of HDL-C significantly decreased ($P < 0.01$), and the Oil Red O staining results showing a large accumulation of lipid droplets also confirmed the above observations. However, after supplementation of DHA-PS, the levels of blood lipids in mice gradually returned to normal, and the hepatic lipid accumulation and pathological damage were also improved in a dose-dependent manner. This indicates that DHA-PS has an ameliorative effect on BPA-induced liver injury.

LPS acts as an active endotoxin in the liver and exhibits strong pro-inflammatory activity [27]. Excessive accumulation of LPS in the body leads to the production of inflammatory cytokines and activation of liver cell necrosis, resulting in inflammation and oxidative stress [28,29]. BPA could disrupt mitochondrial function, leading to the generation of large amounts of reactive oxygen species (ROS) and reducing the defense capabilities of antioxidant enzymes, thereby inducing oxidative stress and toxicity [30,31]. Furthermore, excessive ROS can also trigger inflammation and lipid peroxidation. MDA is a biological marker of lipid peroxidation that quantifies the degree of oxidative stress [32]. Our results indicated that BPA could notably increase the content of MDA in the liver ($P < 0.01$), significantly up-regulate the levels of IL-6, IL-1 β , and TNF- α ($P < 0.05$), and down-regulate the levels of IL-10, which further aggravated the liver damage in mice. Nevertheless, supplementation with DHA-PS can mitigate the liver damage induced by BPA by diminishing oxidative stress and the inflammatory response.

Metabolomics depicts the comprehensive characteristics of metabolism and metabolites in biological systems, playing important roles in exploring the mechanisms of metabolic diseases and identifying biomarkers [33,34]. Lipidomics, a branch of metabolomics,

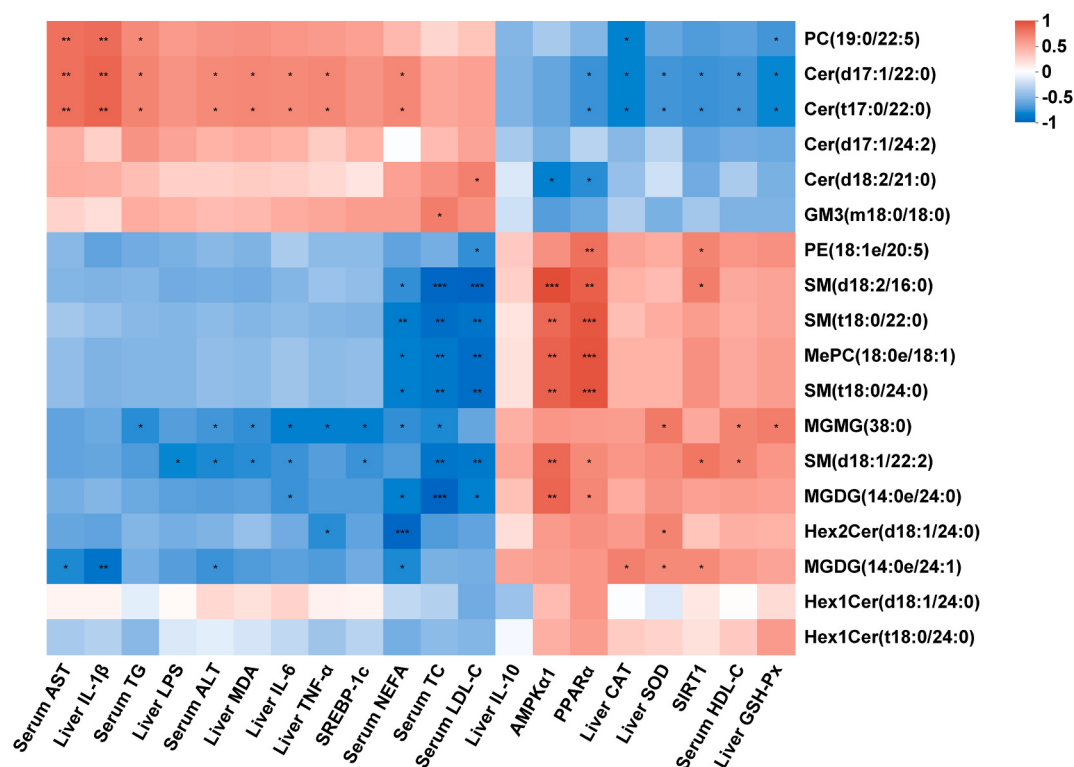


Fig. 7. Spearman correlation heatmap between liver metabolite abundance and biochemical indicators. Different colors in the legend represent the magnitude of the correlation coefficient between attributes, where red indicates a positive correlation, and blue indicates a negative correlation. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

can qualitatively and quantitatively analyze all metabolites in biological samples, elucidating the relationship between metabolites and biochemical indicators and identifying relevant metabolic pathways [18,35]. Thus, we performed lipidomics to explore the effects of BPA on liver metabolites and metabolic pathways and to analyze the alleviating mechanism of DHA-PS. Pathway enrichment analysis showed that glycerophospholipid metabolism is the main metabolic pathway.

Glycerophospholipids, being the primary constituents of cell membranes, play multifaceted roles in living systems, especially in preserving cell structural integrity, as well as in regulating and managing cellular functions and diseases [36,37]. Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are the most abundant phospholipids in animals, and an imbalance between them may disrupt cell membrane integrity, thereby interfering with the signal transduction of glycerophospholipids [38–40]. In this study, BPA decreased the content of PC ((16:1/14:0)/(18:0e/18:1)) in mice liver tissues, and Spearman's correlation calculations showed that PC (19:0/22:5) was positively correlated with liver injury indices and pro-inflammatory factors, and negatively correlated with antioxidant enzymes, which consequently induced lipid metabolism disorders causing liver injury. However, the above phenomena were somewhat improved after DHA-PS administration, indicating that DHA-PS alleviates BPA-induced lipid metabolism abnormalities by regulating glycerophospholipid metabolic pathways.

Lipid accumulation and homeostatic imbalance increase the risk of metabolic diseases [16]. In this experiment, exposure to BPA intensified the accumulation of lipids (TC, TG, and NEFA), resulting in disturbed lipid metabolism. SIRT1 is a NAD⁺-dependent deacetylase widely present in tissues and cells, which can alleviate inflammation, and oxidative stress, and regulate lipid metabolism-related proteins [41,42]. AMPK is an important energy sensor and metabolic regulator that inhibits fatty acid synthesis and regulates lipid homeostasis [43]. SREBP1 is a key transcription factor for hepatic lipid synthesis and is expressed mainly in the liver [44]. PPAR mainly promotes fatty acid β -oxidation [45]. SIRT1 and AMPK have been recognized as interesting targets because they are closely involved in inflammation, and SIRT1 or AMPK activation can inhibit the NF- κ B expression, thus alleviating the inflammatory response [46]. Our results indicated that the expression levels of AMPK α 1, SIRT1, and PPAR α in the MOD group notably decreased, while the expression level of SREBP-1c significantly increased. In addition, the inflammation factor levels (IL-6, IL-1 β , and TNF- α) were also significantly up-regulate ($P < 0.05$). Administering DHA-PS counteracted this effect, suggesting that DHA-PS can alleviate lipid metabolism disorders and inflammation in BPA-induced mouse liver by activating the SIRT1-AMPK pathway.

5. Conclusions

In summary, our results indicate that DHA-PS alleviates BPA-induced liver damage by reducing serum liver injury markers,

decreasing lipid accumulation, inhibiting inflammation, and enhancing antioxidant enzyme activity. Additionally, DHA-PS improves lipid metabolism disorder in mouse liver by regulating glycerophospholipid metabolism and the SIRT1-AMPK pathway, indicating its potential as a dietary supplement for alleviating BPA-induced liver injury.

Funding

This work was financially supported by the Zhoushan Science and Technology Project (No.2022C41004), the Eyas Program Incubation Project of Zhejiang Provincial Administration for Market Regulation (CY2023329), and the Science and Technology Project of Zhejiang Drug Administration (NO.2024008).

International review board statement

All animal procedures were performed under the Animal Ethics Committee of Zhejiang Ocean University (certificate no. 2022021).

Data availability statement

Data supporting our findings can be sent upon request.

CRediT authorship contribution statement

Jing Tian: Writing – original draft, Methodology, Investigation, Formal analysis. **Yun Lu:** Writing – review & editing, Conceptualization. **Qiao-ling Zhao:** Investigation, Funding acquisition, Formal analysis. **Qiu-yan Pu:** Methodology, Investigation, Formal analysis. **Su Jiang:** Investigation, Formal analysis. **Yun-ping Tang:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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