Animal Nutrition 17 (2024) 155–164

Contents lists available at ScienceDirect

Animal Nutrition

journal homepage: http://www.keaipublishing.com/en/journals/aninu/

Original Research Article

Maternal or post-weaning dietary fructo-oligosaccharide supplementation reduces stillbirth rate of sows and diarrhea of weaned piglets

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ARTICLE INFO

Article history:
Received 15 August 2023
Received in revised form
22 January 2024
Accepted 2 April 2024
Available online 8 April 2024

Keywords:
Stillbirth
Diarrhea
Fructo-oligosaccharide
Sow
Weaned piglet

ABSTRACT

Fructo-oligosaccharides (FOS) are well-known prebiotics that have the potential to improve sow reproductive performance and increase piglet growth. However, previous studies were observed in sole FOS-supplemented diets of sows or weaned piglets and did not consider the sow-to-piglet transfer effect on the performance and diarrhea rate of weaned piglets. This study explores the effects of dietary FOS supplementation on the reproductive performance of sows, and the effects of FOS supplementation at different stages on the growth performance and diarrhea rate of weaned piglets. A split-plot experimental design was used with sow diet effect in the whole plot and differing piglet diet effect in the subplot. Fifty-two multiparous sows (223.24 ± 14.77 kg) were randomly divided into 2 groups (0 or 0.2% FOS). The experiment lasted from day 85 of gestation to day 21 of lactation. Reproductive performance, glucose tolerance, placental angiogenesis, and intestinal flora of sows were assessed. At weaning, 192 weaned piglets were grouped in 2 × 2 factorial designs, with the main effects of FOS supplemental level of sow diet (0 and 0.2%), and FOS supplemental level of weaned piglet diet (0 and 0.2%), respectively. The growth performance and diarrhea rate of the weaned piglets were analyzed during a 28-d experiment. Maternal dietary supplementation of FOS was shown to reduce the stillbirth and invalid piglet rates ($P < 0.05$), improve the insulin sensitivity ($P < 0.05$) and fecal scores ($P < 0.05$) of sows, increase the abundance of *Akkermansia muciniphila* ($P = 0.016$), decrease the abundance of *Escherichia coli* ($P = 0.035$), and increase the isovalerate content in feces ($P = 0.086$). Meanwhile, the placental angiogenesis marker *CD31* expression was increased in sows fed FOS diet ($P < 0.05$). Moreover, maternal and post-weaning dietary FOS supplementation reduced the diarrhea rate of weaned piglets ($P < 0.05$) and increased the content of short-chain fatty acids in feces ($P < 0.05$). Furthermore, only post-weaning dietary FOS supplementation could improve nutrient digestibility of weaned piglets ($P < 0.05$). Collectively, FOS supplementation in sows can reduce stillbirth rate, perinatal constipation, and insulin resistance, as well as improve placental vascularization barrier. Additionally, maternal and post-weaning dietary FOS supplementation reduced the diarrhea rate of weaned piglets, but only FOS supplementation in piglets alone at weaning stage could improve their nutrient digestibility.

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Peer review under responsibility of Chinese Association of Animal Science and Veterinary Medicine.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.aninu.2024.04.002

1. Introduction

In recent years, with the improvement of genetic selection and breeding management, the average litter size of modern high yielding sows has been increasing, but so has the stillbirth rate of piglets (Gourley et al., 2020; Van Den Bosch et al., 2019; Vanderhaeghe et al., 2013). One of the main reasons can be attributed to impaired glucose balance of sows with insulin resistance during late gestation. Accumulated evidence suggests that insulin resistance can cause metabolic disorder, leading to the increase of stillbirth and lack of vitality in newborn piglets (Li et al., 2020; Lopez et al., 2022). The transport efficiency of nutrients and the normal growth and development of fetus are directly determined by the normal physiological structure of placenta. Our previous studies have shown that enhancing placental function can improve the sow reproductive performance by promoting fetal survival and growth (Hu et al., 2021; Wu et al., 2023). Likewise, sows are prone to constipation due to less intestinal activity in late gestation, a condition corresponding to obstructed labor or stillbirth (Tabeling et al., 2003).

Diarrhea after weaning is one of the most important factors affecting the growth performance and the survival rate of weaned piglets (Heo et al., 2010). Weaning diarrhea could often cause changes in the morphology and function of small intestine of piglets, damaging digestion and absorption ability and ultimately leading to growth retardation and increased mortality of piglets (Suiryanrayna and Ramana, 2015; Tang et al., 2022). The gut health status determines the health of animal body and is closely related to its production level and efficiency. This suggests a necessity to find effective functional nutrients to alleviate intestinal damage in piglets.

Fructo-oligosaccharides (FOS), as functional oligosaccharides, are fermented by intestinal microorganisms to produce short-chain fatty acids (SCFA), which play an important role in regulating host nutrition and health (Koh et al., 2016; Tolhurst et al., 2012). Several studies have shown that oligosaccharides have the potential to improve the reproductive performance of sows (Cheng et al., 2015; Xie et al., 2015, 2016). FOS have been widely used as a common prebiotic and are reported beneficial to weaned piglets (Luo et al., 2022; Mikkelsen et al., 2003; Oli et al., 1998; Tsukahara et al., 2003). However, previous studies were limited to the sole addition of FOS in diets of sows or in diets of weaned piglets, and did not consider the sow-to-piglet transfer effect and the effects of FOS addition time on the performance and diarrhea rate of weaned piglets.

Therefore, this study aimed to investigate the effects of maternal or post-weaning dietary FOS supplementation on reproductive performance of sows and growth performance of weaned piglets through trials from day 85 of gestation to day 28 after weaning of piglets. Specifically, FOS was added into the diet of sows at day 85 of the gestation period to investigate the effects of FOS on reproductive/lactation performance, constipation, and insulin resistance of sows. Furthermore, the effects of FOS supplementation at different stages on growth performance, diarrhea rate and nutrient digestibility of weaned piglets were investigated by split-plot experiments. This study provides data support for FOS application in pig production.

2. Materials and methods

2.1. Animal ethics statement

All animal experimental design and procedures presented in this study were approved by the Animal Care and Use Committee of the Institute of Subtropical Agriculture, Chinese Academy of Science, and performed according to the Guidelines for Care and Use of Laboratory Animals of South China Agriculture University (2024G009).

2.2. Animal feeding management and experimental design

The management and experimental design followed the animal care rules approved by the South China Agricultural University Animal Care and Use Ethics Committee. Fifty-two multiparous sows (Duroc–Landrace–Yorkshire) (223.24 ± 14.77 kg) were randomly divided into 2 groups at day 85 of gestation. There were 26 sows in each group and one replicate per sow. The experiment lasted from day 85 of gestation to day 21 of lactation. The control group (CON) was fed a basal diet, and the FOS group was fed 0.2% FOS diet. There was no difference in feed intake between the groups from day 85 of gestation to delivery (3.19 ± 0.25 kg/d, 3.17 ± 0.23 kg/d, respectively). The basal diet of test sows was formulated according to the nutritional requirements of NRC (2012), and the composition and nutritional levels of the basal diet are shown in Table S1.

At the end of day 21 of lactation, weaned piglets were assigned into 4 groups by a split-plot experimental design (Fig. 1), and 192 weaned piglets were grouped in 2 × 2 factorial designs. The main effects were FOS supplemental level of sow diet (0 and 0.2%) and FOS supplemental level of weaned piglet diet (0 and 0.2%), coupled with their interaction (sow-to-piglet transfer effect). Each group had 6 pens and each pen had 8 repetitions. The experiment lasted 28 d. The diets were formulated to meet the nutrient requirements for weaned piglets (NRC, 2012), with the basal diet composition and nutrient levels shown in Table S2.

2.3. Intravenous glucose tolerance test (IVGTT)

Twelve sows ($n = 6$ per group) were selected for the experiment at day 110 of gestation as previously reported (Bowe et al., 2014; Yang et al., 2019). After fasting for 8 h, the fasting blood samples of sows were collected from the auricular vein, and the blood glucose value was measured by the automatic blood glucose analyzer (Sinocare Inc., Changsha, China) and recorded at 0 min. Then 0.5 g glucose per kilogram body weight as 50% glucose solution (Sigma, USA) was administered intravenously. The blood glucose of sows was measured at 15, 30, 60, 90 and 120 min after injection.

2.4. Measurements of reproductive performance

The reproductive performance and lactation performance (Table S3) of sows were recorded. Back fat of sows at day 85 and 110 of gestation, day of parturition, and day 21 of lactation were accurately measured for each sow to calculate back fat and body weight change. Reproductive performance of sows was recorded after parturition (total litter size, litter size alive, number of stillbirths, mummified fetus, invalid piglets, litter weight at birth, birth weight and average birth weight). The number of piglets should be adjusted for sows by means of fosterage within 48 h after delivery to ensure that the number of piglets in each litter is about 12. According to sow litter size within 48 h of farrowing, the number and litter weight of piglets on day 1 and 21 of foster care were calculated. The invalid piglets included stillbirth and mummified piglets.

2.5. Sows' intestinal function scores, fecal samples, blood samples and placental samples

The intestinal activity of all sows was monitored from 5 d prior to parturition, and the feces of each sow were visually (qualitatively) evaluated and scored daily (Oliviero et al., 2009). Briefly, we used a scale of 0 to 5, with 0 (absence of feces), 1 (dry and pellet-

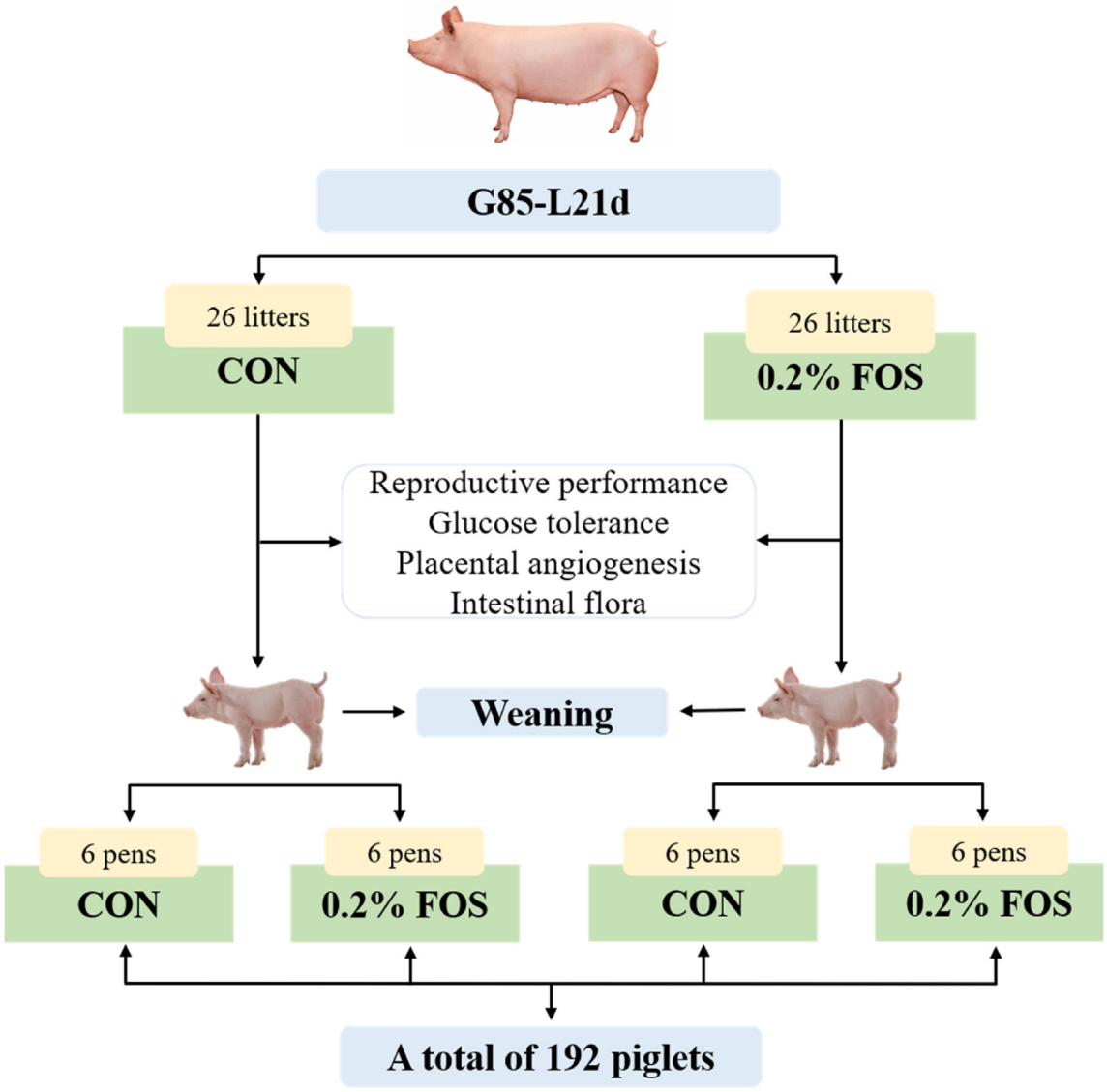

Fig. 1. A split-plot experimental design of dietary fructo-oligosaccharide (FOS) supplementation in pigs. CON = control diet group; G85d = day 85 of gestation; L21d = day 21 of lactation.

shaped), 2 (between dry and normal), 3 (normal and soft, but firm and well formed), 4 (between normal and wet, still formed but not firm), and 5 (very wet feces, unformed and liquid).

Fresh fecal samples were collected directly by massaging the rectum of sows from day 110 of gestation, followed by immediate storage at −80 °C until further analysis.

Fasting blood samples of sows were collected by the ear vein at day 110 of gestation. Then, plasma was isolated by centrifugation at 1500 × *g* and 4 °C for 10 min and stored at −20 °C until chemical analysis.

On parturition day, 8 sows were randomly selected from each group for sampling. After each sow had finished parturition and delivered the placenta, placental samples were collected at 3 to 4 cm around the junction of the umbilical cord and placenta. Finally, the samples were stored in a refrigerator at −80 °C for subsequent experiments.

2.6. Chemical analysis of blood indicators

The fasting plasma glucose concentration of sows was determined using a glucose oxidase assay kit as guided by the manufacturer (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Plasma insulin levels of sows were determined using ultrasensitive pig insulin ELISA kit (Jiangsu Meimian Industry Co., LTD., Jiangsu, China). Insulin resistance and sensitivity were evaluated through homeostasis model assessment (HOMA): HOMA-insulin resistance (HOMA-IR) = fasting insulin (mIU/L) × fasting glucose (mmol/L)/22.5 (coefficient 22.5, a correction factor, which is defined as 5 μU/mL plasma insulin corresponding to a blood glucose level of 4.5 mmol/L in a normal desirable individual) (Hare et al., 2022).

2.7. Growth performance and diarrhea scores of weaned piglets

Feed intake and fasting body weight of each pen were recorded during the experiment to calculate average daily gain (ADG), average daily feed intake (ADFI) and gain/feed ratio (G/F) on day 1, 14 and 28 of the experiment. Fecal scores were monitored each morning and quantified using a scale of 0 to 3, with 0 = solid, 1 = semi-solid, 2 = semi-liquid, and 3 = liquid. A score ≥2 is defined as piglet diarrhea. Diarrhea rate (%) = [total number of diarrhea in each group/(experiment days × number of piglets in

each group)] × 100. Diarrhea index (%) = [diarrhea score sum of each group/(experiment days × number of piglets in each group)] × 100 (Huang et al., 2022).

2.8. Fecal samples of weaned piglets

Fresh fecal samples were collected from piglets on day 24 to 26 after weaning. One pen of piglet feces was placed in one tube, and the fecal samples were stored at −80 °C for subsequent analysis.

2.9. Fecal short-chain fatty acids and branched-short-chain fatty acid analysis

After thawing, the fecal samples (20 mg) were taken for follow-up treatment using the method adopted by Yang et al. (2022). SCFA and branched-short-chain fatty acids (BSCFA) in feces were analyzed by gas–liquid chromatography.

2.10. Fecal DNA isolation and RT-qPCR

Bacterial DNA was extracted from feces using a DNA extraction kit (Magen, Guangdong, China) following the manufacturer's instructions. RT-qPCR analysis of the relative abundance of related bacteria in all samples was performed using SYBR Premix Ex Taq reagents (EZBioscience, Guangdong, China). The universal bacterial reference primer set was selected for calculating the abundance of target bacterial, and the specific sequences are shown in Table S4. The average value of the number of copies was used for statistical analysis. The abundances of related bacteria were calculated as a relative value normalized to the total bacteria of the same sample.

2.11. RT-qPCR analysis of gene expression

According to the manufacturer's instructions, the total placental RNA was extracted using the RNA extraction kit (EZBioscience, Guangzhou, China). The A260/A280 ratio of the RNA used for the experiment should be between 1.8 and 2.0. After reverse transcription using Primer Script RT reagent Kit (EZBioscience, Guangzhou, China), RT-qPCR was performed to analyze the expression levels of related genes on a Quant Studio 6 RealTime PCR System (Thermo Fisher, Waltham, USA). The relative expression was calculated using the comparative method ($2^{-\Delta\Delta Ct}$), with β-actin as the internal control. The primers used in the experiments are listed in Table S4.

2.12. Western blot analysis

Placental samples were processed with RIPA lysis buffer (Beyotime Biotechnology, Shanghai, China) containing phenylmethylsulfonyl fluoride (PMSF) (Beyotime Biotechnology, Shanghai, China). Total protein concentration was detected using the protein assay kit (Beyotime Biotechnology, Shanghai, China). After sodium dodecyl sulfonate polyacrylamide gel electrophoresis (SDS-PAGE), protein samples were transferred to polyvinylidene fluoride (PVDF) membranes. After blocking with 5% nonfat milk for 2 h, the membranes were incubated with the primary antibodies against platelet endothelial cell adhesion molecule-1 (CD31) (ab281583, Abcam, USA, 1:1000) and β-actin (4970, CST, USA, 1:1000) overnight at 4 °C. Next, the membranes were incubated with horseradish peroxidase (HRP) conjugated anti-rabbit immunoglobulin G (IgG) secondary antibody (AS014, Abclonal, China, 1:5,000) for 2 h at room temperature, followed by detection using a BeyoECL Star kit (Beyotime Biotechnology, Shanghai, China). The band intensity was quantified by ImageJ software, and β-actin was used to normalize the relative intensity of target proteins.

2.13. Analysis of digestibility of nutrients

TiO_2 was used as exogenous indicator for digestion test, where 0.2% TiO_2 was added to the diet as exogenous labeled experimental diet. From day 24 after weaning, feed samples and fecal samples were collected continuously for 3 d. Partial feed samples (50 g) were taken from each group every day. After sampling, the feed samples were evenly mixed and stored for each group. Approximately 100 g of freshly excreted feces of piglets were collected daily from each pen, and fecal samples from each pen were mixed with each other. The feed and fecal samples were dried in a forced-draft oven (65 °C) for 72 h, grinding through a 4-mm screen, and thoroughly mixed for chemical analysis. The diet and fecal samples were analyzed in terms of dry matter (DM, AOAC method 930.15), crude protein (CP, AOAC method 990.03), ash (method 938.08) and crude fiber (CF, ISO 6865-2000) (AOAC, 2007). Neutral detergent fiber (NDF) and acid detergent fiber (ADF) were obtained by the method of Van Soest (Van Soest et al., 1991). The diet and fecal samples were also analyzed to establish the TiO_2 content using a UV spectrophotometer as reported by Biasato et al. (2019). Nutrient digestibility was calculated according to the analysis value of nutrient concentration and TiO_2 concentration in feed and feces: apparent total tract digestibility (ATTD, %) = 100 − [100 × ($C1$ × $F2$)/($C2$ × $F1$)], where $C1$ and $F1$ represent TiO_2 and nutrient content (%) in the feed, respectively; $C2$ and $F2$ represent TiO_2 and nutrient content (%) in the feces, respectively.

2.14. Statistical analysis

The number of sows during the experimental period is shown in Table S5. Each sow served as a separate experimental unit. The data were analyzed by the SPSS software package (IMB SPSS v. 27, IBM Corp., Armonk, NY, USA). Experimental data were statistically analyzed by independent t-test. In the experiment of weaned piglets, statistical analysis was conducted with piglets per pen as one experimental unit. The data were analyzed by the SPSS software package, and the two-way analysis of variance (ANOVA) was used to analyze the main effect of FOS in sows, weaned piglets, and interaction effect of FOS in sows and piglets. Diarrhea rate and diarrhea index were analyzed using the Chi-square test. The results are shown as mean ± standard error of the mean (SEM) or mean. A value of $P < 0.05$ was considered as statistically significant difference, with $P < 0.10$ as a trend to significance.

3. Results

3.1. Reproductive performance of sows

As shown in Table 1, dietary FOS supplementation had no effect on the number of live-born piglets and birth weight of litters ($P > 0.05$), but exhibited a tendency to shorten the gestation days of the sows ($P = 0.073$). Additionally, CON group had a larger number of piglets in the weight range of 1.0 to 1.5 kg ($P = 0.071$) (48.4% versus 41.5%), and FOS group had a larger number of piglets with body weight greater than 1.5 kg ($P = 0.072$) (45.7% versus 38.9%).

3.2. Stillbirth and invalid piglet

In Fig. 2, it was shown that compared with CON group, FOS group was signficantly lower ($P < 0.05$) in stillbirth number, stillbirth rate and invalid piglet rate.

Table 1
Effects of dietary fructo-oligosaccharide (FOS) supplementation on reproductive performance of sows.[1]

Item	CON	FOS	SEM	*P*-value
No. of litters	26	25		
Parity	2.8	2.8	0.05	0.953
Gestation days, d	115.3	114.5	0.20	0.073
Litter size	15.3	14.4	0.50	0.398
No. of live-born piglets per litter	13.3	13.4	0.47	0.889
No. of weak piglets (≤0.8 kg) per litter	0.3	0.3	0.09	0.888
No. of mummified fetus per litter	0.1	0.2	0.06	0.332
Birth weight of piglet, kg	1.4	1.4	0.02	0.776
Birth weight of litter, kg	18.8	19.3	0.61	0.672
Birth weight distribution of piglets[2], %				
<1.0 kg	12.7	12.8		0.975
1.0 to 1.5 kg	48.4	41.5		0.071
>1.5 kg	38.9	45.7		0.072

[1] CON group = control diet group; FOS group = 0.2% FOS diet group.
[2] Birth weight distribution of piglets was calculated using chi-square.

Table 2
Effects of dietary fructo-oligosaccharide (FOS) supplementation on fecal score of sows.[1]

Item	CON	FOS	SEM	*P*-value
No. of samples	26	25		
5 d before farrowing	2.0	2.2	0.08	0.179
4 d before farrowing	2.2[b]	2.5[a]	0.07	0.026
3 d before farrowing	2.3	2.5	0.08	0.310
2 d before farrowing	2.3	2.5	0.08	0.189
1 d before farrowing	2.2	2.4	0.07	0.122

[a,b]Different lowercase letters in each row represent significant difference at $P < 0.05$.
[1] CON group = control diet group; FOS group = 0.2% FOS diet group.

Table 3
Effects of dietary fructo-oligosaccharide (FOS) supplementation on fecal volatile fatty acids (VFAs) of sows ($n = 8$) (ng/g).[1]

Item	CON	FOS	SEM	*P*-value
Acetate	1182.1	1336.5	61.34	0.221
Propionate	301.7	326.7	29.38	0.691
Butyrate	140.1	170.3	13.25	0.273
Valerate	44.3	54.2	3.58	0.176
Total SCFA	1668.3	1887.8	101.57	0.306
Isobutyrate	27.3	32.3	1.79	0.177
Isovalerate	34.2	43.3	2.61	0.086
Total BSCFA	61.5	75.6	4.23	0.098
Total VFA	1729.9	1963.4	105.08	0.292

SCFA, short-chain fatty acid; BSCFA, branched-short-chain fatty acid; total SCFA, the sum of acetate, propionate, butyrate, and valerate; total BSCFA, isobutyrate and isovalerate; total VFA, the sum of acetate, propionate, butyrate, isobutyrate, valerate and isovalerate.
[1] CON group = control diet group; FOS group = 0.2% FOS diet group.

3.3. Fecal scores of sows

In Table 2, fecal scoring of sows at 5 d before parturition indicated that compared with CON group, FOS group was significantly higher in the fecal score of sows at 4 d before farrowing ($P = 0.026$).

3.4. Short-chain fatty acids, branched-short-chain fatty acids in feces of sows

The effects of dietary FOS supplementation on sows' fecal volatile fatty acids (VFAs) are shown in Table 3, where FOS group was seen to have an uptrend in isovalerate and total BSCFA relative to CON group ($P = 0.086$ and 0.098, respectively).

3.5. Bacterial populations in feces of sows

Dietary FOS inclusion did not affect total bacteria in the feces of sows (data not shown). In Table 4, compared with CON group, FOS group was significantly lower ($P = 0.035$) in the relative abundance of *Escherichia coli* and higher ($P = 0.016$) in the relative abundance of *Akkermansia muciniphila* in the feces of sows, with an increasing trend in the abundance of *Bifidobacterium* ($P = 0.071$).

3.6. Glucose tolerance and insulin sensitivity

In IVGTT, compared with CON group, FOS group was notably lower at blood glucose value at 60 min after glucose injection ($P = 0.004$; Fig. 3A) and had a smaller area under the curve (AUC) of glucose from 0 to 120 min ($P = 0.022$; Fig. 3B) after intravenous administration of glucose solution. Additionally, compared with CON group, FOS group had significantly lower HOMA-IR values ($P = 0.049$; Fig. 3C).

3.7. Placental angiogenesis, placental barrier, and inflammatory factors

The effects of FOS on placental function were investigated by analyzing the expression of genes related to placental angiogenesis and placental barrier. In Fig. 4A–C, FOS group was shown to have higher mRNA and protein levels of CD31 than CON group ($P < 0.05$). Additionally, compared with CON group, FOS group showed an increasing trend in the mRNA expression of vascular endothelial

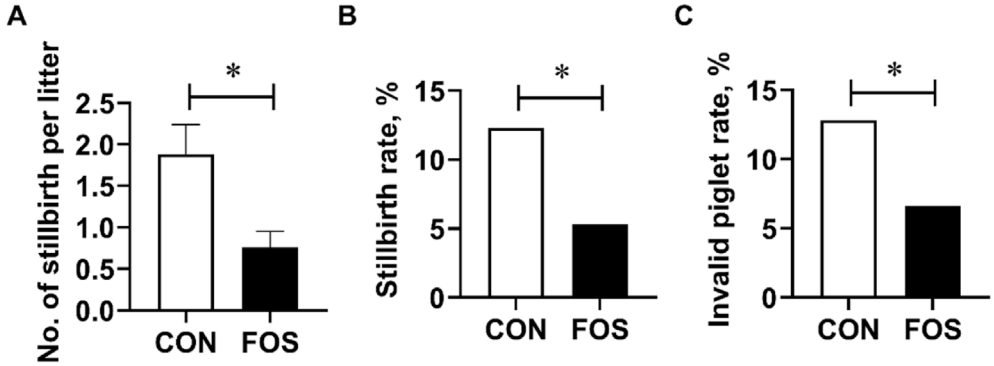

Fig. 2. Effects of dietary fructo-oligosaccharide (FOS) supplementation on stillbirth and invalid piglet of sows ($n = 26, 25$). (A) The number of stillbirth per litter. (B) The stillbirth rate. (C) The invalid piglet rate. Data are expressed as mean ± SEM. CON group = control diet group; FOS group = 0.2% FOS diet group. The invalid piglets include stillbirth and mummified piglets. Stillbirth rates and invalid piglet rates of piglets was calculated using chi-square. *$P < 0.05$.

Table 4
Effects of dietary fructo-oligosaccharide (FOS) supplementation on bacterial population concentration in feces of sows ($n = 8$, relative abundance of CON).[1]

Item	CON	FOS	SEM	*P*-value
Escherichia coli	1.0[a]	0.4[b]	0.14	0.035
Desulfovibrio desulfuricans	1.0	0.9	0.11	0.758
Bifidobacterium	1.0	3.3	0.64	0.071
Lactobacillus	1.0	0.6	0.25	0.529
Faecalibacterium prausnitzii	1.0	0.9	0.16	0.997
Akkermansia muciniphila	1.0[b]	2.5[a]	0.35	0.016
Enterococcus faecium	1.0	1.1	0.27	0.875

[a,b]Different lowercase letters in each row represent significant difference at $P < 0.05$.
[1] CON group = control diet group; FOS group = 0.2% FOS diet group.

growth factor A (*VEGF-A*) ($P = 0.080$; Fig. 4C), and higher expression of placental barrier-related genes ($P < 0.05$; Fig. 4D). However, the 2 groups showed no significant difference in mRNA expression of placental inflammatory factors ($P > 0.05$; Fig. 4E).

3.8. Growth performance of weaned piglets

The growth performance parameters of weaned piglets are shown in Table 5, where dietary FOS supplementation at different stages was shown to have no effect on body weight, ADG, ADFI, and G/F of weaned piglets ($P > 0.05$).

3.9. Diarrhea rate and diarrhea index of weaned piglets

In Table 6, it was shown that on day 1 to 7 of the experiment, dietary FOS supplementation in piglets reduced the diarrhea rate and diarrhea index of weaned piglets ($P = 0.010$). On day 1 to 14, dietary FOS supplementation in sows was shown to decrease the diarrhea rate and diarrhea index of weaned piglets ($P = 0.012$). However, dietary FOS supplementation in both sows and piglets had no notable effect on the diarrhea rate and diarrhea index of weaned piglets ($P > 0.05$).

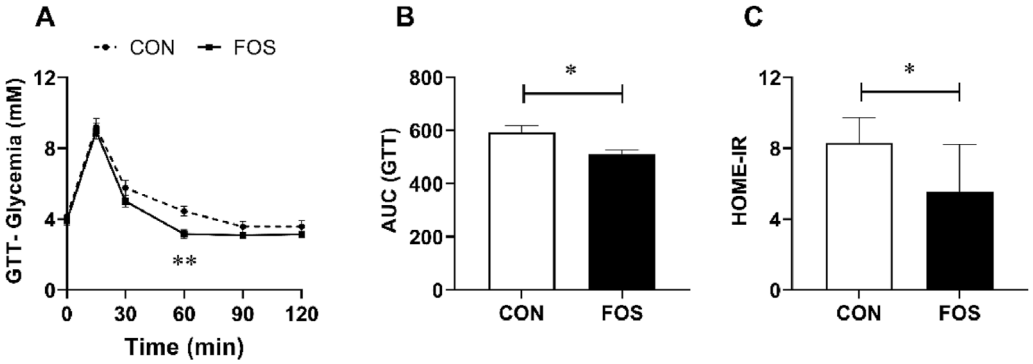

Fig. 3. Glucose tolerance and insulin sensitivity assessment (day 110 of gestation). (A) Intravenous glucose tolerance test (IVGTT) from 0 to 120 min ($n = 6$). (B) Area under the curve (AUC) in glucose tolerance test (GTT). (C) Homeostasis model assessment of insulin resistance (HOMA-IR) ($n = 6$). Data are expressed as mean ± SEM. CON group = control diet group; FOS group = 0.2% FOS diet group. *$P < 0.05$, **$P < 0.01$.

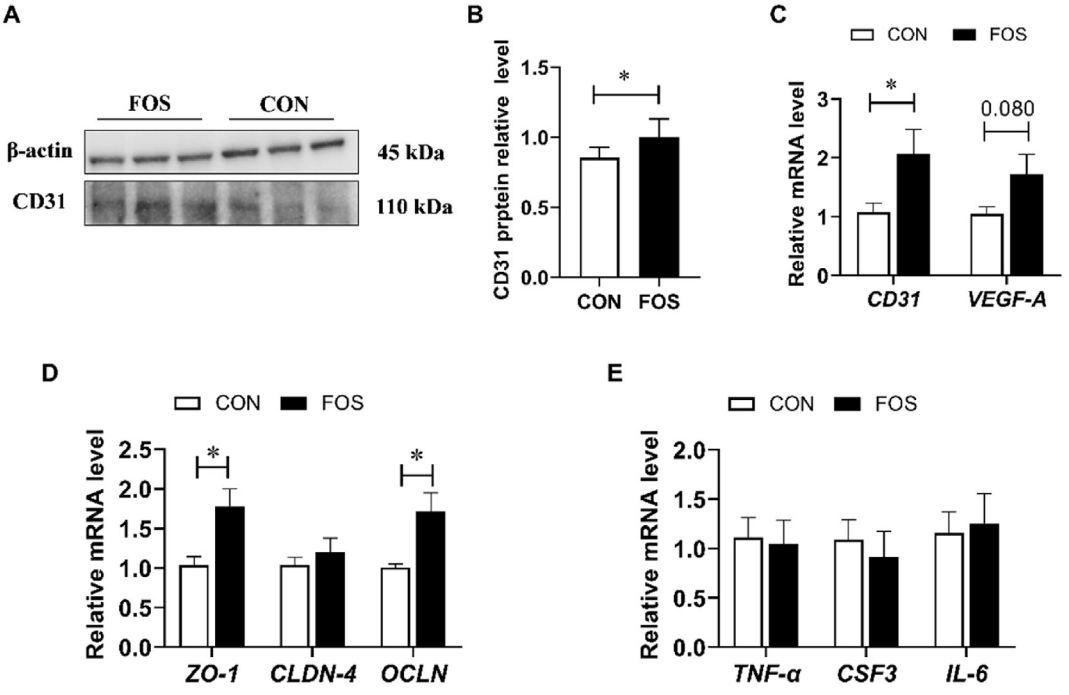

Fig. 4. Effects of dietary fructo-oligosaccharide (FOS) supplementation on placental angiogenesis, placental barrier, and inflammatory factors in sows. (A to B) Protein expression levels of placental angiogenesis CD31 ($n = 6$). (C to E) The mRNA expression of placental angiogenesis, placental barrier, and inflammatory factors in sows ($n = 8$). Data are expressed as mean ± SEM. CON group = control diet group; FOS group = 0.2% FOS diet group. *$P < 0.05$.

Table 5
Effects of combined fructo-oligosaccharide (FOS) supplementation in sows or piglets on growth performance of weaned piglets.[1]

Item	CON sow		FOS sow		SEM	*P*-value[2]		
	CON piglet	FOS piglet	CON piglet	FOS piglet		Sow	Piglet	Sow × piglet
Number of repeats	6	6	6	6				
Body weight, kg								
Initial weight	6.2	6.2	6.2	6.2	0.01	0.122	0.395	0.395
On day 28	13.5	14.3	14.3	14.1	0.30	0.672	0.715	0.453
ADG, g/d								
Day 1 to 14	210.4	222.4	220.9	225.9	5.82	0.573	0.497	0.773
Day 15 to 28	357.4	401.9	403.0	379.8	20.46	0.785	0.811	0.438
Day 1 to 28	273.4	300.6	300.5	291.7	11.07	0.699	0.700	0.444
ADFI, g/d								
Day 1 to 14	249.2	257.4	250.2	251.9	3.65	0.776	0.528	0.683
Day 15 to 28	573.9	628.5	621.6	610.3	24.14	0.775	0.676	0.525
Day 1 to 28	411.6	442.9	435.9	431.1	11.73	0.801	0.595	0.471
G/F								
Day 1 to 14	0.8	0.8	0.8	0.8	0.02	0.302	0.577	0.865
Day 15 to 28	0.6	0.6	0.6	0.6	0.01	0.702	0.610	0.610
Day 1 to 28	0.6	0.6	0.7	0.7	0.01	0.460	0.941	0.656

ADG = average daily gain; ADFI = average daily feed intake; G/F = gain to feed ratio.
[1] CON sow and FOS sow represent basal diet and FOS diet (0.2%) for sows, respectively. CON piglet and FOS piglet represent basal diet and FOS diet (0.2%) for piglets, respectively.
[2] *P*-value for sow, piglet, and sow × piglet represent the main effect of FOS addition in sows, the main effect of FOS addition in piglets, and the interaction effect of FOS addition in sows and piglets, respectively.

3.10. Digestibility of nutrients of weaned piglets

As shown in Table 7, dietary FOS supplementation in piglets alone could improve their apparent total tract digestibility (ATTD) of dry matter (DM) ($P = 0.002$), with an increasing trend in the ATTD of crude protein (CP) ($P = 0.067$). However, dietary FOS supplementation in sows alone had no effect on nutrient digestibility of weaned piglets ($P > 0.05$).

3.11. Short-chain fatty acids and branched-short-chain fatty acids in feces of weaned piglets

In Table 8, dietary FOS supplementation in sows was seen to augment the content of propionate in feces of weaned piglets ($P = 0.045$), coupled with a tendency to increase the acetate, total SCFA, and total VFA content ($0.05 \leq P < 0.10$). Additionally, dietary FOS supplementation in piglets increased the concentration of valerate in feces of weaned piglets ($P = 0.044$) and showed a trend to increase the propionate content ($P = 0.062$). However, the combined FOS supplementation in both sows and piglets had no effect on fecal SCFA of weaned piglets ($P > 0.05$).

4. Discussion

This study investigated whether dietary FOS supplementation in late gestation of sows could improve their reproductive performance. Studies have shown that sow litter size is determined by conception rate in early gestation (Baker et al., 2013; Böhmer et al., 2006). In this study, FOS inclusion in late pregnancy had no effect on total litter size, consistent with our expectations. Studies have shown that low birth weight and stillbirth rates of piglets were very high in sow production, and the late gestation period was the critical period of fetal growth and development (Huang et al., 2021a; Kraeling and Webel, 2015). Our results showed that dietary FOS supplementation could significantly reduce the number of stillbirths, stillbirth rates, and invalid piglet rates.

Constipation is a risk factor for accumulation of toxic substances including pathogenic bacteria in feces, which can increase the absorption of endotoxins in the intestine and eventually lead to

Table 6
Effects of combined fructo-oligosaccharide supplementation in sows or piglets on diarrhea rate and diarrhea index of weaned piglets.

Item	CON Sow		FOS Sow		SEM	*P*-Value		
	CON Piglet	FOS Piglet	CON Piglet	FOS Piglet		Sow	Piglet	S×P
Number of repeats	6	6	6	6				
Diarrhea rate, %								
D 1 to 7	6.5	4.2	7.4	2.1	0.77	0.668	0.010	0.289
D 1 to 14	13.5	11.8	10.1	6.9	0.85	0.012	0.112	0.655
D 1 to 21	19.8	17.8	16.8	12.1	1.37	0.115	0.217	0.632
D 1 to 28	21.8	20.1	18.7	15.6	1.36	0.177	0.387	0.799
Diarrhea index, %								
D 1 to 7	13.1	8.3	14.9	4.2	1.55	0.668	0.010	0.289
D 1 to 14	27.4	23.5	20.4	13.9	1.72	0.012	0.100	0.675
D 1 to 21	39.9	35.5	33.6	24.2	2.75	0.113	0.208	0.638
D 1 to 28	43.8	40.2	37.4	31.1	2.73	0.174	0.376	0.804

Table 7
Effects of combined fructo-oligosaccharide (FOS) supplementation in sows or piglets on apparent total tract digestibility (ATTD) in weaned piglets.[1]

Item	CON sow		FOS sow		SEM	*P*-value[2]		
	CON piglet	FOS piglet	CON piglet	FOS piglet		Sow	Piglet	Sow × piglet
Number of repeats	6	6	6	6				
ATTD, %								
DM	83.5	85.8	84.3	86.1	0.35	0.369	0.002	0.607
CP	76.0	79.2	75.9	77.5	0.64	0.489	0.067	0.515
NDF	54.8	64.4	57.8	56.3	1.73	0.458	0.239	0.113
ADF	49.5	57.4	48.7	55.5	2.21	0.762	0.115	0.895

DM = dry matter; CP = crude protein; NDF = neutral detergent fiber; ADF = acid detergent fiber.
[1] CON sow and FOS sow represent basal diet and FOS diet (0.2%) for sows, respectively. CON piglet and FOS piglet represent basal diet and FOS diet (0.2%) for piglets, respectively.
[2] *P*-value for sow, piglet, and sow × piglet represent the main effect of FOS addition in sows, the main effect of FOS addition in piglets, and the interaction effect of FOS addition in sows and piglets, respectively.

Table 8
Effects of combined fructo-oligosaccharide (FOS) supplementation in sows or piglets on short-chain fatty acids (SCFAs), and branched-short-chain fatty acids (BSCFA) in the feces of weaned piglets.[1]

Item	CON sow		FOS sow		SEM	*P*-value[2]		
	CON piglet	FOS piglet	CON piglet	FOS piglet		Sow	Piglet	Sow × piglet
Number of repeats	6	6	6	6				
Concentration of VFA, ng/g								
Acetate	1147.3	1267.2	1357.5	1417.5	46.40	0.055	0.321	0.738
Propionate	361.7	415.4	423.9	564.9	28.05	0.045	0.062	0.385
Butyrate	261.0	259.7	255.9	318.7	16.74	0.378	0.437	0.357
Valerate	29.3	48.4	40.6	54.8	4.12	0.265	0.044	0.752
Total SCFA	1799.5	1986.9	2081.6	2355.9	86.97	0.059	0.171	0.792
Isobutyrate	23.8	23.1	25.2	30.6	1.65	0.194	0.485	0.356
Isovalerate	35.3	33.6	36.1	47.3	3.01	0.239	0.439	0.298
Total BSCFA	59.1	56.7	61.3	77.9	4.65	0.221	0.454	0.317
Total VFA	1858.6	2043.6	2142.9	2433.9	89.85	0.058	0.172	0.755

SCFA = short-chain fatty acid; BSCFA = branched-short-chain fatty acid; VFA = volatile fatty acid; total SCFA = the sum of acetate, propionate, butyrate, and valerate; total BSCFA = isobutyrate and isovalerate; total VFA = the sum of acetate, propionate, butyrate, isobutyrate, valerate and isovalerate.
[1] CON sow and FOS sow represent basal diet and FOS diet (0.2%) for sows, respectively. CON piglet and FOS piglet represent basal diet and FOS diet (0.2%) for piglets, respectively.
[2] *P*-value for sow, piglet, and sow × piglet represent the main effect of FOS addition in sows, the main effect of FOS addition in piglets, and the interaction effect of FOS addition in sows and piglets, respectively.

dystocia or stillbirth (Gu et al., 2019; Tabeling et al., 2003). Our results showed that FOS could increase the fecal score of sows before parturition, elevate the abundance of *Bifidobacterium*, and reduce the abundance of *E. coli* in feces of sows, suggesting that the intestine was more active and could reduce prolonged constipation during the perinatal period of sows. This agreed with previous reports that oligosaccharides could improve constipation (Lan et al., 2020; Yu et al., 2021) and intestinal flora balance (Gibson and Roberfroid, 1995; Howard et al., 1995). Oligosaccharides are fermented by beneficial bacteria to produce SCFA, which can be used for the maintenance and growth of animals (Xing et al., 2020). In the present study, dietary FOS supplementation showed no effect on the content of SCFA. Most of SCFA in the adult pig intestine can be rapidly absorbed by colon cells before reaching the rectum (Engelhardt et al., 1989), which may be the reason for no effect of FOS supplementation in sows on SCFA in feces. BSCFA are reliable markers for protein fermentation. The results showed that BSCFA in sow feces had a tendency to increase, which may be due to FOS improving the microbial activity of pregnant sows (*Bifidobacterium* and *A. muciniphila*), improves the utilization of dietary protein or endogenous nitrogen by intestinal microbiota (Tian et al., 2020; Yang et al., 2021a; Zhuo et al., 2020). BSCFAs have been reported associated with a reduced risk of neonatal necrotizing enterocolitis development and improved bowel disease status (Ramos-Garcia et al., 2022). They are the main components of the cell membrane of *Bifidobacterium*, *Lactobacillus*, and other bacteria, as well as the important microbial components of neonatal gastrointestinal tract. However, how FOS affects gut microbes on amino acid fermentation to produce BSCFA to reduce the stillbirth rate of sows remains unclear and needs further verification.

Perinatal insulin resistance is a common complication of pregnancy in mammals, and the intestinal flora disturbance in the perinatal period of sows may also aggravate the decrease of insulin sensitivity (Barbour et al., 2007). To our knowledge, this is probably the first report on the correlation between FOS effects on the intestinal flora and insulin sensitivity. FOS addition could increase the abundance of *A. muciniphila* that had been previously reported associated with insulin resistance as evidenced by HOMA-IR value and glucose AUC in glucose tolerance test (GTT). *A. muciniphila* has been increasingly recognized to reduce insulin resistance in different tissues and improve blood glucose balance (Sanjiwani et al., 2022; Zhang et al., 2021). The placenta is a key bridge between mother and fetus and plays an important role in fetal development (Hu et al., 2021). Reduced insulin sensitivity is associated with trophoblast invasion and angiogenesis impairment, resulting in reduction of reproductive efficiency, with further adverse effects on fetal outcomes, such as high stillbirth rates and low birth weight (Huang et al., 2023; Martino et al., 2016; Tan et al., 2016; Tanaka et al., 2018; Yang et al., 2021b). A richer vascular system could efficiently transport oxygen and nutrients from mother to fetus, thus increasing the vitality of piglets (Huang et al., 2021a,b). In this study, we found an increase in the mRNA expression level and protein abundance of vascularized placental markers CD31 in FOS group, as well as an uptrend in the mRNA expression level of *VEGF-A*. This suggested that

the reduction of stillbirth and invalid piglet rates elicited by FOS supplementation in our study was associated with the improvement of insulin sensitivity and placental angiogenesis of sows.

FOS, as a functional oligosaccharide, mainly plays a role in the fermentation of SCFA by microorganisms in the posterior intestine. In most studies of oligosaccharides, researchers have focused on their effects on gut health (Mao et al., 2017; Valpotic et al., 2016; Wan et al., 2018b, Wan et al., 2020a). However, to date, litter information is available about the impact of dietary oligosaccharide supplementation from late gestation to lactation of sows on the diarrhea rate of weaned piglets. In the current study, dietary FOS supplementation in sows or piglets post-weaning had no effect on the growth performance of weaned piglets. Nevertheless, FOS supplementation in sows or piglets alone could reduce the diarrhea rate of piglets in the early weaning period. Diarrhea rate is a direct indicator of intestinal health, which suggests that FOS can improve intestinal health of piglets after weaning.

Oligosaccharide supplementation during pregnancy and lactation could enhance intestinal immune system development and body resistance in suckling piglets (Le Bourgot et al., 2014; Wan et al., 2018a). Accordingly, FOS supplementation of sows may decrease the diarrhea rate of weaned piglets by increasing immunity. Oligosaccharides and their metabolites, such as SCFA, could stimulate the uptake of minerals, electrolytes, and water in the colon, thereby reducing the diarrhea rate (Mikkelsen and Jensen, 2004; Panah et al., 2021). Meanwhile, the organic acids and pH reduction produced by oligosaccharide fermentation could prevent the formation of pathogenic *E. coli* associated with post-weaning diarrhea (Mikkelsen et al., 2003). Our results showed that FOS supplementation in sows or weaned piglets alone could increase the concentration of SCFA in feces of weaned piglets. In this sense, FOS supplementation may decrease the diarrhea rate of weaned piglets by increasing SCFA content. However, the reason why FOS supplementation in late gestation and lactation of sows could increase SCFA content in feces of weaned piglets needs further study.

The high content of protein in feed or undigested protein in intestinal tract may cause allergic reaction and lead to diarrhea of piglets (Wan et al., 2020b). In this experiment, FOS supplementation alone at weaning stage could improve their digestibility of dry matter and crude protein, suggesting that FOS may promote the intestinal protein digestion and absorption and further reduce the diarrhea rate of weaned piglets. FOS supplementation in late gestation and lactation of sows showed no effect on nutrient digestibility of weaned piglets, probably because digestibility can only reflect the ability of an animal to digest and absorb during that time. Therefore, dietary FOS supplementation in sows has no effect on digestibility of weaned piglets.

5. Conclusions

This study investigated the combined effects of maternal and post-weaning dietary FOS supplementation on reproductive performance of sows and diarrhea rate of weaned piglets. Results indicate that FOS supplementation in sows can reduce stillbirth rate, perinatal constipation and insulin resistance, increase fecal abundance of beneficial bacteria, and improve placental vascularization barrier. Additionally, FOS supplementation in both sows and piglets could decrease diarrhea rate and increase SCFA content in feces of weaned piglets. However, only FOS supplementation in weaned piglets alone could increase their nutrient digestibility.

Author contributions

Kaidi Ma: Data curation, formal analysis, investigation, methodology, software and writing – original draft. **Bin Su:** Investigation, formal analysis, data curation, supervision and validation. **Fuyong Li:** Investigation, software and visualization. **Jinfeng Li** and **Jiawei Nie:** Methodology and software. **Wenyu Xiong**, **Jinxi Luo** and **Shuangbo Huang:** Validation. **Tong Zhou, Xide Liang** and **Facai Li:** Visualization. **Jinping Deng** and **Chengquan Tan:** Conceptualization, funding acquisition, project administration, resources, supervision, writing – review and editing.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

Acknowledgments

The authors would like to thank the Guangzhou Pucheng Biological Technology Co. for animal management. This project was funded by National Natural Science Foundation China (32172744 or 32272895).

Appendix supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aninu.2024.04.002.

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