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ORIGINAL RESEARCH

Tussilagone inhibits inflammation and oxidative stress to alleviate acute pancreatitis

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Abstract

Acute pancreatitis (AP) is a clinical emergency characterized by elevated levels of inflammation and oxidative stress, urging the need for the development of new and more efficacious treatments. Tussilagone (TSL), a compound from *Tussilago farfara* flower buds, is known to exhibit diverse properties, including anti-inflammatory activity, but its precise role in AP remains unclear. In this study, we investigated TSL's impact on the progression of AP. To establish AP animal models, mice were intraperitoneally administered hyranolin. Our findings demonstrate that TSL effectively suppresses the progression of AP in these mice and decreases inflammation in their pancreatic tissues, as evidenced by reduced secretion of inflammatory cytokines such as interleukin (IL)-1β, Tumor necrosis factor (TNF)-α and IL-6 ($p < 0.05$). Notably, TSL also mitigates neutrophil infiltration into the pancreatic tissues of AP-afflicted mice and alleviates oxidative stress in AP mice, as confirmed by the measurements of Superoxide dismutase (SOD), malondialdehyde (MDA), glutathione (GSH), and myeloperoxidase (MPO) ($p < 0.05$). Remarkably, TSL exerts its inhibitory effects on inflammation and oxidative stress by blocking the nuclear factor (NF)-κB pathway and activating the NF-E2-related factor 2 (Nrf2) pathway. In conclusion, TSL can mitigate inflammation and oxidative stress, offering potential as a promising therapeutic agent for AP.

Keywords

Acute pancreatitis (AP); Tussilagone; Neutrophil infiltration

1. Background

Acute pancreatitis (AP) is a critical medical emergency characterized by damage to the pancreas [1]. While the exact cause of AP is not fully understood, it is known to trigger oxidative stress and inflammatory responses [2]. In experimental AP models, a significant increase in reactive oxygen species (ROS) levels has been reported [3]. Oxidative stress persists from the early stages of the disease until clinical improvement and is marked by a reduction in glutathione levels, an increase in malondialdehyde (MDA) levels, and decreased Superoxide dismutase (SOD) activity in the pancreas [4, 5]. In addition to its damaging effects, ROS also acts as a signaling molecule, leading to the production of pro-inflammatory cytokines and apoptosis in AP cells [6]. Thus, developing new and more effective treatments for AP remains an important goal to alleviate its symptoms.

Tussilagone (TSL) is derived from the flower buds of *Tussilago farfara* [7], which is the dried flower bud of the Coltsia genus in the Asteraceae family. The underground rhizomes of coltsfoot are transverse and brown. TSL possesses several therapeutic roles in various diseases, such as protecting against acute lung injury by alleviating Hypoxia-inducing factor (Hif)-1α/NF-κB mediated inflammatory responses [8], inhibiting inflammation and improving the survival of mice with cecal ligation and puncture (CLP)-induced sepsis [9], and mitigating atherosclerosis by suppressing mitogen-activated protein kinase (MAPK)-mediated inflammation in macrophages [10]. TSL has also been shown to act on airway epithelial cells by regulating the NF-κB pathway to modulate mucin production and gene expression and alleviate dextran sulfate sodium (DSS)-induced colitis in mice by blocking NF-κB as well as stimulating the NF-E2-related factor 2 (Nrf2) pathway [11]. However, its role in AP remains still unclear.

Nuclear factor-κB (NF-κB) is a pro-inflammatory transcription factor located in the nucleus that governs the expression of genes involved in inflammatory signal transduction pathways [12]. Upon activation, NF-κB is translocated from the cytoplasm into the nucleus, where it initiates the transcription and expression of pro-inflammatory genes [13]. The NF-κB pathway plays a pivotal role in AP [14].

In this study, we investigated the impact of TSL on the progression of AP using an animal model and found that TSL can effectively inhibit inflammation and reduce oxidative stress to ameliorate AP, thereby holding promise as a potential therapeutic agent for the treatment of AP.

2. Materials and methods

2.1 Materials

Tussilagone (TSL) was obtained from Sigma (PHL83299, USA), enzyme-linked immunosorbent assay (ELISA) kits for IL-1β (ab197742), TNF-α (ab208348) and IL-6 (ab222503) were purchased from abcam (Cambridge, UK), kits for measuring MDA (A003-1-2), SOD (A001-3-2), GSH (A005-1-2) and MPO (A044-1-1) levels were bought from Jiancheng Bioengineering (Nanjing, China), TRIzol reagents (15596-018) were acquired from Invitrogen (Carlsbad, California, USA), and M-MLV reverse transcriptase was purchased from Promega Corporation (M1701, Madison, Wisconsin, USA). Antibodies used in this study included p65 (1:1000, ab32536, Abcam, Cambridge, UK), p-p65 (1:1000, ab76302, Abcam, Cambridge, UK), Nrf2 (1:1000, ab62352, Abcam, Cambridge, UK), and β-actin (1:5000, ab8226, Abcam, Cambridge, UK).

2.2 AP animal construction

The AP model was induced in 8-week-old C57BL/6 male mice by intraperitoneal injection of Ceruletide (17650-98-5, Sigma-Aldrich, Silicon Valley, USA) at 50 μg/kg every hour for 12 administrations, with the addition of lipopolysaccharides (LPS, 15mg/kg, HY-D1056, MedChemExpress, New Jersey, USA) during the final Ceruletide injection. In each group, 6 mice received intraperitoneal injections of TSL (10 mg/kg), and LPS was added as appropriate. The mice were allocated to the following groups: (1) Control group: received normal saline injections. (2) AP group: underwent Ceruletide intraperitoneal injections. (3) TSL group: received saline intraperitoneal injections and TSL (20 mg/kg, Sigma, USA) *via* intragastric administration for 7 days. (4) AP + TSL group: subjected to Ceruletide intraperitoneal injections, along with intragastric administration of TSL at a dose of 20 mg/kg for 7 days. After euthanasia *via* cervical dislocation, whole blood and pancreatic tissues were collected for analysis.

2.3 Histological analysis

Pancreatic tissues were fixed in 4% paraformaldehyde, embedded in paraffin and sectioned, followed by staining with hematoxylin and eosin (H&E). Pathological assessment of pancreatitis included four key indicators: inflammation, necrosis, fibrosis and vascular involvement. Each indicator was graded on a scale of 0–3 for severity. The total score, representing the overall severity, was categorized as follows: 0–4 (mild), 4–8 (moderate) or 8–12 (severe).

2.4 ELISA

IL-1β, TNF-α and IL-6 levels in the serum were assessed using an ELISA kit (Beyotime, China), and the optical density of each well was measured at a wavelength of 450 nm using a microplate reader.

2.5 The detection of serum lipase and amylase

Serum lipase and amylase, serving as primary biomarkers, were quantified using the respective kits from Beyotime (Beijing, China).

2.6 Real-Time polymerase chain reaction (PCR)

Total RNA was extracted from arterial samples using TRIzol reagents and reverse transcribed into cDNA using M-MLV reverse transcriptase (Promega Corporation). The cDNA was then amplified using the following primer sequences: TNF-α: Forward: GGTGCCTATGTCTCAGCCTCTT, Reverse: GCCATAGAACTGATGAGAGGGAG; IL-1β: Forward: ACAAGGAGAAGAAAGTAATGAC, Reverse: GCTGTAGAGTGGGCTTAT; IL-6: Forward: AGACAGCCACTCACC, Reverse: TTCTGCCAGTGCCTCTT; chemokine C-C-motif ligand 2 (CCL2): Forward: TAAAAACCTGGATCGGAACCAAA, Reverse: GCATTAGCTTCAGATTTACGGGT; chemokine (C-X-C motif) ligand 12 (CXCL12): Forward: TGCATCAGTGACGGTAAACCA, Reverse: CACAGTTTGGAGTGTTGAGGAT; glyceraldehyde-3-phosphate dehydrogenase (GAPDH): Forward: AGAAGGCTGGGGCTCATTTG, Reverse: AGGGGCCATCCACAGTCTTC.

2.7 SOD, MDA, GSH and MPO detection

Pancreatic tissues were isolated to assess SOD, MDA, GSH and MPO levels. These tissues were homogenized and centrifuged for 20 minutes, after which the supernatant was collected and incubated with indicated samples for 2 hours.

2.8 Immunofluorescence

The tissues were fixed in formaldehyde, washed in phosphate buffered saline (PBS), permeabilized using PBS containing 0.5% Triton X-100, and then stained with the primary antibody. After rinsing with PBS, the cells were exposed to a fluorescent secondary antibody, following which DAPI staining was performed, and fluorescence microscopy was conducted for imaging. The evaluation was based on the percentage of positive cells in a single field of view, with an average derived from 8 fields.

2.9 Immunoblotting

Tissues were lysed to isolate proteins, which were subsequently separated using 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF) membranes. The membranes were then subjected to incubation with 5% bovine serum albumin (BSA) followed by primary antibodies. Horseradish peroxidase (HRP)-conjugated secondary antibodies were applied to the membranes at a 1:1000 dilution for 2 hours. The experimental procedure was conducted as previously described [13].

2.10 Statistics

Statistical analyses were conducted using GraphPad Prism 6.0 (GraphPad, 6.0, La Jolla, CA, USA). Student's *t*-test was employed for group comparisons, with significance defined as

$p < 0.05$.

3. Results

3.1 TSL suppressed AP progression of pancreatic tissue in AP mice

First, we established an AP mouse model by giving the mice daily injections of TSL (20 mg/kg) for 7 days. Evaluation of their pancreatic tissues revealed prominent structural damage, acinar cell necrosis and substantial inflammatory cell infiltration in the AP group (Fig. 1a) compared to the control group (Fig. 1a). Notably, TSL exhibited a modest impact on the observed pathological features (Fig. 1a), while TSL treatment was associated with reduced severity of pancreatitis in AP mice (Fig. 1a). Furthermore, we assessed serum lipase and amylase levels, which serve as indicators of AP severity. The results indicated that TSL treatment had a modest effect on these enzyme levels in mice. In contrast, the AP group showed a significant increase in lipase and amylase levels (Fig. 1b). Importantly, TSL treatment resulted in a decrease in lipase and amylase levels in AP mice (Fig. 1b). Thus, our findings indicate that TSL contributes to the improvement of pancreatic tissue pathology in AP mice.

3.2 TSL suppressed serum and pancreatic tissue inflammation in AP mice

Subsequently, we examined the impact of TSL treatment on inflammation in AP mice by assessing the levels of inflammatory markers, including TNF-α, IL-6 and IL-1β, using both ELISA and qPCR. Our observations revealed that TSL treatment had a modest effect on the secretion of these inflammatory markers in the serum, while TSL treatment significantly reduced the levels of these inflammatory markers in AP mice, indicating a pronounced suppression of inflammation (Fig. 2a). Furthermore, qPCR assays provided additional evidence as TSL treatment led to a decrease in the mRNA levels of TNF-α, IL-6 and IL-1β in AP mice (Fig. 2b). Thus, TSL effectively attenuated inflammation in both serum and pancreatic tissue in AP-afflicted mice.

3.3 TSL blocked neutrophil infiltration in pancreatic tissues of AP mice

Neutrophil infiltration, a critical aspect of AP progression, was assessed using both qPCR and immunostaining. qPCR results showed a significant increase in the mRNA levels of CCL2 and CXCL12 in AP mice (Fig. 3a). However, TSL treatment reduced their mRNA levels in AP mice, indicating inhibition of neutrophil infiltration (Fig. 3a). For a more direct

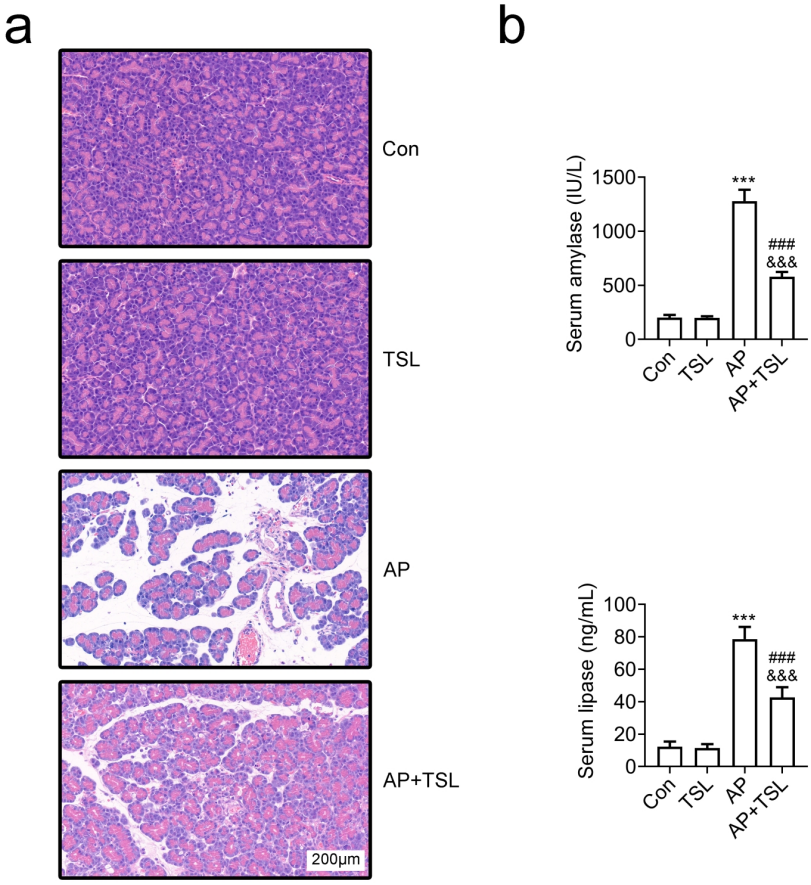

FIGURE 1. Tussilagone improved pathological changes in AP mice pancreatic tissues. (a) Histopathological evaluation using H&E staining illustrating the pancreatic tissue features in mice from the Control, TSL, Acute pancreatitis (AP) and AP + TSL groups. (b) Serum amylase (top) and serum lipase (bottom) levels in mice from the Control, TSL, AP and AP + TSL groups. ***$p < 0.001$, AP *vs.* Con (control); ###$p < 0.001$, AP + TSL *vs.* TSL; &&&$p < 0.001$, AP + TSL *vs.* AP. TSL: Tussilagone.

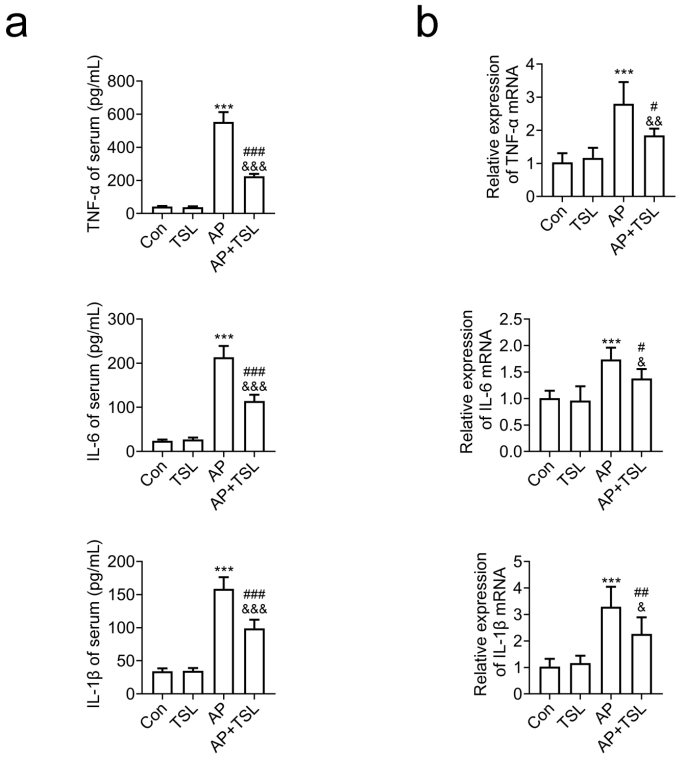

FIGURE 2. Tussilagone suppressed serum and pancreatic tissue inflammation in AP mice. (a) ELISA analysis reveals the secretion levels of the indicated factors in pancreatic tissue among mice from the Control, TSL, Acute pancreatitis (AP) and AP + TSL groups. (b) qPCR assays display the mRNA levels of the indicated factors in pancreatic tissues of mice from the Control, TSL, AP and AP + TSL groups. ***$p < 0.001$, AP *vs.* Con (control); #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$, AP + TSL *vs.* TSL; &$p < 0.05$, &&$p < 0.01$, &&&$p < 0.001$, AP + TSL *vs.* AP. TSL: Tussilagone; TNF: Tumor necrosis factor; IL: interleukin.

assessment, we performed cluster of differentiation (CD)11b immunofluorescence staining. AP mice exhibited a higher presence of CD11b-positive cells in pancreatic tissues, while TSL treatment effectively suppressed CD11b expression in AP-afflicted mice (Fig. 3b). Collectively, the results indicated that TSL could successfully block neutrophil infiltration in AP mice pancreatic tissues.

3.4 TSL restrained oxidative stress in AP mice

Given the significant role of oxidative stress in the progression of AP, we assessed the impact of TSL on oxidative stress in the pancreatic tissues of AP mice. Using ELISA assays, we measured the levels of MDA, SOD and GSH and found elevated levels of MDA and reduced levels of SOD and GSH (Fig. 4), indicative of increased oxidative stress. However, TSL treatment led to a decrease in MDA levels and an increase in the levels of SOD and GSH in pancreatic tissues of AP mice, suggesting effective mitigation of oxidative stress (Fig. 4). Overall, TSL successfully attenuated oxidative stress in AP-afflicted mice.

3.5 TSL blocks the NF-κB pathway and activates the Nrf2 pathway in AP mice

To determine the potential underlying pathways associated with the above findings, we conducted immunoblot assays. The results showed increased levels of p65 phosphorylation in pancreatic tissues of AP mice, which could be effectively reduced with TSL treatment, indicating the suppression of the NF-κB pathway (Fig. 5a). Furthermore, we assessed the impact of TSL on the Nrf2 pathway in AP mice and found that they exhibited elevated levels of Nrf2 expression compared to control mice, and notably, TSL treatment further increased Nrf2 expression, suggesting the activation of the Nrf2 pathway (Fig. 5b). Taken together, Tussilagone exerts its effects by inhibiting the NF-κB pathway and concurrently activating the Nrf2 pathway in AP-afflicted mice.

4. Discussion

AP is characterized by the inflammatory response triggered by the activation of pancreatic enzymes, resulting in pancreatic tissue digestion, edema, bleeding and potential necrosis [15]. The mechanism underlying multiple organ damage in AP remains unclear, contributing to the challenges in achieving satisfactory treatment outcomes and high mortality rates [6]. Commonly employed treatment options for AP include H2 receptor blockers, proton pump inhibitors, somatostatin and its analogs, protease inhibitors, analgesics and antibiotics [4]. A prominent targeted treatment strategy for AP is anti-inflammatory therapy. Given the pivotal role of the inflammatory response in AP pathology, mitigating this response holds promise for alleviating the disease and improving prognosis [3]. During AP, excessive activation of inflammatory cells leads to the release of interleukins and other inflammatory

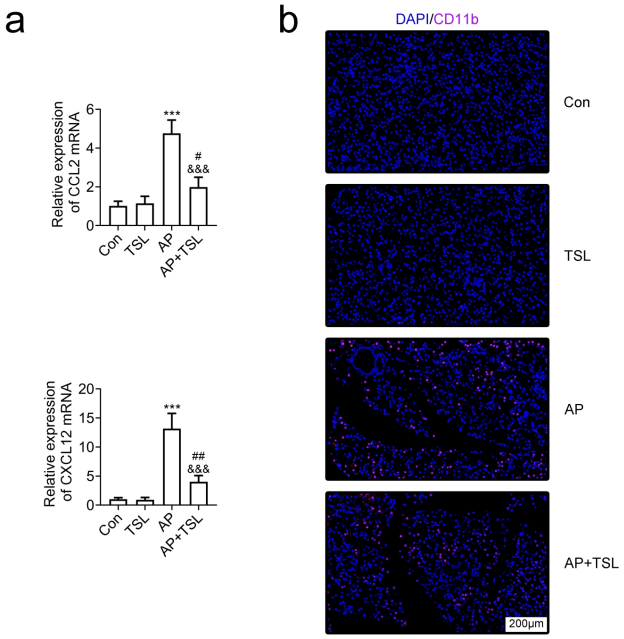

FIGURE 3. Tussilagone blocked neutrophil infiltration in the pancreatic tissues of AP mice. (a) qPCR assay results showing the mRNA levels of CCL-2 and CXCL12 in the pancreatic tissues of mice from the Control, TSL, Acute pancreatitis (AP) and AP + TSL groups. (b) Immunofluorescence assay results of the expression of CD11b (red panel) and DAPI in pancreatic tissues of mice from the Control, TSL, AP and AP + TSL groups. ***$p < 0.001$, AP *vs.* Con (control); #$p < 0.05$, ##$p < 0.01$, AP + TSL *vs.* TSL; &&&$p < 0.001$, AP + TSL *vs.* AP. TSL: Tussilagone; CCL: chemokine C-C-motif ligand; CXCL: chemokine C-X-C-motif ligand; DAPI: 4,6-diamino-2-phenyl indole; CD11b: cluster of differentiation 11b.

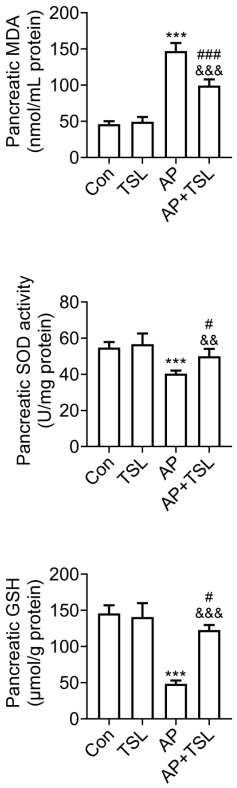

FIGURE 4. Tussilagone suppressed oxidative stress in AP mice. Analysis of the ELISA results reveals the secretion levels of the indicated factors in pancreatic tissues among mice from the Control, TSL, Acute pancreatitis (AP), and AP + TSL groups. ***$p < 0.001$, AP *vs.* Con (control); #$p < 0.05$, ###$p < 0.001$, AP + TSL *vs.* TSL; && $p < 0.01$, &&& $p < 0.001$, AP + TSL *vs.* AP. MDA: malondialdehyde; SOD: Superoxide dismutase; GSH: glutathione; TSL: Tussilagone.

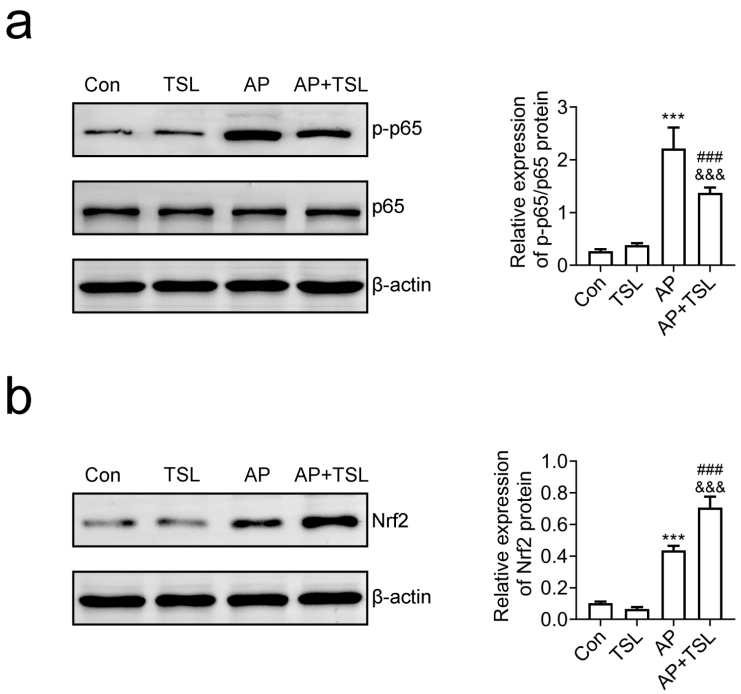

FIGURE 5. Tussilagone blocks the NF-κB pathway and activates the Nrf2 pathway in AP mice. (a) Immunoblot assays showing the expression and phosphorylation levels of p65 in pancreatic tissues of mice from the Control, TSL, Acute pancreatitis (AP) and AP + TSL groups. (b) Immunoblot assays of the expression levels of Nrf2 in pancreatic tissues of mice from the Control, TSL, AP and AP + TSL groups. ***$p < 0.001$, AP *vs.* Con (control); ###$p < 0.001$, AP + TSL *vs.* TSL; &&&$p < 0.001$, AP + TSL *vs.* AP. TSL: Tussilagone; Nrf2: NF-E2-related factor 2.

factors, thereby initiating a systemic inflammatory response and influencing pancreatic tissue cell apoptosis [2]. Importantly, our study demonstrated that TSL effectively attenuated both serum and pancreatic tissue inflammation in AP mice, thereby impeding the progression of AP. Histopathologically, AP is characterized by local glandular duct epithelial injury in the pancreas, marked by substantial neutrophil infiltration and occasionally neutrophil-induced epithelial injury, obstructive vasculitis and local duct epithelial damage [16]. In line with this, our data confirmed that TSL mitigated neutrophil infiltration in AP tissues, potentially contributing to the alleviation of AP symptoms.

Oxidative stress plays a significant role in the pathogenesis of AP and is closely associated with damage to external pancreatic organs, including the heart, liver, lung, kidney and digestive tract [17]. Oxidative stress leads to the generation of a substantial amount of ROS and active nitrogen compounds, resulting in inflammation and microcirculation disturbances, which may in turn lead to cell necrosis or apoptosis through various mechanisms, ultimately causing dysfunction or failure of the pancreas and other organs [18]. Antioxidants can reduce the production of oxygen free radicals or directly eliminate free radicals generated within the body. They also enhance the body's antioxidant capacity and have shown promise in the treatment of AP [19]. According to our data, TSL effectively mitigates oxidative stress in AP-afflicted mice, suggesting that interventions aimed at reducing oxidative stress could be an effective therapeutic approach for the treatment of AP.

NF-κB plays a pivotal role in the pathogenesis of AP by disrupting the expression of inflammatory factors and immune proteins [20]. In this study, we have demonstrated that TSL effectively suppresses inflammation and oxidative stress in AP mice through the modulation of this pathway. Activation of Nrf2 has been shown to have a significant positive impact on AP. Nrf2 is a crucial redox-sensitive transcription factor that responds to the translocation of the Keap1 homodimer from the cytoplasm to the nucleus [21]. In the nucleus, Nrf2 forms a dimer with the Maf protein, subsequently binding to antioxidant response elements in gene promoters and regulating the expression of antioxidant genes to protect cells from the pathological effects induced by oxidative stress [22]. Heme oxygenase (HO)-1 is a rate-limiting enzyme in heme degradation and is considered to be the most vital endogenous enzyme in preventing oxidative stress [23]. HO-1 activation is controlled by the upstream Nrf2/antioxidant response element (ARE) pathway [24]. Interestingly, our results indicated that TSL inhibited the NF-κB pathway and activated the Nrf2 axis, therefore alleviating AP in mice. Notably, TSL was shown to also affect the progression of cancer and angiogenesis, as confirmed by other studies [6, 7].

5. Conclusions

In summary, our study demonstrates that TSL may effectively suppress inflammation and oxidative stress, resulting in the alleviation of AP. Based on these findings, TSL could be considered a promising potential therapeutic drug for the treatment of AP.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

CZ and MRX—designed the study, completed the experiment and supervised the data collection. YMW—analyzed the data, interpreted the data. TYH—prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Ya'An Polytechnic College Affiliated Hospital (Approval No. 2021-049). The animal experiment complies with the ARRIVE guidelines and in accordance with the National Institutes of Health guide for the care and use of Laboratory animals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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