Received: 6 April 2021 | Revised: 24 July 2021 | Accepted: 2 August 2021

DOI: 10.1111/jfbc.13905

ORIGINAL ARTICLE

Journal of Food Biochemistry WILEY

Luzhou-Feier powder reduces inflammatory response and improves intestinal immune barrier in rats with severe acute pancreatitis

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Funding information
The Special Support Program for Young Technologists of Southwest Medical University, Grant/Award Number: 20064; Luzhou Municipal People's Government-Southwest Medical University Science and Technology Strategic Cooperation Project, Grant/Award Number: 2020LZXNYDZ07; Luzhou Municipal People's Government-Southwest Medical University Science and Technology Strategic Cooperation Applied Basic Research Project, Grant/Award Number: 2018LZXNYD-ZK15, and 2017LZXNYD-J05; Cooperation Project of Southwest Medical University and Luzhou Government, Grant/Award Number: 2019LZXNYDJ24

Abstract

As we know, nutritional support plays a key role in the treatment of severe acute pancreatitis (SAP). Since total parenteral nutrition (TPN) was discovered, the mortality of SAP had been greatly reduced. But researchers recently demonstrated that the prognosis of SAP could be improved by early enteral nutrition (EEN), which has been a priority for nutritional support in patients with SAP. However, implementation of total enteral nutrition is often challenging in the early stage of SAP. If the enteral nutrition is overused, the burden on the gastrointestinal tract will be aggravated. Under such circumstances, the combination of enteral and parenteral nutrition for nutritional support of SAP patients would be a better choice. Therefore, in this study, we compared the efficacy of two enteral nutrition agents: traditional nutritional supplement named Luzhou-Feier powder (LZ-FP) and enteral nutritional suspension (TPF) combined with parenteral nutrition to total parenteral nutrition (TPN) in the treatment of SAP rats. Our analysis revealed that the combination of enteral nutrition and parenteral nutrition was more effective than TPN in SAP. And LZ-FP met the requirements for enteral nutrition of SAP supporting its clinical application in SAP.

Practical applications

Luzhou-Feier powder (LZ-FP) is a traditional Chinese nutritional supplement that was originally developed as a nutritional supplement for infants and is currently used for nutritional support in patients with chronic and consumptive diseases. Our research investigated the effect and its possible mechanisms of LZ-FP as early trophic enteral nutrition in SAP rats and compared it with TPF and TPN which have been used clinically. We found that LZ-FP helped to reduce inflammatory response and improve the intestinal immune barrier of SAP. The curative effect of LZ-FP was comparable to that

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of TPF. And this effect may be achieved by inducing the secretion of gut hormones. Our research indicates that LZ-FP should be considered as an enteral nutrition preparation for SAP.

KEYWORDS

inflammatory response, intestinal immune barrier, Luzhou-Feier powder, severe acute pancreatitis, trophic enteral nutrition

1 | INTRODUCTION

Severe acute pancreatitis (SAP) accounts for approximately 5%–10% of all cases of acute pancreatitis (Banks et al., 2013), a common critical illness of the gastrointestinal system. SAP is associated with increased vulnerability to intestinal barrier dysfunction, such as increased intestinal mucosal permeability, endotoxin and bacterial translocation, and inhibition of intestinal immune function, and can even lead to endotoxemia or bacteremia (Cen et al., 2018; Roberts et al., 2017). Conversely, intestinal barrier dysfunction can lead to the progression of infection complications, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS), which are the main causes of high mortality in SAP (Jin et al., 2018; Schietroma et al., 2016; Yong et al., 2016). Therefore, protecting the intestinal barrier function is essential for reducing mortality and improving prognosis in patients with SAP.

Nutritional support plays a key role in the treatment of SAP. Traditionally, parenteral nutrition allows an adequate rest for the pancreas in patients with SAP (Roberts, 2001). However, long-term total parenteral nutrition (TPN) can precipitate intestinal barrier dysfunction and induce or aggravate systemic inflammatory responses and multiple organ dysfunction. In recent years, early enteral nutrition (EEN) was demonstrated to play a significant role in protecting the integrity of intestinal mucosal structures and functions, alleviating systemic inflammatory response, and preventing shifts in bacterial populations (Xu et al., 2018; Zhang et al., 2018). In addition, EEN can alleviate augmented immune responses in the early stages of SAP, thus avoiding the emergence of immunosuppression (Sun et al., 2013). Research suggests that EEN, which can be achieved by nasojejunal feeding, should be the main choice for nutritional support in patients with moderate to severe pancreatitis (Sultan & Forsmark, 2010). Compared with TPN, enteral nutrition can significantly reduce mortality, multiple organ failure, systemic infection, surgical intervention, and length of hospital stays in patients with acute pancreatitis (Alomran et al., 2010).

However, implementation of total enteral nutrition is often challenging in the early stage of SAP. If the enteral nutrition dose is increased excessively, the burden on the gastrointestinal tract will be aggravated, which will lead to the recurrence of the clinical symptoms in patients with SAP. The purpose of EEN in critically ill patients is to protect the gastrointestinal function rather than providing the nutritional dose to meet the demand (Chen et al., 2020). Therefore, it is possible to combine trophic enteral nutrition with supplemental parenteral nutrition for nutritional support in patients with SAP. The European Society of Intensive Care Medicine recommends that critically ill patients should be administered an initial dose of trophic enteral nutrition at 10–20 ml/h, which should be increased gradually to the target dose (Blaser et al., 2017). The Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition recommends that enteral nutrition in patients with SAP requiring nutritional support should begin at a trophic rate (Mcclave et al., 2009). Studies show that early trophic enteral nutrition can reduce the length of intensive care unit stays and the duration of mechanical ventilation in patients with septic shock (Patel et al., 2016).

Elemental enteral nutrition preparations are digested and absorbed easily and thus are not a big burden on the gastrointestinal tract (Tiengou et al., 2006). However, several recent studies demonstrated that non-elemental and elemental preparations did not have significant differences in tolerance, infection, or mortality (Petrov et al., 2009; Poropat et al., 2015). The cost of elemental enteral nutrition is higher; therefore, non-elemental enteral nutrition is recommended as the first choice for enteral nutrition in patients with acute pancreatitis (Lodewijkx et al., 2016). Enteral nutritional suspension (TPF) is a non-elemental enteral nutrition preparation that has been used clinically in patients with SAP; however, TPF cannot be stored conveniently and has to be protected from light at 10℃–30℃ and stored at 4℃ for up to 24 hr after opening.

Luzhou-Feier powder (LZ-FP) is a traditional Chinese nutritional supplement that is high in protein, low in fat and osmotic pressure and is rich in vitamins and minerals but free of cholesterol. Compared with TPF, LZ-FP costs less, and is easier to store, so it has higher economic benefits for patients. Indeed, LZ-FP was originally developed as a nutritional supplement for infants, without contraindications discovered, and has been used for nutritional support in patients with chronic and consumptive disease, like cachexia, but not for SAP. At present, we are applying LZ-FP in clinical practice as an enteral nutrition agent in the early stage of acute pancreatitis, and it shows a certain curative effect. However, the mechanism of LZ-FP applied for SAP remains unclear. Therefore, the purpose of the present study was to investigate the effect and its possible mechanisms of LZ-FP as early trophic enteral nutrition in SAP rats, and compared it with TPF and TPN which have been used clinically.

2 | MATERIALS AND METHODS

2.1 | Animals and surgical procedures

Animal experimental protocols were approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (201906-4, from June 20, 2019 to June 20, 2021; Luzhou, China). Adult male Sprague-Dawley rats weighing 250 to 300 g (Dashuo, Chengdu, China) were housed under standard conditions (21 ± 2°C, 12 hr light/12 hr dark cycle) and provided food and water ad libitum for 1 week before experimentation. 48 rats were randomly assigned to four groups: a sham-operated group receiving normal diet (SO + Normal group, $n = 12$), SAP group receiving early trophic enteral nutrition with TPF (SAP + TPF group, $n = 12$) SAP group receiving early trophic enteral nutrition with LZ-FP (SAP + LZ-FP group, $n = 12$), and SAP group receiving TPN (SAP + TPN group, $n = 12$).

All the animals were starved for 12 hr prior to experimentation except water. Rats were anesthetized with an intraperitoneal injection of 10% chloral hydrate (3 ml/kg). Making a 3 cm midline incision in the upper abdomen, and the major duodenal papilla was identified. Then, a blunt 1 ml syringe needle was retrogradely inserted into the biliopancreatic duct. The 5% sodium taurocholate (Sigma-Aldrich, St. Louis, USA) solution was retrogradely injected into the biliopancreatic duct to induce SAP at a dose of 1 ml/kg, which was injected at a rate of 0.1 ml/min. (sham group underwent the same surgical procedure without intrapancreatic injection of sodium taurocholate; Chen et al., 2016). After the injection, the pancreas was observed for 5 min. The pancreas exhibited exudation, edema, and local bleeding, indicating that SAP was successfully induced. After the gastrostomy, the gastric jejunal tube was placed to establish the EN route. The PN route was established by placing the right external jugular vein catheter. All surgeries were performed using the sterile technique.

Animals were conscious after induction of SAP, they were just anesthetized during the process of inducing SAP and preparation of gastrostomy or insertion of a catheter into the jugular vein. In this experiment, the nutrition and water in the SAP groups (including SAP + TPF group, SAP + LZ-FP group, and SAP + TPN group) were administered through the catheter, while the sham-operated group (SO + Normal) had free access to water and food. After the models were completed, each rat was housed in a separate cage. In order to prevent the damage of the external jugular venous catheter, we placed catheter under the skin of rats, pierced through the skin of the back of the neck, and fixed it. As for catheters inserted into gastric fistula, we did not attach them directly to the abdominal incision, but wound them subcutaneously to the back of the neck, pierced, and fixed them. The length of catheter inserted into the gastric fistula was about 25 cm.

2.2 | Nutritional support

The TPN preparation (as shown in Table 1) was pumped into the SAP + TPN group through the right external jugular vein catheter.

TABLE 1 Formulation of total parenteral nutrition (100 ml)

Composition	Company	Volume (ml)
8.5% Amino acids (18AA-Ⅱ)	Huarui, Wuxi, China	47
20% Fat emulsion (C14~24)	Huarui, Wuxi, China	20
50% Glucose	Kelun, Hubei, China	25
Vitamins	Huarui, Wuxi, China	1
Multi-trace elements	Huarui, Wuxi, China	1
10% Sodium chloride	Rongsheng, Henan, China	1
10% Potassium chloride	Kelun, Hubei, China	1
10% Calcium gluconate	Beite, Chendu, China	1
25% Magnesium sulfate	Tiancheng, Hebei, China	0.1
10% Sodium glycerophosphate	Huarui, Wuxi, China	1
Sterilized water for injection	Meidajiale, Sichuan, China	1.9

Note: Preparation steps of parenteral nutrient solution: (1) Wipe the ultra-clean workbench with 75% alcohol; After all the medicines are wiped with 75% alcohol, they are passed into the parenteral nutrition preparation room through the delivery window, and check whether the label content is consistent with the medicines; Check whether the package of intravenous nutrition infusion bag is complete and expired. (2) Add electrolytes (without phosphate) and trace element preparations to the amino acid solution and mix them thoroughly. (3) Add phosphate to the glucose solution and mix well. (4) Connect the needles of the infusion tube of the nutrition infusion bag to the glucose solution and the amino acid solution, hang them upside down, put the amino acid solution first, and then the glucose solution. After the two solutions have all flowed into the nutrition infusion bag, close the infusion tube clamp. Turn the infusion bag over and mix well. (5) An empty needle is used to extract the fat-soluble vitamins and inject them into the water-soluble vitamins until the water-soluble vitamins are sufficient dissolve and mix. (6) Finally, the fat emulsion containing the vitamin is injected from the third infusion tube into the nutrient infusion bag and gently shake the infusion bag. Caloric value: about 100 kcal/100 ml. Osmolarity: <900 mOsm/L.

TABLE 2 Formulation of enteral nutritional suspension (100 ml)

Composition	Content (g)
Protein	4
Carbohydrate (semi-elemental)	12.3
Fat emulsion	3.89
Dietary fiber	1.5
Water	85
Ion (Na, K, Cl, Ca, Mg, P, and trace elements)	0.52
Vitamins	0.052

Note: The caloric value of TPF is 100 kcal/100 ml, but in order to keep the calorific value consistent with Luzhou-Feier powder, we add 4.3 ml sterilized water for injection to 10 ml TPF to dilute it. Caloric value: about 70 kcal/100 ml. Osmolarity: about 250 mOsm/L.

The SAP + TPF group were given the TPF (Nutricia, Wuxi, China, Table 2) for early trophic enteral nutrition. The SAP + LZ-FP group were given the LZ-FP (Luzhou-Feier powder Co., Ltd., Luzhou, China) for early trophic enteral nutrition. Since LZ-FP has been commercialized and its formula involves a confidentiality mechanism, we only get a list of its ingredients, and we have no way of knowing the specific amount of each ingredient. The ingredients are as follows: brown rice, soybean, mung bean, semen coicis, Yam, Chicken's Gizzard-membrane, lentils, Gorgon fruit, Soy protein, glucose, ferric pyrophosphate, zinc oxide, calcium carbonate, calcium hydrophosphate, vitamins A, D3, B1, B2, and niacin. The preparation method is: 10 g LZ-FP was added to 54.4 ml sterilized water for injection, stir well and form a suspension (caloric value: about 70 kcal/100 ml; Osmolarity: about 300 mOsm/L).

All animals received approximately 200 kcal kg^{-1} day^{-1}, The SAP + TPF group and the SAP + LZ-FP group rats received 20% for trophic enteral nutrition and 80% for parenteral nutrition (Goldberg et al., 2008; Hagiwara et al., 2008). The amount of enteral nutrition and parenteral nutrition was calculated based on the initial weight of each rat, and the pumping speed was adjusted accordingly (as shown in Table 3). Nutritional support was carried out for 6 days, and the rats were sacrificed on the 7th day and samples were collected.

2.3 | Hematoxylin and eosin (H&E) staining

The ileal and pancreatic tissues were collected and stored in 4% paraformaldehyde and subsequently embedded in paraffin for histopathological analysis. Standard hematoxylin and eosin (H&E) staining was performed. Histopathological severity of the pancreas was assessed based on the acute pancreatitis scoring system as previously described (Schmidt et al., 1992). Intestinal mucosal damage was scored according to intestinal villus detachment, lamina propria edema, and hemorrhage.

TABLE 3 The initial weight of each group and the average pumping speed

Group	Weight (g)	Speed
So + Normal	275 ± 4	None
SAP + TPN	280 ± 3	1 ml/min
SAP + TPF	272 ± 3	0.5 ml/min
SAP + LZ-FP	278 ± 5	0.5 ml/min

Abbreviations: LZ-FP, Luzhou-Feier powder; SAP, severe acute pancreatitis; TPN, total parenteral nutrition.

2.4 | Enzyme-linked immunosorbent assay (ELISA)

Serum TNF-α, IL-1β, and IL-6 levels of each group were assayed by ELISA kit (Fanke, Shanghai, China) according to the manufacturer's instructions. Absorbance was measured at a wavelength of 450 nm.

2.5 | Quantitative Real-Time PCR (qRT-PCR)

Total RNA was extracted from pancreatic and intestinal tissues using the RNA extraction kit (BioTeke, Beijing, China). Total RNA was reverse transcribed into cDNA according to the manufacturer's instructions (TOYOBO, Japan). The primers were synthesized by Sangon Biotech (Shanghai, China) as shown in Table 4. Real-time PCR was performed to quantify the expression of several genes using a real-time PCR detection system (LightCycler 96, Roche, Switzerland). Samples were run in triplicates, expression values were normalized against housekeeping genes (GAPDH), and fold-changes were calculated with respect to the control group using the $2^{-\Delta\Delta CT}$ method.

2.6 | Detection of plasma endotoxin

Blood samples were collected and plasma endotoxin was detected using a limulus endotoxin detection kit (Bioendo technology Co., Ltd., Xiamen, China) according to the manufacturer's instructions.

2.7 | Immunohistochemistry

Sections were deparaffinized in xylene, immersed in alcohol, and rehydrated in graded concentrations of ethanol to distilled water. Endogenous peroxidase activity was blocked with 3% H_2O_2. After incubation in normal bovine serum albumin, the sections were incubated with the anti-CD4 antibody (Abcam, UK), anti-CD8 antibody (Abcam, UK), anti-MAdCAM-1 antibody (Santa Cruz, USA), and anti-sIgA antibody (Abcam, UK) overnight at 4°C. DAB was used as chromogen, and counterstaining was performed with hematoxylin. The immunostained sections were examined under light

TABLE 4 Primer sequence

Gene		Primer sequence (5′ to 3′)
TNF-α	Forward primer	CCCTCACACTCAGATCATCTTCT
	Reverse primer	GCTACGACGTGGGCTACAG
IL-1β	Forward primer	GAAATGCCACCTTTTGACAGTG
	Reverse primer	GAAATGCCACCTTTTGACAGTG
IL-6	Forward primer	TAGTCCTTCCTACCCCAATTTCC
	Reverse primer	TTGGTCCTTAGCCACTCCTTC
GAPDH	Forward primer	CCCCCAATGTATCCGTTGTG
	Reverse primer	TAGCCCAGGATGCCCTTTAGT

microscope. Images were analyzed using the computerized color pathological, Analysis of the integrated optical density (IOD) values of immunostaining using imaging software (ImagePro Plus 6.0, Media Cybernetics), The mean IOD values for each group of SAP rats were compared to the sham-operated group to obtain a relative IOD ratio (Wang et al., 2012).

2.8 | Statistical analysis

Statistical analyses were performed using SPSS 21.0 software, data are presented as mean ± standard deviation (*SD*). The data were analyzed by Student's *t*-test or analysis of variance analysis (ANOVA). *p* values of <.05 were accepted as statistically significant.

3 | RESULTS

3.1 | Survival rates

To investigate the safety of early trophic enteral nutrition, we evaluated the survival rates of rats with SAP that were provided different modalities of nutritional support. The survival rates were 100.0%, 41.7%, 58.3%, and 50.0% in the SO + Normal, SAP + TPN, SAP + TPF, and SAP + LZ-FP groups, respectively. The survival rates were higher in the SAP + TPF and SAP + LZ-FP groups compared with the SAP + TPN group. This result showed that enteral nutrition combined with parenteral nutrition could reduce the mortality of SAP rats compared with TPN. And trophic enteral nutrition with LZ-FP had a safe profile comparable to that of TPF (Table 5). However, due to the small amount of data and short observation time, this conclusion may not be convincing, and more research is needed in the future.

3.2 | Pancreatic and intestinal histopathology

Pancreatic and intestinal pathological changes were assessed by the previously reported optical microscopy criteria for SAP. As shown in Figure 1a, there were no remarkable changes suggesting pathologic injury to the pancreatic tissue in the SO + Normal group. Conversely,

TABLE 5 Survival rates of rats with severe acute pancreatitis receiving different nutritional support paradigms

Group	Dead	Alive	Survival rate (%)
SO + Normal	0	12	100.0
SAP + TPN	7	5	41.6
SAP + TPF	5	7	58.3
SAP + LZ-FP	6	6	50.0

Note: SO + Normal, sham-operated group receiving normal diet; SAP + LZ-FP, severe acute pancreatitis group receiving trophic enteral nutrition with LZ-FP; SAP + TPF, severe acute pancreatitis group receiving trophic enteral nutrition with TPF; SAP + TPN, severe acute pancreatitis group receiving total parenteral nutrition.

the pancreatic tissue in the SAP + TPN group exhibited pancreatic interstitial edema, broad necrosis of the acinar cells, nuclear pyknosis, a disordered lobular structure, and inflammatory cell infiltration. Compared with the SAP + TPN group, the pathological changes in the pancreas were significantly alleviated in both the SAP + TPF and SAP + LZ-FP groups. Furthermore, there was no significant difference in the pancreatic pathological scores between the SAP + TPF and SAP + LZ-FP groups ($p > .05$, Figure 1b). These differences among the groups were also observed in the ileal tissue (Figure 1c,d). These results showed that enteral nutrition combined with parenteral nutrition in SAP rats significantly alleviated pancreatic and ileal injury compared with TPN, and the improvement of trophic enteral nutrition with LZ-FP was consistent with TPF, suggesting that LZ-FP is a great enteral nutrition support agent.

3.3 | Changes in the expression of TNF-α, IL-1β, and IL-6

Activation of the inflammatory signaling pathways leads to a strong inflammatory response in acute pancreatitis, which aggravates pancreatic injury (Nieminen et al., 2014; Singh et al., 2009). To study the effect of trophic enteral nutrition on the inflammatory responses in SAP, we examined the changes in mRNA expression levels of TNF-α, IL-1β, and IL-6 in the pancreas and ileum of the rats with SAP. We found that trophic enteral nutrition in both the SAP + TPF and the SAP + LZ-FP groups significantly reduced the relative mRNA expression levels of TNF-α, IL-1β, and IL-6 in the pancreas and ileum compared with those of the SAP + TPN group (Figure 2a,b). To further investigate the changes in the inflammatory responses, we measured the levels of TNF-α, IL-1β, and IL-6 in serum by ELISA, which revealed that the changes in the protein levels were similar to those observed in their mRNA expression levels (Figure 2c). There were no significant differences in the levels of TNF-α, IL-1β, or IL-6 between the SAP + TPF and SAP + LZ-FP groups ($p > .05$). Altogether, these results indicated that trophic enteral nutrition with LZ-FP alleviated local and systemic inflammatory responses compared with TPN in rats with SAP, and this improvement was consistent with TPF. The

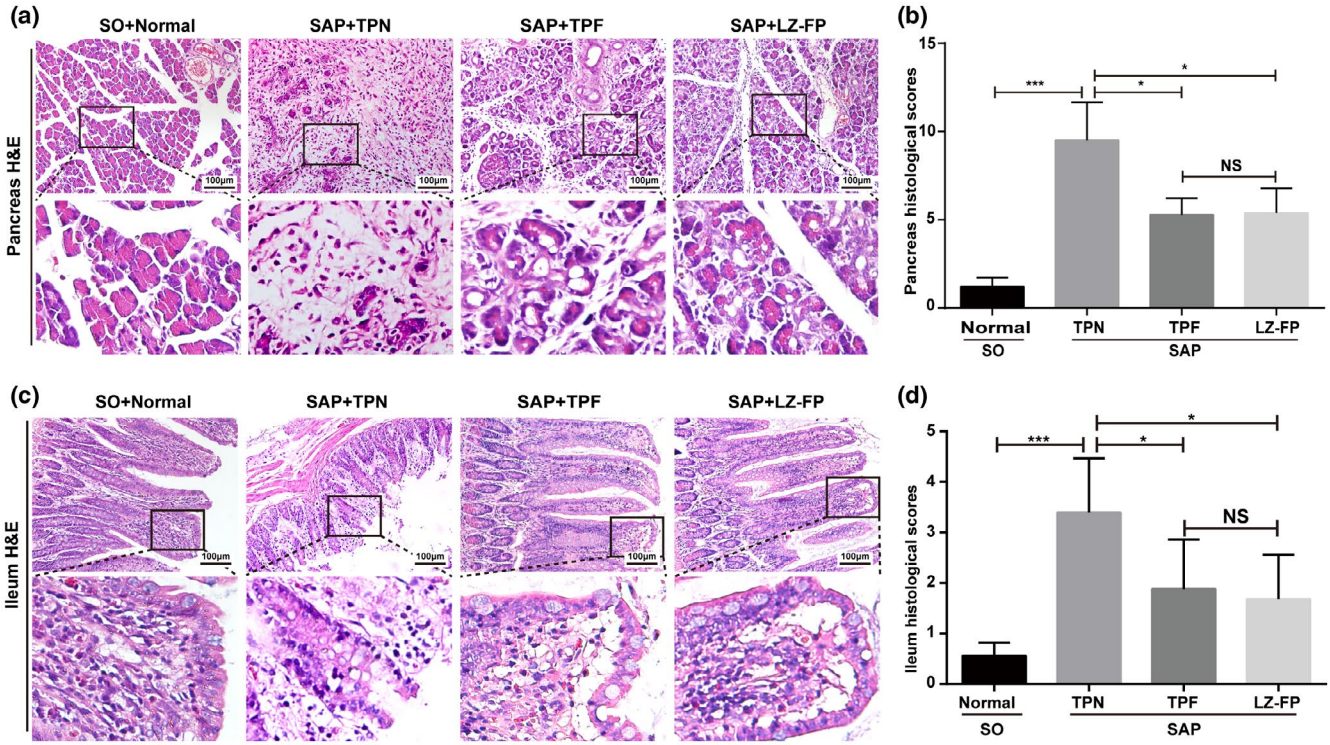

FIGURE 1 Early trophic enteral nutrition with Luzhou-Feier powder (LZ-FP) reduces pathological damage in the pancreas and ileum in rats with severe acute pancreatitis (SAP). (a) Evaluation of pathological pancreatic damage by hematoxylin/eosin staining. (b) Pathological scoring of the pancreas. (c) Detection of pathological ileal damage by hematoxylin/eosin staining. (d) Pathological scoring of the ileum. SO + Normal, sham-operated group receiving normal diet; SAP + LZ-FP, SAP group receiving trophic enteral nutrition with LZ-FP; SAP + TPF, SAP group receiving trophic enteral nutrition with TPF; SAP + TPN, SAP group receiving total parenteral nutrition. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. NS, not statistically significant

combination of enteral nutrition and parenteral nutrition is more conducive to the relief of SAP inflammation.

3.4 | Endotoxin levels in plasma

Plasma endotoxin levels were measured by limulus test. The plasma endotoxin levels were significantly lower in the groups receiving trophic enteral nutrition compared to the SAP + TPN group, whereas there was no significant difference in the plasma endotoxin levels between the SAP + TPF and SAP + LZ-FP groups ($p > .05$, Figure 3). These findings indicated that enteral nutrition combined with parenteral nutrition reduced the intestinal mucosal permeability and reduced the endotoxin translocation compared with TPN, and LZ-FP had a similar effect to TPF.

3.5 | Expression levels of $CD4^+$ and $CD8^+$ cells, MAdCAM-1, and sIgA

Intestinal mucosa exerts immunity through lymphocyte homing, which requires the adhesion molecule MAdCAM-1 (Shale et al., 2013). Therefore, we next evaluated the expression levels of $CD4^+$ cells, $CD8^+$ cells, and MAdCAM-1 in Peyer's patches by immunohistochemistry. We found that trophic enteral nutrition upregulated the expression levels of $CD4^+$ cells, $CD8^+$ cells, and MAdCAM-1 compared with SAP + TPN ($p < .05$, Figure 4a,c). We also measured sIgA, the main immunoglobulin of the intestinal mucosa that plays a key role in intestinal mucosal immunity. We found that, compared with TPN, trophic enteral nutrition also upregulated the expression of sIgA (Figure 4b,c). There were no significant differences in the expression levels of $CD4^+$ and $CD8^+$ cells, MAdCAM-1, or sIgA between the SAP + TPF and SAP + LZ-FP groups ($p > .05$, Figure 4c).

4 | DISCUSSION

SAP is characterized by high mortality, rapid progression, and numerous complications, often accompanied by single or multiple organ failure. The treatment for SAP requires multidisciplinary participation, and nutritional support therapy plays an important role in the management of patients with SAP. Several recent studies confirmed the safety and efficacy of EEN in patients with SAP (Bakker et al., 2011; Dijk et al., 2018; Peng et al., 2016; Shen et al., 2017). Clinical studies highlighted that EEN significantly reduced the incidence of complications and mortality in SAP (Wereszczynskasiemiatkowska et al., 2013). However, one study

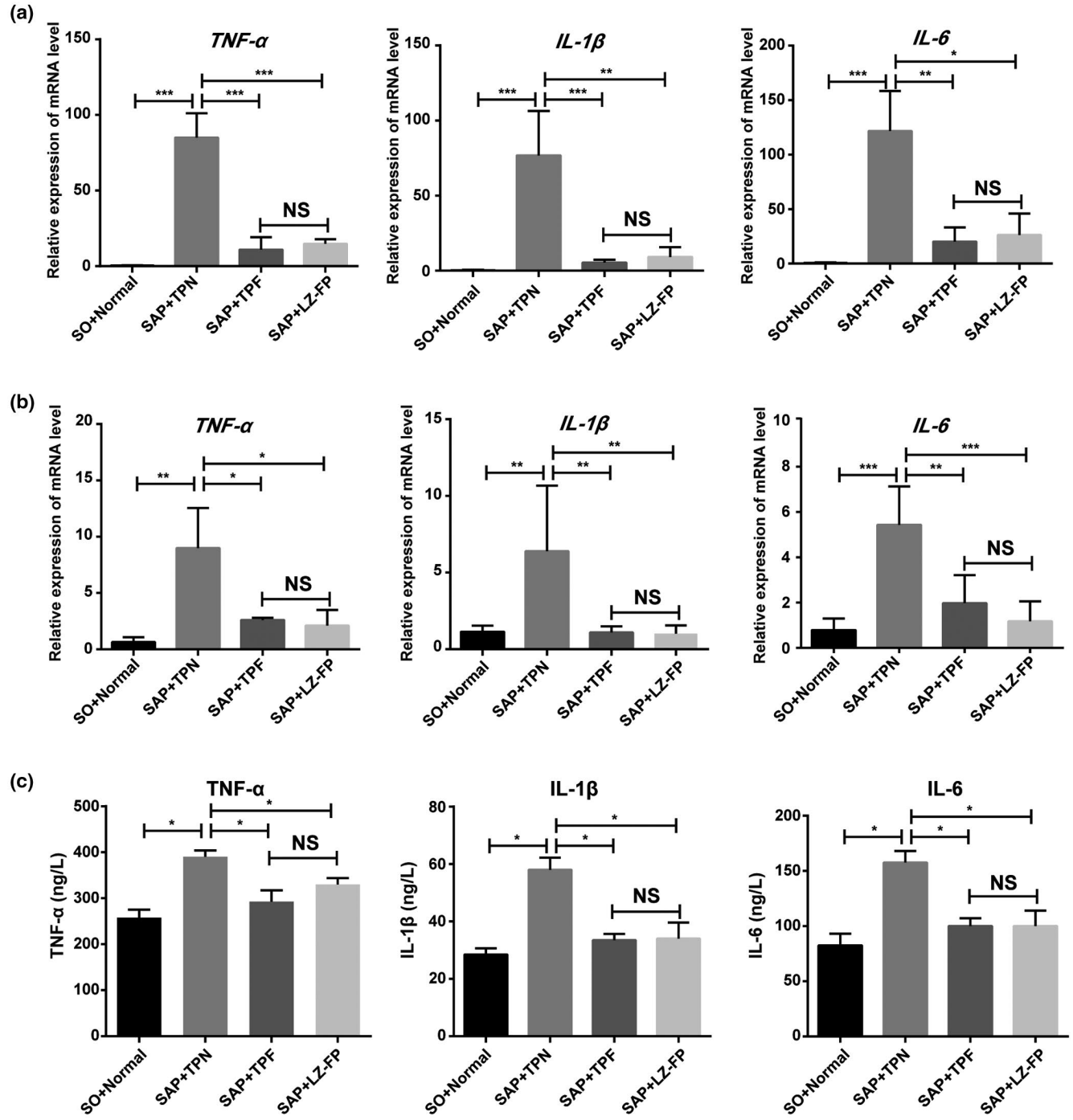

FIGURE 2 Early trophic enteral nutrition with Luzhou-Feier powder reduces the inflammatory response of rats with severe acute pancreatitis. (a) Relative mRNA expression levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 in the pancreas. (b) Relative mRNA expression levels of TNF-α, IL-1β, and IL-6 in the ileum. (c) Serum levels of TNF-α, IL-1β, and IL-6. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. NS, not statistically significant

found that EEN did not reduce in-hospital mortality, albeit improvements in the clinical outcomes of patients with SAP. In the current study, the safety of trophic enteral nutrition with LZ-FP or TPF in the early stage of SAP was compared with TPN. Although enteral nutrition combined with parenteral nutrition improved the survival rates in rats with SAP. But the data and the time is limited, more research is needed in the future.

Overproduction of inflammatory mediators is an important pathogenic event in SAP (Silvavaz et al., 2020). Impaired pancreatic acinar cells in acute pancreatitis activate multiple inflammatory signaling pathways, resulting in strong local and systemic inflammatory responses (Gu et al., 2013; Gukovsky et al., 2013; Habtezion, 2015). The inflammatory cascade reaction causes increased production of inflammatory mediators, leading to SIRS and MODS. Among the

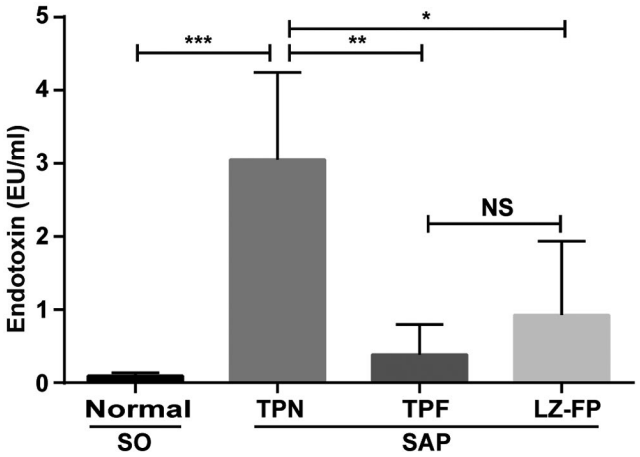

FIGURE 3 Early trophic enteral nutrition with Luzhou-Feier powder reduces endotoxin translocation. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. NS, not statistically significant

mediators, TNF-α, IL-1, and IL-6 promote neutrophil adhesion, attachment, and extravasation as well as increased capillary permeability, aggravating pancreatic injury and the inflammatory responses (Hoque et al., 2011; Perides et al., 2011; Rotstein, 2014). The results of the present study indicated that enteral nutrition combined with parenteral nutrition could effectively reduce the levels of serum inflammatory factors and systemic inflammatory response compared to TPN. In addition, early trophic enteral nutrition with LZ-FP reduced the relative mRNA expression levels of TNF-α, IL-1β, and IL-6 and alleviated the inflammatory changes and pathological damage in the pancreas and ileum. Importantly, we also compared the effects of TPF and LZ-FP on the inflammatory responses in rats with SAP and found that LZ-FP and TPF had comparable effects on the inflammatory response.

During SAP, intestinal barrier dysfunction is one of the most critical pathophysiological events caused by inflammatory mediators and cytokine release, microcirculatory dysfunction, ischemia-reperfusion injury, and other factors (Jia et al., 2015; Pinhu et al., 2014; Wang et al., 2016; Zerem, 2014). Regulating intestinal immune function and restoring the normal intestinal mucosal barrier are important measures for the treatment of SAP (Xiong et al., 2018). MAdCAM-1 belongs to the immunoglobulin superfamily and binds directly to its receptor, integrin α4β7, to participate in lymphocyte homing (Tanida et al., 2011); therefore, MAdCAM-1 contributes to the immune function of the intestinal mucosa. As the main immunoglobulin on the surface of intestinal mucosa, sIgA is secreted by B lymphocytes after antigen stimulation and activation into plasma cells and plays an important role in intestinal immunity. Importantly, sIgA expression is inversely proportional to the severity of SAP. Therefore, we investigated the effects of early trophic enteral nutrition on the intestinal immune barrier by evaluating the expression of $CD4^{+}$cells, $CD8^{+}$cells, MAdCAM-1, and sIgA and found that the expression of all four was reduced significantly in the rats with SAP; this finding indicated that the intestinal immune barrier was impaired in the rats with SAP. The data of the current study suggested that enteral nutrition combined with parenteral nutrition improved the intestinal immune barrier by upregulating the expression of MAdCAM-1, $CD4^{+}$, and $CD8^{+}$ cells, and sIgA compared with TPN. Moreover, our analyses revealed that LZ-FP reduced the intestinal permeability and endotoxin translocation. The effect of LZ-FP in improving the intestinal immune barrier was comparable to that of TPF.

Our study found that LZ-FP, as an enteral nutrition agent combined with parenteral nutrition had an effectiveness on the improvement of inflammatory response and intestinal immune barrier in SAP. It has been reported that enteral feeding induces the secretion of gut hormones. And gut hormones generate signals related to the rate of nutrient absorption, the composition of the luminal milieu, the cell proliferation, and the integrity of the epithelial barrier (Gribble & Reimann, 2019; Zeng et al., 2020). Among gut hormones, gastrin and cholecystokinin (CCK) were discovered early. Gastrin is produced and released by G cells in the stomach. Although the primary physiological effect of gastrin is the stimulation of gastric acid, its trophic effect on gastric and colonic mucosa was also crucial. Gastrin stimulates mucosal proliferation. In its absence, these tissues will go atrophy. CCK is synthesized principally in the open-type I cells of the duodenum and proximal 2/3 of the jejunum and has numerous physiological functions. It stimulates insulin secretion from pancreas and exhibits trophic effect in the small bowel mucosa (Ceranowicz et al., 2015). In addition, CCK has shown trophic effect on the pancreas by increasing the synthesis of pancreatic DNA, the content of DNA, RNA, and protein, and pancreatic weight. In addition, Tim Lubbers et al. found that the activation of CCK-1 receptor on afferent vagal fibers by CCK released in response to enteral nutrients could attenuate inflammation and intestinal injury in rats exposed to hemorrhagic shock (Lubbers et al., 2010). In this study, although we did not obtain the changes in the contents of gastrin and cholecystokinin, this may be the potential mechanism of LZ-FP as an EEN preparation for SAP to protect the intestinal barrier, reduce pancreatic injury and inflammation. In the subsequent studies, we will further verify this mechanism.

Furthermore, Previous experimental and clinical observations have shown that disturbance of pancreatic blood flow may be the primary cause of AP (Waldner, 1992). The degree of pancreatic blood flow disruption was correlated with the severity of AP, when pancreatic microcirculation disturbance occurs rapidly, it may progress to SAP (Knoefel et al., 1994). Dembinski et al demonstrated this in animal studies. They found that transient pancreatic ischemia followed by immediate reperfusion also leads to acute necrotizing pancreatitis (Dembiński et al., 2001). In addition, clinical studies have shown pancreatic hypoperfusion due to a variety of causes, including shock and abdominal surgery may also be the critical factor that causes the progression from edema to necrosis in pancreatitis (Lonardo et al., 1999; Warshaw & O'Hara, 1978). Therefore, improving pancreatic blood flow has a protective effect on pancreas (Warzecha et al., 1997). We actively hydrated early in SAP through parenteral and enteral pathways, which brought a positive effect to some extent. However, osmotic diarrhea caused by enteral nutrition was ignored. Osmotic diarrhea leads to hypovolemia which can disrupt

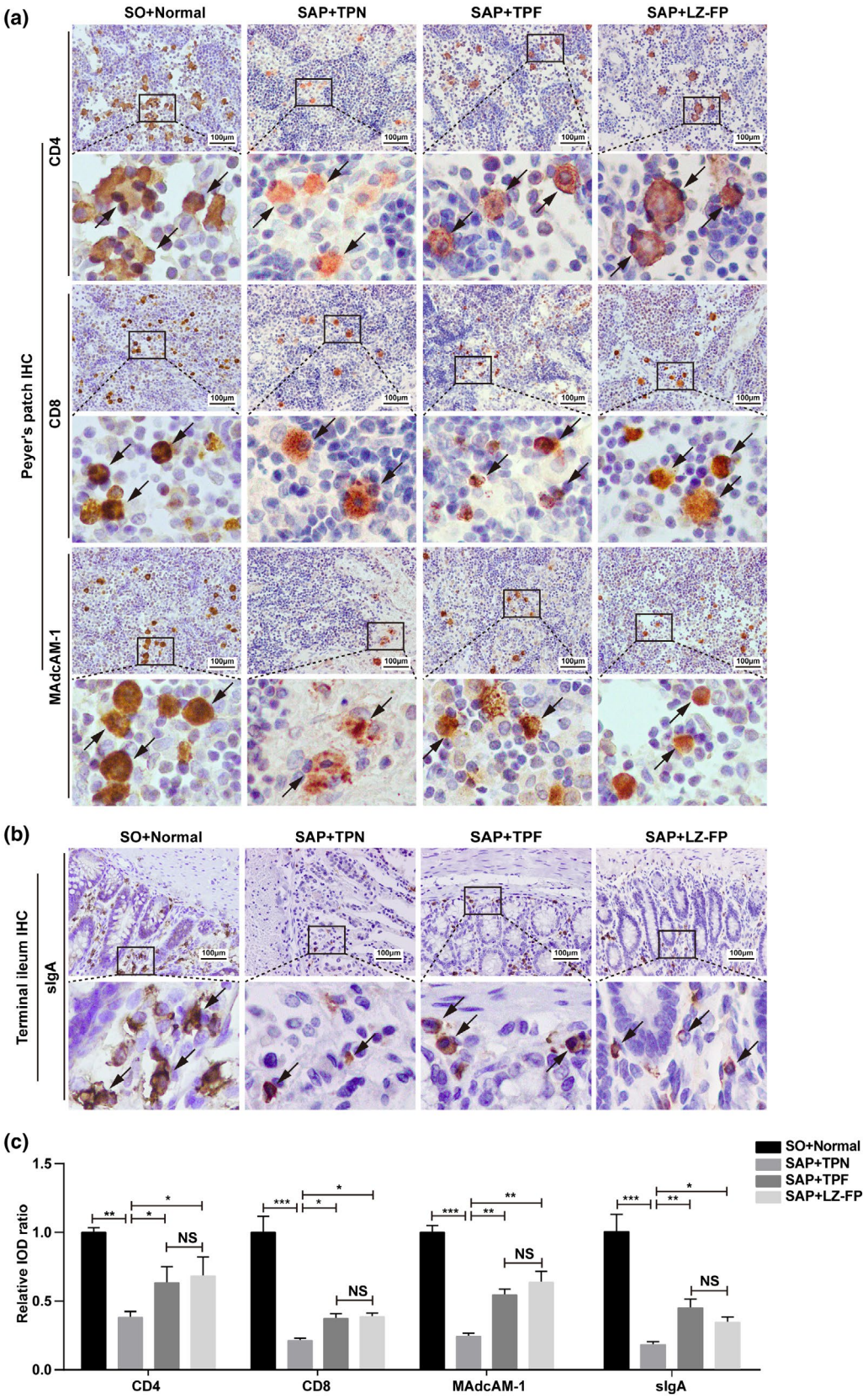

FIGURE 4 Early trophic enteral nutrition with Luzhou-Feier powder up-regulates the expression levels of CD4, CD8, MAdCAM-1, and secretory immunoglobulin A (sIgA). (a) Expression levels of CD4, CD8, and MAdCAM-1 in Peyer's patches. (b) Expression levels of sIgA in the terminal ileum. (c) Relative integrated optical density ratios of $CD4^+$ cells, $CD8^+$ cells, MAdCAM-1, and sIgA. $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$. NS, not statistically significant

pancreatic blood flow. Given this, the frequency and consistency of stools deserve our attention. On the other hand, pancreatic injury leads to local vascular damage, manifesting as endothelial damage and activation, increased vascular permeability, as well as activation of coagulation. Maduzia et al creatively used warfarin pretreatment to inhibit the development of acute pancreatitis caused by pancreatic ischemia. These findings indicate that activation of coagulation is involved in the mechanism of acute pancreatitis and anticoagulant therapy may bring some benefits (Maduzia et al., 2020). However, there may be some risks and side effects, and further research in this field is needed.

5 | CONCLUSIONS

In the current study, we used sodium taurocholate to induce SAP in rats, which exhibited specific manifestations including decreased intestinal immune function, increased pathological damage, inflammatory response, and intestinal permeability. LZ-FP as early trophic enteral nutrition may induce the secretion of gastrin and cholecystokinin in SAP rats, further reduce the local and systemic inflammatory response; alleviate the pathological damage to the pancreas and ileum; improve the intestinal immune barrier by upregulating the expression of $CD4^+$ and $CD8^+$ cells, MAdCAM-1, and sIgA; and reduce the intestinal permeability and endotoxin translocation. Therefore, LZ-FP should be considered as a novel enteral nutrition preparation for SAP. However, clinical studies and specific mechanisms are necessary to confirm the safety and efficacy of LZ-FP for trophic enteral nutrition in humans with SAP.

ACKNOWLEDGMENTS

This work was supported by Luzhou Municipal People's Government-Southwest Medical University Science and Technology Strategic Cooperation Applied Basic Research Project (NO. 2018LZXNYD-ZK15, 2017LZXNYD-J05), Luzhou Municipal People's Government-Southwest Medical University Science and Technology Strategic Cooperation Project (No. 2020LZXNYDZ07), The Special Support Program for Young Technologists of Southwest Medical University (20064), Cooperation Project of Southwest Medical University, and Luzhou Government (No. 2019LZXNYDJ24).

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Data curation; *Methodology*; *Resources*: Zhiwei Huang. *Data curation*; *Resources*; *Writing-original draft*: Xiaodong Guo. *Methodology*: Peng Tan. *Resources*: Min Wang. *Writing-review & editing*: Hao Chen. *Funding acquisition*: Yan Peng. *Validation*: Xianming Xia. *Conceptualization*; *Supervision*: Xiaowei Tang. *Conceptualization*; *Resources*; *Supervision*: Qiu Li. *Conceptualization*; *Project administration*; *Resources*; *Supervision*: Wenguang Fu.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Huang, Z., Guo, X., Tan, P., Wang, M., Chen, H., Peng, Y., Xia, X., Tang, X., Li, Q., & Fu, W. (2021). Luzhou-Feier powder reduces inflammatory response and improves intestinal immune barrier in rats with severe acute pancreatitis. *Journal of Food Biochemistry*, 45, e13905. https://doi.org/10.1111/jfbc.13905