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Sheng-Jiang-Yi-You decoction inhibits the inflammatory response by down-regulating the p38MAPK signaling pathway to alleviate *Helicobacter pylori*-associated gastritis

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Summary. Background. *Helicobacter pylori* (HP)-associated gastritis is an important factor in development of stomach cancer. Components of Sheng-Jiang-Yi-You decoction (SJYYD) exert gastroprotective effects. However, the effects and mechanism of SJYYD in HP-associated gastritis remain uncertain.

Methods. HP bacterial solution (1×10^9 CFU/mL) was gavaged every other day for 14 days to construct an HP-associated gastritis mouse model. Male BALB/c mice were randomized into Sham, HP, HP+Standardized triple therapy (HP+Triplet), HP+SJYYD (0.4 mL/20 g), HP+Triplet+SJYYD, HP+anisomycin (ANI) (2.5 mg/kg/d, p38MAPK agonist, HP+ANI), and HP+SJYYD+ANI groups (n=6). Gastric mucosal injury detection and rapid urease test for HP infection were conducted. HE staining for pathological damage and ELISA for pro-inflammatory factors and immunoglobulin G (IgG) content were performed. Measurement of p38 mitogen-activated protein kinase (p38MAPK) pathway-related factor expression was performed by qRT-PCR and western blot.

Results. The increased IgG content and HP colonization rate indicated successful modeling. SJYYD caused attenuated gastric mucosal damage, with decreased ulcer index (UI), HP colonization rate, inflammatory cell infiltration, tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β levels in HP-associated gastritis mice. Moreover, SJYYD reduced p38MAPK, c-Jun N-terminal kinase (JNK), and extracellular regulated protein kinase (ERK) mRNA expression, as well as p-p38MAPK/p38MAPK, p-JNK/JNK, and p-ERK/ERK protein expression in gastric mucosa tissues of HP-associated gastritis mice. The above effects were reversed by further ANI treatment.

Conclusion. SJYYD may attenuate HP-associated gastritis by inhibiting inflammatory response by down-regulating p38MAPK pathway, providing scientific evidence for clinical application of SJYYD in HP-associated gastritis treatment and promoting the development of therapeutic approaches in HP-associated gastritis.

Key words: Helicobacter pylori, Gastritis, Sheng-Jiang-Yi-You, Inflammatory response, p38MAPK

Introduction

As a Gram-negative microaerobic bacterium, *Helicobacter pylori* (HP) is closely associated with gastrointestinal disorders (Sousa et al., 2023). Approximately 50% of the global population suffers from HP infection, with 30-50% of prevalence in developed countries and 85-95% in developing countries (Sharndama and Mba, 2022). Notably, almost all HP-infected individuals suffer from chronic gastritis of varying severity, with gastric mucous membrane damage, glandular atrophy, and severe cases progressing to gastric cancer (Yang and Hu, 2022; Zhang et al., 2022b). Thus, the importance of eradicating HP infections has led to the rapid development of HP-associated gastritis treatments. Until now, HP treatment

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regimens mainly consist of strong acid inhibitors with antibiotics and/or bismuth, but increasing resistance, recurrent flare-ups, and the gastrointestinal adverse effects have made its treatment a major challenge (Malfertheiner et al., 2023). Therefore, improving the eradication rate of HP is an urgent global problem, and more effective means of eradication are urgently needed.

In fact, the exact mechanism of HP-associated gastritis is still in the stage of continuous exploration, but it is certain that the inflammatory response is one of the important mechanisms (Zhang et al., 2022b). Mice with HP-associated gastritis exhibited significantly increased interleukin (IL)-1β, IL-6, 1L-8, tumor necrosis factor-alpha (TNF-α), and immunoglobulin G (IgG) levels; leaf extract of *Cudrania tricuspidata* reversed the above effects, thereby mitigating the progression of HP-associated chronic gastritis (Lee et al., 2023). Cordycepin was found to exert anti-inflammatory and antibacterial effects in HP-associated chronic gastritis mice with reduced IL-1β and IL-6 expression (Kong et al., 2022). Therefore, inhibition of the inflammatory response is essential for alleviation of HP-associated gastritis.

The p38 mitogen-activated protein kinase (p38MAPK) belongs to the MAPK family and plays an important biological role in the modulation of inflammatory responses, cell proliferation, apoptosis, and other pathological processes (Li et al., 2022). Several studies have demonstrated that activation of the p38MAPK signaling pathway is involved in the development of HP-associated chronic gastritis (Song et al., 2021; Tang et al., 2021). HP promoted its colonization in the gastric mucosa and increased the levels of pro-inflammatory factors like IL-1, IL-6, IL-1β, and TNF-α by up-regulating heparanase, accompanied by activation of the p38MAPK signaling pathway, leading to exacerbation of gastritis lesions (Tang et al., 2021). Song et al. (2021) demonstrated that the effects of *Polygonum capitatum* in improving HP-associated gastritis were correlated with p38MAPK, extracellular regulated protein kinases 1/2 (ERK1/2), and nuclear factor kappa-B p65 (NF-κB p65), and further confirmed, with *in vivo* and *in vitro* experiments, that *Polygonum capitatum* may exert anti-HP-associated gastritis effects by inhibiting the phosphorylation of p38MAPK and ERK1/2, with lowered TNF-α levels. According to the above findings, suppression of the inflammatory response through inhibition of the p38MAPK pathway may be a potential avenue for HP-associated gastritis treatment.

HP infection is generally recognized as "damp-heat pathogenic Qi" or "toxins from pathogenic bacteria", mainly including a type of dampness-heat syndrome in the spleen and stomach, type of deficiency of spleen and stomach, type of blood stasis in the stomach collaterals, type of liver-stomach disharmony, and type of stomach-Yin deficiency (Li et al., 2021b). In Chinese medicine theory, HP-associated gastritis belongs to "root deficiency and branch excess", and the principle of treatment is focused on invigorating the spleen and Qi, clearing heat, and eliminating dampness, as well as harmonizing the stomach (Li et al., 2021b). Sheng-Jiang-Yi-You decoction (SJYYD) consists of seventeen kinds of Chinese herbal medicines, including *Pseudostellariae Radix*, *Campsis grandiflora* (Thunb.) K. Schum, *Atractylodes macrocephala Koidz*, *Bombyx Batryticatus*, *Cicadae Periostracum*, *Caryophylli Flos*, *Mentha haplocalyx* Briq., *Endoconcha Sepiae*, *Concha Arcae*, *Halloysitum Rubrum*, *Rhei Radix et Rhizoma*, *Curcuma longa* L., *Smilacis Glabrae Rhizom*a, *Taraxacum mongolicum* Hand.-Mazz., *Coptis chinensis Franch*, Massa Medicata Fermentata, and *Agastache rugosa* (Fisch. & C.A. Mey.) Kuntze. Yang et al. (2019) revealed through network pharmacology that *Atractylodes macrocephala Koidz* may ameliorate chronic gastritis via the TNF-α pathway and IL-17 signaling pathway, while down-regulation of IL-6 and IL-1β levels were confirmed *in vitro*. Curcumin was proven to inhibit HP growth and has the potential to be an adjunct for treating HP-related diseases and promoting HP eradication (Boyanova et al., 2024). In addition, palmatine, an alkaloid extracted from Coptidis Rhizoma, played an enteroprotective role by inhibiting the inflammatory response in the gastric mucosa, thereby ameliorating HP-associated chronic atrophic gastritis, with a reduction of pro-inflammatory factor chemokine 16 (CXCL-16) and IL-8 levels (Chen et al., 2020). Therefore, SJYYD may be a potential new therapeutic approach for HP-associated gastritis treatment, primarily leading to gastric mucosal protection mediated through inhibited inflammatory responses.

Furthermore, besides the anti-HP effects of modified pectic polysaccharide from turmeric, the inflammatory response was also suppressed in rats with gastric ulcers, with decreased TNF-α, IL-8, and p-p38MAPK/p38MAPK expression, to exhibit gastric mucosal protective effects (Rajagopal et al., 2018). As an active ingredient in *Taraxacum mongolicum* (Zheng et al., 2022), quercetin was demonstrated to improve reflux esophagitis by suppressing the inflammatory response through down-regulation of the p38 signaling pathway, which was mainly reflected in the reduction of IL-6, IL-8, TNF-α, IL-1β, JNK, and p38MAPK expression (Zhao et al., 2022). Thus, SJYYD may attenuate HP-associated gastritis progression by suppressing inflammation through down-regulation of the p38MAPK signaling pathway.

In this study, we constructed a mouse model of HP-associated gastritis and used a p38MAPK agonist, anisomycin (ANI), to clarify that the ameliorative effects of SJYYD in HP-associated gastritis may be related to inhibition of the p38MAPK signaling pathway-mediated inflammatory response, providing scientific evidence for clinical application of SJYYD in HP-associated gastritis treatment and advancing the development of therapeutic means for HP-associated gastritis.

Materials and methods

Animals

Fifty-three Specific pathogen-free (SPF) grade eight-week-old male BALB/c mice, obtained from the Shanghai SLAC Laboratory Animal Co., Ltd, were housed at 22±2°C, 50-60% relative humidity, and a light-dark cycle every 12 h. The mice were kept by Hangzhou Hunter Testing Biotechnology Co., Ltd (No. SYXK (Zhe) 2024-0003).

Preparation of HP solution

The *Helicobacter pylori* Sydney Strain 1 (Hp SS1) was clinically obtained from children with HP-associated gastritis from the Hangzhou Children's Hospital, China (ethics approval No. 2021-24). HP was incubated for 72 h at 37°C under microaerobic conditions with a gas mixture (O_2 5%, N_2 85%, and CO_2 10%). Then, the bacteria were collected, and the concentration was adjusted to 1×10^9 CFU/mL (Kong et al., 2020).

Preparation of SJYYD

The composition of SJYYD was presented in Table 1. Among them, except for the two Chinese medicines of *Caryophylli Flos* and *Mentha haplocalyx* Briq., the rest was first decocted medicines. The medicines were decocted twice in water, and the two decoction times were mixed, a total of 400 mL, for taking twice in the morning and evening 1h after meals. The clinical dose was converted to a mouse dose based on 70 kg of adult body weight (Yang et al., 2022), and the mouse dose was 33.8 g/kg.

HP-associated gastritis mouse modeling and grouping

After one week of acclimatization, the HP-associated gastritis mouse modeling was conducted (Kong et al., 2022). Firstly, gavage of the mixed antibiotic solution, consisting of 10 mg/mL of ampicillin (B28636, Shanghai Yuanye), 10 mg/mL of azithromycin (B20006, Shanghai Yuanye), and 1.2 mg/mL of gentamicin (E003632, Sigma), was given to the mice once a day for 3 days. One week later, HP bacterial solution was administered by gavage with 0.5 mL (approximately 1×10^9 CFU/mL) once every other day for a total of seven times for 14 days (Kong et al., 2022). After completion of gavage, five mice were randomly selected to undergo a rapid urease assay and ELISA to determine the presence of HP infection.

Following confirmation of successful modeling, all mice were randomly sorted into seven groups: Sham, HP-associated gastritis (HP), HP+Standardized triple therapy (amoxicillin+clarithromycin+omeprazole, HP+Triplet), HP+SJYYD, HP+Triplet+SJYYD, HP+ANI (p38MAPK agonist, HP+ANI), and HP+SJYYD+ANI (n=6). The liquid from the two decoctions in water was mixed and concentrated to 200 mL, and each mouse (20 g) was treated with a dose of approximately 0.4 mL of SJYYD per gavage twice daily. Similar to the dose conversion for SJYYD, the mouse dose of amoxicillin in this study was calculated as 455 mg/kg/d for amoxicillin (S26786, Shanghai Yuanye), 136.5 mg/kg/d for clarithromycin (B25481, Shanghai Yuanye), and 7.28 mg/kg/d for omeprazole (B24391, Shanghai Yuanye) dissolved in saline and administered twice a day, based on the equivalent dose formula for humans and mice converted by body surface area. Mice in the ANI group were treated with intraperitoneal injections of 2.5 mg/kg/d of anisomycin (T90619, Shanghai Yuanye) once a day for 14 days (Li et al., 2021a). The Sham and HP groups were gavaged with equal amounts of saline.

Table 1. Composition of SJYYD.

Latin name	Chinese Name	Amount (g)
Endoconcha Sepiae	Hai-Piao-Xiao	20
Concha Arcae	Wa-Leng-Zi	20
Pseudostellariae Radix	Tai-Zi-Shen	30
Smilacis Glabrae Rhizoma	Tu-Fu-Ling	30
Taraxacum mongolicum Hand.-Mazz.	Pu-Gong-Ying	30
Campsis grandiflora (Thunb.) K. Schum	Ling-Xiao-Hua	15
Atractylodes macrocephala Koidz	Bai-Zhu	15
Massa Medicata Fermentata	Shen-Qu	15
Bombyx Batryticatus	Jiang-Can	15
Agastache rugosa (Fisch. & C.A. Mey.) Kuntze	Huo-Xiang	15
Cicadae Periostracum	Chan-Tui	10
Coptis chinensis Franch	Huang-Lian	10
Halloysitum Rubrum	Chi-Shi-Zhi	10
Rhei Radix et Rhizoma	Da-Huang	10
Curcuma longa L.	Jiang-Huang	6
Caryophylli Flos	Ding-Xiang	3
Mentha haplocalyx Briq.	Bo-He	3

Detection of gastric mucosal injury and ulcer index (UI)

After anesthesia, the abdominal cavity was incised in the midline of the abdomen below the xiphoid process to locate the stomach and extract it. The gastric cavity was cut along the greater curvature of the stomach to spread the gastric mucosa, and then the gastric mucosa was rinsed with saline three times. The changes in morphology of the gastric mucosa damage were visualized and photographed. The evaluation of UI was performed according to GUTH criteria (Song et al., 2024). The specific score criteria were as follows: damage length ≤ 1 mm as 1 point; 1 mm < damage length ≤ 2 mm as 2 points; 2 mm < damage length ≤ 3 mm as 3 points; 3 mm < damage length ≤ 4 mm as 4 points; and 4 mm < damage length ≤ 5 mm as 5 points. The score was doubled for an injury width > 2 mm, and the UI for each mouse was the cumulative sum of the scores.

Sample collection

After 14 days of treatment, the mice were

anesthetized with isoflurane and the observation of the gastric mucosa damage status was carried out. CO_2 inhalation was employed for the euthanasia of mice, and the whole stomach was removed by dissection, and cut longitudinally along the side of the greater curvature of the stomach. Following rinsing off a little food residue with saline, the gastric mucosal lesion tissues were extracted, one part of which was fixed with 4% paraformaldehyde to prepare paraffin sections, and the other part was kept at -80°C.

Rapid urease test

The collected mouse stomach tissues were prepared into a homogenate and dropped on the urease test paper (Corfu Medical Technology Co., China). After 5 min at room temperature, the reagent color was observed. The change in reagent color from yellow to pink or red represented positive HP infection (Zhang et al., 2022a). When the reagent remained yellow, it proved negative for the urease test.

ELISA assay

According to the procedures of the Mouse TNF-α ELISA Kit (RX202412M, Ruixin), Mouse IL-6 ELISA Kit (RX203049M, Ruixin), Mouse IL-1β ELISA Kit (RX203063M, Ruixin), and Mouse IgG ELISA Kit (RX202736M, Ruixin), the determination of TNF-α, IL-6, IL-1β, and IgG content in the mouse gastric mucosa tissues was carried out.

HE staining

The gastric mucosa tissue paraffin sections were sequentially placed into xylene I, xylene II, anhydrous ethanol I, anhydrous ethanol II, and 75% ethanol, and hematoxylin (H3136, Sigma) was added for 5 min, followed by washing with tap water. After completion of differentiation and reblueing (Bry-0001-03, Bry-0001-04, Shanghai Runner), the sections were dehydrated in ethanol and then immersed in eosin staining solution (E4009, Sigma) for 5 min. Subsequently, the slices were sequentially placed in anhydrous ethanol I, anhydrous ethanol II, anhydrous ethanol III, xylene I, and xylene II. The sealing of sections and image visualization under the microscope (Nikon Eclipse Ci-L, Nikon) were performed. Histopathology scoring of gastric mucosal tissues mainly included observation of chronic inflammation, atrophy, intestinal metaplasia and dysplasia (Cai et al., 2021; Shen et al., 2023), which were classified into four grades according to the degree of lesion: none, mild, moderate, and severe, with scores of 0, 1, 2, and 3, respectively (Shen et al., 2023).

qRT-PCR assay

Following extraction of total RNA from mouse gastric mucosa using the Universal Genotype RNA Extraction Kit (AG21024, Amyjet), the RNA was reversed to cDNA using the HiFiScript cDNA First Strand Synthesis Kit (CW2569M, Jiangsu Cowin Biotech). After dilution, 2 μL of cDNA was taken and the PCR reaction was performed according to the instructions of the SYBR Green qPCR Kit (11201ES08, Yeasen Biotech). β-actin was employed as an internal reference, and the reaction system was 20 μL. The amplification conditions were 95°C, 10 min denaturation; 95°C, 15 s; 60°C, 60 s; 40 cycles. After the calculation of Ct values, the determination of p38MAPK, JNK, and ERK mRNA expression levels was made by the $2^{-\Delta\Delta Ct}$ assay. Table 2 showed the primer sequences.

Western blot assay

Pre-cooled lysis buffer was added to the sheared gastric mucosal tissues, which were then homogenized and kept on ice for 30 min. The total protein concentration of the samples was determined by the BCA method after centrifugation at 12000 g for 5 min at 4°C. After gel preparation, the samples were added to the wells, electrophoresed, and transferred to the PVDF membrane. The membrane was immersed in 5% skimmed milk powder and blocked with shaking for 1.5 h. Subsequently, the primary antibody (Table 3) was added and incubated overnight at 4°C, and then the secondary antibody was added (Table 3) the next day, incubating for 1 h at room temperature. ECL reagents were added to cover the PVDF membrane, and images were saved after exposure. The bands' gray values were detected by ImageJ software.

Statistical analysis

SPSS statistical software (version 20.0, IBM) was utilized for data analysis. Measures between multiple groups meeting the normal distribution and the chi-

Table 2. Primer sequence information.

Gene	Forward Primer (5'-3')	Reverse Primer (5'-3')
Mouse *p38MAPK*	TGCCCGAACGATACCAGAAC	GTGGTGGCACAAAGCTGATG
Mouse *JNK*	AGGCTCAGGAGCTCAAGGAA	GCTGCACCTGTGCTAAAGGA
Mouse *ERK*	CCAACCTCTCGTACATCGGAG	GAATGGCGCTTCAGCAATGG
Mouse *β-actin*	GTGTGATGGTGGGAATGGGT	ACTCCTGCTTGCTGATCCAC

square test were analyzed by one-way ANOVA, with further two-by-two comparisons between groups using Turkey's test. The Kruskal-Wallis H test was adopted for data that did not conform to a normal distribution. All data was reported as mean ± standard deviation. $p<0.05$ was considered a statistically significant difference.

Table 3. Western blot assay antibody information.

Antibody	Company	Article number
p-p38MAPK	Affinity	AF4001
p38MAPK	Affinity	AF6456
p-JNK	Affinity	AF3318
JNK	Affinity	AF6318
p-ERK	Affinity	AF1015
ERK	CST	4695s
Anti-rabbit IgG, HRP-linked	CST	7074
β-actin	Proteintech	81115-1-RR

Results

SJYYD treatment ameliorated gastric mucosal injury in mice with HP-associated gastritis

The IgG content and Hp colonization rate were used as criteria to assess the modeling. ELISA was employed to test IgG content and the rapid urease test was used to examine the Hp colonization rate. In Figure 1A, the mouse gastric mucosal tissue of the HP group exhibited higher IgG content than that of mice in the Sham group (6.87±0.76 vs. 2.31±0.29, $p<0.01$). Meanwhile, the HP colonization rate was 100%, indicating successful modeling.

Subsequently, observation of the appearance and

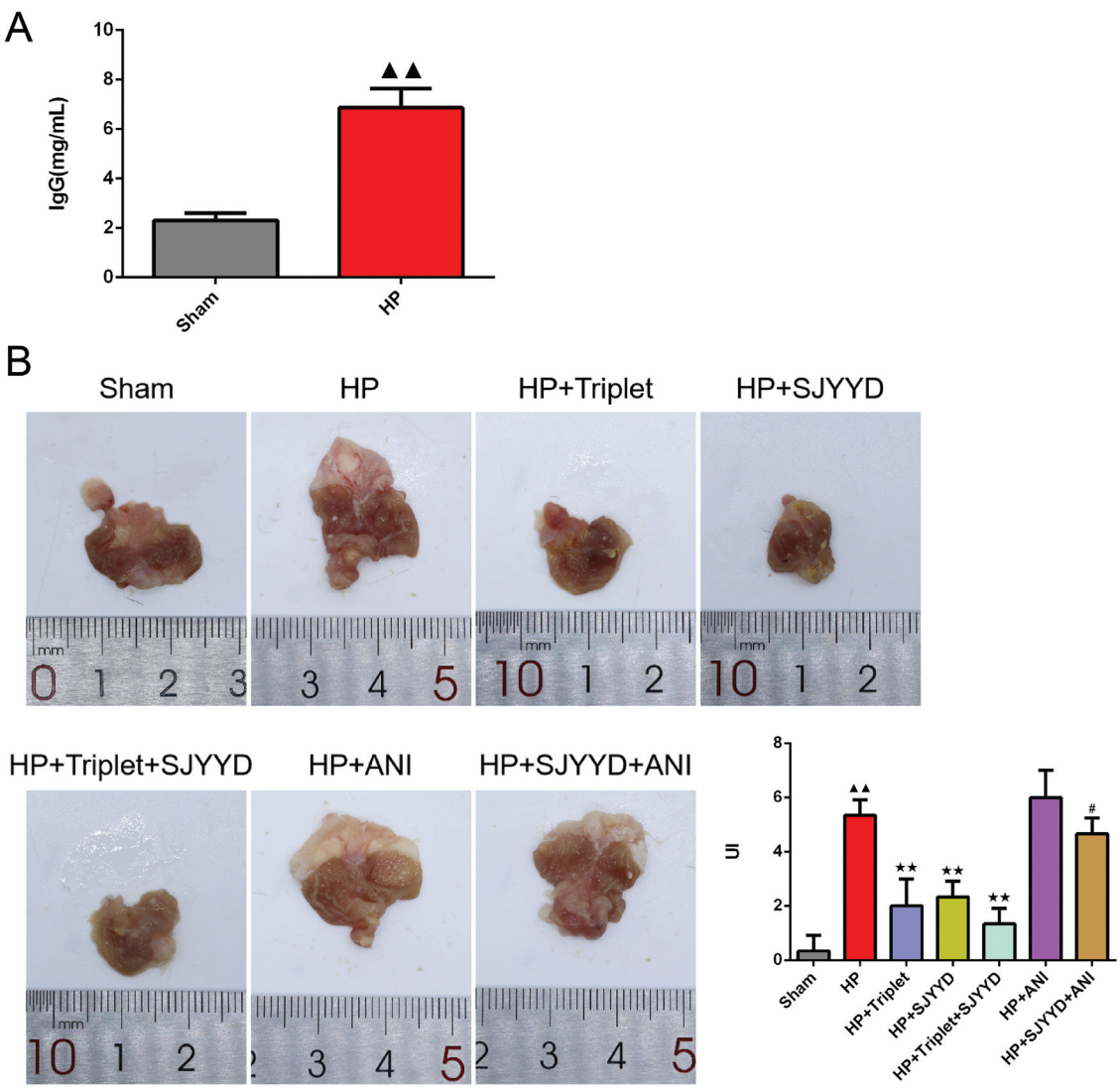

Fig. 1. SJYYD treatment ameliorated gastric mucosal injury in mice with HP-associated gastritis. **A.** ELISA was employed to test the IgG content, n=5. **B.** Observation of the appearance and morphology of the gastric mucosa and evaluation of gastric mucosal lesion UI was performed, n=3; ▲$p<0.05$ and ▲▲$p<0.01$ vs. Sham group; ★$p<0.05$ and ★★$p<0.01$ vs. HP group; #$p<0.05$ and ##$p<0.01$ vs. HP+SJYYD group; Note: SJYYD: Sheng-Jiang-Yi-You decoction; IgG: immunoglobulin G; UI: ulcer index; ANI: anisomycin.

morphology of the gastric mucosa and evaluation of gastric mucosal lesion UI was performed (Fig. 1B, Table 4). Mice in the Sham group had a relatively thick layer of gastric mucosa. HP mice in the HP and HP+ANI groups exhibited thinning of the gastric mucosal layer, visible blood vessels, shallow folds, mucosal wall hemorrhages, ulcers, and erosions. The morphology and structure of the gastric mucosa of mice in the HP+Triplet, HP+SJYYD, and HP+Triplet+SJYYD groups were improved to different degrees. There were higher UI levels in HP mice than in the Sham group (p<0.01), and reduced UI in HP mice with further Triplet, SJYYD, and Triplet+SJYYD treatment (5.33±0.58 vs. 2.00±1.00, 2.33±0.58, and 1.33±058, respectively; p<0.01). ANI treatment reversed the effects of SJYYD treatment in HP mice, with increased UI (p<0.05). Moreover, the HP+Triplet, HP+SJYYD, and HP+Triplet+SJYYD groups had decreased HP colonization rates in comparison with the HP group (33.33%, 50.00%, and 16.67% vs. 100%). The HP colonization rates of the HP+ANI and HP+SJYYD+ANI groups were 100% and 66.67%, respectively.

Table 4. Evaluation of gastric mucosal lesion UI.

Group	UI
Sham	0.33±058
HP	5.33±0.58▲▲
HP+Triplet	2.00±1.00★★
HP+SJYYD	2.33±0.58★★
HP+Triplet+SJYYD	1.33±058★★
HP+ANI	6.00±1.00
HP+SJYYD+ANI	4.67±0.58#

▲▲p<0.01 vs. Sham group; ★★p<0.01 vs. HP group; #p<0.05 vs. HP+SJYYD group. SJYYD: Sheng-Jiang-Yi-You decoction; ANI: anisomycin; UI: ulcer index.

SJYYD treatment alleviated pathological damage and the inflammatory response of gastric mucosa in mice with HP-associated gastritis

Detection of pathological damage of gastric mucosal tissues was conducted by HE staining (Fig. 2A). The structure of the gastric mucosa in the Sham group was almost normal, with relatively thick gastric mucosa, clear gastric notches, and abundant glands. In the HP and HP+ANI groups, there was a thinned gastric mucous membrane layer, shallow folds, a large number of detached epithelial cells, as well as inflammatory cell infiltration visible in the lamina propria, with atrophied, disorganized, and reduced glands. Mouse gastric mucosal tissues in other administration groups showed different degrees of improvement. In addition, HP mice demonstrated higher inflammation scores than those of mice in the Sham group (9.00±1.00 vs. 1.00±1.00, p<0.01). Further Triplet, SJYYD, and Triplet+SJYYD

Table 5. Measurement of TNF-α, IL-6, and IL-1β levels in mouse gastric mucosa tissues.

Group	TNF-α (pg/mg prot)	IL-6 (pg/mg prot)	IL-1β (pg/mg prot)
Sham	31.06±5.81	37.73±5.95	25.44±5.18
HP	58.00±6.57▲▲	172.96±23.55▲▲	92.14±6.97▲▲
HP+Triplet	26.70±4.97★★	104.14±5.85★★	65.23±6.11★★
HP+SJYYD	27.78±1.56★★	113.49±9.65★★	61.77±5.37★★
HP+Triplet+SJYYD	22.71±2.34★★	89.20±12.58★★	42.46±4.78★★
HP+ANI	66.66±8.45	189.66±29.02	92.16±14.09
HP+SJYYD+ANI	65.21±8.61##	154.81±18.19##	78.69±10.65#

▲▲p<0.01 vs. Sham group; ★★p<0.01 vs. HP group; #p<0.05 and ##p<0.01 vs. HP+SJYYD group. SJYYD: Sheng-Jiang-Yi-You decoction; ANI: anisomycin; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6.

Table 6. Detection of p38MAPK, JNK, and ERK mRNA expression in mouse gastric mucosa tissues.

Group	p38MAPK	JNK	ERK
Sham	1.009±0.166	1.008±0.154	1.001±0.062
HP	2.617±0.343▲▲	3.221±0.391▲▲	2.165±0.098▲▲
HP+Triplet	1.792±0.176★	1.980±0.206★★	1.472±0.253★
HP+SJYYD	1.469 ±0.087★★	2.189±0.317★	1.465±0.243★
HP+Triplet+SJYYD	1.168±0.109★★	1.229±0.445★★	1.139±0.290★★
HP+ANI	2.981±0.324	4.360±0.187★	2.977±0.097★★
HP+SJYYD+ANI	2.191±0.288#	3.236±0.467#	2.215±0.280##

▲▲p<0.01 vs. Sham group; ★p<0.05 and ★★p<0.01 vs. HP group; #p<0.05 and ##p<0.01 vs. HP+SJYYD group. SJYYD: Sheng-Jiang-Yi-You decoction; ANI: anisomycin; MAPK: mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; ERK: extracellular regulated protein kinases.

intervention caused a reduction in inflammation scores in HP mice (3.33±0.58, 3.67±0.58, and 1.67±0.58 vs. 9.00±1.00, $p<0.01$).

The TNF-α, IL-6, and IL-1β levels were measured by ELISA assay (Fig. 2B, Table 5). HP-associated gastritis led to higher TNF-α, IL-6, and IL-1β levels than in the Sham group ($p<0.01$). The TNF-α, IL-6, and IL-1β levels of the HP+Triplet, HP+SJYYD, and HP+Triplet+SJYYD groups were lower than those of the HP group ($p<0.01$). The ANI treatment intervention weakened the effects of SJYYD in HP mice, with higher TNF-α, IL-6, and IL-1β levels than mice in HP+SJYYD

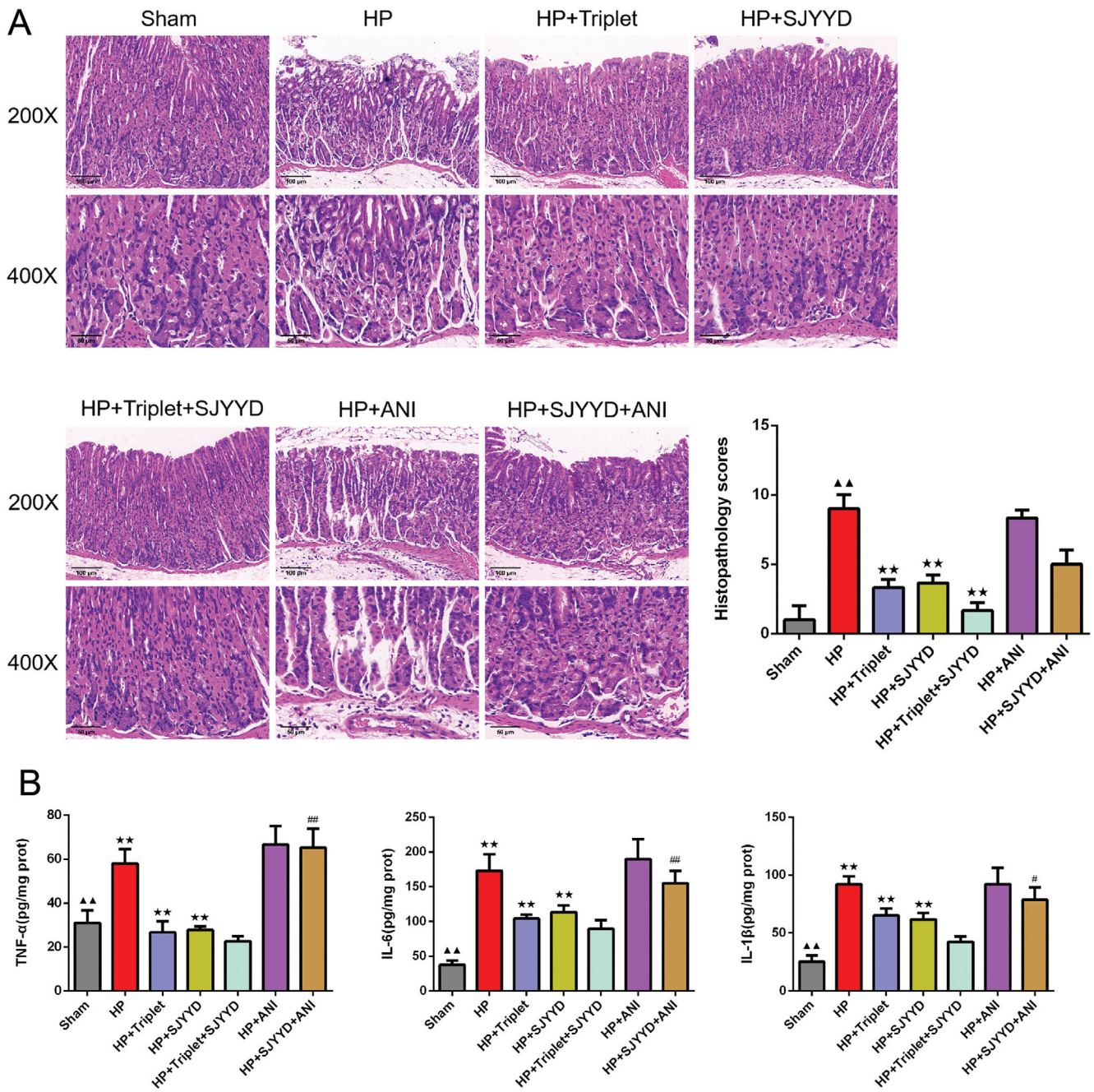

Fig. 2. SJYYD treatment alleviated the pathological damage and inflammatory response of gastric mucosa in mice with HP-associated gastritis. **A.** Detection of pathological damage of gastric mucosal tissues was conducted by HE staining, magnification 200×, scale bar=100 μm; magnification 400×, scale bar=50 μm, n=3. **B.** TNF-α, IL-6, and IL-1β levels were measured by ELISA assay, n=6; ▲$p<0.05$ and ▲▲$p<0.01$ vs. Sham group; ★$p<0.05$ and ★★$p<0.01$ vs. HP group; #$p<0.05$ and ##$p<0.01$ vs. HP+SJYYD group; Note: SJYYD: Sheng-Jiang-Yi-You decoction; IgG: immunoglobulin G; UI: ulcer index; ANI: anisomycin; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6.

group (p<0.01 or p<0.05).

SJYYD treatment exerted ameliorative effects on HP-associated gastritis through activation of the p38MAPK signaling pathway

Determination of p38MAPK, JNK, and ERK mRNA expression in mouse gastric mucosa tissues was made by qRT-PCR (Fig. 3A and Table 6). The p38MAPK, JNK, and ERK mRNA expression of HP mice were elevated in comparison with the Sham group (p<0.01). The HP+Triplet, HP+SJYYD, and HP+Triplet+SJYYD groups exhibited lower p38MAPK, JNK, and ERK mRNA expression than the HP group (p<0.05 or p<0.01). Further ANI treatment resulted in higher p38MAPK, JNK, and ERK mRNA expression in HP+SJYYD+ANI group than in HP+SJYYD group (p<0.05 or p<0.01).

Moreover, p-p38MAPK/p38MAPK, p-JNK/JNK, and p-ERK/ERK protein expression was measured by western blot (Fig. 3B and Table 7). There was increased p-p38MAPK/p38MAPK, p-JNK/JNK, and p-ERK/ERK protein expression in HP mice than in Sham mice (p<0.01). The p-p38MAPK/p38MAPK, p-JNK/JNK, and p-ERK/ERK protein levels of the HP+Triplet, HP+SJYYD, and HP+Triplet+SJYYD groups were reduced compared with HP mice (p<0.05 or p<0.01). Further ANI intervention led to an increase in p-p38MAPK/p38MAPK, p-JNK/JNK, and p-ERK/ERK protein expression in mice of the HP+SJYYD group p<0.05).

Discussion

With the development of scientific technology and life quality, the drug resistance rate of HP is increasing, whereas the eradication rate is decreasing (Li et al., 2023). In recent years, the significant advantages of traditional Chinese medicine formulas in treating HP-associated gastritis have been explored and have

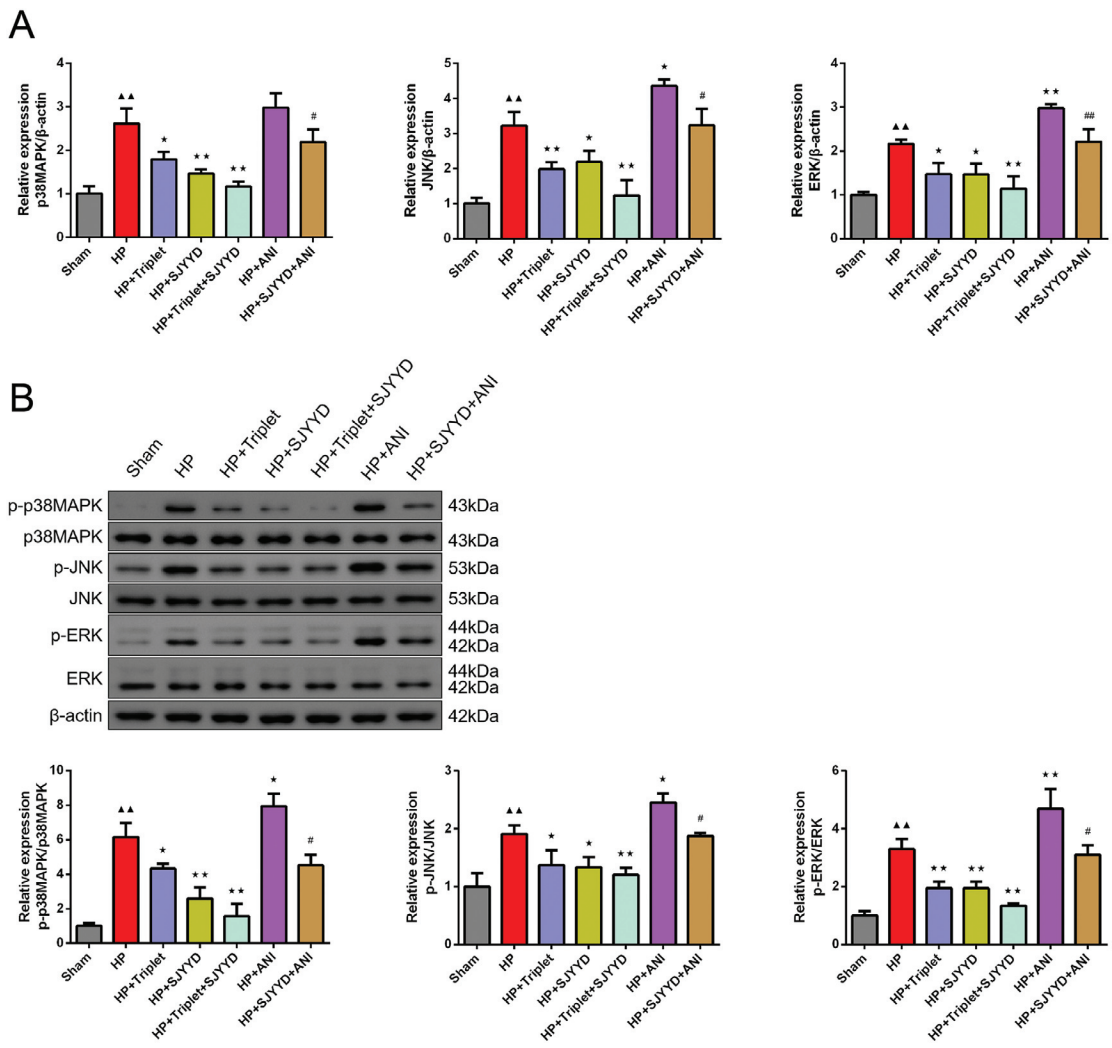

Fig. 3. SJYYD treatment exerted ameliorative effects on HP-associated gastritis through activation of the p38MAPK signaling pathway. **A.** Determination of p38MAPK, JNK, and ERK mRNA expression in mouse gastric mucosa tissues was made by qRT-PCR, n=3; **B.** p-p38MAPK/p38MAPK, p-JNK/JNK, and p-ERK/ERK protein expression was measured by western blot, n=3; ▲p<0.05 and ▲▲p<0.01 vs. Sham group; ★p<0.05 and ★★p<0.01 vs. HP group; #p<0.05 and ##p<0.01 vs. HP+SJYYD group; Note: SJYYD: Sheng-Jiang-Yi-You decoction; ANI: anisomycin; MAPK: mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; ERK: extracellular regulated protein kinases.

gradually become a major trend in the world market (Li et al., 2021c). In the present study, we determined that SJYYD ameliorated HP-associated gastritis and observed that an enhanced inflammatory response and activated p38MAPK pathway in HP-associated gastritis were weakened with further SJYYD intervention. Hence, SJYYD is a promising treatment option for HP-associated gastritis.

There is still no gold standard for the diagnosis of HP infection, as a result, it is usually evaluated using at least two diagnostic tests to improve accuracy and sensitivity (Liao et al., 2023). As a useful tool for assessing HP infection, serologic testing for changes in IgG levels helps determine HP infection, with high sensitivity, but it also indicates previous HP infection, making it difficult to accurately reflect whether or not a patient is currently infected (Liao et al., 2023). The invasive rapid urease test, also named the campylobacter-like organism test (CLO) test, has high specificity and sensitivity (Qi et al., 2024). The successful model construction was demonstrated by the results of IgG detection and the rapid urease test in our study. The results of the rapid urease test by Shen et al. (2023) showed that *Lactobacillus acidophilus* NCFM and *Lactiplantibacillus plantarum* Lp-115 reduced HP colonization, in line with our findings. Additionally, Silibinin was able to exert antimicrobial effects and reduce HP colonization levels in HP-associated gastritis mouse models (Cho et al., 2021), further confirming the anti-HP-associated gastritis of SJYYD in the present study.

Based on the "monarch, minister, assistant, and envoy" theory (Wang et al., 2024), in the SJYYD formula, *Pseudostellariae Radix*, *Campsis grandiflora* (Thunb.) K. Schum, *Atractylodes macrocephala Koidz*, *Bombyx Batryticatus*, *Cicadae Periostracum*, *Caryophylli Flos,* and *Mentha haplocalyx* Briq. as monarch drugs, are mainly transporting spleen-Yang and invigorating spleen Qi; *Endoconcha Sepiae*, *Concha Arca*e, *Halloysitum Rubrum*, *Rhei Radix et Rhizoma*, and *Curcuma longa* L. as minister drugs, are mainly clearing stomach heat and lowering stomach Qi; *Smilacis Glabrae Rhizoma*, *Taraxacum mongolicum* Hand.-Mazz., and *Coptis chinensis* Franch as assistant drugs, are mainly clearing heat and eliminating dampness; and *Massa Medicata Fermentata* and *Agastache rugosa* (Fisch. & C.A. Mey.) Kuntze as envoy drugs, are mainly aromatizing, eliminating dampness, regulating Qi, and harmonizing the stomach. The ethanolic extract of *Taraxacum mongolicum* Hand.-Mazz. showed anti-HP effects and urease inhibition activity, and down-regulated TNF-α and IL-6 levels, thereby playing a gastroprotective role (Dong et al., 2024). Berberine, an isoquinoline alkaloid, the main active component of *Coptis chinensis* Franch, was able to alleviate HP-associated gastritis by modulating macrophage polarization, with decreased TNF-α levels and increased IL-4 and IL-10 levels (Yang et al., 2021). The above findings were consistent with our results, which indicated that SJYYD amelioration for HP-associated gastritis may be mediated by inhibition of the inflammatory response.

The interaction between p38MAPK and pro-inflammatory factors has gradually attracted extensive attention. As an important component of the MAPK cascade, the p38MAPK signaling pathway induces TNF-α expression to promote apoptosis and *vice versa* (Zhang et al., 2019). Moreover, the substrates of p38MAPK mainly include activating transcription factor 2 (ATF2) (Li et al., 2022). Activated p38MAPK promotes ATF2, which in turn modulates the production of inflammation-associated factors, like TNF-α and IL-6 (Zhu et al., 2024). Notably, p38MAPK agonist (ANI) treatment reversed the anti-inflammatory effects of SJYYD in our study. In fact, HP infection led to an activated MAPK signaling pathway, with higher p-p38MAPK/p38MAPK, p-JNK1/2/JNK1/2, and p-ERK1/2/ERK1/2 protein expression (Bi et al., 2022). In the present study, SJYYD intervention inhibited the inflammatory response mediated by the p38MAPK signaling pathway, in accordance with the findings of Park et al. (2018). Furthermore, berberine reduced inflammation by suppressing the p38MAPK pathway to improve periodontitis, as evidenced by reduced TNF-α and IL-1β levels, as well as higher IL-10 levels (Gu et al., 2021). The extract of *Curcuma longa* L., curcumin, improved chronic colitis by regulating B-cell differentiation through inhibition of p38MAPK expression, with higher

Table 7. Detection of p-p38MAPK/p38MAPK, p-JNK/JNK, and p-ERK/ERK protein expression in mouse gastric mucosa tissues.

Group	p38MAPK	JNK	ERK
Sham	1.000±0.166	1.000±0.234	1.000±0.157
HP	6.165±0.807▲▲	1.910±0.151▲▲	3.297±0.345▲▲
HP+Triplet	4.322±0.296★	1.372±0.258★	1.951±0.220★★
HP+SJYYD	2.587±0.658★★	1.331±0.176★	1.943±0.223★★
HP+Triplet+SJYYD	1.574±0.715★★	1.203±0.122★★	1.343±0.070★★
HP+ANI	7.939±0.731★	2.453±0.157★	4.688±0.682★★
HP+SJYYD+ANI	4.524±0.614#	1.876±0.049#	3.096±0.336#

▲▲$p<0.01$ vs. Sham group; ★$p<0.05$ and ★★$p<0.01$ vs. HP group; #$p<0.05$ vs. HP+SJYYD group. SJYYD: Sheng-Jiang-Yi-You decoction; ANI: anisomycin; MAPK: mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; ERK: extracellular regulated protein kinases.

IL-4, IL-10, and IL-13 levels, as well as lower TNF-α, IL-1β, and IL-6 levels (Huang et al., 2023), in agreement with our findings.

In conclusion, SJYYD may attenuate HP-associated gastritis by inhibiting the inflammatory response through down-regulation of the p38MAPK pathway, building a foundation for the clinical application of SJYYD in HP-associated gastritis treatment, expanding the new mechanisms of SJYYD, and promoting the development of therapeutic approaches in HP-associated gastritis.

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Data availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' contributions. Ze Li: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Supervision, Writing-original draft, Writing-review & editing. Ruirui Chen: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing-original draft. Weihong Tang: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Writing-original draft. Xiaoya Zheng: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing-original draft. Xuefeng Jin: Formal analysis, Investigation, Visualization. Zhongmin Wang: Investigation, Methodology, Validation. Qiao Wu: Investigation, Validation, Visualization.

References

Bi Y., Wu D., Wu X., Wang F., Yu H., Liu P., Cui G. and Chen Z. (2022). Phycocyanin inhibits *Helicobacter pylori*-induced hyper-proliferation in AGS cells via activation of the ROS/MAPK signaling pathway. Ann. Transl. Med. 10, 176.

Boyanova L., Medeiros J., Yordanov D., Gergova R. and Markovska R. (2024). Turmeric and curcumin as adjuncts in controlling *Helicobacter pylori*-associated diseases: A narrative review. Lett. Appl. Microbiol. 77, ovae049.

Cai Q., Shi P., Yuan Y., Peng J., Ou X., Zhou W., Li J., Su T., Lin L., Cai S., He Y. and Xu J. (2021). Inflammation-associated senescence promotes *Helicobacter pylori*-induced atrophic gastritis. Cell. Mol. Gastroenterol. Hepatol. 11, 857-880.

Chen X., Wang R., Bao C., Zhang J., Zhang J., Li R., Wu S., Wen J., Yang T., Wei S., Li H., Wei Y., Ren S. and Zhao Y. (2020). Palmatine ameliorates *Helicobacter pylori*-induced chronic atrophic gastritis by inhibiting MMP-10 through ADAM17/EGFR. Eur. J. Pharmacol. 882, 173267.

Cho K., Lee H.G., Piao J.Y., Kim S.J., Na H.K. and Surh Y.J. (2021). Protective effects of silibinin on *Helicobacter pylori*-induced gastritis: NF-κB and STAT3 as potential targets. J. Cancer Prev. 26, 118-127.

Dong H., Qiao J., Hou S., Ran H., Sun W., Lin B., Han Y., Yu C. and Li Y. (2024). Potentialities of dandelion (Taraxacum Mongolicum Hand.-Mazz.) flower extracts on gastric protection against *Helicobacter pylori* and characterization of its bioactive constituents. Chem. Biodivers. 21, e202400140.

Gu L., Ke Y., Gan J. and Li X. (2021). Berberine suppresses bone loss and inflammation in ligature-induced periodontitis through promotion of the G protein-coupled estrogen receptor-mediated inactivation of the p38MAPK/NF-κB pathway. Arch. Oral Biol. 122, 104992.

Huang J., Wu T., Zhong Y., Huang J., Kang Z., Zhou B., Zhao H. and Liu D. (2023). Effect of curcumin on regulatory B cells in chronic colitis mice involving TLR/MyD88 signaling pathway. Phytother. Res. 37, 731-742.

Kong H., You N., Chen H., Teng Y.S., Liu Y.G., Lv Y.P., Mao F.Y., Cheng P., Chen W., Zhao Z., Zou Q.M., Guo G., Zhang J.Y. and Zhuang Y. (2020). *Helicobacter pylori*-induced adrenomedullin modulates IFN-γ-producing T-cell responses and contributes to gastritis. Cell Death Dis. 11, 189.

Kong W., Liu W., Wang M., Hui W., Feng Y., Lu J., Miranbieke B., Liu H. and Gao F. (2022). Cordycepin exhibits anti-bacterial and anti-inflammatory effects against gastritis in *Helicobacter pylori*-infected mice. Pathog. Dis. 80, ftac005.

Lee J.Y., Son H.G., Koo Y., Jung S.H., Park S.D., Shim J.J., Lee J.L. and Lee Y.H. (2023). Protective effects of *Cudrania tricuspidata* against *Helicobacter pylori*-induced inflammation in C57BL/6 mice. J. Med. Food 26, 224-231.

Li J., Sun Q., Zheng C., Bai C., Liu C., Zhao X., Deng P., Chai L. and Jia Y. (2021a). Lipoxin A4-Mediated p38 MAPK signaling pathway protects mice against collagen-induced arthritis. Biochem. Genet. 59, 346-365.

Li R.J., Dai Y.Y., Qin C., Huang G.R., Qin Y.C., Huang Y.Y., Huang Z.S., Luo X.K. and Huang Y.Q. (2021b). Application of traditional Chinese medicine in treatment of *Helicobacter pylori* infection. World J. Clin. Cases. 9, 10781-10791.

Li Y., Li X. and Tan Z. (2021c). An overview of traditional Chinese medicine therapy for *Helicobacter pylori*-related gastritis. Helicobacter 26, e12799.

Li Z., Dai A., Yang M., Chen S., Deng Z. and Li L. (2022). p38MAPK signaling pathway in osteoarthritis: Pathological and therapeutic aspects. J. Inflamm. Res. 15, 723-734.

Li X.H., Xu J.Y., Wang X., Liao L.J., Huang L., Huang Y.Q. and Zhang Z.F. (2023). BanXiaXieXin decoction treating gastritis mice with drug-resistant *Helicobacter pylori* and its mechanism. World J. Gastroenterol. 29, 2818-2835.

Liao E.C., Yu C.H., Lai J.H., Lin C.C., Chen C.J., Chang W.H. and Chien D.K. (2023). A pilot study of non-invasive diagnostic tools to detect *Helicobacter pylori* infection and peptic ulcer disease. Sci. Rep. 13, 22800.

Malfertheiner P., Camargo M.C., El-Omar E., Liou J.M., Peek R., Schulz C., Smith S.I. and Suerbaum S. (2023). *Helicobacter pylori* infection. Nat. Rev. Dis. Primers 9, 19.

Park H.S., Wijerathne C.U.B., Jeong H.Y., Seo C.S., Ha H. and Kwun

H.J. (2018). Gastroprotective effects of Hwanglyeonhaedok-tang against *Helicobacter pylori*-induced gastric cell injury. J. Ethnopharmacol. 216, 239-250.

Qi X., Kuan K., El Jabbour T., Lo Y., Liu Q. and Fang Y. (2024). Retrospective analysis of discordant results between histology and other clinical diagnostic tests on *Helicobacter pylori* infection. World J. Gastrointest. Endosc. 16, 64-71.

Rajagopal H.M., Manjegowda S.B., Serkad C. and Dharmesh S.M. (2018). A modified pectic polysaccharide from turmeric (Curcuma longa) with antiulcer effects via anti-secretary, mucoprotective and IL-10 mediated anti-inflammatory mechanisms. Int. J. Biol. Macromol. 118, 864-880.

Sharndama H.C. and Mba I.E. (2022). *Helicobacter pylori*: An up-to-date overview on the virulence and pathogenesis mechanisms. Braz. J. Microbiol. 53, 33-50.

Shen S., Ren F., Qin H., Bukhari I., Yang J., Gao D., Ouwehand A.C., Lehtinen M.J., Zheng P. and Mi Y. (2023). *Lactobacillus acidophilus* NCFM and *Lactiplantibacillus plantarum* Lp-115 inhibit *Helicobacter pylori* colonization and gastric inflammation in a murine model. Front. Cell. Infect. Microbiol. 13, 1196084.

Song X., He Y., Liu M., Yang Y., Yuan Y., Yan J., Zhang M., Huang J., Zhang S. and Mo F. (2021). Mechanism underlying Polygonum capitatum effect on *Helicobacter pylori*-associated gastritis based on network pharmacology. Bioorg. Chem. 114, 105044.

Song H., Xiong M., Yu C., Ren B., Zhong M., Zhou S., Gao Q., Ou C., Wang X., Lu J., Zeng M., Cai X. and Peng Q. (2024). Huang-Qi-Jian-Zhong-Tang accelerates healing of indomethacin-induced gastric ulceration in rats via anti-inflammatory and antioxidant mechanisms. J. Ethnopharmacol. 319, 117264.

Sousa C., Ferreira R., Santos S.B., Azevedo N.F. and Melo L.D.R. (2023). Advances on diagnosis of *Helicobacter pylori* infections. Crit. Rev. Microbiol. 49, 671-692.

Tang L., Tang B., Lei Y., Yang M., Wang S., Hu S., Xie Z., Liu Y., Vlodavsky I. and Yang S. (2021). *Helicobacter pylori*-induced heparanase promotes *H. pylori* colonization and gastritis. Front. Immunol. 12, 675747.

Wang Y., Cui J., Jiang Y., Zhang S., Chen L., Ma Z., Yang D., Zhang Z., Huang X., Yang Y., Guo J., Lu Z. and Li C. (2024). Jiawei Yanghe Decoction attenuate allergic airway inflammation by suppressing group 2 innate lymphoid cells responses. J. Ethnopharmacol. 326, 117927.

Yang H. and Hu B. (2022). Immunological perspective: *Helicobacter pylori* infection and gastritis. Mediators Inflamm. 2022, 2944156.

Yang S., Zhang J., Yan Y., Yang M., Li C., Li J., Zhong L., Gong Q. and Yu H. (2019). Network pharmacology-based strategy to investigate the pharmacologic mechanisms of *Atractylodes macrocephala* Koidz. For the treatment of chronic gastritis. Front. Pharmacol. 10, 1629.

Yang T., Wang R., Liu H., Wang L., Li J., Wu S., Chen X., Yang X. and Zhao Y. (2021). Berberine regulates macrophage polarization through IL-4-STAT6 signaling pathway in *Helicobacter pylori*-induced chronic atrophic gastritis. Life Sci. 266, 118903.

Yang M., Jiao H., Li Y., Zhang L., Zhang J., Zhong X. and Xue Y. (2022). Guanmaitong granule attenuates atherosclerosis by inhibiting inflammatory immune response in ApoE$^{-/-}$ mice fed high-fat diet. Drug Des. Devel. Ther. 16, 3145-3168.

Zhang M., Hu J., Li H., Zhang S., Hu W., Wu L. and Han B. (2019). High TNF-α and/or p38MAPK expression predicts a favourable prognosis in patients with $T_1N_0M_0$ hepatocellular carcinoma: An immunohistochemical study. Oncol. Lett. 17, 4948-4956.

Zhang X., Wang C., He Y., Xing J., He Y., Huo X., Fu R., Lu X., Liu X., Lv J., Du X., Chen Z. and Li C. (2022a). Establishment of noninvasive methods for the detection of *Helicobacter pylori* in Mongolian Gerbils and application of main laboratory gerbil populations in China. Biomed. Res. Int. 2022, 6036457.

Zhang Y., Wang M., Zhang K., Zhang J., Yuan X., Zou G., Cao Z. and Zhang C. (2022b). 6'-O-Galloylpaeoniflorin attenuates *Helicobacter pylori*-associated gastritis via modulating Nrf2 pathway. Int. Immunopharmacol. 111, 109122.

Zhao Y., Cao Y., Yang X., Guo M., Wang C., Zhang Z., Zhang Q., Huang X., Sun M., Xi C., Tangthianchaichana J., Bai J., Du S. and Lu Y. (2022). Network pharmacology-based prediction and verification of the active ingredients and potential targets of Huagan Decoction for reflux esophagitis. J. Ethnopharmacol. 298, 115629.

Zheng Y., Ji S., Li X. and Feng Q. (2022). Active ingredients and molecular targets of *Taraxacum mongolicum* against hepatocellular carcinoma: Network pharmacology, molecular docking, and molecular dynamics simulation analysis. PeerJ 10, e13737.

Zhu M., Long S., Tao Y., Zhang Z., Zhou Z., Wang X. and Chen W. (2024). The P38MAPK/ATF2 signaling pathway is involved in PND in mice. Exp. Brain Res. 242, 109-121.

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