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Taurine mitigates bisphenol A-induced maternal-fetal oxidative stress and improves fetal weight by regulating Nrf2-Keap1 pathway, gut microbiota and bile acid metabolism

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ABSTRACT

Bisphenol A (BPA) exposure disrupts the maternal-fetal environment, resulting in fetal growth restriction and tissue damage. While taurine is recognized for its protective effects and its role in regulating tauro-conjugated bile acid (TCBA) metabolism, its specific mechanism of action underlying BPA exposure remains unclear. This study systematically investigated whether taurine alleviates BPA-induced placental dysfunction, oxidative stress, and fetal weight restriction at gestation day (GD) 18.5 by regulating TCBA metabolism using a murine pregnancy model. Our results showed that gestational BPA exposure significantly inhibits the Nrf2-Keap1 signaling pathway, triggering a vicious cycle of oxidative stress and inflammation. This cascade disrupted placental nutrient transport, impaired hepatic detoxification, and perturbed the gut microbiota-bile acid (BA) axis, ultimately leading to fetal weight restriction at GD18.5. Taurine supplementation exerted multi-level protective effects by activating the Nrf2-Keap1 pathway, upregulating the expression of antioxidant genes (*CAT*, *SOD1*, *SOD2*), inhibiting pro-inflammatory factors (*IL-6*, *IL-8*), and simultaneously mitigated oxidative stress and inflammatory damage in the placenta and liver; restoring the expression of nutrient transport genes such as syncytin B (*SynB*) and insulin-like growth factor 2 (*IGF2*) to repair placental function and ensure fetal nutrient supply, while upregulating cytochrome P450 family 27 subfamily A member 1 (*CYP27A1*) expression to maintain hepatic BA synthesis homeostasis; and remodeling the gut microbial community structure by restoring the abundance of beneficial bacteria (Muribaculaceae, *Ruminococcus*), inhibiting the abnormal proliferation of *Bifidobacterium*, and improving BA metabolic imbalance, thereby normalizing the "liver-gut microbiota-BA" metabolic axis. Our findings indicate that taurine mitigates BPA-induced maternal-fetal toxicity by targeting the microbiota-BA-oxidative stress axis. This study highlights taurine as a promising nutritional intervention strategy for protecting pregnancy against environmental toxicant exposure.

Keywords: Taurine; Bisphenol A; Fetal growth restriction; Gut microbiota; Oxidative stress; Bile acid metabolism

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Introduction

Bisphenol A (BPA) is a ubiquitous environmental endocrine disruptor widely used in food packaging, plastic products, and various industrial materials. Sufficient evidence has demonstrated that BPA is extensively present in the environment, and humans are exposed to BPA via multiple routes, including diet, skin contact, and inhalation [1]. A growing body of data indicates that BPA can be detected in various human tissues [2]. In addition, BPA has also been identified in maternal serum, breast milk, umbilical cord blood, placental tissues [3], and even fetal livers [4]. These findings clearly suggest that pregnancy represents a critically sensitive window for BPA exposure.

Epidemiological studies have consistently shown that exposure to environmental chemicals, including BPA, can induce a series of adverse pregnancy outcomes in both mothers and developing fetuses, such as miscarriage [5], low birth weight [6], placental abnormalities [7], and an increased risk of pregnancy-related complications [8]. Accumulating evidence confirms that maternal BPA exposure during pregnancy can cross the placental barrier and interfere with fetal development [9]. Animal experimental studies have further validated the adverse effects of BPA: early pregnancy exposure to BPA in mice can induce fetal intrauterine growth restriction (IUGR) and reduce birth weight [10]; BPA exposure during the embryonic and infant stages in mice causes oxidative damage to the brain, liver, and kidneys [11]. Recent studies have also emphasized that BPA exposure can induce gut microbial dysbiosis in mice, thereby increasing disease susceptibility [12]. As a multifaceted regulator, gut microbiota participates in various host physiological processes, including metabolism, immune response, and barrier function; its dysbiosis is closely associated with pathological conditions. Specifically, a study on pregnant ewes demonstrated that maternal BPA exposure alters the composition of gut microbiota, which in turn promotes placental apoptosis and oxidative stress, reduces placental efficiency, and ultimately leads to fetal growth restriction [13].

Taurine (2-aminoethanesulfonic acid) is a conditionally essential amino acid and one of the most abundant amino acids in humans and rodents, widely distributed in

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various tissues [14]. A large body of evidence has demonstrated that taurine exerts prominent physiological functions primarily through antioxidant defense and anti-inflammatory pathways, thereby preventing various diseases and repairing damage induced by toxic substances [15]. For instance, dietary taurine supplementation has been reported to alleviate deoxynivalenol-induced hepatic oxidative stress, mitochondrial dysfunction, apoptosis, and inflammatory responses in weaned piglets [16]. Another study confirmed that taurine can mitigate hepatic inflammatory responses, apoptosis, and oxidative stress in weaned piglets challenged with lipopolysaccharide [17]. Importantly, taurine is crucial for fetal development. Mammals are unable to synthesize taurine endogenously and thus rely entirely on exogenous sources [18]. Previous studies have shown that intraperitoneal injection of taurine into pregnant mice can deliver this amino acid to both the fetal brain and liver simultaneously, indicating that maternal taurine is capable of crossing the placental barrier to reach the fetus [19]. Recent research further reported that prenatal/postnatal taurine supplementation improves neurodevelopment and brain function in mouse offspring [20]. Additionally, maternal taurine supplementation has been shown to ameliorate maternal metabolic disorders induced by fructose, such as insulin resistance and systemic inflammatory dysregulation, and partially improve adverse developmental outcomes in offspring [21]. These findings collectively suggest that taurine has potential protective effects on the maternal body and fetus during pregnancy. However, it remains unclear whether maternal taurine supplementation can ameliorate BPA-induced placental oxidative stress damage and promote fetal health.

Taurine serves as an indispensable and pivotal precursor for the synthesis of tauro-conjugated bile acids (TCBAs), whose content and biological activity are directly regulated by exogenous taurine supply levels. Accumulating evidence has confirmed that exogenous taurine supplementation can directly facilitate TCBA synthesis and accumulation [22]. Specifically, duodenal taurine administration has been shown to markedly increase the taurocholic acid conjugation rate in patients by 2.5% to 10% [23]. In animal models, TCBAs represent the predominant form of BAs in rodents, with over 95% of BAs conjugated to taurine in mice [24]. Dietary taurine

supplementation modulates BA metabolism in *ApoE*$^{-/-}$ mice, which not only elevates TCBA levels in the liver and serum significantly but also upregulates the expression of hepatic genes related to TCBA synthesis; additionally, it alleviates atherosclerosis by mitigating trimethylamine N-oxide-induced inflammatory responses [25]. As the core bioactive form of BAs, TCBAs exert multiple beneficial regulatory functions via activating farnesoid X receptor (*FXR*) and G protein-coupled BA receptor (*TGR5*) [26]. These functions specifically include maintaining glucose metabolic homeostasis, regulating the structural balance of gut microbiota [27], alleviating oxidative stress-induced damage, and reducing inflammatory responses [28], thereby providing critical support for systemic health.

Although the maternal-fetal protective effects of taurine and the regulatory functions of TCBAs have been independently verified, systematic investigations remain scarce regarding whether taurine can exert maternal-fetal protective effects by regulating TCBA metabolism under gestational BPA exposure. Specifically, it is unclear if taurine can alleviate BPA-induced placental dysfunction, maternal-fetal oxidative stress, and fetal low birth weight. In view of this, the present study hypothesizes that maternal taurine supplementation during pregnancy can synergistically activate antioxidant and anti-inflammatory pathways by promoting TCBA synthesis, thereby attenuating BPA-induced placental injury and relieving maternal-fetal oxidative stress. This study aims to clarify the protective effects of taurine against BPA-induced maternal-fetal oxidative stress, placental dysplasia, and fetal low birth weight, as well as to elucidate the underlying mechanisms. Collectively, findings from this study will provide novel insights into the preventive and interventional strategies for BPA-induced adverse pregnancy outcomes.

Material and methods

Animal welfare statement

The animal experimental protocol employed in this study was approved by the Animal Care of the Feed Research Institute, Chinese Academy of Agricultural Sciences (Approval No.: IFR-CAAS20240702).

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Experimental animals and design

In the present study, 30 specific pathogen-free (SPF) grade C57BL/6J female mice and 15 male mice were selected and caged overnight for mating at a female-to-male ratio of 2:1. On the following day, the formation of vaginal plugs was checked; female mice with visible vaginal plugs were confirmed as pregnant, housed individually, and the day of vaginal plug detection was designated as gestation day (GD) 0.

The pregnant mice were randomly divided into three groups (n = 10 per group): the control group, the BPA group, and the BPA+Tau group. All pregnant mice were fed a basal breeding diet, and interventions were administered via intragastric gavage: the control group was gavaged with 0.2 mL of corn oil daily; the BPA group was gavaged with 0.2 mL of corn oil containing 200 mg/kg BW BPA daily; and the BPA+Tau group was gavaged with 0.2 mL of corn oil containing 200 mg/kg BW BPA and 500 mg/kg BW taurine daily. The experimental procedure is illustrated in **Fig. 1**. The doses of BPA and taurine were selected in accordance with previous studies [29, 30]. BPA (≥ 99% purity) was purchased from Sigma-Aldrich; Taurine (≥ 99% purity) and corn oil were purchased from Shanghai Yuanye Biotechnology Co., Ltd. The experimental period lasted for 18.5 days; during this period, the body weights of the pregnant mice were recorded on the 1st day of pregnancy and the 18.5th day of pregnancy, respectively.

Sample collection

On GD 18.5, blood samples were collected from the retro-orbital venous plexus, followed by euthanasia of the pregnant mice via cervical dislocation for subsequent sample processing. The collected whole blood was placed in sterile anticoagulant-free centrifuge tubes and allowed to stand at room temperature for 2 h to ensure complete coagulation. Subsequently, the samples were centrifuged at 4000 r/min for 10 min at 4 °C. The upper pale yellow serum was carefully aspirated, aliquoted into sterile cryopreservation tubes, and stored at -80 °C for subsequent detection and analysis of maternal-fetal related oxidative stress, inflammatory factors, and metabolic indicators. For tissue samples, fetal placentas of pregnant mice and livers from both dams and

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fetuses were harvested. The litter size was recorded, and fetal, placental weights were measured. IUGR was defined as fetal body weight below the mean − 2 SD of the control group, and the IUGR rate was calculated accordingly [31]. The placental and hepatic tissues were placed in cryovials and preserved at -80°C for subsequent gene expression analysis.

Determination of serum and placental antioxidant enzyme activity and inflammatory cytokines

Before detection, the placental tissues were fully ground. An appropriate amount of placental tissue was homogenized in 1.0 mL of pre-chilled phosphate-buffered saline (PBS, pH 7.4) using a tissue homogenizer. Subsequently, the homogenate was centrifuged at 3500 rpm for 10 min at 4°C, and the supernatant was collected for subsequent assays. The protein concentration of tissue supernatant was determined by BCA (Bicinchoninic Acid) protein assay kit (Huaxing Bio, Beijing, China) in strict accordance with the manufacturer's instructions. Bovine serum albumin (BSA) was used as the standard to establish a standard curve, and the absorbance value was measured at 562 nm with a microplate reader (BioTek Epoch, Agilent Technologies, USA). The protein concentration of each sample was calculated according to the standard curve. The activities of antioxidant enzymes, including superoxide dismutase (SOD) and total antioxidant capacity (T-AOC), as well as the oxidative damage marker malondialdehyde (MDA), were determined in serum and placental tissue using specific commercial assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). The concentrations of inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in serum and placental tissue were measured by mouse-specific enzyme-linked immunosorbent assay (ELISA) kits (Enzyme-Linked Biotechnology Co., Ltd., Shanghai, China).

RT-qPCR

Total RNA was extracted from the placental and hepatic tissues of pregnant mice using the i-presci Scientific RNA Extraction Kit. Following the determination of RNA concentration and quality, reverse transcription was performed with the PrimeScript® RT Reagent Kit with gDNA Eraser (Takara, Japan) to eliminate genomic DNA

contamination before complementary DNA (cDNA) synthesis. Quantitative real-time polymerase chain reaction (RT-qPCR) was subsequently conducted on a Bio-Rad CFX96 Real-Time PCR System. Relative mRNA expression levels were normalized to β-actin and calculated using the 2^(–ΔΔCt) method [32]. The sequences of the primers used in this study are provided in **Table S1**.

16S rRNA gene sequencing analysis of fecal microbiome

Following the procedures described in previous studies [33], Total microbial DNA was extracted from frozen fecal samples using the Fast DNA Extraction Kit (Omega Bio-Tek, Norcross, GA, USA) in accordance with the manufacturer's optimized protocol. DNA quality was comprehensively evaluated: integrity was verified by 1.0% agarose gel electrophoresis, while concentration and purity were determined using a NanoDrop™ 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) by measuring the absorbance ratios A260/A280 (1.8–2.0, indicating minimal protein contamination) and A260/A230 (>1.5, reflecting low polysaccharide or salt interference). Only DNA samples with intact electrophoretic bands (no obvious degradation) and a concentration ≥50 ng/μL were selected as templates for PCR amplification. The specific primer pairs 338F (5'-ACTCCTACGGGAGGCAGCAG-3') and 806R (5'-GGACTACHVGGGTWTCTAAT-3') were used to amplify the hypervariable V3-V4 regions of the bacterial 16S rRNA gene [34].

Paired-end sequencing (2×250 bp) was performed on the Illumina MiSeq platform to acquire raw sequence data. Raw reads were quality-controlled and denoised using the DADA2 plugin integrated in QIIME 2 (v2022.2) with customized parameters to generate high-resolution amplicon sequence variants (ASVs). Taxonomic assignment of ASVs was achieved by alignment against the SILVA 138.2 database with a confidence threshold of 80%.

Subsequently, systematic bioinformatics analyses were performed using the Majorbio Cloud Platform (https://cloud.majorbio.com/), encompassing taxonomic composition analysis, microbial community diversity assessment (α-diversity and β-diversity), intergroup difference testing, correlation analysis, phylogenetic tree

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construction, and functional potential prediction. α-diversity indices, including Shannon, Chao1, ACE, and Simpson, were calculated to quantify the species richness and evenness of the community. β-diversity was visualized via principal coordinate analysis (PCoA) based on weighted UniFrac distances, intuitively reflecting intergroup differences in community structure. For intergroup microbial community difference testing, the Kruskal–Wallis test was employed for multiple-group comparisons; Spearman's rank correlation analysis was used for correlation analysis. Based on 16S rRNA gene sequencing data, the PICRUSt2 tool (version 2.2.0-b) was employed with default parameters to predict functional potential. Amplicon sequences were projected to functional profiles using the built-in IMG reference genome database, followed by annotation against the Kyoto Encyclopedia of Genes and Genomes (KEGG) database for classification.

Serum BA profile detection

The targeted BA metabolomics detection was performed with reference to the methods previously reported in the literature [33]. Due to serum hemolysis in the CON group and BPA + Tau group, one sample from each group was excluded from subsequent analyses to ensure data reliability.

Before detection, serum samples were subjected to preprocessing procedures, including protein precipitation, liquid-liquid extraction, and centrifugation (detailed parameters were consistent with the referenced method), to remove interfering substances and enrich the target BA components. The pretreated samples were then analyzed using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS, ACQUITY UPLC Xevo TQ-S, Waters Corp., Milford, MA, USA) for the qualitative and quantitative determination of analytes.

Raw mass spectrometry data were collected and processed using MassLynx software (v4.1, Waters Corp., Milford, MA, USA), including peak alignment, peak picking, and peak area integration. Subsequent targeted metabolomics analysis of the identified BAs was conducted on the Majorbio Cloud Platform (https://cloud.majorbio.com/) for data visualization and systematic interpretation.

Statistical analysis

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Statistical analyses of reproductive performance, antioxidant enzyme indices, inflammatory cytokines in serum and placental tissues, and quantitative real-time PCR results were performed using SPSS statistical software (Version 25.0). One-way ANOVA was performed for multi-group comparisons, with the least significant difference (LSD) test used to determine significant differences. Intergroup comparisons of α-diversity (Shannon index, Simpson index) and relative abundances of dominant taxa (phylum and genus levels) were conducted via the Wilcoxon rank-sum test. Spearman's rank correlation analysis was applied to explore associations among serum oxidative stress markers, inflammatory cytokines, gut microbiota (at the genus level), and serum BAs, and correlation heatmaps were generated using R software (v4.4.2). Data are presented as the mean ± standard error (SE), with a P-value < 0.05 considered statistically significant and a P-value between 0.05 and 0.10 regarded as a significant trend.

Results

Maternal taurine supplementation on reproductive performance in pregnant mice exposed to bisphenol A (BPA)

The results of reproductive performance are presented in **Table 1**. Compared with the control group, maternal BPA exposure did not significantly affect the incidence of IUGR, but it markedly reduced the average placental weight, fetal weight and total litter size ($P < 0.05$). In contrast, taurine supplementation significantly increased fetal weight and total litter size relative to the BPA-exposed group ($P < 0.05$).

Maternal taurine supplementation on serum and placental tissues antioxidant enzyme activities and inflammation-related markers in pregnant mice exposed to bisphenol A (BPA)

The activities of antioxidant enzymes and levels of inflammation-related markers in serum and placental tissues of pregnant mice are shown in **Fig. 2**. In terms of antioxidant capacity (**Fig. 2-A**, **2-C**), BPA exposure significantly disrupted the redox balance in serum and placental tissues. Compared with the CON group, the BPA-exposed group showed significantly decreased SOD activity in serum ($P < 0.01$)

and placental tissue ($P < 0.05$), along with significantly increased serum MDA levels ($P < 0.001$), and a significant decrease in T-AOC in placental tissue ($P < 0.05$). Taurine supplementation effectively reversed these BPA-induced abnormalities: it significantly upregulated SOD activity in serum and placental tissue ($P < 0.05$), while downregulating serum MDA levels ($P < 0.001$), and enhancing serum T-AOC ($P < 0.05$). These findings indicate that taurine supplementation effectively alleviates BPA-induced placental oxidative stress.

Regarding inflammatory cytokine responses, BPA exposure triggered abnormal inflammatory responses in serum and placental tissues (**Fig. 2-B**, **2-D**). Compared with the CON group, the BPA-exposed group showed a significant increase in the levels of the pro-inflammatory cytokine IL-6 in serum ($P < 0.01$) and placental tissue ($P < 0.05$), while taurine supplementation significantly reduced IL-6 levels in serum ($P < 0.001$) and placental tissue ($P < 0.05$). Furthermore, compared with the BPA group, the taurine-supplemented group exhibited a significant decrease in serum IL-1β ($P < 0.01$) and TNF-α levels ($P < 0.05$). These results suggest that taurine supplementation exerts a prominent mitigating effect on BPA-induced placental inflammation.

Maternal taurine supplementation on the expression levels of placental function, antioxidant, and inflammatory cytokine-critical genes in placental tissues of BPA-exposed pregnant mice

Placental development-related genes directly determine the structural integrity and physiological function of the placenta, which is essential for maternal-fetal nutrient exchange and barrier protection. To systematically evaluate the protective effects of taurine against BPA-induced placental impairment, we analyzed the mRNA expression of placental function-critical genes, antioxidant pathway genes, and inflammatory cytokine genes (**Fig. 3**).

As shown in **Fig 3-A**, BPA exposure significantly impaired the expression of genes essential for placental development and function. Compared with the CON group, the BPA-exposed group exhibited a significant downregulation of *syncytinB* and *IGF2* mRNA expression in the placenta ($P < 0.05$). Taurine supplementation

effectively reversed these deficits, significantly upregulating *syncytinB* and *IGF2* mRNA expression ($P < 0.05$). In contrast, neither BPA exposure nor taurine supplementation exerted significant effects on the mRNA expression of *PLGF* or *FGF15*.

Concurrent with the impairment of placental development genes, BPA exposure significantly disrupted the Nrf2-Keap1 antioxidant axis in placental tissues (**Fig. 3-B**). Compared with the CON group, *Nrf2* mRNA expression was remarkably downregulated ($P < 0.01$), while its negative regulator *Keap1* ($P < 0.01$) and downstream target gene *NQO1* ($P < 0.001$) were significantly upregulated. This suggests that BPA impairs placental antioxidant capacity by suppressing Nrf2-mediated cytoprotective signaling. In addition, taurine supplementation effectively reversed these BPA-induced abnormalities: it significantly elevated *Nrf2* mRNA expression ($P < 0.01$) and inhibited *Keap1* overexpression ($P < 0.01$), while exerting no significant effect on *NQO1*. Furthermore, relative to the BPA group, taurine supplementation markedly enhanced the mRNA expression of core antioxidant enzymes *CAT* and *SOD1* ($P < 0.01$). Collectively, these results indicate that taurine alleviates BPA-induced placental oxidative stress through activating the Nrf2-Keap1 pathway, thereby enhancing the transcriptional levels of downstream antioxidant enzymes to restore placental redox homeostasis.

In addition to oxidative stress, BPA exposure triggered a robust pro-inflammatory response in the placenta (**Fig. 3-C**), which may synergistically damage placental function with oxidative stress. Compared with the CON group, BPA exposure significantly upregulated the mRNA expression of pro-inflammatory cytokines *IL-6* ($P < 0.01$), *IL-8* ($P < 0.01$), and *IL-1β* ($P < 0.001$). Relative to the BPA group, Taurine supplementation exerted a potent anti-inflammatory effect by significantly attenuating the BPA-induced overexpression of *IL-6*, *IL-8*, and *IL-1β*. Additionally, taurine slightly increased anti-inflammatory *IL-10* expression ($P = 0.071$), which may contribute to rebalancing the placental inflammatory microenvironment. Collectively, these regulatory effects of taurine mitigate BPA-induced placental damage.

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Maternal taurine supplementation on the expression levels of antioxidant, inflammatory cytokine, and bile acid synthesis-critical genes in liver tissues of BPA-exposed pregnant mice

As the core organ of metabolism and detoxification in the maternal body, the liver plays a pivotal role in regulating systemic redox balance, inflammatory responses, and bile acid synthesis. So, we analyzed the mRNA expression profiles of key genes involved in antioxidant defense, inflammatory regulation, and BA synthesis in the liver tissues of BPA-exposed pregnant mice (**Fig. 4**).

As shown in **Figure 4-A**, BPA exposure significantly disrupted the Nrf2-mediated antioxidant signaling pathway in the maternal liver. Compared with the CON group, BPA exposure significantly downregulated *Nrf2* mRNA expression in maternal liver ($P < 0.05$), while its negative regulator *Keap1* ($P < 0.05$) and downstream gene *NQO1* ($P < 0.001$) were significantly upregulated. Taurine supplementation effectively reversed these BPA-induced abnormalities, significantly elevated *Nrf2* mRNA expression, and inhibited *Keap1* overexpression ($P < 0.05$), with a trend toward decreased *NQO1* expression ($P = 0.055$). Additionally, versus the BPA group, taurine supplementation significantly elevated the mRNA expression of antioxidant enzymes *CAT* ($P < 0.05$) and *SOD1* ($P < 0.01$), and also significantly elevated the mRNA expression of *SOD2* ($P < 0.05$). Collectively, these results indicate that taurine antagonizes BPA-induced hepatic oxidative stress by activating Nrf2, suppressing Keap1, and thereby enhancing the transcriptional levels of downstream antioxidant enzymes, which Consistent with the oxidative stress observed in placental tissues.

Parallel to the placental inflammatory response, BPA exposure also triggered a prominent pro-inflammatory cascade in maternal liver (**Fig. 4-B**). compared with the CON group, BPA exposure significantly upregulated the mRNA expression of pro-inflammatory cytokines *IL-6* and *IL-8* ($P < 0.001$). Taurine supplementation exerted a potent anti-inflammatory effect by significantly suppressing the BPA-induced overexpression of *IL-6* and *IL-8* ($P < 0.01$). Furthermore, no significant differences in *IL-1β* or *TNF-α* mRNA expression were observed among all

experimental groups. Intriguingly, taurine also significantly upregulated the transcription of *PPARγ*, a nuclear receptor known to cross-talk with inflammatory and oxidative stress pathways.

As the core organ responsible for BA synthesis, the liver's BA metabolic homeostasis is critical for maintaining maternal nutrient absorption and detoxification functions. Regarding BA synthesis-critical genes (**Fig. 4-C**), BPA exposure had no significant impact on the mRNA expression of core genes in the FXR signaling pathway—including *FXR*, *CYP7A1*, and *CYP7B1* ($P > 0.05$), which suggested that BPA does not disrupt FXR-mediated BA synthesis in maternal liver (**Fig. 4-C**). However, relative to the BPA group, taurine supplementation significantly elevated the mRNA expression of *CYP27A1* ($P < 0.05$), which indicates that taurine specifically targets CYP27A1 to enhance BA synthesis.

Maternal taurine supplementation on the expression levels of antioxidant, inflammatory cytokine, and bile acid synthesis-critical genes in fetal liver tissues of BPA-exposed pregnant mice

Maternal BPA exposure is known to potentially impair fetal liver development. Thus, we detected the mRNA expression of key genes involved in antioxidant defense and inflammatory regulation in fetal liver tissues (**Fig. 5**). As shown in **Fig. 5-A**, BPA-induced maternal hepatic and placental oxidative stress were mirrored in the fetal liver. Compared with the CON group, the BPA group significantly downregulated the mRNA expression of *CAT* ($P < 0.05$) and *SOD2* ($P < 0.01$). Taurine supplementation significantly upregulated *SOD2* mRNA expression ($P < 0.05$), thereby restoring fetal hepatic antioxidant capacity. Similar results regarding inflammatory responses (**Fig. 5-B**), BPA exposure triggered pro-inflammatory activation in the fetal liver. Compared with the CON group, the BPA group significantly upregulated the mRNA expression of pro-inflammatory cytokines *IL-8* and *TNF-α* ($P < 0.05$), which promoted inflammatory reactions. Taurine supplementation exerted targeted anti-inflammatory effects: relative to the BPA group, which significantly suppressed the overexpression of *IL-8* and *TNF-α* ($P < 0.05$), thus mitigating BPA-induced fetal hepatic inflammation. Additionally, no significant

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differences in *IL-6* or *IL-1β* mRNA expression were observed among all groups ($P > 0.05$).

Maternal taurine supplementation on fecal microbiota in BPA-exposed pregnant mice

To investigate the effect of taurine supplementation on the gut microbiota of pregnant mice, we analyzed the composition, structure, and functional potential of the fecal microbiota in pregnant mice, as well as its correlation with maternal serum oxidative stress and inflammatory markers (**Fig. 6-7**). Alpha diversity analysis (**Fig. 6 A-B**) demonstrated that maternal BPA exposure significantly disrupted the diversity of the fecal gut microbiota. Compared with the BPA-exposed group, taurine supplementation notably increased the Shannon index ($P < 0.05$) and concurrently decreased the Simpson index ($P < 0.05$) of the fecal gut microbiota. Given that the Shannon index reflects the species richness and evenness of the microbial community, while the Simpson index characterizes community dominance, these results suggest that taurine can effectively reverse BPA-induced alpha diversity dysbiosis of the gut microbiota and contribute to maintaining the homeostasis of the intestinal microecosystem.

Furthermore, PCoA based on weighted UniFrac distance (**Fig. 6-C**) revealed distinct clustering patterns among the three groups. The microbial community structure of the BPA-exposed group was significantly separated from that of the CON group. In contrast, the community of the BPA+Tau group clustered closely with the CON group and exhibited a distinct structural difference from the BPA group (ANOSIM: R = 0.2217, $P < 0.05$). This result confirms that taurine supplementation remarkably reverses the overall community structure disorder of fecal gut microbiota caused by BPA treatment.

As shown in the Venn diagram analysis of ASVs (**Fig. S1A**), a total of 489 shared ASVs were identified among the three groups. Regarding the number of unique ASVs, the CON group (1574) had a higher count than the BPA group (1453), while the BPA+Tau group (1572) showed a count comparable to that of the CON

group, indicating that taurine is conducive to reversing the microbial community disorder induced by BPA.

Analysis of community composition at the phylum level revealed that the fecal microbiota of the three treatment groups was predominantly composed of five phyla, namely Bacteroidota, Firmicutes, Actinobacteriota, Verrucomicrobiota, and Proteobacteria (**Fig. S1-B**). Specifically, their relative abundances were as follows: in the CON group, Bacteroidota accounted for 60.54%, Firmicutes for 30.61%, Actinobacteriota for 1.42%, Verrucomicrobiota for 2.34%, and Proteobacteria for 1.74%; in the BPA group, the relative abundances were 39.08% (Bacteroidota), 47.95% (Firmicutes), 5.25% (Actinobacteriota), 2.84% (Verrucomicrobiota), and 2.83% (Proteobacteria); in the BPA+Tau group, they were 55.55% (Bacteroidota), 36.23% (Firmicutes), 2.11% (Actinobacteriota), 2.17% (Verrucomicrobiota), and 1.43% (Proteobacteria). Additionally, the Firmicutes/Bacteroidota ratio (F/B) ratio was 0.5, 1.22, and 0.65 in the CON, BPA, and BPA+Tau groups, respectively. This suggests BPA exposure significantly increased the F/B ratio, which was mitigated by taurine supplementation.

Further analysis of phylum-level differences (**Fig. S1C**) showed that compared with the CON group, the BPA group exhibited significant alterations in gut microbiota composition: the relative abundances of Firmicutes and Actinobacteria were significantly increased ($P < 0.05$), while the relative abundance of Bacteroidota was significantly decreased ($P < 0.05$). These results indicate that BPA exposure induces structural imbalance of gut microbiota at the phylum level. Notably, relative to the BPA group, the BPA+Tau group showed significantly reduced relative abundances of Actinobacteria and Firmicutes ($P < 0.05$) and a significantly increased relative abundance of Bacteroidota ($P < 0.05$).

At the genus level, the three treatment groups were dominated by three taxa with the highest relative abundances: norank_f__Muribaculaceae (Muribaculaceae family, unclassified genus), *Lactobacillus*, and *Dubosiella* (**Fig. 7-A**). Specifically, the relative abundance of norank_f__Muribaculaceae was 52.88% in the CON group, 35.80% in the BPA group, and 50.72% in the BPA+Tau group; *Lactobacillus*

accounted for 8.69% (CON), 12.73% (BPA), and 9.39% (BPA+Tau); *Dubosiella* exhibited relative abundances of 2.86% (CON), 15.60% (BPA), and 8.96% (BPA+Tau).

Genus-level differential analysis (**Fig. 7B-C**, **Fig. S1D**) revealed that compared with the CON group, the BPA group significantly upregulated the relative abundances of *Dubosiella*, *Bacillus*, and *Bifidobacterium* ($P < 0.05$), while significantly downregulating the abundances of *norank_f__Muribaculaceae*, *Alistipes*, *Rikenella*, and *Ruminococcus* ($P < 0.05$). In contrast, taurine supplementation alleviated the aforementioned abnormal changes in certain genera. Compared with the BPA group, the BPA+Tau group significantly increased the abundances of *norank_f__Muribaculaceae* and *Ruminococcus* that were previously suppressed by BPA ($P < 0.05$). Meanwhile, it significantly reduced the overexpressed abundance of *Bifidobacterium* in the BPA group ($P < 0.05$).

In addition, a correlation analysis was performed to explore the potential associations between serum oxidative stress, inflammatory markers, and fecal microbiota in BPA-exposed pregnant mice supplemented with taurine (**Fig. 7-D**). The results showed that SOD activity positively correlated with *norank_f__Muribaculaceae* abundance ($P < 0.05$) and negatively correlated with *Bifidobacterium* and norank_o__Clostridia_UCG-014 abundances; MDA positively correlated with unclassified_f__Atopobiaceae abundance and negatively correlated with *norank_f__Muribaculaceae* and *Alistipes* abundances; TNF-α positively correlated with Lachnospiraceae_NK4A136_group and *Helicobacter* abundances; IL-1β positively correlated with *Ileibacterium* and *Parasutterella* abundances; IL-6 positively correlated with *Dubosiella* and *Bifidobacterium* abundances and negatively correlated with *Alistipes* abundance.

Functional prediction analysis based on KEGG pathway abundance (**Fig. S1 E**) and enzyme abundance (**Fig. S1 F**) revealed that compared with the CON group, the BPA group significantly downregulated the predicted abundance of the bile acid: Na+ symporter (BASS family) gene pathway ($P < 0.05$) and significantly upregulated the functional abundance of 7α-hydroxysteroid dehydrogenase (7α-HSDH), an enzyme

involved in BA metabolism ($P < 0.05$). In contrast, taurine supplementation increased the abundance of the bile acid: Na+ symporter (BASS family) gene pathway, though this change did not reach statistical significance. Taurine supplementation significantly downregulated the functional abundance of 7α-HSDH, restoring it to the normal level observed in the CON group ($P < 0.05$).

Maternal taurine supplementation on the serum bile acid metabolism of BPA-exposed pregnant mice

Targeted ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was employed to comprehensively profile the serum BA metabolism in pregnant mice (**Fig. 8**). Principal component analysis (PCA) (**Fig. 8-A**) revealed distinct separation of BA metabolic profiles among the CON group, BPA-exposed group, and BPA+Tau group, indicating pronounced inter-group differences in BA homeostasis. Further analysis of serum BA relative abundance showed that all three groups shared a core composition dominated by five key BAs (**Fig. 8-B**): taurocholic acid (TCA), 23-nordeoxycholic acid (23_NDCA), tauro-β-muricholic acid (TβMCA), β-muricholic acid (βMCA), and cholic acid (CA). Differential BA analysis (**Fig. 8C-Q**) demonstrated that BPA exposure induced significant metabolic dysregulation relative to the CON group: specifically, the serum concentrations of conjugated BAs (including glycocholic acid (GCA), TCA, taurochenodeoxycholic acid (TCDCA), tauro-α-muricholic acid (TαMCA), TβMCA, tauro-γ-muricholic acid (TγMCA), and tauro-ω-muricholic acid (TωMCA)) as well as total TCBAs were markedly downregulated; in contrast, the concentration of apocholic acid (ACA) was significantly elevated ($P < 0.05$), while tauoursodeoxycholic acid (TUDCA) and deoxycholic acid (DCA) exhibited a non-significant downward trend ($0.05 < P < 0.10$). For the BPA+Tau group, significant reductions were observed in the concentrations of TCDCA, TUDCA, ACA, taurolithocholic acid (TLCA), glycodeoxycholic acid (GDCA), isolithocholic acid (ILCA), DLCA, TωMCA ($P < 0.05$), while TCBA, GCA, TαMCA, and TβMCA showed a non-significant decreasing trend ($0.05 < P < 0.10$). These results suggest that taurine can partially restore the BPA-induced reduction in these BA levels. Compared with the BPA group,

the BPA+Tau group effectively reversed the abnormal elevation of ACA. In addition, all BA constituents created an interconnected network characterized by dense positive correlations, notably with taurine-conjugated BAs aggregating into a separate cluster (**Fig. 8R**). This pattern suggests a highly synergistic nature of BA metabolism, where changes in individual components can trigger cascading effects on others, elucidating the mechanism behind the widespread metabolic dysregulation caused by BPA.

Correlation analysis between differential BAs, oxidative stress markers (MDA, T-AOC, SOD), and inflammatory cytokines (IL-6, IL-1β, TNF-α) identified several significant associations (**Fig. 8S**): glycochenodeoxycholic acid (GCDCA) was positively correlated with SOD ($P < 0.05$) and negatively correlated with MDA ($P < 0.05$); glycoursodeoxycholic acid (GUDCA) was negatively correlated with MDA ($P < 0.05$); TβMCA was positively correlated with SOD ($P < 0.05$); TγMCA was negatively correlated with IL-6 ($P < 0.05$); ILCA was positively correlated with TNF-α ($P < 0.01$); and TωMCA was negatively correlated with both IL-6 ($P < 0.01$) and MDA ($P < 0.05$), while positively correlated with SOD ($P < 0.05$).

Discussion

Bisphenol A, a ubiquitous environmental endocrine disruptor, can perturb the physiological homeostasis of the maternal-fetal unit during the critical developmental sensitive window of pregnancy, triggering a variety of adverse pregnancy outcomes and posing a significant threat to maternal reproductive health and fetal growth and development. Fetal weight at GD18.5 and total litter size are key indicators for evaluating maternal reproductive performance and fetal developmental potential. Consistent with previous studies reporting adverse effects of maternal BPA exposure during pregnancy on both dams and fetuses [9, 10], our findings demonstrated that maternal BPA exposure during gestation significantly reduced fetal weight at GD18.5 and total litter size. Taurine supplementation effectively reversed these BPA-induced adverse phenotypes, which highlights the critical role of taurine in antagonizing BPA-induced maternal-fetal toxicity and protecting maternal-fetal health. Herein, we systematically explore the potential protective mechanisms of taurine by integrating

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the main findings of the present study.

Oxidative stress and aberrant inflammatory responses are well recognized as key mediators of BPA-induced multi-organ toxicity, and their synergistic effects constitute an important pathological mechanism triggering tissue damage and adverse outcomes. Accumulating evidence has indicated that prenatal BPA exposure elicits maternal inflammatory responses, exacerbates oxidative stress, and impairs antioxidant capacity [35, 36]. Disruption of redox homeostasis and the occurrence of aberrant inflammatory responses in maternal and fetal tissues are closely associated with the pathogenesis of adverse pregnancy outcomes. Previous studies have reported that low-dose BPA can induce liver damage in pregnant mice and their offspring through the synergistic effects of oxidative stress and inflammatory responses, including downregulating the activity of hepatic antioxidant enzymes and upregulating the expression of the proinflammatory cytokine *IL-1β* as well as the proapoptotic factors AIF and Bax [37]. Consistent with these findings, analogous results were observed in our study: gestational BPA exposure significantly disrupted the redox balance and promoted inflammatory responses in maternal serum and placental tissues. Specifically, the activity of SOD, a key antioxidant enzyme, was markedly decreased in serum and placental tissues, the level of MDA, a lipid peroxidation product, was significantly elevated in serum, and the level of the proinflammatory cytokine *IL-6* was also notably increased in both serum and placental tissues. In contrast, taurine supplementation effectively reversed these BPA-induced abnormalities by significantly upregulating SOD activity in serum and placenta to enhance antioxidant defense capacity, downregulating serum MDA levels to alleviate oxidative damage, and simultaneously reducing the levels of the proinflammatory cytokines *IL-6*, *IL-1β* and *TNF-α* in serum. These results suggested that taurine can break the "oxidative stress-inflammation" vicious cycle via inhibiting oxidative stress and alleviating aberrant inflammatory responses.

To further elucidate the molecular mechanisms underlying taurine-mediated antagonism of oxidative stress and attenuation of inflammatory responses, the present study focused on analyses of the core regulatory Nrf2-Keap1 pathway and the

modulation of proinflammatory cytokines. The Nrf2 signaling pathway serves as the central cellular pathway for regulating oxidative stress and plays a pivotal role in maintaining redox homeostasis in the organism [38]. Under physiological conditions, Nrf2 forms an inactive complex with Keap1 in the cytoplasm; upon exposure to oxidative stress stimuli, the Nrf2-Keap1 complex dissociates, and free Nrf2 translocates into the nucleus, where it binds to antioxidant response elements (AREs) to activate the transcriptional expression of various downstream antioxidant enzyme genes. This process enhances the organism's antioxidant capacity, thereby scavenging excessive reactive oxygen species (ROS) and restoring redox homeostasis [39, 40]. Accumulating evidence has confirmed that BPA exposure induces oxidative stress damage in multiple tissues by inhibiting the activation of the Nrf2-Keap1 pathway and downregulating the expression of antioxidant genes [37], whereas taurine exerts antioxidant protective effects by activating the Nrf2-Keap1 pathway [16]. As a critical interface for material exchange between the mother and fetus, the placenta's redox and inflammatory homeostasis, along with its normal physiological function, are essential for sustaining normal fetal development. In this study, gestational BPA exposure significantly inhibited the mRNA expression of Nrf2 in placental tissue, while markedly upregulating the expression of its negative regulator Keap1 and the downstream target gene *NQO1*, and significantly downregulating the transcriptional levels of key downstream antioxidant enzymes (*CAT*, *SOD1*). These changes led to a decline in placental antioxidant capacity and exacerbated oxidative stress damage. In contrast, taurine supplementation significantly upregulated the mRNA expression of *Nrf2* in placental tissue, suppressed the overexpression of *Keap1,* and simultaneously enhanced the transcriptional levels of downstream antioxidant enzymes (*CAT*, *SOD1*, *SOD2*). These results demonstrate that taurine enhances the antioxidant defense capacity of placental tissue by activating the Nrf2-Keap1 signaling pathway and upregulating the expression of downstream antioxidant genes, thereby effectively alleviating BPA-induced placental oxidative stress damage—consistent with previous findings that taurine exerts antioxidant protection via modulation of the Nrf2-Keap1 pathway [41, 42]. Inflammatory responses and oxidative stress often act synergistically:

BPA-induced placental oxidative stress can further activate inflammatory signaling pathways, and aberrant inflammatory responses can in turn exacerbate oxidative stress damage. Together, these two processes compound placental dysfunction. The present study also found that BPA exposure induced a robust proinflammatory response in placental tissue, significantly upregulating the mRNA expression of the proinflammatory cytokines *IL-6*, *IL-8*, and *IL-1β* in placental tissue. In contrast, taurine supplementation significantly reduced the overexpression of these proinflammatory cytokines and exhibited a trend toward upregulating the expression of the anti-inflammatory cytokine *IL-10*. These findings indicate that taurine rebalances the placental inflammatory microenvironment by inhibiting proinflammatory factor expression and promoting anti-inflammatory factor secretion, thereby alleviating inflammation-mediated placental damage and exerting a synergistic effect with its antioxidant properties.

BPA-induced placental oxidative stress and inflammatory responses can further impair placental nutrient transport function, a pathological process closely associated with the downregulated expression of key placental functional genes. Syncytin B (SynB) is a critical syncytin involved in the formation of the trophoblast layer at the maternal-fetal interface of the mouse placenta and plays an essential role in fetal material exchange [43]. Previous studies have reported that SynB deficiency leads to placental dysfunction, which in turn causes embryonic growth retardation and reduced neonatal survival rates [44]. Insulin-like growth factor 2 (IGF2) is a key regulator of fetal nutrient supply and exerts a vital role in the normal functional development of the mouse placenta; it maintains placental nutrient transport function by regulating the proliferation and differentiation of placental trophoblast cells [45]. Moreover, IGF2 deficiency in the placenta impairs the maternal insulin resistance response, leading to fetal growth restriction and further affecting postnatal metabolic function in offspring [46]. Our findings demonstrated that BPA exposure significantly downregulated the mRNA expression of S*ynB* and *IGF2* in placental tissue, indicating that BPA impairs placental nutrient transport function by inhibiting the expression of functional genes related to placental nutrient transport, thereby resulting in impaired fetal growth and

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development and reduced birth weight. In contrast, taurine supplementation effectively reversed these abnormalities and markedly upregulated the mRNA expression of *SynB* and *IGF2*. These results suggest that taurine not only alleviates placental damage by inhibiting oxidative stress and rebalancing the inflammatory microenvironment, but also ensures material exchange and nutrient supply between the mother and fetus by restoring the expression of key functional genes associated with placental nutrient transport, thus providing critical support for normal fetal growth and development.

The liver, as the body's core detoxification organ and metabolic hub, is critical for maintaining systemic metabolic homeostasis and eliminating exogenous toxicants. The normal functioning of hepatic function during pregnancy not only safeguards maternal health per se but also exerts a pivotal role in fetal metabolic development. Accumulating evidence has indicated that direct BPA exposure or indirect exposure following maternal ingestion can reduce *Nrf2* expression in the liver of male offspring rats, thereby exacerbating hepatic oxidative stress and inducing liver injury [47]. The findings of the present study further confirm that BPA exposure similarly disrupts the oxidative stress balance and aggravates inflammatory responses in the maternal and fetal livers. The antioxidant and anti-inflammatory regulatory effects of taurine in the placenta are consistent with those observed in the maternal and fetal livers: excessive hepatic oxidative stress induced by BPA can inhibit Nrf2-mediated antioxidant responses, whereas taurine alleviates BPA-induced hepatic oxidative damage by activating the Nrf2 signaling pathway and upregulating the expression of antioxidant genes.

Consistent with previous findings [37], the present study confirmed that BPA-induced liver injury is mediated by the synergistic effects of oxidative stress and inflammatory responses. Furthermore, our results further demonstrated that taurine supplementation can significantly activate the expression of key factors in the Nrf2 signaling pathway and simultaneously inhibit the overexpression of proinflammatory factors in both maternal and fetal livers, exerting a systemic hepatoprotective effect. In the fetal liver, taurine specifically suppressed BPA-induced overexpression of *IL-8*

and *TNF-α* and upregulated the expression level of *SOD2*, effectively alleviating hepatic inflammation and oxidative damage to ensure the normal development of the fetal liver. In the maternal liver, taurine not only activated the Nrf2-Keap1 pathway and inhibited the expression of the proinflammatory factors *IL-6* and *IL-1β*, but also significantly upregulated the transcriptional level of peroxisome proliferator-activated receptor γ (*PPARγ*). As a nuclear receptor, PPARγ mediates the bidirectional regulation of inflammatory responses and redox homeostasis either by directly binding to the promoters of target genes or through protein-protein interactions with signaling molecules such as NF-κB and Nrf2 [48, 49], which contributes to the coordinated regulation of inflammatory responses and the maintenance of homeostasis in maternal hepatic detoxification and metabolic functions. These results are consistent with previous reports that taurine alleviates liver injury induced by various toxic substances via its antioxidant and anti-inflammatory properties [50].

Furthermore, as the primary organ for bile acid synthesis, the liver's BA metabolic homeostasis directly modulates maternal nutrient absorption and detoxification functions. Our study found that taurine supplementation significantly upregulated the mRNA expression of *CYP27A1*; as a key rate-limiting enzyme in BA synthesis, the upregulated expression of *CYP27A1* enhances BA synthetic capacity, which contributes to the maintenance of BA metabolic homeostasis. These results further confirm that taurine preserves BA metabolic homeostasis by activating the Nrf2-Keap1 signaling pathway and rebalancing the inflammatory microenvironment, thereby exerting a systemic protective effect on maternal and fetal livers. In turn, this maintains the metabolic homeostasis of the maternal-fetal unit and provides a favorable internal environment for fetal growth and development.

The gut microbiota, as a core component of the body's microecological system, directly regulates nutrient metabolism and immune homeostasis between the mother and fetus via the gut-placental axis, and serves as a critical microecological foundation for ensuring normal fetal development [51]. Dysbiosis of the maternal gut microbiota induces fetal metabolic abnormalities and immune developmental disorders, ultimately increasing the risk of adverse pregnancy outcomes such as fetal

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growth restriction [52, 53]. The findings of the present study demonstrated that BPA exposure significantly reduced the α-diversity index of the maternal murine gut microbiota, altered the microbial community structure, and markedly increased the Firmicutes/Bacteroidetes (F/B) ratio, severely disrupting the homeostasis of the maternal gut microbiota. These results are consistent with previous reports that BPA exposure reduces gut microbial diversity in animals, and our study is the first to confirm the association of this effect with hormonal regulatory network dysregulation in a pregnancy model. Taurine supplementation significantly reversed the aforementioned abnormal indices, indicating its ability to effectively restore microbial diversity and maintain gut microecological homeostasis during the unique physiological stage of pregnancy.

Further analysis revealed that taurine supplementation alleviates BPA-induced specific dysbiosis of *norank_f__Muribaculaceae*, *Ruminococcus* and *Bifidobacterium*. As a core beneficial bacterial family within the phylum Bacteroidetes, Muribaculaceae produces short-chain fatty acids (SCFAs) via the fermentation of dietary fiber and endogenous mucin glycans [54], and also participates in intestinal barrier maintenance and mucin metabolism regulation [55], serving as a key biomarker of intestinal homeostasis. In the present study, BPA exposure significantly downregulated the abundance of Muribaculaceae, which may lead to a reduction in SCFA synthesis capacity and impairment of intestinal barrier integrity, thereby exacerbating inflammatory responses—an observation consistent with the decreased abundance of Muribaculaceae reported in models of inflammatory bowel disease (IBD) and type 2 diabetes (T2D)-associated metabolic disorders [56, 57]. In contrast, taurine supplementation markedly upregulated the abundance of *norank_f__Muribaculaceae*; by restoring SCFA synthetic function and intestinal barrier maintenance capacity, taurine inhibits aberrant inflammatory responses, enhances intestinal barrier integrity, and thereby exerts a protective effect. Concomitantly, the restored abundance of *norank_f__Muribaculaceae* promotes the renewal and thickening of the intestinal mucus layer, which further consolidates the intestinal physical barrier and creates a favorable microenvironment for the

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colonization and proliferation of other beneficial bacteria.

Furthermore, taurine reverses BPA-induced over-enrichment of *Bifidobacterium* and inhibition of *Ruminococcus*. As a classic probiotic genus, *Bifidobacterium* is significantly upregulated upon BPA exposure, and this response represents a compensatory proliferation following microbial dysbiosis rather than a beneficial adaptive reaction. Such excessive proliferation disrupts the competitive balance of the gut microbiota and consequently exacerbates microecological disorder, a phenomenon that may be associated with microbial metabolic abnormalities induced by BPA exposure. In contrast, taurine supplementation effectively suppresses the aberrant proliferation of *Bifidobacterium*, restoring its abundance to physiological levels and thus facilitating the re-establishment of microbial homeostasis. *Ruminococcus*, a core functional genus within the phylum Firmicutes that modulates BA metabolism, maintains host BA metabolic homeostasis by mediating BA transformation and the enterohepatic circulation. *Ruminococcus torques*, a strain of this genus closely linked to intestinal inflammation, elicits insufficient synthesis of secondary BAs when its abundance is imbalanced; this deficiency disrupts intestinal immune homeostasis and promotes the initiation and progression of inflammatory responses [58]. This study further confirms that the reduced abundance of *Ruminococcus* induced by BPA exposure is not merely a disruption of microbial community structure, but a core trigger for the imbalance of the microbiota-BA metabolism axis. Functional prediction analysis revealed that BPA exposure concurrently elicits bidirectional dysregulation of BA metabolism-related pathways, significantly downregulating the gene expression of the BA sodium symporter (BASS) family and aberrantly upregulating the functional activity of 7α-hydroxysteroid dehydrogenase (7α-HSDH). The BASS family proteins mediate the intestinal absorption and transport of BAs; the inhibition of their pathway expression directly impairs the integrity of the BA enterohepatic circulation and disrupts the physiological balance of the intestinal BA pool. As a key rate-limiting enzyme catalyzing the conversion of primary BAs to secondary BAs, the non-physiological elevation of 7α-HSDH activity leads to an imbalance in the conversion ratio of secondary BAs, driving the excessive

accumulation of toxic BAs such as lithocholic acid and further exacerbating inflammatory responses. In contrast, taurine can target the restoration of *Ruminococcus* abundance, significantly reduce the abnormally elevated 7α-HSDH activity in the intestine, further repair the microbiota-mediated BA metabolic function, and reverse BPA-induced metabolic disorders.

Targeted metabolomic analysis further validated the dysregulation of the microbiota-BA regulatory axis and the reparative effects of taurine on this pathological process. BPA exposure significantly downregulated the concentrations of conjugated BAs (including GCA, TCA and TCDCA) and total tauro-conjugated bile acids (Total-TCBA), while concomitantly inducing an abnormal elevation in apocholic acid (ACA) levels. This metabolic profile was consistent with the functional prediction results of reduced *Ruminococcus* abundance, upregulated 7α-HSDH activity and downregulated BASS family expression. The decreased serum levels of conjugated BAs resulted from the combined effects of impaired synthesis and defective transport. More importantly, the synthesis of Total-TCBA requires taurine as an essential precursor, and maternal metabolic disorders induced by BPA exposure may indirectly inhibit the de novo synthesis and utilization of endogenous taurine, which further exacerbates the insufficient production of Total-TCBA. The abnormal elevation of ACA may further aggravate oxidative stress and inflammatory damage in maternal and fetal tissues by activating proinflammatory signaling pathways. Additionally, our correlation analysis further confirmed that aberrant alterations in BA components can amplify BPA-induced toxicity through oxidative stress and inflammatory pathways. This finding indicates that BA metabolic dysregulation can directly disrupt maternal-fetal immune homeostasis, trigger oxidative stress damage, and exacerbate local and systemic inflammatory responses. Notably, taurine exerts its BA-modulating effects through a dual mechanism: on the one hand, exogenous taurine supplementation provides an abundant precursor for the synthesis of Total-TCBA and simultaneously targets the regulation of gut microbiota and metabolic pathways, which synergistically mitigates the decline in Total-TCBAs and exerts a positive effect on elevating the concentrations of conjugated BAs and

Total-TCBAs; on the other hand, it significantly suppresses the accumulation of BAs such as ACA and LCA, and blocks the proinflammatory and oxidative stress pathways mediated by these BAs. Although some indicators have not been fully restored to the levels of the control group, taurine has significantly ameliorated BPA-induced BA metabolic dysregulation, thereby providing crucial metabolic support for its antagonism of BPA-induced maternal-fetal toxicity. Though taurine is a key precursor of TCBA that promotes BA synthesis, total TCBA levels were not significantly restored in the BPA+Tau group, likely due to systemic hepatic BA metabolic disruption (impaired synthetic enzymes, transport and enterohepatic circulation) induced by BPA exposure, which taurine only partially alleviates. Notably, taurine still significantly regulated specific TCBA subtypes and corrected BPA-induced BA profile imbalance, the core of its protective effect against maternal-fetal toxicity. The marginal increasing trend of total TCBA in the BPA+Tau group ($0.05 \leq P < 0.10$) also suggests that a larger sample size may verify the restorative effect of taurine on total TCBA levels in future studies.

In summary, taurine potently reverses the BPA-induced imbalance of the microbiota-BA-oxidative stress/inflammation axis, effectively antagonizes BPA-elicited maternal-fetal damage, and preserves maternal-fetal microecological and metabolic homeostasis (**Fig. 9**).

Conclusion

This study confirms that taurine can effectively alleviate BPA-induced maternal-fetal oxidative stress by targeting the “gut microbiota-BA-oxidative stress/inflammation” axis, protect liver and placental functions, and improve intestinal microbiota imbalance and BA metabolism disorders. Through multi-dimensional synergistic regulation, taurine comprehensively ensures the nutritional absorption and metabolic development of the fetus, and ultimately reverses the fetal weight loss and adverse pregnancy outcomes caused by BPA. As a safe and non-toxic conditionally essential amino acid, taurine is expected to become a potential candidate for preventing and intervening in maternal-fetal toxicity caused by BPA exposure. This study not only

clarifies the intrinsic mechanism of taurine antagonizing BPA-induced maternal-fetal toxicity, but also provides new ideas and theoretical references for maintaining maternal-fetal health during pregnancy and promoting normal fetal development.

Author contributions

Conceptualization, Yu Pi. and Xilong Li. and Chenggang Yin.; methodology, Yu Pi. and Xilong Li. and Wenjuan Sun.; validation, Yu Pi. and Xilong Li. and Yanpin Li.; formal analysis, Chenggang Yin. and Lei Xu. and Yuyang Fan.; investigation, Chenggang Yin. and Lei Xu. and Jiaqi Yang.; data curation, Chenggang Yin. and Lei Xu.; writing—original draft preparation, Lei Xu.; writing—review and editing, Yu Pi. and Xilong Li. and Yanpin Li. and Dongxu Ming.; supervision, Yu Pi. and Xilong Li.; project administration, Yu Pi. and Yanpin Li.; funding acquisition, Yu Pi. and Xilong Li. All authors have read and agreed to the published version of the manuscript.

Data availability statement

All data used for this study appear in the illustrated figures, and the raw data will promptly be made available upon request.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

1. S. Almeida, A. Raposo, M. Almeida-González and C. Carrascosa, Bisphenol A: Food Exposure and Impact on Human Health, 2018, **17**, 1503-1517.
2. J. R. Rochester, Bisphenol A and human health: A review of the literature, *Reproductive Toxicology*, 2013, **42**, 132-155.
3. G. Schönfelder, W. Wittfoht, H. Hopp, C. E. Talsness, M. Paul and I. Chahoud, Parent bisphenol A accumulation in the human maternal-fetal-placental unit, *Environmental health perspectives*, 2002, **110**, A703-707.
4. M. S. Nahar, C. Liao, K. Kannan, D. C. J. J. o. b. Dolinoy and m. toxicology, Fetal liver bisphenol A concentrations and biotransformation gene expression reveal variable exposure and altered capacity for metabolism in humans, 2013, **27**, 116-123.
5. S. A. Krieg, L. K. Shahine and R. B. Lathi, Environmental exposure to endocrine-disrupting chemicals and miscarriage, *Fertility and sterility*, 2016, **106**, 941-947.
6. C. Philippat, M. Mortamais, C. Chevrier, C. Petit, A. M. Calafat, X. Ye, M. J. Silva, C. Brambilla, I. Pin, M. A. Charles, S. Cordier and R. Slama, Exposure to phthalates and phenols during pregnancy and offspring size at birth, *Environmental health perspectives*, 2012, **120**, 464-470.
7. F. Fischer, T. Kretschmer, P. Seifert, J. Howanski, E. Krieger, J. Rödiger, B. Fink, Z. Yin, M. Bauer, M. L. Zenclussen, N. Meyer, A. Schumacher and A. C. Zenclussen, Single and combined exposures to bisphenol A and benzophenone-3 during early mouse pregnancy have differential effects on fetal and placental development, *The Science of the total environment*, 2024, **922**, 171386.
8. D. Yan, Y. Jiao, H. Yan, T. Liu, H. Yan and J. Yuan, Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: a systematic review and meta-analysis, *Environmental health : a global access science source*, 2022, **21**, 53.
9. O. Takahashi and S. J. E. h. p. Oishi, Disposition of orally administered 2, 2-Bis (4-hydroxyphenyl) propane (Bisphenol A) in pregnant rats and the placental transfer to fetuses, 2000, **108**, 931.
10. J. E. Müller, N. Meyer, C. G. Santamaria, A. Schumacher, E. H. Luque, M. L. Zenclussen, H. A. Rodriguez and A. C. Zenclussen, Bisphenol A exposure during early pregnancy impairs uterine spiral artery remodeling and provokes intrauterine growth restriction in mice, *Scientific Reports*, 2018, **8**, 9196.
11. H. Kabuto, M. Amakawa and T. Shishibori, Exposure to bisphenol A during embryonic/fetal life and infancy increases oxidative injury and causes underdevelopment of the brain and testis in mice, *Life Sciences*, 2004, **74**, 2931-2940.
12. A. B. Javurek, W. G. Spollen, S. A. Johnson, N. J. Bivens, K. H. Bromert, S. A. Givan and C. S. Rosenfeld, Effects of exposure to bisphenol A and ethinyl estradiol on the gut microbiota of parents and their offspring in a rodent model, *Gut microbes*, 2016, **7**, 471-485.
13. H. Zhang, X. Zha, B. Zhang, Y. Zheng, M. Elsabagh, H. Wang and M. Wang, Gut microbiota contributes to bisphenol A-induced maternal intestinal and placental apoptosis, oxidative stress, and fetal growth restriction in pregnant ewe model by regulating gut-placental axis, *Microbiome*, 2024, **12**, 28.
14. C. Wen, F. Li, L. Zhang, Y. Duan, Q. Guo, W. Wang, S. He, J. Li and Y. Yin, Taurine is Involved in Energy Metabolism in Muscles, Adipose Tissue, and the Liver, *Molecular*

View Article Online
DOI: 10.1039/D6FO00521G

nutrition & food research, 2019, **63**, e1800536.

15. B. N. Ames, Prolonging healthy aging: Longevity vitamins and proteins, *Proceedings of the National Academy of Sciences of the United States of America*, 2018, **115**, 10836-10844.
16. X. Ji, Z. Tang, F. Zhang, F. Zhou, Y. Wu and D. Wu, Dietary taurine supplementation counteracts deoxynivalenol-induced liver injury via alleviating oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation in piglets, *Ecotoxicology and Environmental Safety*, 2023, **253**, 114705.
17. D. D. Zhao, J. J. Wang, J. J. Fan, Y. Fu, Y. D. Ma, C. Li, G. F. Wu, M. Liu, S. M. Lin and J. M. Hu, Taurine Prevents LPS-Induced Liver Injury in Weaned Piglets, *Advances in experimental medicine and biology*, 2022, **1370**, 497-505.
18. S. Tochitani, Functions of Maternally-Derived Taurine in Fetal and Neonatal Brain Development, *Advances in experimental medicine and biology*, 2017, **975 Pt 1**, 17-25.
19. J. A. Sturman, D. K. Rassin and G. E. Gaull, Taurine in developing rat brain: maternal-fetal transfer of [35 S] taurine and its fate in the neonate, *Journal of neurochemistry*, 1977, **28**, 31-39.
20. M. M. Ommati, H. Rezaei, R.-M. Socorro, W. Tian, J. Zhao, A. Rouhani, S. Sabouri, F. Ghaderi, A. M. Niknahad, A. Najibi, S. Mazloomi, M. Safipour, Z. Honarpishefard, H.-W. Wang, H. Niknahad and R. Heidari, Pre/postnatal taurine supplementation improves neurodevelopment and brain function in mice offspring: A persistent developmental study from puberty to maturity, *Life Sciences*, 2024, **336**, 122284.
21. M. Li, C. M. Reynolds, D. M. Sloboda, C. Gray and M. H. Vickers, Maternal taurine supplementation attenuates maternal fructose-induced metabolic and inflammatory dysregulation and partially reverses adverse metabolic programming in offspring, *The Journal of nutritional biochemistry*, 2015, **26**, 267-276.
22. J. J. P. o. t. S. f. E. B. Sjövall and Medicine, Dietary glycine and taurine on bile acid conjugation in man. Bile acids and steroids 75, 1959, **100**, 676-678.
23. W. G. J. G. Hardison, Hepatic taurine concentration and dietary taurine as regulators of bile acid conjugation with taurine, 1978, **75**, 71-75.
24. K. Duszka, Versatile Triad Alliance: Bile Acid, Taurine and Microbiota, 2022, **11**, 2337.
25. J.-Y. Yang, T.-T. Zhang, Z.-L. Yu, C.-C. Wang, Y.-C. Zhao, Y.-M. Wang, C.-H. J. J. o. A. Xue and F. Chemistry, Taurine alleviates trimethylamine N-oxide-induced atherosclerosis by regulating bile acid metabolism in ApoE–/–mice, 2022, **70**, 5738-5747.
26. J. Münzker, N. Haase, A. Till, R. Sucher, S.-B. Haange, L. Nemetschke, T. Gnad, E. Jäger, J. Chen, S. J. Riede, R. Chakaroun, L. Massier, P. Kovacs, M. Ost, U. Rolle-Kampczyk, N. Jehmlich, J. Weiner, J. T. Heiker, N. Klöting, G. Seeger, M. Morawski, V. Keitel, A. Pfeifer, M. von Bergen, J. Heeren, U. Krügel and W. K. Fenske, Functional changes of the gastric bypass microbiota reactivate thermogenic adipose tissue and systemic glucose control via intestinal FXR-TGR5 crosstalk in diet-induced obesity, *Microbiome*, 2022, **10**, 96.
27. H. Wang, Y. Guo, W. Han, M. Liang, X. Xiao, X. Jiang, W. J. J. o. a. Yu and f. chemistry, Tauroursodeoxycholic acid improves nonalcoholic fatty liver disease by regulating gut microbiota and bile acid metabolism, 2024, **72**, 20194-20210.
28. N. A. Mohamed, M. T. Ithmil, A. I. Elkady and S. Abdel Salam, Tauroursodeoxycholic Acid (TUDCA) Relieves Streptozotocin (STZ)-Induced Diabetic Rat Model via Modulation of Lipotoxicity, Oxidative Stress, Inflammation, and Apoptosis, 2024, **25**, 6922.

View Article Online
DOI: 10.1039/D6FO00521G

29. P. Singh, K. Gollapalli, S. Mangiola, D. Schranner, M. A. Yusuf, M. Chamoli, S. L. Shi, B. Lopes Bastos, T. Nair and A. Riermeier, Taurine deficiency as a driver of aging, *Science*, 2023, **380**, eabn9257.

30. Y. Sun, M. Sha, Y. Qin, J. Xiao, W. Li, S. Li and S. Chen, Bisphenol A induces placental ferroptosis and fetal growth restriction via the YAP/TAZ-ferritinophagy axis, *Free Radical Bio Med*, 2024, **213**, 524-540.

31. M. Janot, M. L. Cortes-Dubly, S. Rodriguez and U. Huynh-Do, Bilateral uterine vessel ligation as a model of intrauterine growth restriction in mice, *Reproductive biology and endocrinology : RB&E*, 2014, **12**, 62.

32. Y. Pi, Y. J. Wu, X. Y. Zhang, D. D. Lu, D. D. Han, J. C. Zhao, X. J. Zheng, S. Y. Zhang, H. Ye, S. Lian, Y. Bai, Z. Y. Wang, S. Y. Tao, D. J. Ni, X. H. Zou, W. Jia, G. L. Zhang, D. F. Li and J. J. Wang, Gut microbiota-derived ursodeoxycholic acid alleviates low birth weight-induced colonic inflammation by enhancing M2 macrophage polarization, *Microbiome*, 2023, **11**.

33. C. Yin, L. Xu, Z. Wei, Y. Zhao, R. Bai, G. Gao, Y. Fan, Y. Li, W. Sun, X. Li and Y. Pi, Gut microbiota and bile acid profiles in purebred vs. crossbred sows: links to oxidative stress and inflammation in late gestation, *Microbial genomics*, 2025, **11**.

34. Y. Pi, X. Y. Zhang, Y. J. Wu, Z. Y. Wang, Y. Bai, X. Y. Liu, D. D. Han, J. B. Zhao, I. Tobin, J. C. Zhao, G. L. Zhang and J. J. Wang, Alginate Alleviates Dextran Sulfate Sodium-Induced Colitis by Promoting Bifidobacterium animalis and Intestinal Hyodeoxycholic Acid Synthesis in Mice, *Microbiology spectrum*, 2022, **10**.

35. Y. F. Huang, P. W. Wang, L. W. Huang, C. H. Lai, W. Yang, K. Y. Wu, C. A. Lu, H. C. Chen and M. L. Chen, Prenatal Nonylphenol and Bisphenol A Exposures and Inflammation Are Determinants of Oxidative/Nitrative Stress: A Taiwanese Cohort Study, *Environmental science & technology*, 2017, **51**, 6422-6429.

36. K. K. Ferguson, D. E. Cantonwine, T. F. McElrath, B. Mukherjee and J. D. Meeker, Repeated measures analysis of associations between urinary bisphenol-A concentrations and biomarkers of inflammation and oxidative stress in pregnancy, *Reproductive toxicology (Elmsford, N.Y.)*, 2016, **66**, 93-98.

37. B. Linillos-Pradillo, L. Rancan, S. D. Paredes, M. Schlumpf, W. Lichtensteiger, E. Vara and J. Á. F. Tresguerres, Low Dose of BPA Induces Liver Injury through Oxidative Stress, Inflammation and Apoptosis in Long–Evans Lactating Rats and Its Perinatal Effect on Female PND6 Offspring, 2023, **24**, 4585.

38. T. Suzuki, J. Takahashi and M. Yamamoto, Molecular Basis of the KEAP1-NRF2 Signaling Pathway, *Molecules and cells*, 2023, **46**, 133-141.

39. S. Adinolfi, T. Patinen, A. Jawahar Deen, S. Pitkänen, J. Härkönen, E. Kansanen, J. Küblbeck and A. L. Levonen, The KEAP1-NRF2 pathway: Targets for therapy and role in cancer, *Redox biology*, 2023, **63**, 102726.

40. M. Yamamoto, T. W. Kensler and H. Motohashi, The KEAP1-NRF2 System: a Thiol-Based Sensor-Effector Apparatus for Maintaining Redox Homeostasis, *Physiological reviews*, 2018, **98**, 1169-1203.

41. G. Wu, J. San, H. Pang, Y. Du, W. Li, X. Zhou, X. Yang, J. Hu and J. Yang, Taurine attenuates AFB1-induced liver injury by alleviating oxidative stress and regulating mitochondria-mediated apoptosis, *Toxicon : official journal of the International Society on*

View Article Online
DOI: 10.1039/D6FO00521G

Toxinology, 2022, **215**, 17-27.

42. C. Chen, M. Qi, W. Zhang, F. Chen, Z. Sun, W. Sun, W. Tang, Z. Yang, X. Zhao and Z. Tang, Taurine alleviated paraquat-induced oxidative stress and gut-liver axis damage in weaned piglets by regulating the Nrf2/Keap1 and TLR4/NF-κB signaling pathways, *Journal of animal science and biotechnology*, 2025, **16**, 117.
43. G. Mousseau, N. Préault, S. Souquere, C. Bireau, P. Cassonnet, A. Bacquin, L. Beck, G. Pierron, Y. Jacob, A. Dupressoir and T. Heidmann, Sodium-dependent phosphate transporter PiT1/SLC20A1 as the receptor for the endogenous retroviral envelope syncytin-B involved in mouse placenta formation, *Journal of virology*, 2024, **98**, e0091524.
44. A. Dupressoir, C. Vernochet, F. Harper, J. Guégan, P. Dessen, G. Pierron and T. Heidmann, A pair of co-opted retroviral envelope syncytin genes is required for formation of the two-layered murine placental syncytiotrophoblast, *Proceedings of the National Academy of Sciences of the United States of America*, 2011, **108**, E1164-1173.
45. C. P. Sibley, P. M. Coan, A. C. Ferguson-Smith, W. Dean, J. Hughes, P. Smith, W. Reik, G. J. Burton, A. L. Fowden and M. Constância, Placental-specific insulin-like growth factor 2 (Igf2) regulates the diffusional exchange characteristics of the mouse placenta, *Proceedings of the National Academy of Sciences of the United States of America*, 2004, **101**, 8204-8208.
46. J. Lopez-Tello, H. E. J. Yong, I. Sandovici, G. K. C. Dowsett, E. R. Christoforou, E. Salazar-Petres, R. Boyland, T. Napso, G. S. H. Yeo, B. Y. H. Lam, M. Constancia and A. N. Sferruzzi-Perri, Fetal manipulation of maternal metabolism is a critical function of the imprinted Igf2 gene, *Cell metabolism*, 2023, **35**, 1195-1208.e1196.
47. J.-X. Liao, Y.-W. Chen, M.-K. Shih, Y.-L. Tain, Y.-T. Yeh, M.-H. Chiu, S. K. C. Chang and C.-Y. Hou, Resveratrol Butyrate Esters Inhibit BPA-Induced Liver Damage in Male Offspring Rats by Modulating Antioxidant Capacity and Gut Microbiota, 2021, **22**, 5273.
48. M. Fang, Q. Yu, J. Ou, J. Lou, J. Zhu and Z. Lin, The Neuroprotective Mechanisms of PPAR-γ: Inhibition of Microglia-Mediated Neuroinflammation and Oxidative Stress in a Neonatal Mouse Model of Hypoxic-Ischemic White Matter Injury, *CNS neuroscience & therapeutics*, 2024, **30**, e70081.
49. W. Cai, T. Yang, H. Liu, L. Han, K. Zhang, X. Hu, X. Zhang, K. J. Yin, Y. Gao, M. V. L. Bennett, R. K. Leak and J. Chen, Peroxisome proliferator-activated receptor γ (PPARγ): A master gatekeeper in CNS injury and repair, *Progress in neurobiology*, 2018, **163-164**, 27-58.
50. G. Ouyang, N. Wang, J. Tong, W. Sun, J. Yang and G. Wu, Alleviation of taurine on liver injury of type 2 diabetic rats by improving antioxidant and anti-inflammatory capacity, *Heliyon*, 2024, **10**, e28400.
51. D. Kelly, T. King and R. Aminov, Importance of microbial colonization of the gut in early life to the development of immunity, *Mutation research*, 2007, **622**, 58-69.
52. M. Levy, A. A. Kolodziejczyk, C. A. Thaiss and E. Elinav, Dysbiosis and the immune system, *Nature reviews. Immunology*, 2017, **17**, 219-232.
53. S. Giugliano, A. Gatti, M. Rusin, T. Schorn, S. Pimazzoni, M. Calanni-Pileri, V. Fraccascia, S. Carloni and M. Rescigno, Maternal gut microbiota influences immune activation at the maternal-fetal interface affecting pregnancy outcome, *Nature communications*, 2025, **16**, 4326.
54. C. Xu, J. Liu, J. Gao, X. Wu, C. Cui, H. Wei, R. Zheng and J. Peng, Combined Soluble Fiber-Mediated Intestinal Microbiota Improve Insulin Sensitivity of Obese Mice, *Nutrients*,

View Article Online
DOI: 10.1039/D6FO00521G

2020, **12**.

55. F. C. Pereira, K. Wasmund, I. Cobankovic, N. Jehmlich, C. W. Herbold, K. S. Lee, B. Sziranyi, C. Vesely, T. Decker, R. Stocker, B. Warth, M. von Bergen, M. Wagner and D. Berry, Rational design of a microbial consortium of mucosal sugar utilizers reduces Clostridiodes difficile colonization, *Nature communications*, 2020, **11**, 5104.

56. J. K. Volk, E. E. L. Nyström, S. van der Post, B. M. Abad, B. O. Schroeder, Å. Johansson, F. Svensson, S. Jäverfelt, M. E. V. Johansson, G. C. Hansson and G. M. H. Birchenough, The Nlrp6 inflammasome is not required for baseline colonic inner mucus layer formation or function, *The Journal of experimental medicine*, 2019, **216**, 2602-2618.

57. Y. Du, D. X. Li, D. Y. Lu, R. Zhang, X. X. Zheng, B. J. Xu, Y. L. Zhao, S. Ji, M. Z. Guo, L. Wang and D. Q. Tang, Morus alba L. water extract changes gut microbiota and fecal metabolome in mice induced by high-fat and high-sucrose diet plus low-dose streptozotocin, *Phytotherapy research : PTR*, 2022, **36**, 1241-1257.

58. Y. Lou, Y. Lv, X. Wang, Y. Luo, J. Lou, Y. Yu, W. Gu, J. Yu, Y. Fang, H. Zhao, K. Peng, J. Chen and Y. Ni, Ruminococcus torques ameliorates the inflammation bowel disease and gut barrier dysfunction by modulating gut microbiota and bile acid metabolism, *Journal of translational medicine*, 2025, **23**, 1162.

Table 1. Maternal taurine supplementation on reproductive performance in pregnant mice exposed to bisphenol A (BPA)

Items	Groups			SEM	*P*-value
	CON	BPA	BPA+Tau		
Initial BW (gestation day 0), g	20.27	20.27	20.27	0.224	1.000
BW (gestation day 18.5), g	33.96	32.01	33.55	0.640	0.092
Average placenta weight, g	0.10^{a}	0.08^{b}	0.09^{ab}	0.004	0.014
Average fetal weight, g	0.85^{a}	0.60^{b}	0.81^{a}	0.046	0.001
Total number of fetal	7.70^{a}	6.50^{b}	7.70^{a}	0.219	0.012
IUGR rate, %	20.79	28.05	19.56	2.726	0.098

Notes: Values are presented as mean ± standard error of the mean (SEM).

Within each row, values with different superscript lowercase letters (a, b) indicate a statistically significant difference at the level of $P < 0.05$, while values sharing the same superscript letter indicate no significant difference ($P \geq 0.05$). CON, control group; BPA, bisphenol A-exposed group; BPA+Tau, bisphenol A-exposed+ taurine; IUGR, intrauterine growth restriction; BW, body weight.

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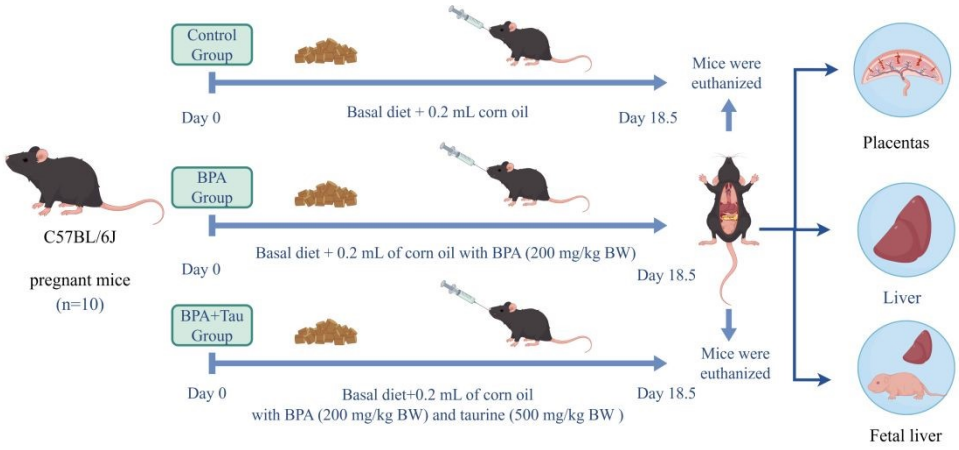

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1050 **Fig. 1.** Schematic diagram of the experimental process.

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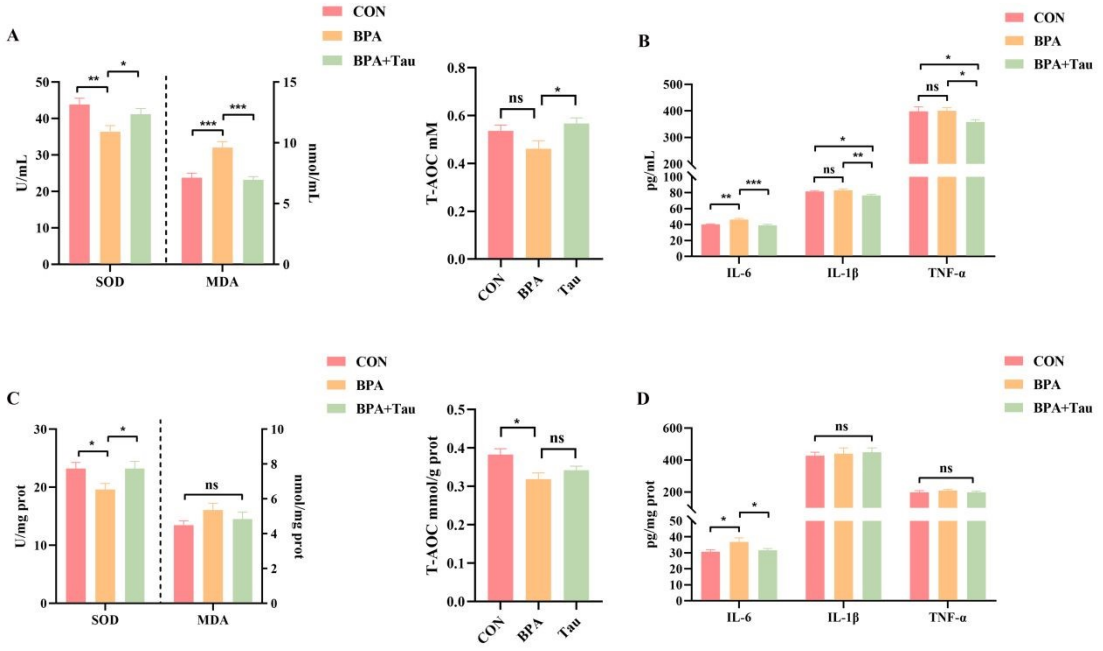

Fig. 2. Maternal taurine supplementation on oxidative stress and inflammation-related biomarkers in serum and placental tissues of BPA-exposed pregnant mice. (A) Serum antioxidant enzyme activity and malondialdehyde (MDA) level; (B) Serum inflammatory cytokines; (C) Placental antioxidant enzyme activity and malondialdehyde (MDA) level; (D) Placental inflammatory cytokines. CON, control group; BPA, bisphenol A-exposed group; BPA+Tau, bisphenol A-exposed+ taurine. ns, no significance; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

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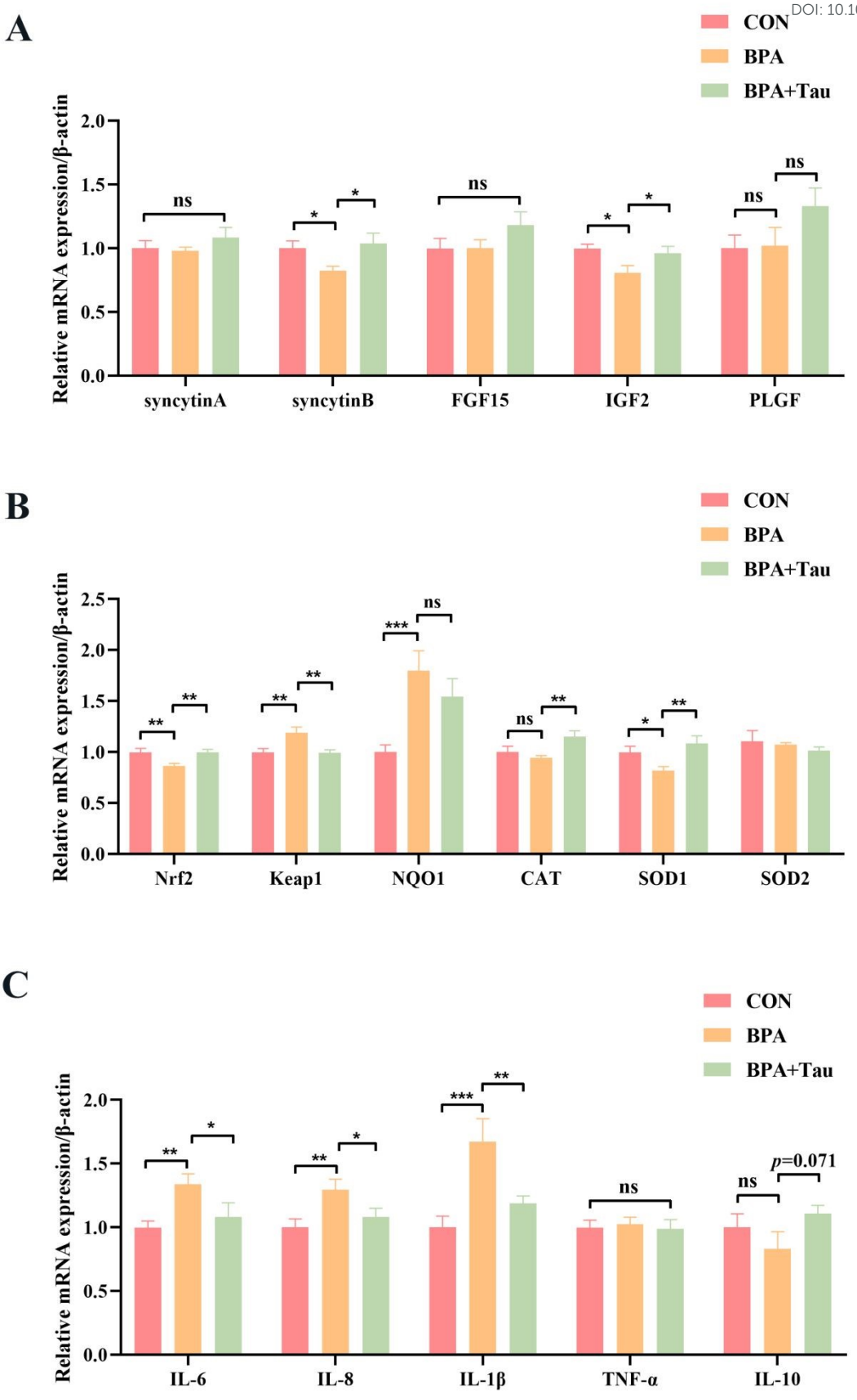

1062 **Fig. 3. Maternal taurine supplementation on the expression levels of placental**

function-associated genes, antioxidant and inflammatory cytokine in placental tissues of BPA-exposed pregnant mice. (A) The mRNA abundance of placental function-related genes; (B) The mRNA abundance of antioxidant cytokine-related genes; (C) The mRNA abundance of inflammatory-related genes. CON, control group; BPA, bisphenol A-exposed group; BPA+Tau, bisphenol A-exposed+ taurine. ns, no significance; $0.05 \leq P < 0.10$, tendency towards significance; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

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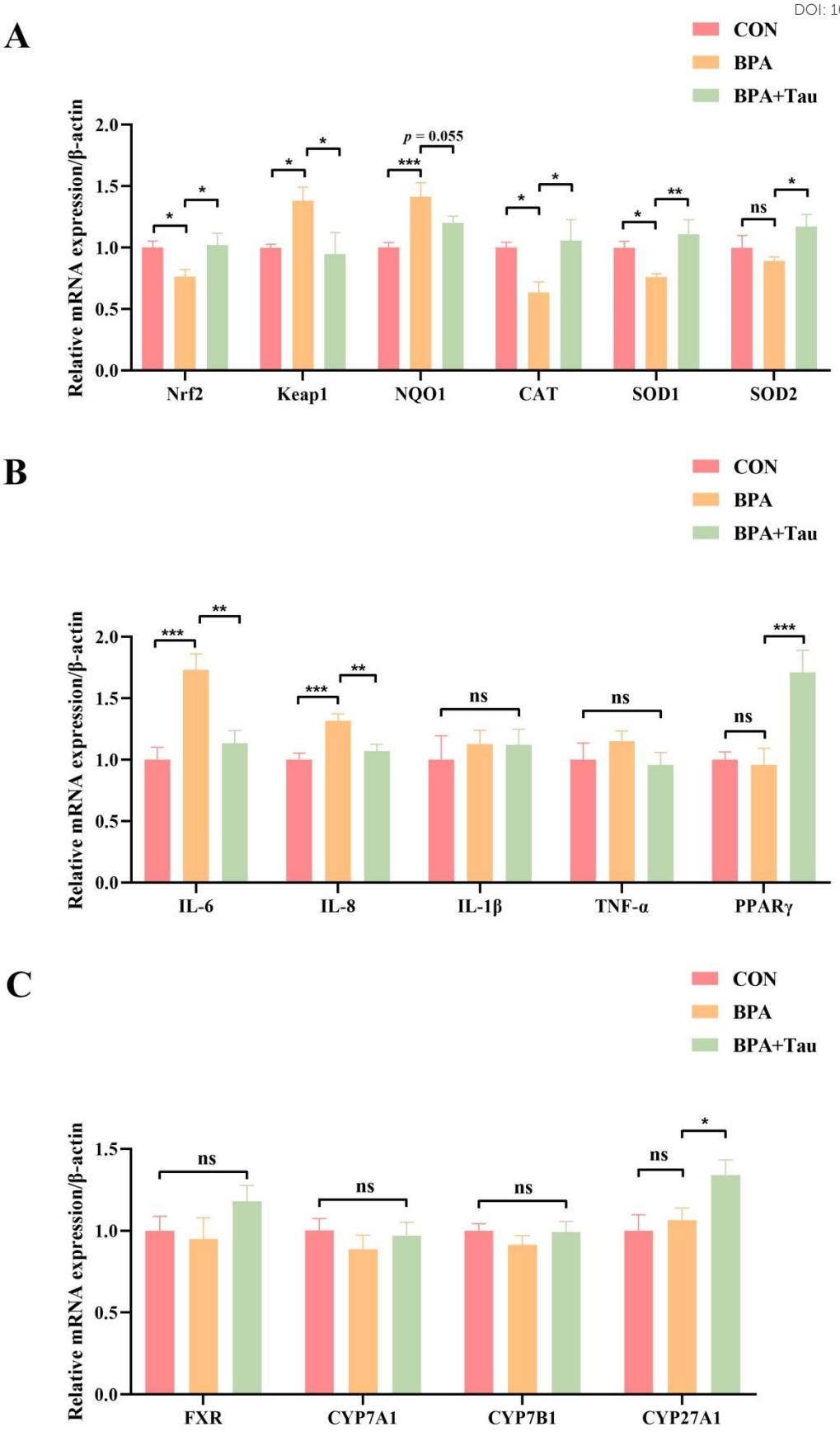

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Fig. 4. Maternal taurine supplementation on the expression levels of antioxidant, inflammatory cytokine, and bile acid (BA) synthesis associated genes in liver tissues of BPA-exposed pregnant mice. (A) The mRNA abundance of antioxidant-related genes; (B) The mRNA abundance of inflammatory cytokine-related genes; (C) The mRNA abundance of BA synthesis-related genes; CON, control group; BPA, bisphenol A-exposed group; BPA+Tau, bisphenol A-exposed+ taurine. ns, no significance; $0.05 \leq P < 0.10$, tendency towards significance; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

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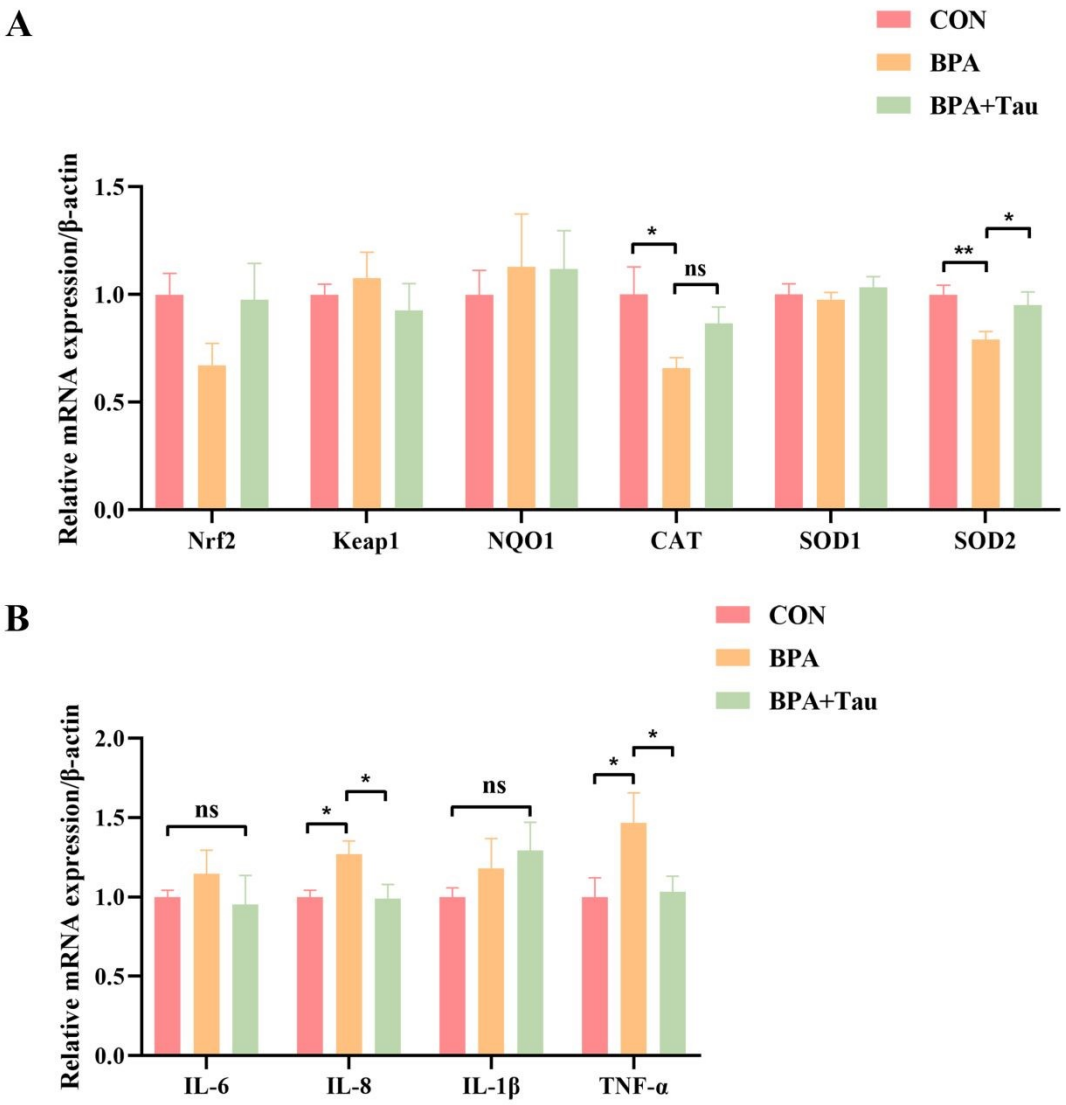

Fig. 5. Maternal taurine supplementation on the expression levels of antioxidant and inflammatory cytokine genes in fetal liver tissues of BPA- exposed pregnant mice. (A) The mRNA abundance of antioxidant-related genes; (B) The mRNA abundance of inflammatory cytokine-related genes. CON, control group; BPA, bisphenol A-exposed group; BPA+Tau, bisphenol A-exposed+ taurine. ns, no significance; *$P < 0.05$; **$P < 0.01$.

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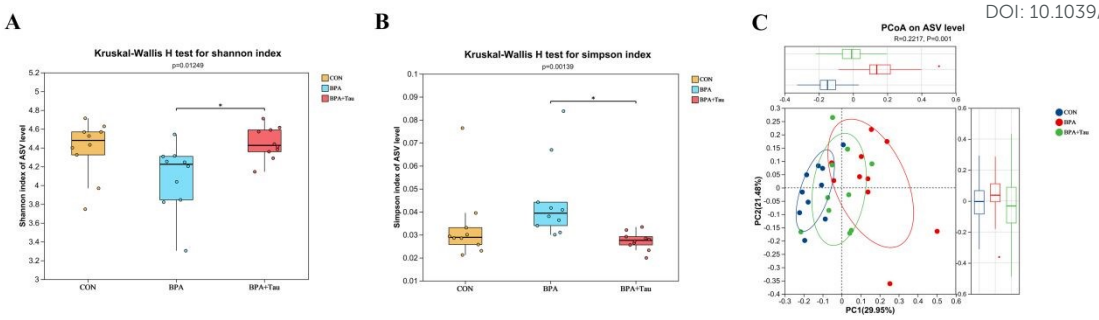

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1091 **Fig. 6. Maternal taurine supplementation on fecal microbiota community**
1092 **diversity in BPA-exposed pregnant mice.** (A) Shannon index; (B) Simpson index;
1093 (C) Principal Coordinates Analysis (PCoA) based on weighted UniFrac distances at
1094 the ASV level.

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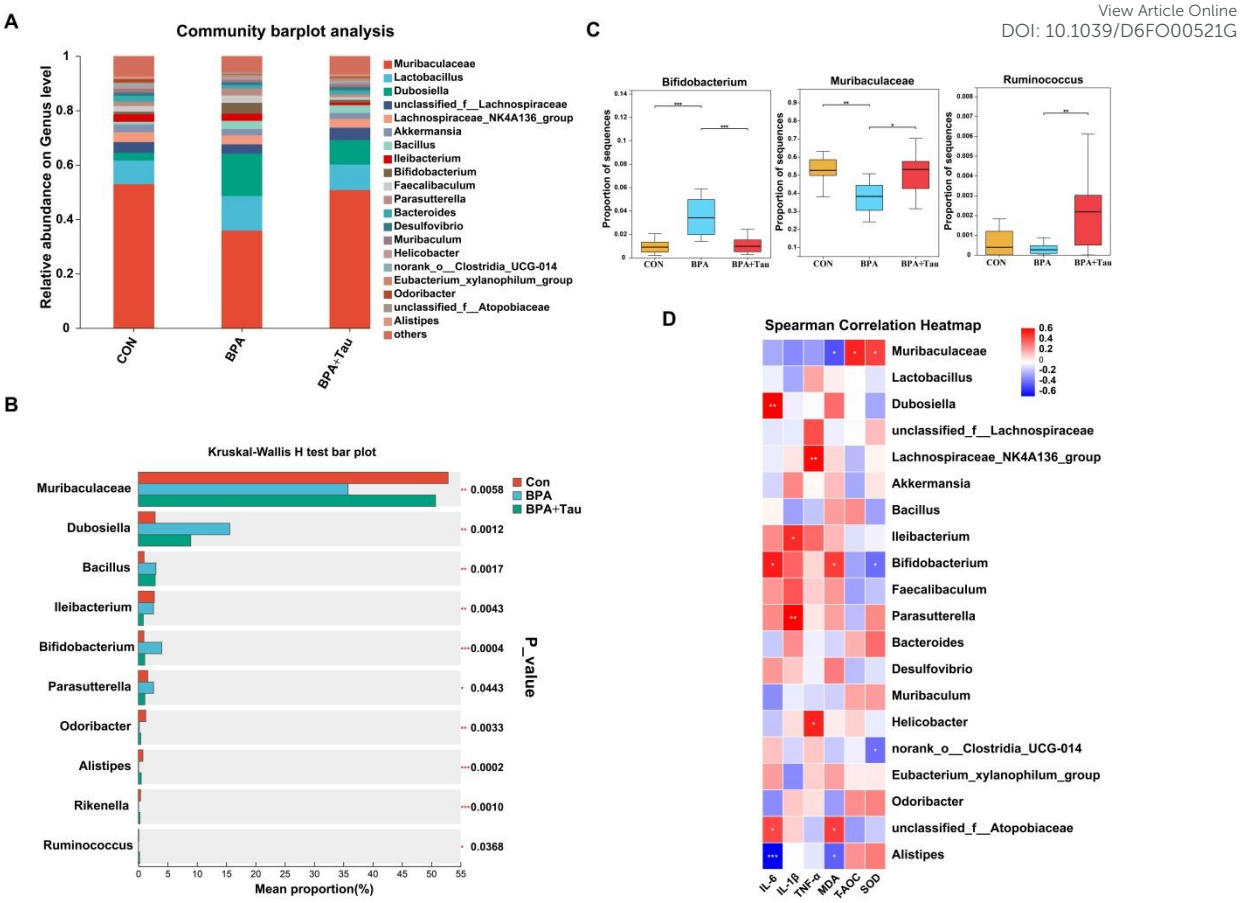

Fig. 7. Maternal taurine supplementation on fecal microbiota in BPA-exposed pregnant mice. (A) Microbial composition at the genus level; (B-C) Differential analysis of microbial composition at the genus level; (D) Correlation analysis between serum antioxidant enzyme activity, inflammatory markers, and fecal microbiota. CON, control group; BPA, bisphenol A-exposed group; BPA+Tau, bisphenol A-exposed+ taurine. ns, no significance; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

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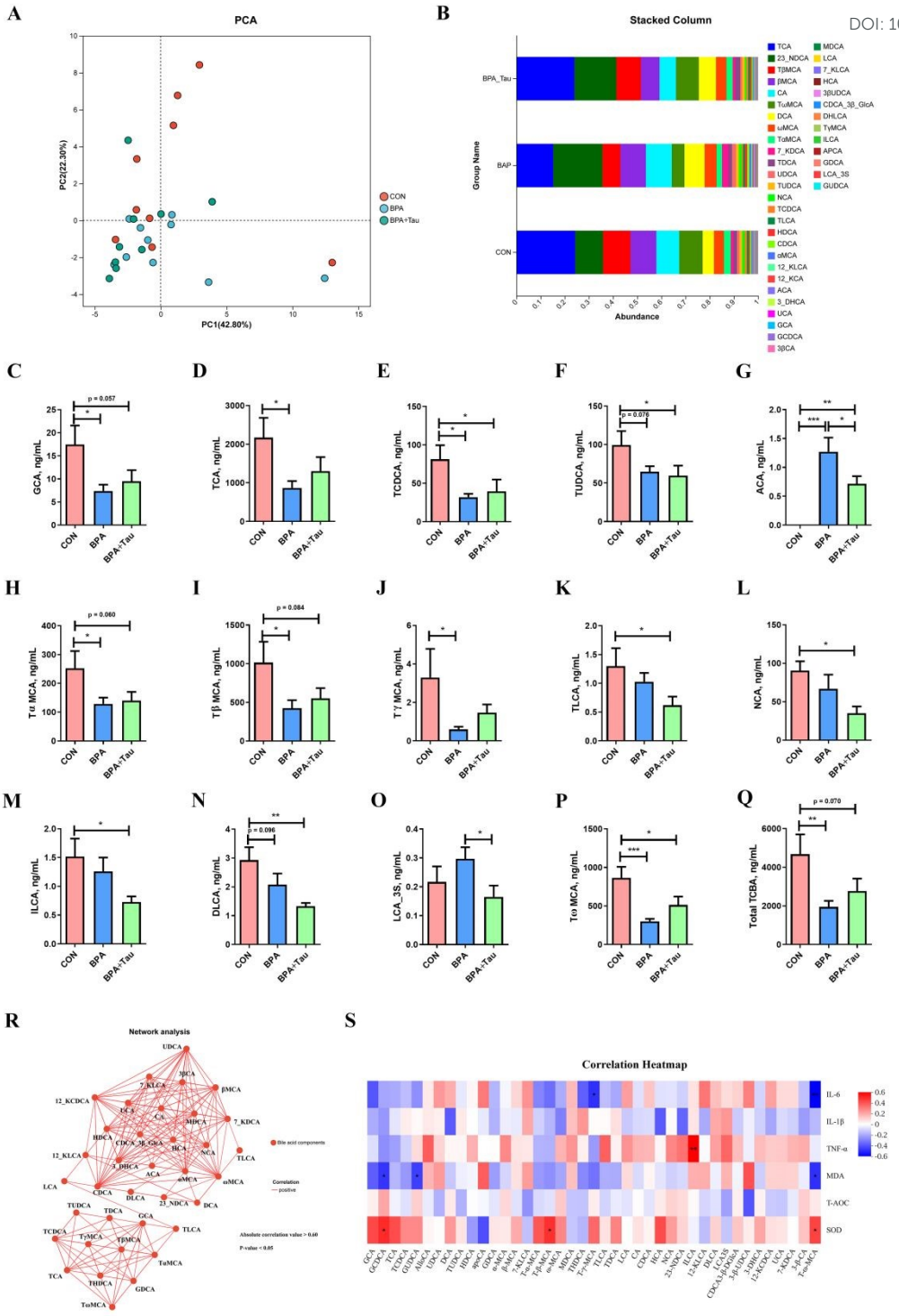

Fig. 8. Maternal taurine supplementation on the bile acid (BA) metabolism in serum of BPA-exposed pregnant mice. (A) PCA analysis; (B) Composition of BAs; (C-Q) Composition of differential serum BAs. GCA, Glycocholic acid; TCA, Taurocholic acid; TCDCA, Taurochenodeoxycholic acid; TUDCA, Tauroursodeoxycholic acid; ACA, Apocholic acid; T-α-MCA, Tauro-alpha-muricholic acid; T-β-MCA, Tauro-beta-muricholic acid; T-γ-MCA,

Tauro-gamma-muricholic acid; TLCA, Taurolithocholic acid; NCA, Norcholic acid; ILCA, Isolithocholic acid; DLCA, Dehydrolithocholic acid; LCA-3S, Lithocholic acid 3-sulfate; T-ω-MCA, Tauro-omega-muricholic acid; Total-TCBA, Total Tauro-conjugated bile acid; (R) Network analysis related to BA components; (S) Correlation analysis between differential BAs, oxidative stress markers, and inflammatory cytokines. MDA, Malondialdehyde; T-AOC, Total antioxidant capacity; SOD, Superoxide dismutase; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-1β, Interleukin-1beta. One sample from the CON group and one sample from the BPA+Tau group were excluded due to hemolysis; final sample sizes were n = 9 (CON), n = 10 (BPA), and n = 9 (BPA+Tau). $0.05 \leq P < 0.10$, tendency towards significance; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

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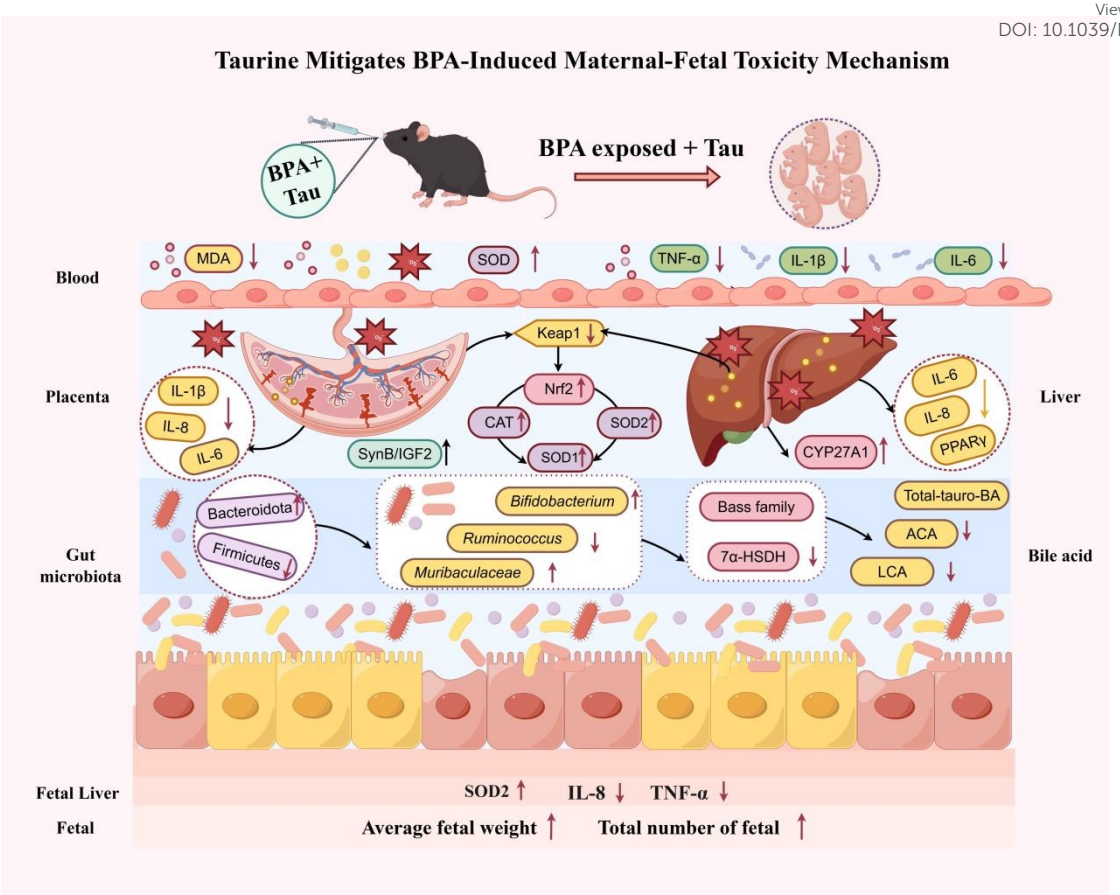

Fig. 9. Summary chart for taurine mitigates BPA-induced maternal-fetal oxidative stress and improves fetal weight by regulating Nrf2-Keap1 pathway, inflammation, gut microbiota, and bile acid (BA) metabolism. This schematic illustrates how taurine mitigates BPA-induced maternal-fetal toxicity through multi-organ, synergistic regulation. BPA exposure disrupts the Nrf2-Keap1 pathway, triggering oxidative stress and inflammation that impair placental and hepatic function, disturb gut microbiota, and dysregulate BA metabolism, leading to fetal growth restriction. Taurine counteracts these effects by activating the Nrf2-Keap1 pathway to reduce oxidative stress and inflammation, restoring placental nutrient transport and hepatic metabolic homeostasis, while also remodeling gut microbiota and regulating the liver-gut microbiota-BA axis to normalize BA metabolism. These actions collectively reverse fetal growth restriction and maintain maternal-fetal metabolic and microecological homeostasis. BPA, Bisphenol A; Tau, Taurine; MDA, Malondialdehyde; SOD, Superoxide dismutase; Nrf2, Nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; SOD1, Superoxide

dismutase 1; SOD2, Superoxide dismutase 2; CAT, Catalase; TNF-α, Tumor necrosis factor-alpha; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IL-8, Interleukin-8; SynB, Syncytin B; IGF2, Insulin-like growth factor 2; PPARγ, Peroxisome proliferator-activated receptor γ; CYP27A1, Cytochrome P450 family 27 subfamily A member 1; 7α-HSDH, 7α-Hydroxysteroid dehydrogenase; Bass family, bile acid sodium symporter family; ACA, Apocholic acid; LCA, Lithocholic acid.

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Data availability statement

All data used for this study appear in the illustrated figures, and the raw data will promptly be made available upon request.