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Effects of dietary dihydroartemisinin supplementation on growth performance, hepatic inflammation, and lipid metabolism in weaned piglets with intrauterine growth retardation

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Abstract

The aims of this study were to investigate the effects of dietary supplementation with dihydroartemisinin (DHA) on growth performance, hepatic inflammation, and lipid metabolism in intrauterine growth retardation (IUGR)-affected weaned piglets. Eight piglets with normal birth weight (NBW) and 16 IUGR-affected piglets were selected and fed either a basal diet (NBW and IUGR groups) or the basal diet supplemented with 80 mg/kg DHA (IUGR-DHA group) from 21 to 49 day of age. Blood and liver samples were collected on day 49. DHA supplementation significantly alleviated the compromised growth performance and liver damage in IUGR-affected piglets. Additionally, DHA supplementation decreased the activities of alanine aminotransferase and aspartate aminotransferase, as well as the serum levels of non-esterified fatty acids (NEFA), very-low-density lipoprotein, and total cholesterol. In the liver, the concentrations of interleukin 1 beta, interleukin 6, tumor necrosis factor alpha, triglycerides, and NEFA were decreased. Fatty acid synthesis was decreased by DHA supplementation, whereas the activities of lipoprotein lipase, hepatic lipase, and total lipase were increased. Dietary DHA supplementation led to upregulation of the expression of AMPK/SIRT1 signaling pathway-related genes, whereas that of inflammatory factor-related genes were downregulated. In conclusion, dietary inclusion of 80 mg/kg DHA can alleviate IUGR-induced impairments in piglets.

KEYWORDS
dihydroartemisinin, inflammation, intrauterine growth retardation, lipid metabolism, liver

1 | INTRODUCTION

Growth and development of the fetus are complex biological processes that can be affected by genetics, maternal nutrition, maternal maturity, and environmental factors, among others (Redmer, Wallace, & Reynolds, 2004). These factors directly or indirectly affect the birth weight of the fetus, whereas birth weight is an important risk factor affecting preweaning mortality rate in pigs. Intrauterine growth retardation (IUGR) is usually defined as fetal growth below the tenth percentile for gestational age (Robert, 2002) and results in impaired growth and development of the fetus and/or its organs during gestation (Longo, Borghesi, Tzialla, & Stronati, 2014). The most notable feature of neonates following IUGR is the lower birth weight that is due mainly to placental insufficiency. IUGR

is one of the most common pregnancy complications, affecting more than 15% of all pregnancies in some developed countries, and the probability of IUGR in developing countries is approximately sixfold higher than that in developed countries (Ananth & Vintzileos, 2009; Saleem et al., 2011). In addition to having a permanent effect on postnatal growth and long-term health, IUGR can also result in high fetal mortality and morbidity. Previous studies have shown that IUGR can lead to lipid dysfunction, a fatty liver, and inflammation (Magee et al., 2008). He et al. (2015) demonstrated that piglets with IUGR can lead to disorder of lipid catabolism in the liver and Liu et al. (2014) found mRNA expression abundances of hepatic inflammatory factor were significantly upregulated in IUGR pigs. However, the mechanism underlying abnormal lipid metabolism and inflammation in the livers of weaned IUGR-affected piglets remains unclear, and investigating IUGR has important implications for both animals and humans.

Dihydroartemisinin (DHA), an antimalarial drug prepared by reduction of artemisinin with sodium borohydride, displays a wide range of pharmacological properties, including antibacterial, antitumorigenic, and antifibrotic activities (Akpaloo & Purssell, 2014; Feng et al., 2016; Zhang et al., 2014), and is the main metabolite of artemisinin drugs in vivo (Klayman, 1985). Compared to artemisinin, DHA has better water solubility, easier absorption, faster excretion and metabolism, higher efficiency, and lower toxicity. Previous reports have suggested that, in addition to its antimalarial effects, DHA can also help prevent obesity and improve obesity-related metabolic disorders (Lu et al., 2016). Gao et al. (2017) showed that dietary supplementation with 0.25 mg/kg artemisinin can reduce adipose weight in an inflammatory obese mouse model, demonstrating for the first time that artemisinin can reduce the risk of non-alcoholic fatty liver disease. Furthermore, recent studies have revealed that DHA can prevent the inflammatory cascade by inhibiting TNF, an inflammatory mediator, and influencing NF-κB activation and its translocation to the nucleus (Li, Dong, Tu, & Lin, 2006; Wei et al., 2013). Zhang, Guo, Zhao, Shao, and Zheng (2016) found that DHA might protect the liver against CCl_4-induced injury by inhibiting the production and release of inflammatory cytokines. However, to the best of our knowledge, the effects of DHA on IUGR-induced hepatic damage, inflammation, and lipid metabolism in weaned piglets have not been investigated. Based on published studies, we hypothesized that DHA treatment would have protective effects against IUGR-induced hepatic damage and alter the expression of genes related to inflammation and lipid metabolism. Therefore, the objective of this study was to investigate whether dietary DHA supplementation can alleviate the negative effects of IUGR on growth performance, inflammation, lipid metabolism, and associated gene expression in weaned piglets.

2 | MATERIALS AND METHODS

2.1 | Dihydroartemisinin preparation

The dihydroartemisinin used in this study was purchased from the Dasf Biotechnology Co., Ltd.

2.2 | Animal experiment design

The experimental design and procedures used in this study were approved by the Animal Care Committee of Nanjing Agricultural University (Nanjing, Jiangsu, China) following the Guidelines on Ethical Treatment of Experimental Animals (2006) set by the Ministry of Science and Technology in China.

The piglets were selected from 10 litters [Duroc × (Landrace × Yorkshire)] of newborn piglets. These piglets were born from sows of similar weight (197.53 ± 1.68 kg) and parity (3 or 4 births). All the sows were fed the same commercial diet based on the nutritional requirements stipulated by the National Research Council (NRC, 2012). Two IUGR-affected piglets and one normal birth weight (NBW) piglet were selected for each litter. A piglet was defined as intrauterine growth-restricted when its birth weight was two standard deviations below the mean birth weight of the total population, as described by Wang et al. (2012). Pigs of NBW were selected according to the standard deviation range of the birth weight of the IUGR-affected pigs. Specific determination methods were based on previous studies in the laboratory, namely, the normal piglet weight was 1.56 ± 0.02 kg, whereas the birth weight of IUGR-affected piglets was 0.99 ± 0.03 kg. All piglets were allowed to suckle naturally until weaning age (21 day old). At weaning, the piglets were divided into three experimental groups (n = 10), as follows: NBW (normal birth weight group given a basal diet), IUGR (intrauterine growth retardation group given the basal diet), and IUGR-DHA (IUGR group given the basal diet +80 mg/kg DHA). There were 10 piglets in each group, half of which were male and half female, with one replicate for each group. Table 1 shows the chemical composition of the diet, which was formulated to meet the nutritional requirements of the piglets according to NRC (2012). The piglets were housed individually in pens with plastic floors (1 × 0.6 m) at 28°C and were given ad libitum access to feed and water.

2.3 | Growth performance measurement and sample collection

Body weight and feed intake were recorded and measured on a pen basis at weaning and sampling to calculate body weight gain (BWG) and feed intake (FI). The gain to feed ratio (G:F) was calculated as the ratio between BWG and FI.

At 49 day of age, blood was collected by jugular vein puncture and serum samples were obtained from the blood by centrifugation at 3,000 *g* for 15 min at 4°C. Eight weaned piglets weighing close to the average body weight were selected from each pen for euthanasia. All the piglets were euthanized by exsanguination after electrical stunning. Liver samples from the left lobe were removed immediately after sacrifice, frozen in liquid nitrogen after snipping, and stored at −80°C for further analysis. The liver samples were homogenized in 0.9% (w/v) ice-cold physiological saline for 10 s and centrifuged at 3,000 *g* for 15 min at 4°C, after which the supernatant was rapidly analyzed.

TABLE 1 Compositions of the basal diets (as-fed basis)

Items	Content (%)
Ingredients (%)	
Corn	65.00
Soybean meal	10.00
Fish meal	4.00
Extruded soybean	8.00
Whey power	5.00
Fermented soybean meal	4.00
Premix[†]	4.00
Total	100.00
Nutrient level[‡]	
Crude protein (%)	18.15
Gross energy (MJ/kg)	9.00
Digestible energy (MJ/kg)	14.58
Metabolizable energy (MJ/kg)	11.41
Lysine (%)	1.30
Methionine (%)	0.32
Methionine + Cystine (%)	0.60
Threonine (%)	0.83
Ca (%)	0.71
Total phosphorus (%)	0.72
Available phosphorus (%)	0.27

[†]The premix provided the following per mg/kg diet: retinyl acetate, 4.79; cholecalciferol, 0.075; all-rac-α-tocopherol acetate, 100; menadione, 3; thiamin, 3; riboflavin, 8; nicotinamide, 5; cobalamin, 0.04; biotin, 0.3; pantothenic acid, 20; niacin, 45; folic acid, 2; choline chloride, 450; Fe (as $FeSO_4 \cdot H_2O$), 180; Cu (as $CuSO_4.5H_2O$), 230; Zn (as ZnO), 65; Mn (as $MnSO_4 \cdot H_2O$), 50; I (as KIO_3), 0.5; Se (as Na_2SeO_3), 0.2.
[‡]All nutrient content values, except DE and ME values, were analyzed values.

The protein content of liver samples was measured using the bicinchoninic acid protein assay kit (Beyotime Institute of Biotechnology).

2.4 | Assessment of serum aminotransferase activities

The serum activities of alanine aminotransferase (ALT; Alanine Aminotransferase Assay Kit, C009-2-1) and aspartate aminotransferase (AST; Aspartate Aminotransferase Assay Kit, C010-2-1) were determined using the corresponding kits obtained from the Nanjing Jiancheng Institute of Bioengineering.

2.5 | Analysis of lipid metabolism in the serum and liver

Serum concentrations of high-density lipoprotein cholesterol (HDL-C; High-Density Lipoprotein Cholesterol Assay Kit, A112-1-1), low-density lipoprotein cholesterol (LDL-C; Low-Density Lipoprotein Cholesterol Assay Kit, A113-1-1), total cholesterol (TC; Total Cholesterol Assay Kit, A111-1-1), and triglycerides (TG; Triglyceride Assay Kit, A110-1-1) were measured using commercial assay kits obtained from the Nanjing Jiancheng Institute of Bioengineering. The serum concentration of very-low-density lipoprotein cholesterol (VLDL-C) was measured by commercial enzymatic methods (Roche Diagnostics GmbH). The liver samples were homogenized in 0.9% (w/v) ice-cold physiological saline for 10 s and centrifuged at 3,000 *g* for 15 min at 4°C, after which the supernatant was rapidly analyzed. The TC, TG, and non-esterified fatty acid (NEFA; Non-Esterified Free Fatty Acids Assay Kit, A042-1-1) levels and total lipase (TL; Lipoprotein Lipase and Hepatic Lipase Assay Kit, A067-1-2), hepatic lipase (HL; Lipoprotein Lipase and Hepatic Lipase Assay Kit, A067-1-2), and lipoprotein lipase (LPL; Lipoprotein Lipase and Hepatic Lipase Assay Kit, A067-1-2) activities in the liver were measured using kits obtained from the Nanjing Jiancheng Institute of Bioengineering. Hepatic fatty acid synthase (FAS) activity was measured using a Porcine Fatty Acid Synthase ELISA Kit (F4818-A) purchased from Shanghai YILI Biological Technology Co., Ltd.

2.6 | Analysis of liver cytokine levels

The levels of interferon gamma (IFN-γ; Porcine Interferon γ ELISA Kit, F4859-B), interleukin 1beta (IL-1β; Porcine Interleukin 1β ELISA Kit, F4869-B), interleukin 6 (IL-6; Porcine Interleukin 6 ELISA Kit, F4865-B), and tumor necrosis factor alpha (TNF-α; Porcine Tumor Necrosis Factor α ELISA Kit, F4830-B) in the liver were determined using ELISA (pig-specific) kits purchased from Shanghai YILI Biological Technology Co., Ltd, according to the manufacturer's instructions. The protein content of each sample was measured using the bicinchoninic acid protein assay (Beyotime Institute of Biotechnology). ELISA results were expressed as picograms per gram of protein.

2.7 | Assay of gene expression

Total RNA was isolated from liver samples using TRIzol Reagent (TaKaRa Biotechnology). RNA integrity was assessed on 1% agarose gels with ethidium bromide staining. The concentration and purity of the total RNA were assessed from OD 260/280 readings (ratio > 1.8) using a spectrophotometer (NanoDrop Technologies). Total RNA (1 μg) was reverse-transcribed into cDNA using the PrimeScript RT Reagent Kit (TaKaRa Biotechnology) according to the manufacturer's guidelines. Quantitative real-time polymerase chain reaction (qRT-PCR) was performed on an ABI StepOnePlus Real-Time PCR System (Applied Biosystems) according to the manufacturer's instructions. The sequences of primers used in this experiment are shown in Table 2. All the primer sequences were designed using NCBI primer blast (http://www.ncbi.nlm.nih.gov/tools/primerblast/index.cgi?LINK_LOC=BlastHome) according to Guan, Liang, Martin, and Guan (2017). The cDNA samples were amplified by qRT-PCR with SYBR Premix Ex Taq reagents (Takara Biotechnology). Briefly, a

TABLE 2 Sequences for real-time PCR primers

Gene	Accession number.	Sequences (5′→3′)	Product length (bp)	Amplification efficiency
SCD	NM_213781.1	F: AGAATGGAGGGGGCAAGTTG R: CTTCTCTTTGACGGCTGGGT	503	1.00
ACCβ	NM_001206399.1	F: CCCAACTCTCGCTCGTTTCA R: AACCCAACCATGGAGAGGAG	80	1.00
AMPKα	XM_021076522.1	F: GGAGGTTCTCAGCTGCCTTT R: GAATCAGGTGGGCTTGTTGC	132	1.01
FAS	NM_213839.1	F: TGATGCCCAAGTGACTGACC R: CAGCATGTTTCCGTTTGCCA	140	1.02
CPT-1	NM_001129805.1	R: GTCCATCGACAGCTTTCAGC F: TGGGGTATGGAATGTTGGGG	80	1.00
SIRT1	NM_001145750.2	R: CCGACGACTTCTACGACGAC F: GAACTGGCATGTGAGGCTCT	172	1.00
SREBP-1	AY338729.1	R: GCTACCGCTCCTCCATCAAT F: CTGCTTGAGCTTCTGGTTGC	146	1.03
TNF-α	NM_214022.1	R: ATCGGCCCCCAGAAGGAAGAG F: GATGGCAGAGAGGAGGTTGAC	351	1.01
IFN-γ	NM_213948.1	R: TCAGCTTTGCGTGACTTTGTG F: GCTCTCTGGCCTTGGAACAT	462	0.98
IL-1β	NM_214029.1	R: TGCCAGCTATGAGCCACTTCC F: TGACGGGTCTCGAATGATGCT	337	1.00
IL-6	NM_214399.1	R: AGATGCCAAAGGTGATGCCA F: CTCAGGCTGAACTGCAGGAA	519	1.02
β-actin	XM_003124280.4	R: CAGTCGGTTGGATGGAGCAT F: AGGCAGGGACTTCCTGTAAC	146	1.00

Abbreviations: *ACCβ*, acetyl-CoA carboxylase beta; *AMPKα*, adenosine monophosphate-activated protein kinase alpha; *CPT-1*, carnitine palmityl transferase 1; *FAS*, fatty acid synthesis; *IFN-γ*, interferon gamma; *IL-1β*, interleukin 1 beta; *IL-6*, interleukin 6; *SCD*, stearoyl-CoA desaturase; *SIRT1*, sirtuin 1; *SREBP-1*, sterol regulatory element-binding protein 1; *TNF-α*, tumor necrosis factor alpha.

20 μl reaction mixture was prepared using 2 μl of cDNA, 0.4 μl each of forward and reverse primers, 0.4 μl of ROX reference dye (50×; Life Technologies), 10 μl of SYBR Premix Ex Taq (2 ×), and 6.8 μl of double-distilled H2O. Each sample was tested in duplicate. The qRT-PCR conditions consisted of an initial denaturation at 95°C for 30 s, followed by 40 cycles of denaturation at 95°C for 5 s and annealing at 60°C for 30 s. The conditions of the melting curve analysis were one cycle of denaturation at 95°C for 10 s, followed by an increase in temperature from 65 to 95°C at a rate of 0.5°C/s. For melting curve analysis, we compared the amplification efficiencies of the target genes with those of the housekeeping genes. The melt curves of a single gene in the different samples showed one single, overlapping peak, and the amplification efficiency of each of the target genes and the housekeeping gene were all similar and within a range of 0.9 and 1.1 (Table 2). The relative mRNA expression levels were calculated using the 2-ΔΔCT method, with *β-actin* as the internal standard and the values for pigs in the NBW group were used as a calibrator.

2.8 | Statistical analysis

One-way analysis of variance (ANOVA) was performed in SPSS ver. 20.0 to determine the main effects of IUGR and the diets, followed by multiple pairwise comparisons (Duncan's multiple range test, used for multigroup comparisons). *p*-values smaller than .05 were considered significant. Data were presented as means ± standard error of the means.

3 | RESULTS

3.1 | Growth performance

Growth performance is shown in Table 3. The IUGR and IUGR-DHA groups had lower BW at 21 day of age ($p < .05$) than the NBW group. At 49 day of age, the BW of the NBW and IUGR-DHA groups did not differ ($p > .05$) and were greater than that of the IUGR group ($p < .05$). Compared to NBW piglets, IUGR-affected piglets exhibited lower ($p < .05$) total body weight gain and feed intake during the entire experimental period. However, dietary supplementation with DHA increased ($p < .05$) the total body weight gain and feed intake in the IUGR-DHA group compared to those in the IUGR group.

3.2 | Serum AST and ALT activities and the AST/ALT ratio

As shown in Table 4, IUGR-affected piglets had higher ($p < .05$) serum AST and ALT activities than NBW piglets. The AST/ALT ratio was

TABLE 3 Effects of dietary dihydroartemisinin (DHA) supplementation on growth performance of IUGR weaned piglets

Item	Experiment groups		
	NBW	IUGR	IUGR-DHA
BW (kg): 21 days	6.96 ± 0.05[a]	6.08 ± 0.09[b]	6.08 ± 0.06[b]
BW (kg): 49 days	12.80 ± 0.60[a]	10.24 ± 0.38[b]	12.11 ± 0.46[a]
BWG (kg)	5.84 ± 0.62[a]	4.17 ± 0.35[b]	6.03 ± 0.49[a]
FI (kg)	8.00 ± 0.13[b]	6.55 ± 0.15[c]	9.13 ± 0.13[a]
G:F (kg/kg)	0.73 ± 0.08	0.64 ± 0.06	0.66 ± 0.06

Abbreviations: BW, body weight; BWG, body weight gain; FI, feed intake; G:F, body weight gain:feed intake; IUGR, Intrauterine growth retardation group given a basal diet; IUGR-DHA, IUGR group given diets supplemented with 80 mg/kg dihydroartemisinin; NBW, normal birth weight group given a basal diet.

[a,b,c]Mean values within a row with unlike superscript letters were significantly different ($p < .05$).

TABLE 4 Effects of dietary dihydroartemisinin (DHA) supplementation on activities of ALT, AST, and the ratio of AST to ALT in the serum of IUGR weaned piglets

Item	Experiment groups		
	NBW	IUGR	IUGR-DHA
AST (U/L)	8.679 ± 0.374[b]	16.782 ± 0.420[a]	8.206 ± 0.433[b]
ALT (U/L)	9.187 ± 0.224[c]	14.517 ± 0.405[a]	12.110 ± 0.367[b]
AST/ ALT	0.944 ± 0.032[b]	1.160 ± 0.035[a]	0.599 ± 0.055[c]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AST/ALT, AST to ALT ratio; IUGR, Intrauterine growth retardation group given a basal diet; IUGR-DHA, IUGR group given diets supplemented with 80 mg/kg dihydroartemisinin; NBW, normal birth weight group given a basal diet.

[a,b,c]Mean values within a row with unlike superscript letters were significantly different ($p < .05$).

significantly increased ($p < .05$) in the IUGR group. Dietary DHA supplementation decreased ($p < .05$) AST and ALT activities in piglets of the IUGR group, whereas the AST/ALT ratio was also decreased ($p < .05$) in the IUGR-DHA group compared to that in the IUGR group.

3.3 | Assessment of lipid metabolism in the serum and liver

As shown in Table 5, compared to the NBW group, IUGR significantly increased ($p < .05$) the serum concentrations of TC, VLDL-C and NEFA and decreased ($p < .05$) that of HDL-C. In the IUGR-DHA group, the TC, VLDL-C and NEFA concentrations were lower ($p < .05$) than those in the IUGR group, whereas the HDL-C concentration was higher ($p < .05$). Compared to NBW piglets, the hepatic TG and NEFA concentrations in IUGR-affected piglets were significantly increased ($p < .05$), whereas HL and TL activities were significantly decreased ($p < .05$). DHA supplementation significantly decreased ($p < .05$) the TG and NEFA concentrations in the IUGR-DHA group. The activities of LPL, HL, and TL were higher in the IUGR-DHA group than in the IUGR group, whereas that of FAS was lower.

3.4 | Levels of hepatic inflammation-related cytokines

The concentrations of hepatic TNF-α and IL-1β in the IUGR-affected piglets were significantly higher ($p < .05$) than those in the NBW piglets (Table 6). Dietary DHA supplementation reduced ($p < .05$) the concentrations of hepatic TNF-α, IL-1β, and IL-6 in the IUGR-DHA group compared to the IUGR group. In addition, the IFN-γ concentration was not different between the IUGR-affected and NBW.

3.5 | Gene expression

The expression of hepatic genes is presented in Figures 1 and 2. The mRNA expression levels of stearoyl-CoA desaturase (*SCD*), adenosine monophosphate-activated protein kinase alpha (*AMPKα*), carnitine palmitoyltransferase 1 (*CPT-1*), and sirtuin 1 (*SIRT1*) were lower ($p < .05$) in the IUGR-affected piglets than in the NBW piglets, whereas those of acetyl-CoA carboxylase beta (*ACCβ*), *FAS*, sterol regulatory element binding transcription factor 1 (*SREBP-1*), *IFN-γ*, *IL-1β*, *IL-6*, and *TNF-α* were higher ($p < .05$). Dietary DHA supplementation significantly decreased ($p < .05$) the mRNA expression levels of *ACCβ*, *FAS*, *SREBP-1*, *IFN-γ*, *IL-1β*, *IL-6*, and *TNF-α* and increased ($p < .05$) those of *AMPKα*, *CPT-1*, and *SIRT1*.

4 | DISCUSSION

Intrauterine growth retardation has been reported to result in inflammation and abnormal lipid metabolism in the liver (He et al., 2015; Liu et al., 2014). When used as a dietary supplement, DHA can reduce body adipose weight and improve hepatic immune function (Qian et al., 2017; Zhang et al., 2016). However, relatively few studies have investigated the effect of DHA on the liver of IUGR-affected piglets. In this study, we investigated hepatic inflammation and lipid metabolism in weaned IUGR-affected piglets and assessed the effects of DHA supplementation on the above indexes of IUGR-affected piglets during the post-weaning period.

TABLE 5 Effects of dietary dihydroartemisinin (DHA) supplementation on lipid metabolism in the serum and liver of IUGR weaned piglets

Item	Experiment groups		
	NBW	IUGR	IUGR-DHA
Serum			
TC (mmol/L)	5.40 ± 0.41[b]	7.28 ± 0.29[a]	5.33 ± 0.39[b]
TG (mmol/L)	0.60 ± 0.07	0.61 ± 0.05	0.58 ± 0.06
HDL-C (mmol/L)	2.43 ± 0.16[a]	1.56 ± 0.11[b]	2.42 ± 0.10[a]
LDL-C (mmol/L)	1.09 ± 0.04	1.06 ± 0.15	0.88 ± 0.09
VLDL-C (mmol/L)	0.85 ± 0.09[b]	1.77 ± 0.12[a]	1.11 ± 0.13[b]
NEFA (μmol/L)	550.15 ± 36.58[b]	794.17 ± 28.27[a]	382.52 ± 40.70[c]
Liver			
TC (mmol/g prot)	0.11 ± 0.002	0.104 ± 0.01	0.107 ± 0.01
TG (mmol/g prot)	0.16 ± 0.004[b]	0.197 ± 0.01[a]	0.127 ± 0.01[c]
NEFA (μmol/g prot)	60.88 ± 5.37[b]	111.13 ± 5.79[a]	73.65 ± 4.78[b]
LPL (U/mg prot)	0.80 ± 0.04[b]	0.62 ± 0.07[b]	1.14 ± 0.10[a]
HL (U/mg prot)	1.35 ± 0.10[a]	0.62 ± 0.06[c]	1.14 ± 0.05[b]
TL (U/mg prot)	2.15 ± 0.10[a]	1.24 ± 0.11[b]	2.28 ± 0.12[a]
FAS (U/mg prot)	226.81 ± 11.04[a]	230.40 ± 11.80[a]	141.96 ± 11.39[b]

Abbreviations: FAS, fatty acid synthesis; HDL-C, high-density lipoprotein cholesterol; HL, hepatic lipase; IUGR, Intrauterine growth retardation group given a basal diet; IUGR-DHA, IUGR group given diets supplemented with 80 mg/kg dihydroartemisinin; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; NBW, normal birth weight group given a basal diet; NEFA, non-esterified fatty acid; TC, total cholesterol; TG, triglyceride; TL, total lipase; VLDL-C, very low-density lipoprotein cholesterol.

[a,b,c]Mean values within a row with unlike superscript letters were significantly different ($p < .05$).

TABLE 6 Effects of dietary dihydroartemisinin (DHA) supplementation on hepatic inflammation cytokines of IUGR weaned piglets

Item	Experiment groups		
	NBW	IUGR	IUGR-DHA
IFN-γ (pg/mg)	6.15 ± 0.25[a]	5.50 ± 0.38[ab]	4.76 ± 1.06[b]
IL–1β (pg/mg)	48.29 ± 2.75[b]	66.28 ± 2.56[a]	45.27 ± 1.06[b]
IL–6 (pg/mg)	100.53 ± 1.76[a]	105.03 ± 1.89[a]	79.98 ± 2.71[b]
TNF-α (pg/mg)	22.13 ± 0.76[b]	30.10 ± 1.29[a]	23.13 ± 1.30[b]

Abbreviations: IFN-γ, interferon-γ; IL-1β, interleukin-1 β; IL-6, interleukin-6; IUGR, Intrauterine growth retardation group given a basal diet; IUGR-DHA, IUGR group given diets supplemented with 80 mg/kg dihydroartemisinin; NBW, normal birth weight group given a basal diet; TNF-α, tumor necrosis factor-α.

[a,b]Mean values within a row with unlike superscript letters were significantly different ($p < .05$).

The data show that IUGR significantly reduced BW, BWG, and FI in piglets after weaning. These findings indicate that IUGR negatively affected the body weight and post-weaning growth of the piglets, consistent with previously reported results. Several studies have shown that IUGR-affected piglets exhibit poor growth performance compared to normal piglets (Han et al., 2013; Li, Zhang, et al., 2018; Yao et al., 2013). Interestingly, we found that dietary DHA supplementation could ameliorate the inferior growth performance associated with IUGR by significantly increasing BW, BWG, and FI. Dietary supplementation with *Artemisia annua* L. has been demonstrated to improve growth performance in broiler chickens (Wan et al., 2017). Windisch, Schedle, Plitzner, and Kroismayr (2008) reported that phytogenic products, as feed additives, have growth-promoting effects on swine and poultry. Studies have also indicated that dietary inclusion of phytogenic feed additives with various advantageous characteristics could improve the growth performance of pigs, and that DHA might play a similar beneficial role (Li et al., 2016). However, the mechanisms related to the effects of DHA on IUGR growth performance are poorly understood and require further investigation.

The activities of serum AST and ALT, as well as the AST/ALT ratio, are important indicators of liver function. When the structure of the liver is severely damaged, ALT and AST are released and their levels in the blood circulation increase (Nyblom et al., 2004). In this study,

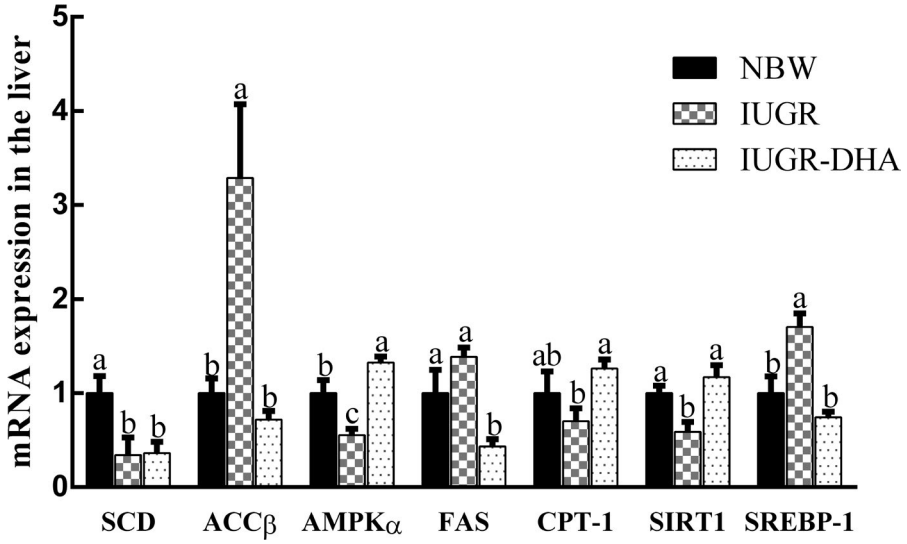

FIGURE 1 Effects of dietary dihydroartemisinin (DHA) supplementation on the hepatic lipid metabolism related mRNA expressions in IUGR piglets. *ACCβ*, acetyl-CoA carboxylase beta; *AMPKα*, adenosine monophosphate-activated protein kinase alpha; *CPT-1*, carnitine palmityl transferase 1; *FAS*, fatty acid synthesis; IUGR, Intrauterine growth retardation group given a basal diet; IUGR-DHA, IUGR group given diets supplemented with 80 mg/kg dihydroartemisinin; *SCD*, stearoyl-CoA desaturase; *SIRT1*, sirtuin; *SREBP-1*, sterol regulatory element-binding protein 1. NBW, normal birth weight group given a basal diet. [a,b,c]Mean values within a column with unlike superscript letters were significantly different ($p < .05$)

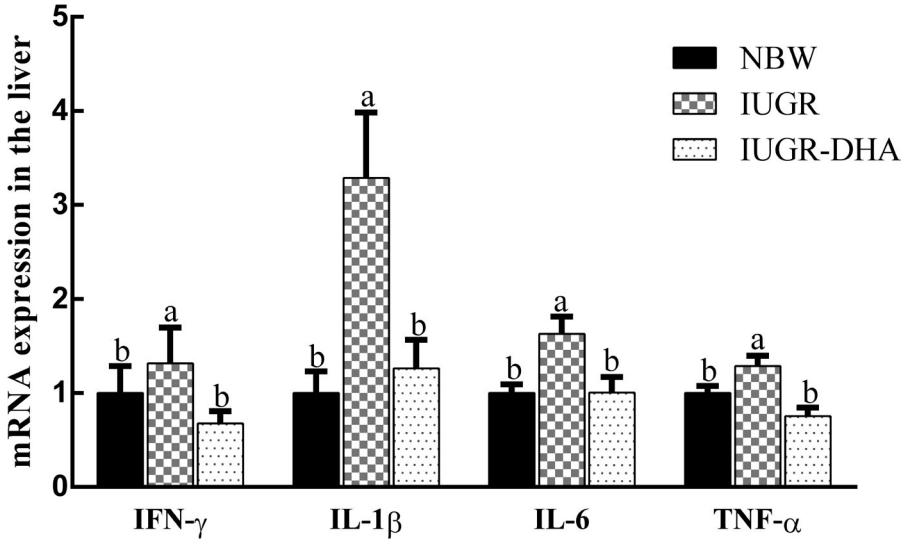

FIGURE 2 Effects of dietary dihydroartemisinin (DHA) supplementation on the mRNA expressions of proinflammatory cytokines in the liver of IUGR piglets. *IFN-γ*, interferon gamma; *IL-1β*, interleukin 1 beta; *IL-6*, interleukin 6; IUGR, Intrauterine growth retardation group given a basal diet; IUGR-DHA, IUGR group given diets supplemented with 80 mg/kg dihydroartemisinin; NBW, normal birth weight group given a basal diet; *TNF-α*, tumor necrosis factor alpha. [a,b]Mean values within a column with unlike superscript letters were significantly different ($p < .05$)

the activities of serum AST and ALT and the AST/ALT ratio were higher in the IUGR group than in the NBW group. Similarly, He et al. (2018) reported that IUGR-affected rats showed a greater increase in plasma aminotransferase activity and impaired liver function compared to normal rats. In our study, we found that DHA supplementation could attenuate hepatic damage in IUGR-affected piglets. Reduced AST and ALT activities and AST/ALT ratio in the serum suggested that IUGR-associated hepatic injury was ameliorated in response to DHA administration. Zhao et al. (2017) also found that artemisinin can decrease the levels of AST and ALT, as well as reduce liver cell and liver cell membrane damage. The serum aminotransferase activities and histological changes strongly implied that IUGR-induced liver damage can be alleviated by DHA administration.

Several studies have shown that IUGR affects the proteome, thereby reducing the capacity for detoxification in the liver of IUGR-affected fetuses, and leading to a high risk of inflammation (Liu et al.,

2013; Tarry-Adkins et al., 2015). TNF-α is the most prominent inflammatory mediator, and can activate inflammatory responses in the innate immune system, including inducing the production of cytokines like IL-1β and IL-6 (Hehlgans & Pfeffer, 2005). Higher TNF-α and IL-1β levels were observed in the livers of IUGR-affected piglets, indicative of a shift toward proinflammation. Reports have indicated that a stronger proinflammatory bias exists with IUGR, and that IUGR resulted in a high risk of inflammation in the liver (van Deventer, 2000; He et al., 2018). Dietary DHA supplementation significantly decreased the concentrations of TNF-α, IL-1β, and IL-6, suggesting that DHA can reduce hepatic inflammatory responses. These results are similar to those previously reported (Li et al., 2006; Zhao et al., 2017). We also examined the mRNA expression levels of *IFN-γ*, *TNF-α*, *IL-1β*, and *IL-6* and found that all these genes were upregulated in the livers of IUGR-affected piglets. Importantly, dietary DHA supplementation clearly downregulated the expression of these genes in the livers of IUGR-affected piglets. These observations support that IUGR-affected piglets fed a diet supplemented with DHA can mitigate hepatic inflammation by decreasing the production of proinflammatory cytokines through transcriptional regulation of hepatic I*FN-γ*, *TNF-α*, *IL-1β*, and *IL-6* expression.

An imbalance between lipid utilization and disposal is the main cause of lipid accumulation in the liver, which eventually triggers lipoperoxidative stress and hepatic injury (Musso, Gambino, & Cassader, 2009). Total cholesterol is an important component of lipid metabolism, whereas HDL-C particles promote vascular health by extracting cholesterol from tissues and returning it to the liver. Therefore, an increased TC level and a reduced level of HDL-C are risk factors in the pathogenesis of coronary heart disease, as well as of some metabolic diseases (Li, Li, et al., 2018). In this study, IUGR resulted in significantly increased serum TC, VLDL-C and NEFA concentrations and a decreased HDL-C concentration, suggesting that IUGR may lead to hyperlipidemia. The increase in VLDL-C may be the reason for the increase in TC. Similarly, Lin et al. (2012) observed that IUGR-affected fetuses have higher TC and HDL-C concentrations than normal fetuses on days 90 and 110 of gestation. However, He et al. (2011) reported that the serum HDL-C level was lower in IUGR-affected than normal-weight piglets after birth, which was consistent with our results. We also found that TG and NEFA concentrations were significantly increased in the livers of IUGR-affected piglets. Studies have demonstrated that hepatic lipidosis is associated with increased concentrations of NEFAs and reduced levels of circulating TGs (Gerloff, Herdt, Wells, Liesman, & Emery, 1986). However, after DHA treatment, lipogenesis could be efficiently attenuated to a normal state, and showed no obvious differences compared to NBW piglets. Similar to our results, recent studies have shown that artemisinins can decrease lipid biosynthesis in adipose tissue (Wang et al., 2015). Importantly, in this study, HL and TL activities were decreased in the livers of IUGR-affected piglets. Hepatic lipase is essential for the hydrolysis of TG-rich lipoproteins, and is predominantly active in the liver. Hepatic lipase plays a major role in lipoprotein metabolism as a lipolytic enzyme that catalyzes the hydrolysis of TGs and phospholipids in chylomicron remnants, intermediate-density lipoprotein, and HDL (Schneider, Maximilian, Stephan, Nawroth, & Dugi, 2005). He et al. (2015) also observed that IUGR-affected piglets exhibit lower hepatic HL and TL activities than normal piglets. After DHA treatment, HL, LPL, and TL activities were all increased, whereas that of FAS was decreased in the liver of IUGR-affected piglets, which alleviated hepatic lipid accumulation. Artemisinin is reported to play adipose weight-reducing roles by rectifying inflammation-driven mitochondrial dysfunction. Gao et al. (2017) showed that 0.25 mg/kg artemisinin can reduce adipose weight in an inflammatory obese mouse model. In this study, we showed that DHA may reduce lipid accumulation through the regulation of lipid metabolism.

We also examined the expression of lipid metabolism-associated genes. AMPK and SIRT1 are well-known regulators of glucose and lipid metabolism, stimulating fatty acid oxidation and inhibiting hepatic lipid accumulation via a bidirectional interaction (Ruderman et al., 2010; Tessari, Coracina, Cosma, & Tiengo, 2009). SIRT1 activation can help prevent non-alcoholic fatty liver disease and reduce the expression of adipogenic genes like *SREBP-1*, *ACACB*, and *FAS* (Bruckbauer et al., 2017). Studies have shown that activation of AMPK in the upstream target of SIRT1 can inhibit lipid accumulation and decrease fatty acid synthesis, indicating that the AMPK/SIRT1 signaling pathway is important for the regulation of lipid metabolic balance. In this study, *ACCβ* and *SREBP-1* mRNA expression levels were upregulated, whereas those of *AMPKα*, *SIRT1*, and *SCD* were downregulated in the livers of IUGR-affected piglets. These results indicate that NFFA and TG accumulation in the liver of IUGR-affected piglets may be associated with suppression of the AMPK/SIRT1 signaling pathway. Importantly, we found that DHA supplementation resulted in significant downregulation of *FAS*, *ACCβ* and *SREBP-1* mRNA expression levels in IUGR-affected piglets and in significant upregulation of the mRNA expression levels of *AMPKα*, *SIRT1*, and *CPT-1*. Exposure to the SIRT1 activator (SRT 1720) in NAFLD mice reportedly resulted in decreased expression of *SREBP-1c*, *ACC*, and *FAS*, as well as reduced lipid accumulation in the liver (Lee et al., 2012; Podrini et al., 2013). In addition, activated AMPK has been reported to inhibit the decomposition and nuclear translocation of SREBP-1, ultimately leading to reduced plasma TC and TG levels (Huang et al., 2013). Moreover, AMPK was shown to indirectly increase the activity of CPT-1 by inhibiting acetyl-CoA carboxylase activity (Assifi et al., 2005; Xue & Kahn, 2006). Carnitine palmitoyltransferase is a rate-limiting enzyme for fatty acid beta-oxidation, a process that can enhance lipid mobilization (Korman, Waterham, Gutman, Jakobs, & Wanders, 2005). Overall, these results indicate that DHA can inhibit lipid synthesis and accelerate fatty acid beta-oxidation in the liver by activating the AMPK/SIRT1 signaling pathway, thereby improving abnormal lipid metabolism and attenuating IUGR-induced lipid accumulation.

In summary, our study showed that IUGR impaired piglet growth performance and led to a high risk of hepatic injury and disturbance of lipid metabolism in the livers of piglets. However, dietary DHA supplementation improved growth performance and attenuated hepatic injury in IUGR-affected piglets; these effects

were exerted through decreased proinflammatory cytokine production and regulation of abnormal hepatic lipid metabolism *via* transcriptional regulation of the AMPK/SIRT1 signaling pathway. Our research may aid in finding new strategies to treat IUGR in both animals and humans.

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REFERENCES

Akpaloo, W., & Purssell, E. (2014). Does the use of dihydroartemisinin-piperaquine in treating patients with uncomplicated falciparum malaria reduce the risk for recurrent new falciparum infection more than artemether-lumefantrine? *Malaria Research and Treatment*, *2014*, 263674–263674. https://doi.org/10.1155/2014/263674

Ananth, C. V., & Vintzileos, A. M. (2009). Distinguishing pathological from constitutional small for gestational age births in population-based studies. *Early Human Development*, *85*, 653–658. https://doi.org/10.1016/j.earlhumdev.2009.09.004

Assifi, M. M., Suchankova, G., Constant, S., Prentki, M., Saha, A. K., & Ruderman, N. B. (2005). AMP-activated protein kinase and coordination of hepatic fatty acid metabolism of starved/carbohydrate-refed rats. *American Journal of Physiology-endocrinology and Metabolism*, *289*, E794–E800. https://doi.org/10.1152/ajpendo.00144.2005

Bruckbauer, A., Banerjee, J., Cao, Q., Cui, X., Jing, J., Zha, L., … Zemel, M. B. (2017). Erratum: Leucine-nicotinic acid synergy stimulates AMPK/Sirt1 signaling and regulates lipid metabolism and lifespan in *Caenorhabditis elegans*, and hyperlipidemia and atherosclerosis in mice. *American Journal of Cardiovascular Disease*, *7*, 97.

Feng, M. X., Hong, J. X., Wang, Q., Fan, Y. Y., Yuan, C. T., Lei, X. H., … Hong, D. (2016). Dihydroartemisinin prevents breast cancer-induced osteolysis via inhibiting both breast cancer cells and osteoclasts. *Scientific Reports*, *6*, 46935. https://doi.org/10.1038/srep19074

Gao, Q., He, J., Liao, T., Chen, Y. P., Tian, L. L., Zhang, J. D., … Zeng, Q. P. (2017). Artemisinin mimics nitric oxide to reduce adipose weight by targeting mitochondrial complexes. *BioRxiv*, *157396*. https://doi.org/10.1101/157396

Gerloff, B. J., Herdt, T. H., Wells, W. W., Liesman, J. S., & Emery, R. S. (1986). Inositol and hepatic lipidosis. I. Effect of inositol supplementation and time from parturition on liver and serum lipids in dairy cattle. *Journal of Animal Science*, *62*, 1682–1692. https://doi.org/10.2527/jas1986.6261682x

Guan, Y., Liang, G., Martin, G. B., & Guan, L. L. (2017). Functional changes in mRNA expression and alternative pre-mRNA splicing associated with the effects of nutrition on apoptosis and spermatogenesis in the adult testis. *BMC Genomics*, *18*, 64–64. https://doi.org/10.1186/s12864-016-3385-8

Han, F., Hu, L., Xuan, Y., Ding, X., Luo, Y., Bai, S., … Che, L. (2013). Effects of high nutrient intake on the growth performance, intestinal morphology and immune function of neonatal intra-uterine growth-retarded pigs. *The British Journal of Nutrition*, *110*, 1819–1827. https://doi.org/10.1017/S0007114513001232

He, J., Dong, L. I., Xu, W., Bai, K., Lu, C., Wu, Y., … Wang, T. (2015). Dietary tributyrin supplementation attenuates insulin resistance and abnormal lipid metabolism in suckling piglets with intrauterine growth retardation. *PLoS ONE*, *10*, e0136848–e0136848. https://doi.org/10.1371/journal.pone.0136848

He, J., Niu, Y. U., Wang, F., Wang, C., Cui, T., Bai, K., … Wang, T. (2018). Dietary curcumin supplementation attenuates inflammation, hepatic injury and oxidative damage in a rat model of intra-uterine growth retardation. *British Journal of Nutrition*, *120*(5), 537–548. https://doi.org/10.1017/S0007114518001630

He, Q., Ren, P., Kong, X., Xu, W., Tang, H., Yin, Y., & Wang, Y. (2011). Intrauterine growth restriction alters the metabonome of the serum and jejunum in piglets. *Molecular BioSystems*, *7*, 2147–2155. https://doi.org/10.1039/c1mb05024a

Hehlgans, T., & Pfeffer, K. (2005). The intriguing biology of the tumour necrosis factor/tumour necrosis factor receptor superfamily: Players, rules and the games. *Immunology*, *115*, 1–20. https://doi.org/10.1111/j.1365-2567.2005.02143.x

Huang, C. H., Shiu, S. M., Wu, M. T., Chen, W. L., Wang, S. G., & Lee, H. M. (2013). Monacolin K affects lipid metabolism through SIRT1/AMPK pathway in HepG2 cells. *Archives of Pharmacal Research*, *36*, 1541–1551. https://doi.org/10.1007/s12272-013-0150-2

Klayman, D. L. (1985). Qinghaosu (artemisinin): An antimalarial drug from China. *Science*, *228*, 1049–1055. https://doi.org/10.1126/science.3887571

Korman, S. H., Waterham, H. R., Gutman, A., Jakobs, C., & Wanders, R. J. (2005). Novel metabolic and molecular findings in hepatic carnitine palmitoyltransferase I deficiency. *Molecular Genetics and Metabolism*, *86*, 337–343. https://doi.org/10.1016/j.ymgme.2005.07.022

Lee, C.-W., Wong, L.-L.-Y., Tse, E.-Y.-T., Liu, H.-F., Leong, V.-Y.-L., Lee, J.-M.-F., … Ching, Y.-P. (2012). AMPK promotes p53 acetylation via phosphorylation and inactivation of SIRT1 in liver cancer cells. *Cancer Research*, *72*, 4394–4404. https://doi.org/10.1158/0008-5472.CAN-12-0429

Li, H. L., Zhao, P. Y., Lei, Y., Hossain, M. M., Kang, J., & Kim, I. H. (2016). Dietary phytoncide supplementation improved growth performance and meat quality of finishing pigs. *Asian-Australasian Journal of Animal Sciences*, *29*(9), 1314–1321. https://doi.org/10.5713/ajas.15.0309

Li, W., Dong, Y., Tu, Y., & Lin, Z. (2006). Dihydroarteannuin ameliorates lupus symptom of BXSB mice by inhibiting production of TNF-alpha and blocking the signaling pathway NF-kappa B translocation. *International Immunopharmacology*, *6*, 1243–1250. https://doi.org/10.1016/j.intimp.2006.03.004

Li, W., Li, B., Lv, J., Dong, L., Zhang, L., & Wang, T. (2018a). Choline supplementation improves the lipid metabolism of intrauterine-growth-restricted pigs. *Asian-Australasian Journal of Animal Sciences*, *31*, 686–695. https://doi.org/10.5713/ajas.15.0810

Li, Y., Zhang, H., Su, W., Ying, Z., Chen, Y., Zhang, L., … Wang, T. (2018b). Effects of dietary *Bacillus amyloliquefaciens* supplementation on growth performance, intestinal morphology, inflammatory response, and microbiota of intra-uterine growth retarded weanling piglets. *Journal of Animal Science and Biotechnology*, *9*, 22–22. https://doi.org/10.1186/s40104-018-0236-2

Lin, G., Liu, C., Feng, C., Fan, Z., Dai, Z., Lai, C., … Wang, J. (2012). Metabolomic analysis reveals differences in umbilical vein plasma metabolites between normal and growth-restricted fetal pigs during late gestation. *The Journal of Nutrition*, *142*, 990–998. https://doi.org/10.3945/jn.111.153411

Liu, C., Lin, G., Wang, X., Wang, T., Wu, G., Li, D., & Wang, J. (2013). Intrauterine growth restriction alters the hepatic proteome in fetal pigs. *Journal of Nutritional Biochemistry*, *24*, 954–959. https://doi.org/10.1016/j.jnutbio.2012.06.016

Liu, J., He, J., Yang, Y., Yu, J., Mao, X., Yu, B., & Chen, D. (2014). Effects of intrauterine growth retardation and postnatal high-fat diet on hepatic inflammatory response in pigs. *Archives of Animal Nutrition*, *68*, 111–125. https://doi.org/10.1080/1745039X.2014.897532

Longo, S., Borghesi, A., Tzialla, C., & Stronati, M. (2014). IUGR and infections. *Early Human Development*, *90*, S42–S44. https://doi.org/10.1016/S0378-3782(14)70014-3

Lu, P., Zhang, F., Qian, S., Li, X., Cui, Z., Dang, Y., & Tang, Q. (2016). Artemisinin derivatives prevent obesity by inducing browning of WAT and enhancing BAT function. *Cell Research*, *26*, 1169–1172. https://doi.org/10.1038/cr.2016.108

Magee, T. R., Han, G., Cherian, B., Khorram, O., Ross, M. G., & Desai, M. (2008). Down-regulation of transcription factor peroxisome proliferator-activated receptor in programmed hepatic lipid dysregulation and inflammation in intrauterine growth-restricted offspring. *American Journal of Obstetrics & Gynecology*, *199*, 271.e1–271.e5. https://doi.org/10.1016/j.ajog.2008.05.022

Musso, G., Gambino, R., & Cassader, M. (2009). Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD). *Progress in Lipid Research*, *48*, 1–26. https://doi.org/10.1016/j.plipres.2008.08.001

NRC. (2012). *Nutrient requirements of swine* (Vol. *44*(3)).

Nyblom, H., Berggren, U., Balldin, J., Olsson, R., Göteborgs, U., Gothenburg, U., … Institutionen, F. K. N. (2004). High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. *Alcohol and Alcoholism*, *39*, 336–339. https://doi.org/10.1093/alcalc/agh074

Podrini, C., Borghesan, M., Greco, A., Pazienza, V., Mazzoccoli, G., & Vinciguerra, M. (2013). Redox homeostasis and epigenetics in non-alcoholic fatty liver disease (NAFLD). *Current Pharmaceutical Design*, *19*, 2737–2746. https://doi.org/10.2174/1381612811319150009

Qian, G., Jiang, H., Tao, L., Chen, Y. P., Tan, L. L., Zhang, J. D., … Huang, S. Q. (2017). Artemisinin mimics nitric oxide to reduce adipose weight by targeting mitochondrial complexes. *BioRxiv*, *157396*, 157396.

Redmer, D. A., Wallace, J. M., & Reynolds, L. P. (2004). Effect of nutrient intake during pregnancy on fetal and placental growth and vascular development. *Domestic Animal Endocrinology*, *27*, 199–217. https://doi.org/10.1016/j.domaniend.2004.06.006

Robert, R. (2002). Intrauterine growth restriction. *Obstetrics & Gynecology*, *99*, 490–496. https://doi.org/10.1097/00006250-200203000-00020

Ruderman, N. B., Xu, X. J., Nelson, L., Cacicedo, J. M., Saha, A. K., Lan, F., & Ido, Y. (2010). AMPK and SIRT1: A long-standing partnership? *American Journal of Physiology-endocrinology and Metabolism*, *298*, E751–E760. https://doi.org/10.1152/ajpendo.00745.2009

Saleem, T., Sajjad, N., Fatima, S., Habib, N., Ali, S. R., & Qadir, M. (2011). Intrauterine growth retardation–small events, big consequences. *Italian Journal of Pediatrics*, *37*, 41. https://doi.org/10.1186/1824-7288-37-41

Schneider, J. G., Maximilian, V. E., Stephan, S., Nawroth, P. P., & Dugi, K. A. (2005). Low plasma adiponectin levels are associated with increased hepatic lipase activity in vivo. *Diabetes Care*, *28*, 2181–2186. https://doi.org/10.2337/diacare.28.9.2181

Tarry-Adkins, J. L., Fernandez-Twinn, D. S., Hargreaves, I. P., Neergheen, V., Aiken, C. E., Martin-Gronert, M. S., … Ozanne, S. E. (2015). Coenzyme Q10 prevents hepatic fibrosis, inflammation, and oxidative stress in a male rat model of poor maternal nutrition and accelerated postnatal growth. *American Journal of Clinical Nutrition*, *103*, 579. https://doi.org/10.3945/ajcn.115.119834

Tessari, P., Coracina, A., Cosma, A., & Tiengo, A. (2009). Hepatic lipid metabolism and non-alcoholic fatty liver disease. *Scientia Sinica*, *19*, 291–302. https://doi.org/10.1016/j.numecd.2008.12.015

van Deventer, S. J. (2000). Cytokine and cytokine receptor polymorphisms in infectious disease. *Intensive Care Medicine*, *26*(Suppl. 1), S98–S102. https://doi.org/10.1007/s001340051125

Wan, X., Jiang, L., Zhong, H., Lu, Y., Zhang, L., & Wang, T. (2017). Effects of enzymatically treated\r Artemisia annua\r L. on growth performance and some blood parameters of broilers exposed to heat stress. *Animal Science Journal*, *88*. https://doi.org/10.1111/asj.12766

Wang, J., Zhang, C.-J., Chia, W. N., Loh, C. C. Y., Li, Z., Lee, Y. M., … Lin, Q. (2015). Haem-activated promiscuous targeting of artemisinin in *Plasmodium falciparum*. *Nature Communications*, *6*, 10111. https://doi.org/10.1038/ncomms10111

Wang, Y., Zhang, L., Zhou, G., Liao, Z., Ahmad, H., Liu, W., & Wang, T. (2012). Dietary L-arginine supplementation improves the intestinal development through increasing mucosal Akt and mammalian target of rapamycin signals in intra-uterine growth retarded piglets. *British Journal of Nutrition*, *108*, 1371–1381. https://doi.org/10.1017/S0007114511006763

Wei, M., Xie, X., Chu, X., Yang, X., Guan, M., & Wang, D. (2013). Dihydroartemisinin suppresses ovalbumin-induced airway inflammation in a mouse allergic asthma model. *Immunopharmacology and Immunotoxicology*, *35*, 382–389. https://doi.org/10.3109/08923973.2013.785559

Windisch, W., Schedle, K., Plitzner, C., & Kroismayr, A. (2008). Use of phytogenic products as feed additives for swine and poultry. *Journal of Animal Science*, *86*, 140–148. https://doi.org/10.2527/jas.2007-0459

Xue, B., & Kahn, B. B. (2006). AMPK integrates nutrient and hormonal signals to regulate food intake and energy balance through effects in the hypothalamus and peripheral tissues. *Journal of Physiology*, *574*, 73–83. https://doi.org/10.1113/jphysiol.2006.113217

Yao, Y., Yu, B., Chen, D., Tian, G., Mao, X., Zheng, P., & Liu, J. (2013). Effect of dietary folic acid supplementation on growth performance and hepatic protein metabolism in early-weaned intrauterine growth retardation piglets. *Journal of Integrative Agriculture*, *12*, 862–868. https://doi.org/10.1016/S2095-3119(13)60262-2

Zhang, X. G., Li, G. X., Zhao, S. S., Xu, F. L., Wang, Y. H., & Wang, W. (2014). A review of dihydroartemisinin as another gift from traditional Chinese medicine not only for malaria control but also for schistosomiasis control. *Parasitology Research*, *113*, 1769–1773. https://doi.org/10.1007/s00436-014-3822-z

Zhang, Z., Guo, M., Zhao, S., Shao, J., & Zheng, S. (2016). ROS-JNK1/2-dependent activation of autophagy is required for the induction of anti-inflammatory effect of dihydroartemisinin in liver fibrosis. *Free Radical Biology and Medicine*, *101*, 272–283. https://doi.org/10.1016/j.freeradbiomed.2016.10.498

Zhao, X., Wang, L., Zhang, H., Zhang, D., Zhang, Z., & Zhang, J. (2017). Protective effect of artemisinin on chronic alcohol induced-liver damage in mice. *Environmental Toxicology and Pharmacology*, *52*, 221–226. https://doi.org/10.1016/j.etap.2017.04.008

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