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ORIGINAL RESEARCH

Yangweishu Ameliorates Chronic Atrophic Gastritis with Stomach Yin Deficiency Syndrome Through IL-6/STAT3 Signaling Pathway

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Background: Chronic atrophic gastritis of stomach yin deficiency syndrome (YDCAG) is a precancerous lesion characterized by inflammation of gastric mucosa and atrophy of gastric adenocytes. Yangweishu (YWS) is widely used to treat gastrointestinal diseases.
Objective: This study was to investigate the mechanism of YWS in YDCAG.
Methods: The YDCAG rat model was established using a comprehensive modeling approach, and a human gastric epithelial cell (GES-1) injury model was induced by MNNG stimulation. Hematoxylin-eosin staining (HE), enzyme-linked immunosorbent assay (ELISA), real-time polymerase chain reaction (RT-PCR), immunohistochemistry and Western blotting were performed to observe the effects of YWS on YDCAG rats and GES-1 cells. Network pharmacology was conducted to identify potential core targets and signaling pathways involved in the anti-YDCAG effects of YWS. RT-PCR and Western blotting were employed to measure the gene and protein expression in the IL-6/STAT3 signaling pathway in vivo and in vitro. Apoptosis in GES-1 cells was evaluated through flow cytometry, immunofluorescence, RT-PCR, and Western blotting.
Results: YWS significantly improved gastric morphology in YDCAG rats and alleviated GES-1 cell injury induced by MNNG. YWS treatment also reduced serum, tissue, and cellular levels of inflammatory cytokines, while enhancing antioxidant capacity. Network pharmacology analysis suggested that YWS modulates apoptosis and inhibits the IL-6/STAT3 signaling pathway. Furthermore, YWS has an ameliorative effect on apoptosis and inhibits the expression of IL-6/STAT3 signaling pathway genes and proteins in vitro and in vivo.
Conclusion: YWS has a good therapeutic effect on YDCAG, which may be closely related to the inhibition of IL-6/STAT3 signaling pathway.
Keywords: Yangweishu, chronic atrophic gastritis with stomach yin deficiency syndrome, network pharmacology, IL-6/STAT3 signaling pathway, cell apoptosis

Introduction

Chronic atrophic gastritis (CAG) is a form of chronic gastritis characterized by localized or widespread atrophy of the gastric mucosal intrinsic glands. Key pathological changes include a reduction in glandular number, thinning of the mucosal layer, and thickening of the muscular layer.[1,2] Clinically, CAG presents with abdominal pain, discomfort, loss of appetite, weight loss, and secondary anemia.[3] Pathologically, CAG is marked by chronic inflammation of the gastric mucosa, a reduction or loss of gastric glandular cells, and often intestinal metaplasia, which can ultimately lead to gastric cancer.[4,5] While the exact pathogenesis of CAG remains unclear, chronic *Helicobacter pylori* (Hp) infection, bile reflux, and gastric mucosal inflammation are widely considered to be primary causes.[6,7] Treatment options primarily include

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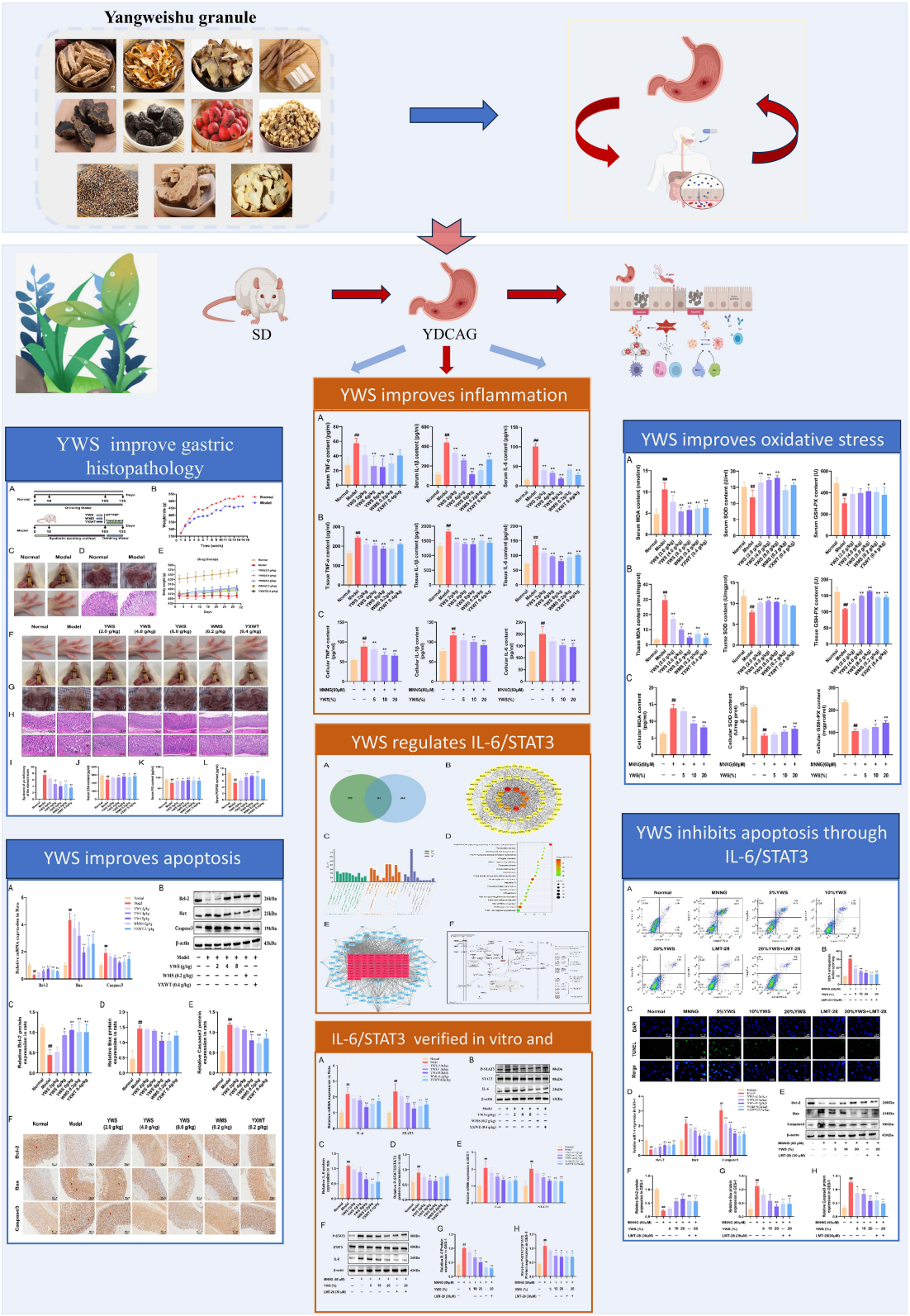
Graphical Abstract



antibiotics, proton pump inhibitors, and gastric mucosal protectants,[8] which can alleviate symptoms and improve mucosal inflammation. However, prolonged use of these drugs may lead to adverse effects, including drug resistance, significantly impacting patients' health and quality of life.[9] Therefore, there is an urgent need to develop alternative and complementary treatment methods for CAG.

In traditional Chinese medicine (TCM), CAG is categorized under "epigastric pain" "fullness" "noisy" "acid reflux" and "vomiting." The differentiation and classification of CAG vary among modern practitioners. The "Consensus Opinions on the Diagnosis and Treatment of CAG Combined with Traditional Chinese and Western Medicine" (2017) classifies the disease into five syndromes: liver-stomach disharmony, spleen-stomach dampness-heat, spleen-stomach weakness, stomach Yin deficiency, and stomach collateral stasis. Chronic atrophic gastritis with stomach Yin deficiency (YDCAG) is primarily caused by dysfunction of the spleen and stomach. TCM, with its long history and unique advantages, has been widely utilized in treating gastrointestinal diseases.[10] Yangweishu (YWS), a Chinese patent medicine, is derived from Li Dongyuan's "Warm Stomach Decoction" written during the Jin and Yuan periods. The formula of YWS comprises 11 herbs, namely *Codonopsis Radix, Crataegi Fructus, Atractylodis Macrocephalae Rhizoma, Polygonati Rhizoma, Dioscoreae Rhizoma, Scrophulariae Radix, Citri Reticulatae Pericarpium, Zingiberis Rhizoma, Mume Fructus, Cuscutae Semen* and *Glehniae Radix*, YWS nourishes Yin, strengthens the stomach, regulates gastric function, and alleviates pain.[8] *Codonopsis Radix*, a key ingredient in YWS, possesses significant pharmacological properties, including gastric mucosal protection and anti-inflammatory activities.[11,12] It plays a crucial role in inhibiting inflammatory mediators and alleviating oxidative stress. Clinical studies have shown that the combination of YWS and folic acid in the treatment of CAG can effectively alleviate the clinical symptoms of patients and improve their quality of life.[13] However, the mechanisms underlying YWS's therapeutic effects in YDCAG, particularly its anti-inflammatory, glandular regeneration, and anti-apoptotic functions, remain poorly understood.

Network pharmacology, a discipline based on systems biology, offers innovative strategies for understanding complex biological systems.[14,15] It is particularly valuable in deciphering the components of TCM and their potential mechanisms in treating diseases. Through network pharmacology, a comprehensive model can be constructed that maps multiple molecules, targets, and interactions, linking drugs to active compounds and their respective targets.[16] This approach enables the effective screening of candidate pathways and target genes.[17]

This study established the rat YDCAG model and the MNNG-induced human gastric epithelial cell (GES-1) injury model using a comprehensive modeling approach. Various techniques, including hematoxylin-eosin staining (HE), enzyme-linked immunosorbent assay (ELISA), real-time reverse transcription–polymerase chain reaction (RT-PCR), immunohistochemistry, and Western blotting, were employed to assess inflammation, oxidative stress, and apoptosis in YDCAG. To evaluate the therapeutic effects of YWS on YDCAG, network pharmacology was used to predict the potential mechanisms. These were subsequently verified through both in vivo and in vitro experiments. The relative expression of genes and proteins in the IL-6/STAT3 signaling pathway was analyzed to deepen our understanding of YWS's therapeutic effects and its underlying mechanism. The findings aim to provide a theoretical foundation for the rational application of YWS in clinical settings.

Materials and Methods

Chemicals and Reagents

YWS Granule (2304349) was obtained from China Resources Shen Lu Pharmaceutical Co., Ltd. The components of YWS were identified using high-performance liquid chromatography (HPLC). The YWS extract was diluted to 0.45 g/mL with 50% methanol and subjected to ultrasonic mixing for 30 minutes. The resulting solution was filtered and used for HPLC analysis. Chlorogenic acid, hesperidin, harpagoside, and cinnamic acid were used as standard controls (Supplementary Figure 1). Sodium deoxycholate (127N021) was purchased from Beijing Solaibao Technology Co., Ltd. Indomethacin enteric-coated tablets (G220901), Vitacoenzyme tablets (WMS) (221205), Yin deficiency stomach pain capsules (YXWT) (20230301), and liquid (20220326) were obtained from the market. MNNG (294350) was purchased from MCE Biotechnology Limited. PGI (F07837), PGII (F07838), and GAS (F05353) kits were supplied by Shanghai Yan Jin Biological Co., Ltd. TNF-α (MM-0122H2), IL-1β (MM-0181H2), and IL-6 (MM-0049H2)

antibodies were obtained from Jiangsu Enzyme Free Biotechnology Co., Ltd. Malondialdehyde (MDA) (A003-1-2), Superoxide dismutase (SOD) (A001-3-1), and Glutathione peroxidase (GSH-PX) (A005-1-2) kits were purchased from Nanjing Jian Cheng Biotechnology Co., Ltd. Bcl-2 (26593-1-AP), Bax (AF0120), Caspase-3 (19677-1-AP), and IL-6 (DF6087) antibodies were obtained from Wuhan San Ying Co., Ltd. and Jiangsu Qin Ke Biology Co., Ltd. The STAT3 (1000859–36) and P-STAT3 (1000205–21) antibodies were sourced from Abcam, USA. GES-1 cell (CL0352) was purchased from the Shanghai Institute of Pharmaceutical Research.

Experimental Animals

Overall, 120 healthy male SPF rats (6–8 weeks old, weighing 180 ± 20 g) were purchased from Liaoning Chang Sheng Biotechnology Co., Ltd. (experimental animal certificate number: SCXK (Liaoning) 2020–0001). All rats were housed at the SPF Laboratory Animal Center of Anhui University of Chinese Medicine under controlled conditions (temperature: 20–25°C, humidity: 50–70%, natural light). The experimental protocol was approved by the Ethics Committee of Anhui University of Traditional Chinese Medicine and complied with guidelines for the care and use of laboratory animals (AHUCM-rats-2022151).

YDCAG Modelling and Treatments

After 7 days of isolation and adaptation, the 120 rats were randomly divided into two groups: 10 in the normal group and 110 in the model group. A 2 g/mL liquid decoction was prepared from dried ginger, aconite and cinnamon (1:1:1 ratio) and administered by gavage for 14 days to establish a stomach Yin deficiency syndrome. Following this, a CAG model was induced using a comprehensive approach. Briefly, 6-week-old male rats were treated with 20 mmol/L sodium deoxycholate and 0.05% indomethacin daily. Additionally, 52°C liquor was administered by gavage twice weekly on an empty stomach, while 0.05% ammonia water was provided ad libitum. Irregular fasting (2 days of feeding followed by 1 day of fasting) was applied, continuing for 105 days. The success of the YDCAG model was verified by the significant increase in the score of stomach Yin deficiency and the reduction in the number of mucosal intrinsic glands and epithelial cells. The Scoring Criteria for Rats in stomach yin deficiency syndrome were presented in Supplementary Table 1. The YDCAG rats were then divided into six groups: model group, positive control groups (WMS: 0.2 g/kg, YXWT: 0.4 g/kg), and YWS groups (2.0 g/kg, 4.0 g/kg, and 8.0 g/kg doses). In addition to the normal group and the model group, all other treatment groups underwent 30-day intragastric administration treatment, and then were sacrificed for analysis.

Preparation of YWS Containing Drug Serum

The 24 rats (180~200 g) were randomly divided into two groups, a blank normal group and an YWS group (8.0 g/kg), after 7 days of adaptive feeding. Normal saline and YWS (8.0 g/kg) were given by gavage at the dose of 1 mL/100g, once a day, for consecutive 7 days. 2 hours after the last dose, rats were anesthetized with pentobarbital sodium in advance, and whole blood was collected from the abdominal aorta. The serum was collected after centrifugation at 3000 r/min for 10 minutes and inactivated by a water bath at 56 °C for 30 minutes. Finally, the serum was filtered through a 0.22μm microporous membrane and stored at −20°C.[18,19]

Cell Culture and Drug Concentration Determination

GES-1 were cultured in RPMI-1640 medium containing 10% fetal bovine serum, 100 IU/mL penicillin, and 100 μg/mL streptomycin in a 37°C incubator with 5% CO_2. During the logarithmic growth phase, GES-1 cells were treated with different concentrations of MNNG (5, 10, 20, 40, 60, 80, 100, and 160 μM) for 24 hours, and cell viability was assessed via MTT assay. Next, GES-1 were exposed to different concentrations of YWS drug-containing serum (2.5%, 5%, 10%, 20%, 40%) for 24 hours, and cell viability was measured using the MTT assay. Finally, GES-1 cells were co-cultured with 60 μM MNNG and treated with YWS drug-containing serum at 2.5%, 5%, 10%, and 20%. The cell viability was calculated using the following formula: cell viability (%) = (OD treatment/OD control) × 100.

The experimental group included: Normal group (20% blank serum), Model group (MNNG+ 20% blank serum), 5% YWS group (MNNG+ 5%YWS drug-containing serum), 10%YWS group (MNNG+ 10%YWS drug-containing serum),

20%YWS group (MNNG+ 20%YWS drug-containing serum), LMT-28 group (MNNG+LMT-28), 20%YWS+LMT-28 group (MNNG+ 20%YWS drug-containing serum +LMT-28).

HE Staining

Rat stomach specimens were fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned at 5μm for HE staining, following standard histological procedures.

Biochemical Index Detection

After a 24-hour fasting period post-treatment, rats were anesthetized with pentobarbital sodium. Blood was collected via the abdominal aorta, centrifuged at 3500 rpm for 15 minutes at 4°C, and serum was separated. Serum, gastric tissue, and cell supernatant levels of GSA, PGI, PGII, TNF-α, IL-1β, IL-6, MDA, SOD, and GSH-PX were quantified using ELISA and biochemical kits, according to the manufacturer's instructions.

Immunohistochemistry Study

For immunostaining of Bcl-2, Bax, and Caspase-3, 5-μm-thick tissue sections were deparaffinized and rehydrated. Antigen retrieval was performed using a microwave oven. After washing with PBS 3 times, endogenous peroxidase activity was blocked by incubation with 3% hydrogen peroxide for 25 minutes. The sections were then washed again with PBS three times and blocked with 5% bovine serum albumin for 30 minutes. Next, the sections were incubated overnight at 4°C with Bcl-2, Bax, and Caspase-3 rat monoclonal antibodies (1:250 dilution). Following PBS washes, the sections were incubated with a secondary antibody and stained with DAB substrate-chromogen solution for 2 minutes. After rinsing with PBS, the sections were counterstained with hematoxylin. Immunohistochemistry images were observed under a microscope.

Detection of mRNA Expression by RT-PCR

Total RNA was extracted from rat tissues using the HiPure Total RNA Mini Kit, and cDNA synthesis was performed using the BioRT Master HiSensi cDNA First Strand Synthesis Kit following the manufacturer's instructions. mRNA expression levels were analyzed by RT-PCR using 2×SYBR Green PCR Master Mix, with β-actin as the endogenous reference. Relative mRNA levels were quantified using the $2^{-\Delta\Delta CT}$ method. The primer sequences were described in Supplementary Table 2.

Western Blot Assay

Western blot assay for the expression of IL-6, STAT3, P-STAT3, Bcl-2, Bax and Caspase- 3 in gastric tissue: 100 mg of gastric tissue at the site of obvious injury was taken and mixed with protein phosphatase inhibitor, PMSF and RIPA lysis buffer and then homogenized under an ice bath. It was allowed to stand for 30 minutes and centrifuged at 12,000 rpm for 15 minutes at 4°C. Protein concentration was determined using the BCA kit with bovine serum albumin as a standard. Samples were loaded onto a 10% gel and proteins were separated by polyacrylamide gel electrophoresis before transfer to a PVDF membrane. The PVDF membrane was sealed with a sealing solution containing 5% skimmed milk powder for 1.5 hours. Then incubate overnight at 4°C with the corresponding primary antibody, wash with TBST buffer, and incubate with the secondary antibody for 2 hours at room temperature. The bands were imaged using the ECL chemiluminescence detection kit, and the grey scale values of the bands were analyzed using ImageJ software, and the relative expression of the target proteins was expressed as the ratio of the target proteins to the internal reference proteins.

Network Pharmacology Predicts the Relationship Between YWS and YDCAG

To identify the active components of YWS, the TCMSP database (https://old.tcmsp-e.com/tcmsp.php) was used. The Swiss Target Prediction (http://swisstargetprediction.ch/) and Herb (http://herb.ac.cn/) databases helped identify the targets of these active ingredients.[20] Using "chronic atrophic gastritis" as a keyword, potential targets associated with this condition were retrieved from the GeneCards (https://www.genecards.org/) and DisGeNET databases

(https://disgenet.com/).[21,22] A Venn diagram created with the online tool Venny 2.1 (http://www.bioinformatics.com.cn/) illustrates overlapping targets between YWS and YDCAG, revealing their shared therapeutic goals. The common YWS targets within the YDCAG context were further identified. With *Homo sapiens* as the study focus, common targets were entered into the STRING database to construct a protein-protein interaction (PPI) network, using a confidence level of 0.4. Cytoscape 3.7.1 software visualized the PPI network, arranging targets by degree with varying color and size to map the active factor-target-disease interaction network. Finally, the DAVID platform (https://davidbioinformatics.nih.gov/) enabled GO function and KEGG pathway enrichment analyses of the shared drug and disease targets, with the results visualized for further interpretation.

Flow Cytometry

The cells were washed once with PBS, gently suspended and counted, centrifuged at 300 g for 5 min, and the supernatant was discarded. The cell suspension was added with 2.5μL Annexin V-FITC and 2.5μL PI staining solution, gently swirled and mixed, incubated at room temperature and away from light for 15~20 min, and detected by flow cytometry.

TUNEL Staining

Paraffin-embedded sections of gastric tissue were dewaxed and rehydrated through standard procedures. Next, 20μg/mL protease K was applied to the wet box and incubated at 37°C for 25 minutes. The sections were then washed with PBS three times. Following this, 50μL of TUNEL solution was added to the samples and incubated at 37°C for 60 minutes. After incubation, the sections were washed three times with PBS, sealed with DAPI solution, and observed under a microscope after 20 minutes.

Data Statistics

Data were analyzed by GraphPad Prism 8.0, and *T*-test and one-way analysis of variance were used. The results are graphically expressed as Mean ±SD. $P < 0.05$ was considered statistically significant.

Results

YWS Improved the General Signs and Pathological Changes in YDCAG Rats

To examine the effect of YWS on CAG, we established an YDCAG rat model using the comprehensive modeling method as mentioned in the Materials and methods (Figure 1A). After 15 weeks of modeling, the normal group remained in good condition, active, with smooth coats, normal diet, and steady weight gain. In contrast, rats in the model group exhibited poor health, slow responses, and a tendency to curl up. They ate less, drank more water, and gained weight more slowly (Figure 1B). Their coats were dull and loose, tongues appeared dark red (Figure 1C). Gastric mucosa morphology was observed both macroscopically and microscopically. The normal group's gastric mucosa was healthy, with deep folds and a rich mucosal layer. In the model group, gastric tissue was pale, folds were shallow, and the mucosal epithelium showed necrosis and atrophy, with disrupted mucosal glands (Figure 1D). These observations confirm the successful establishment of the YDCAG rat model. Following YWS intervention, the therapeutic effects of YWS on YDCAG were evident, including improved mobility, glossy coats, a ruddy tongue, and weight recovery (Figure 1E). Indicators of stomach Yin deficiency significantly improved (Figure 1F and I), and gastric tissue pallor and fold deepening were also restored (Figure 1G). Histological examination showed that YWS alleviated epithelial cell shedding, mucosal thinning, gland reduction, and inflammatory cell infiltration (Figure 1H), with the high-dose group showing the most significant improvement. Serum biomarkers are the gold standard for non-invasive diagnosis and clinical evaluation of CAG progression. Compared with the control group, the levels of GAS, PG-I and the ratio of PG-I/PG-II in the model group were significantly decreased ($P<0.01$); it is noteworthy that after treatment with YWS, these indicators were significantly restored ($P<0.01$ or $P<0.05$). These findings indicate that YWS can improve serum biomarkers and protect gastric tissue from damage (Figure 1J–L).

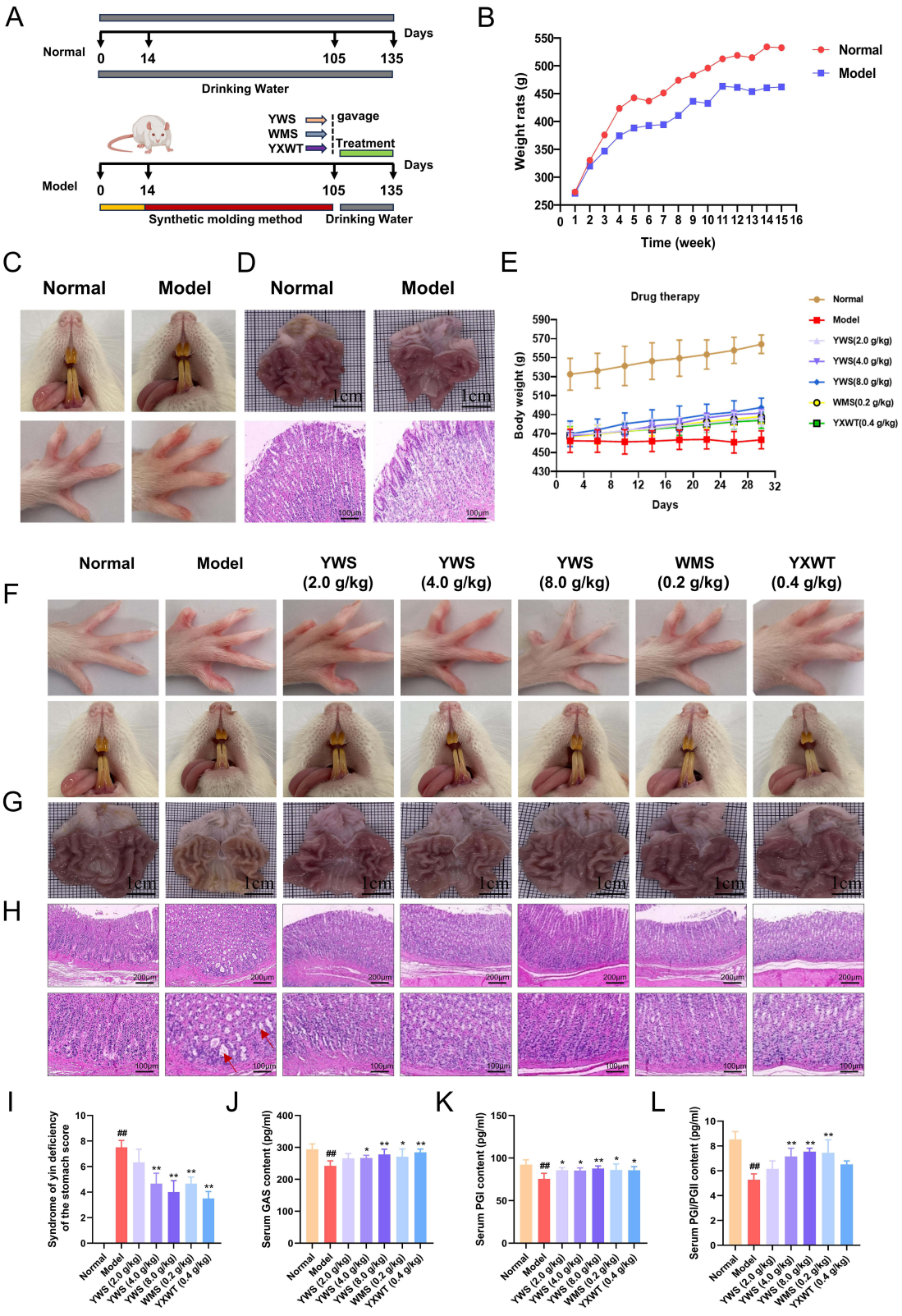


Figure 1 YWS improved the general signs and pathological changes in YDCAG rats. (**A**) The animal experimental protocol of this study. (**B**) Changes in body weight during modeling. (**C**) A representative picture of a rat tongue and foot paw. After modeling, the normal group was compared with the model group. (**D**) Rat stomach morphology and HE representative pictures of stomach tissue. After modeling, the normal group was compared with the model group. (**E**) Weight changes of rats in each group after YWS intervention. (**F**) Representative pictures of rat tongue and foot paw, 4 weeks after YWS administration, the model group was compared with the YWS group. (**G** and **H**) Gastric morphology of rats, HE representative images of gastric tissue, 4 weeks after YWS administration, the model group and YWS group were compared, the scale = 200μm. (**I**) Gastric Yin deficiency syndrome score. (**J–L**) ELISA was used to determine GAS, PGI and PGI/PGII levels (n=6). The data were expressed as the means ± SD. $^{\#\#}p<0.01$, compared with the normal group; $^{*}p<0.05$, $^{**}p<0.01$, compared with the model group.

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Drug Concentration and Cell Viability

GES-1 cell viability and the concentrations of MNNG and YWS drug-containing serum were assessed using an MTT assay. First, we identified the optimal concentration of MNNG for GES-1 exposure, selecting a concentration that maintained a cell survival rate above 60%. This was achieved with a 60μM MNNG concentration (Figure 2A). Next, we examined the effects of various YWS drug-containing serum concentrations on GES-1 cell viability after 24 hours. No significant effect on viability was observed at YWS drug-containing serum concentrations ≤20% (P>0.05) (Figure 2B). Based on these findings, GES-1 cells were co-cultured with MNNG and different concentrations of YWS drug-containing serum. The MTT assay revealed that 20% YWS drug-containing serum provided the best protection for GES-1 cells (P<0.01) (Figure 2C). Consequently, YWS drug-containing serum concentrations of 5%, 10%, and 20% were selected for subsequent experiments. They were then divided into seven groups to observe the effect of YWS drug-containing serum on the morphology of GES-1 cells injured by MNNG. The results showed as shown in (Figure 2D), the morphological characteristics of GES-1 cells were mainly polygon, which grew at the bottom of the cell bottle and had a moderate karyotoplasmic ratio. Under MNNG stimulation, the morphology of GES-1 cells became irregular and moved closer to the edge. The cells shed; After the intervention of YWS drug-containing serum, the cell morphology gradually returned to normal. The above results indicate that the YWS drug-containing serum has a protective effect on GES-1 cells.

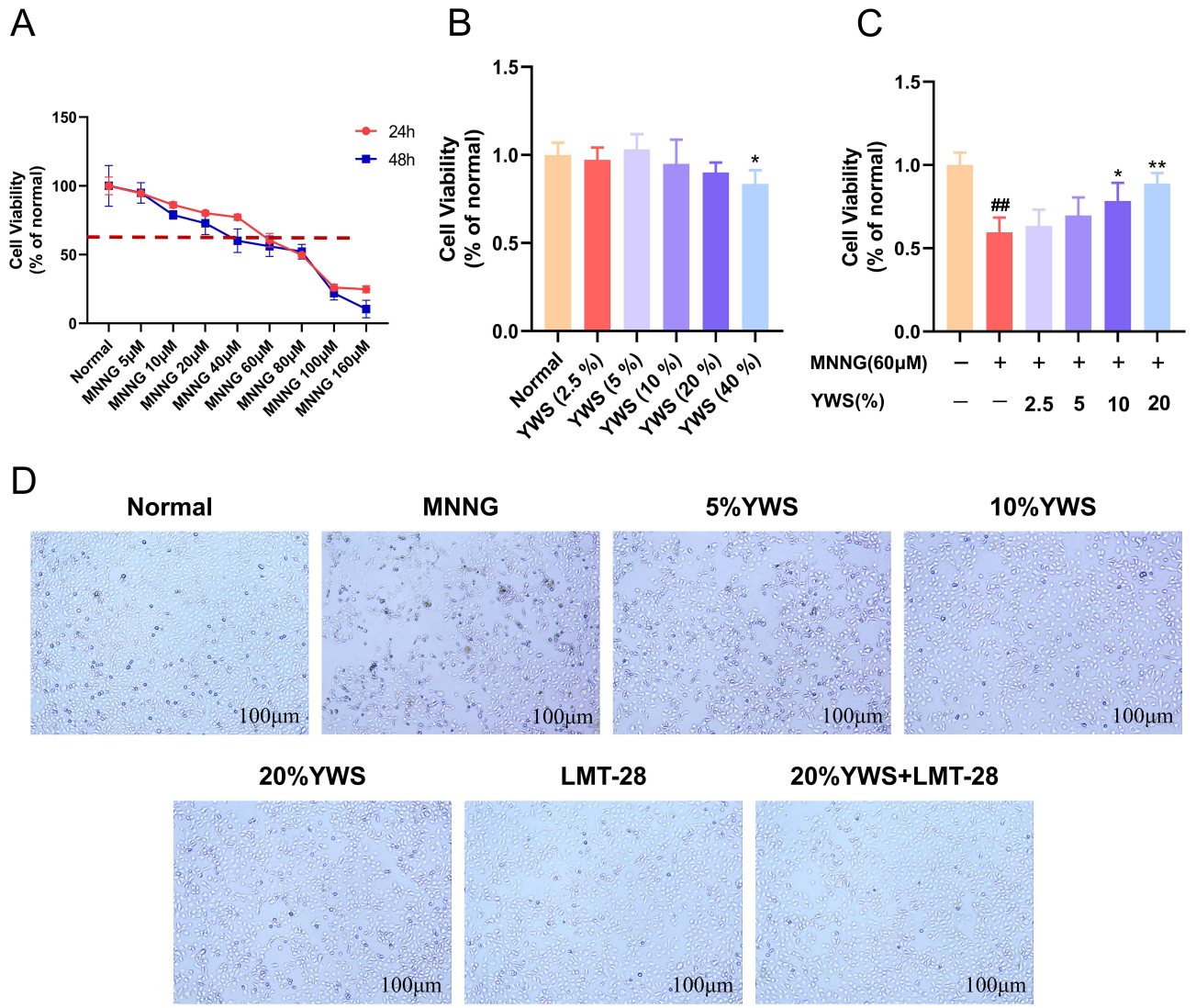

Figure 2 Drug concentration and cell viability. (**A**) The effect of different concentrations of MNNG on the 24h/48h survival rate of GES-1 cells. (**B**) Effects of different concentrations of YWS on 24h survival rate of GES-1 cells. (**C**) Effects of different concentrations of YWS on the viability of GES-1 cells co-cultured with 60μM MNNG. (**D**) The morphological changes of cells in each group were observed by inverted microscope. Data expressed as means ± SD (n = 6). $^{\#\#}p<0.01$, compared with the normal group; $^{*}p<0.05$, $^{**}p<0.01$, compared with the model group.

YWS Improved the Levels of Inflammatory Factors in the Serum and Gastric Tissue of YDCAG Rats and in GES-1 Cells

Inflammation plays a critical role in the development of YDCAG.[23] Serum, gastric tissue, and GES-1 cell levels of TNF-α, IL-1β, and IL-6 were measured using ELISA. Compared with the normal group, the model group showed significantly elevated expression of these cytokines in serum, tissue, and GES-1 cells (P<0.01). YWS intervention notably reduced inflammatory cytokine levels (P<0.01 or P<0.05) (Figure 3A–C), suggesting that inflammation is present in both

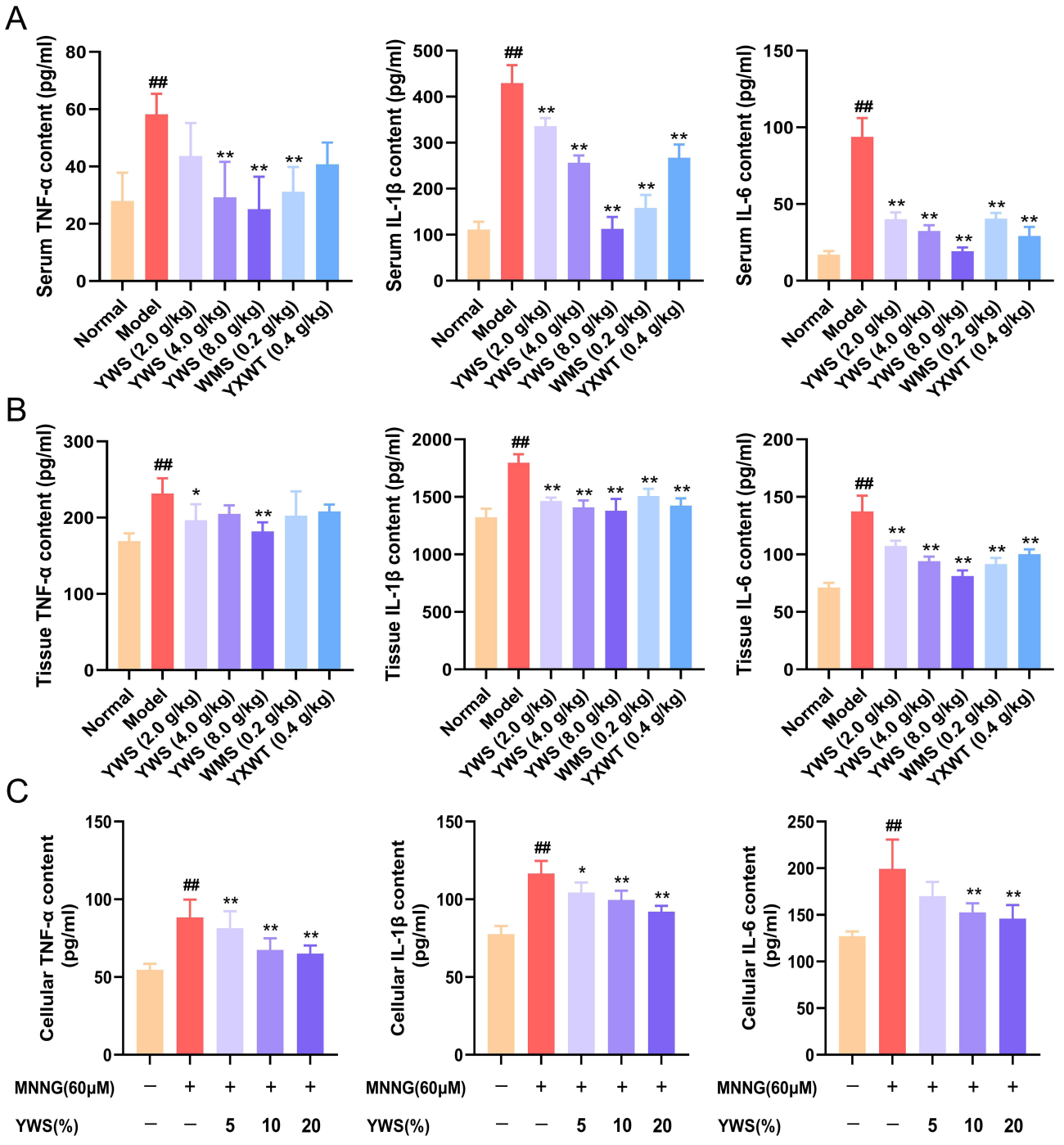

Figure 3 YWS improved the levels of inflammatory factors in the serum and gastric tissue of YDCAG rats and in GES-1 cells. (**A**) ELISA kit was used to detect the levels of TNF-α, IL-1β and IL-6 in serum (n=6). (**B**) ELISA kit was used to detect the levels of TNF-α, IL-1β and IL-6 in gastric tissue (n=6). (**C**) ELISA kit was used to detect the levels of TNF-α, IL-1β and IL-6 in GES-1 cells (n=6). The data were expressed as the means ± SD, $^{\#\#}p<0.01$, compared with the normal group; $^{*}p<0.05$, $^{**}p<0.01$, compared with the model group.

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YDCAG rat and GES-1 cell injury models. Furthermore, YWS effectively alleviates the inflammatory response in these models.

YWS Increased the Level of Oxidative Stress in the Serum and Gastric Tissue of YDCAG Rats and in GES-1 Cells

Oxidative stress is a key contributor to YDCAG.[24] The levels of MDA, SOD, and GSH-PX in serum, gastric tissue, and GES-1 cells were assessed by TBA method and colorimetric method. In the model group, MDA levels were significantly higher in all tested samples compared to the normal group ($P<0.01$), but YWS treatment significantly reduced MDA levels ($P<0.01$ or $P<0.05$). Conversely, SOD and GSH-PX levels were notably lower in the model group ($P<0.01$), while YWS intervention significantly elevated these antioxidants. These findings indicate that YWS can mitigate oxidative stress in serum, gastric tissue, and GES-1 cells (Figure 4A–C).

YWS Prevented YDCAG by Inhibiting Cell Apoptosis

Apoptosis is a key factor in the progression of YDCAG. Bcl-2, Bax, and Caspase-3 are crucial apoptotic markers. To investigate the protective effects of YWS on gastric mucosa, we examined the expression of these genes and proteins through RT-PCR, Western blot, and immunohistochemistry. RT-PCR results showed that Bcl-2 expression was significantly reduced in gastric tissue of the model group ($P<0.01$), while Bax and Caspase-3 expressions were increased ($P<0.01$). YWS intervention effectively increased Bcl-2 expression and decreased Bax and Caspase-3 levels ($P<0.01$ or $P<0.05$) (Figure 5A). To further explore apoptosis at the protein level, Western blot and Immunohistochemistry analyses confirmed that YWS increased Bcl-2 protein expression ($P<0.01$ or $P<0.05$) while reducing Bax and Caspase-3 protein levels ($P<0.01$ or $P<0.05$) (Figure 5B–F). These results suggest that YWS inhibits apoptosis in gastric mucosa cells and mitigates damage caused by YDCAG.

Network Pharmacological Analysis Showed That YWS Alleviated YDCAG by Inhibiting IL-6/STAT3 Signaling Pathway

To explore the primary mechanism of YWS in treating YDCAG, network pharmacology was employed. A total of 882 YWS targets were identified from the Herb and Swiss Target Prediction databases, and 345 YDCAG-related targets were sourced from GeneCards and DisGeNet. A Venn diagram (Figure 6A) revealed 83 overlapping targets between YWS and YDCAG. These targets underwent GO enrichment and KEGG pathway analyses, identifying the HIF-1 signaling pathway as a major pathway (Figure 6C and D). The 83 common targets were further analyzed through the STRING database, which generated a PPI network. Cytoscape 3.7.1 software identified 10 core targets, with IL-6, STAT3 and Bcl-2 standing out (Figure 6B). STAT3 plays a pivotal role in gastritis, supporting the hypothesis that the IL-6/STAT3 pathway is central to the anti-YDCAG effects of YWS. A drug-composition-target-disease network diagram was also constructed to clarify YWS's mechanism of action (Figure 6E). The results indicate that the activation of the IL-6/STAT3 signaling pathway may promote cell apoptosis by increasing the level of Bcl-2, further strengthening the view that IL-6/STAT3 plays a central role in the therapeutic effect of YWS on YDCAG (Figure 6F).

YWS Inhibited IL-6 and STAT3 Gene and Protein Levels in the Gastric Tissue of Rats with YDCAG in vivo

To evaluate the in vivo efficacy of YWS in inhibiting the IL-6/STAT3 signaling pathway, we assessed gene and protein expression levels in the gastric tissues of rats with YDCAG. RT-PCR analysis revealed a significant reduction in the expression of IL-6 and STAT3 genes following YWS treatment ($P<0.01$ or $P<0.05$) (Figure 7A). Western blot analysis further confirmed that the protein levels of IL-6 and P-STAT3 were notably elevated in the gastric tissue of YDCAG rats, but these levels were downregulated after YWS administration ($P<0.05$) (Figure 7B–D). The research results indicate that YWS inhibits the expression of the IL-6/STAT3 signaling pathway, thereby preventing the occurrence of YDCAG in vivo.

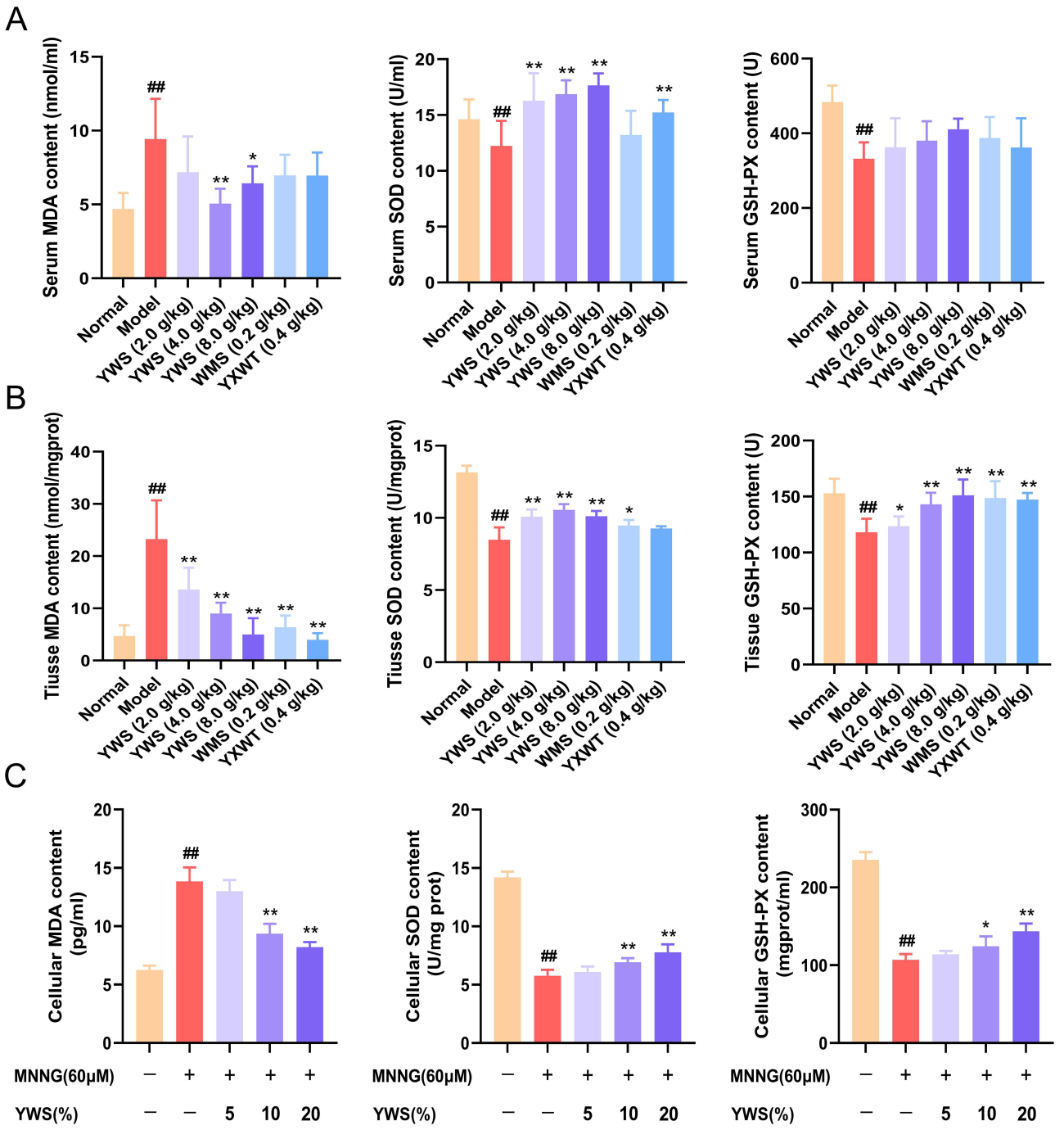

Figure 4 YWS increased the level of oxidative stress in the serum and gastric tissue of YDCAG rats and in GES-1 cells. (**A**) Biochemical kit was used to detect the levels of MDA, SOD and GSH-PX in serum (n=6–8). (**B**) Biochemical kit was used to detect the levels of MDA, SOD and GSH-PX in gastric tissue (n=6). (**C**) Biochemical kit was used to detect the levels of MDA, SOD and GSH-PX in GES-1 cells (n=6). The data were expressed as the means ± SD, $^{\#\#}p<0.01$, compared with the normal group; $^{*}p<0.05$, $^{**}p<0.01$, compared with the model group.

YWS Exerted Anti-Apoptotic Effect by Inhibiting the IL-6/STAT3 Signaling Pathway of GES-1 Cells

It is widely recognized that both macrophages and epithelial cells secrete IL-6, which induces apoptosis in GES-1 cells and contributes to CAG development. Our findings indicated a marked increase in the gene expression of IL-6 and STAT3 in GES-1 cells 24 hours after MNNG treatment, which was subsequently reduced upon YWS intervention (P<0.01) (Figure 8A). Western blot analysis corroborated these findings, showing a decrease in IL-6 and STAT3 protein

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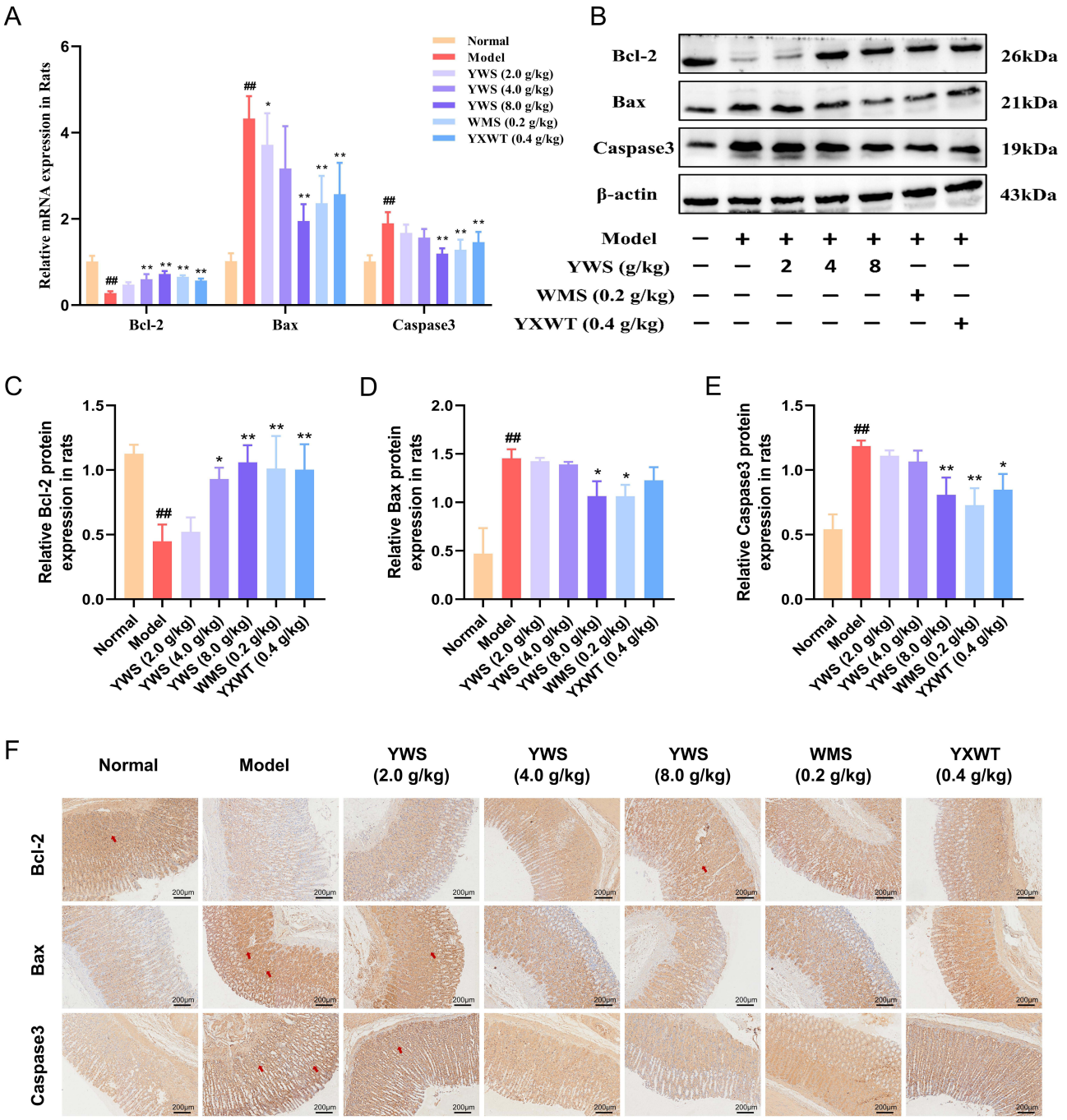

Figure 5 YWS prevented YDCAG by inhibiting cell apoptosis. (**A**) RT-PCR was used to detect Bcl-2, Bax and Caspase3 gene levels in gastric tissue. (**B**) Western blot analysis of Bcl-2, Bax and Caspase3 protein expression in gastric tissue (n = 3). (**C–E**) Gray value analysis of the expression of Bcl-2, Bax and Caspase3 proteins in (**C–E**) respectively. (**F**) Immunohistochemistry expression of Bcl-2, Bax and Caspase3 in gastric tissues of rats in each group, scale = 200μm (n = 3) (The red arrows indicated the expression of the positive protein). The data were expressed as the means ± SD, $^{\#\#}p<0.01$, compared with the normal group; $^{*}p<0.05$, $^{**}p<0.01$, compared with the model group.

levels following YWS treatment (P<0.01 or P<0.05) (Figure 8B–D). This is consistent with the results of the in vivo experiments. To further investigate the mechanism by which YWS regulates apoptosis, we used the IL-6 inhibitor LMT-28. Flow cytometry and TUNEL assays were used to explore the relationship between the IL-6/STAT3 pathway and apoptosis. The number of apoptotic GES-1 cells decreased with LMT-28 treatment; However, when YWS was combined with LMT-28 for treatment, the number of cell apoptosis was also reduced (P<0.01) (Figure 9A–C). These findings were confirmed by RT-PCR and Western blot results (P<0.01 or P<0.05) (Figure 9D–H). Compared to the normal group, the

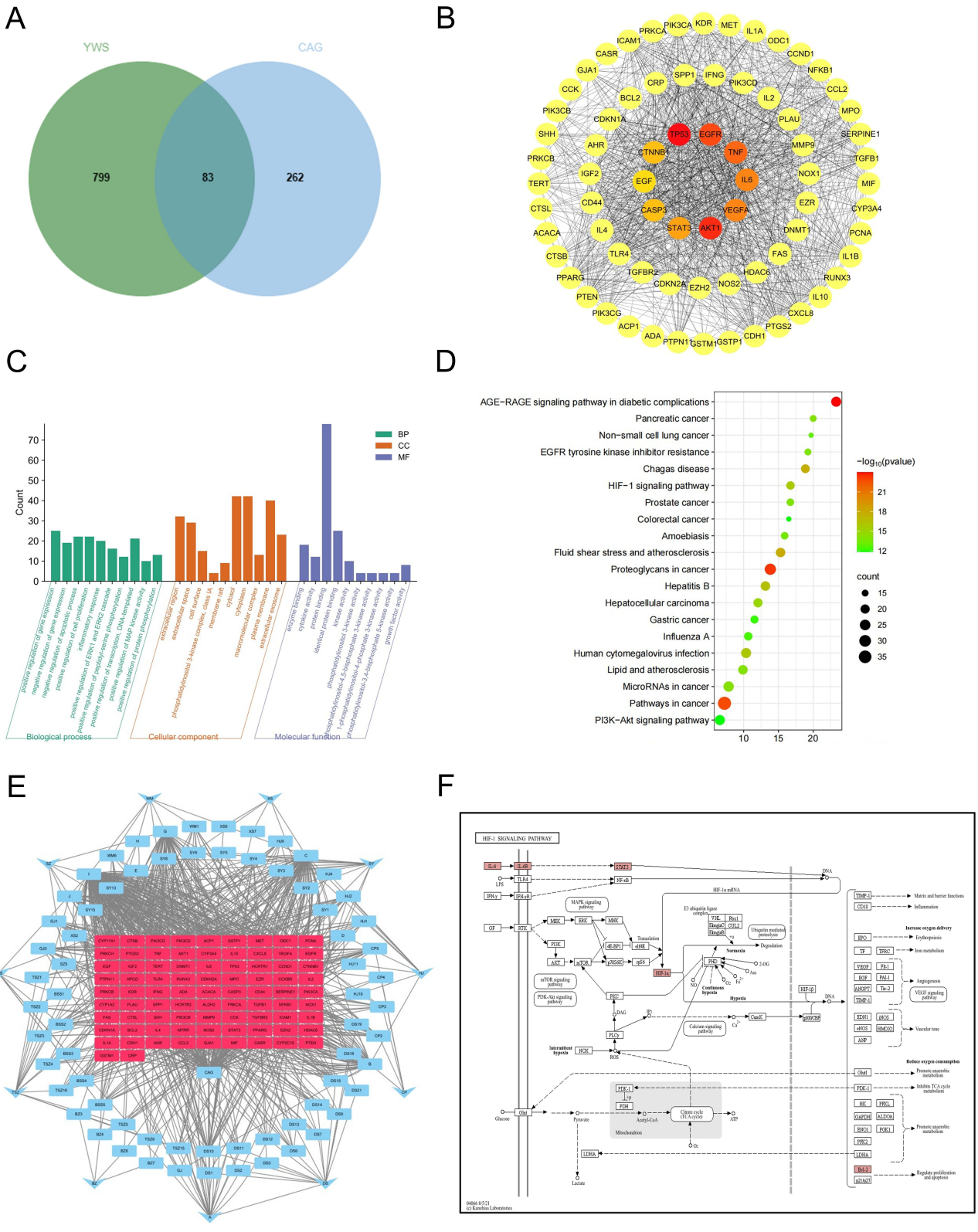

Figure 6 Network pharmacological analysis showed that YWS alleviated YDCAG by inhibiting IL-6/STAT3 signaling pathway. (**A**) Venn diagram showing YWS and CAG targets (green for YWS targets, blue for CAG targets), overlapping areas indicate common goals. (**B**) PPI network diagram. (**C**) Functional enrichment analysis of common targets showed that BP, CC and MF had significant enrichment in the top 10 in GO analysis. (**D**) KEGG pathway enrichment analysis highlighted the top 20 significantly enriched pathways. (**E**) Drug-composition-gene-disease network diagram. (**F**) Schematic diagram of IL-6/STAT3 signaling pathway.

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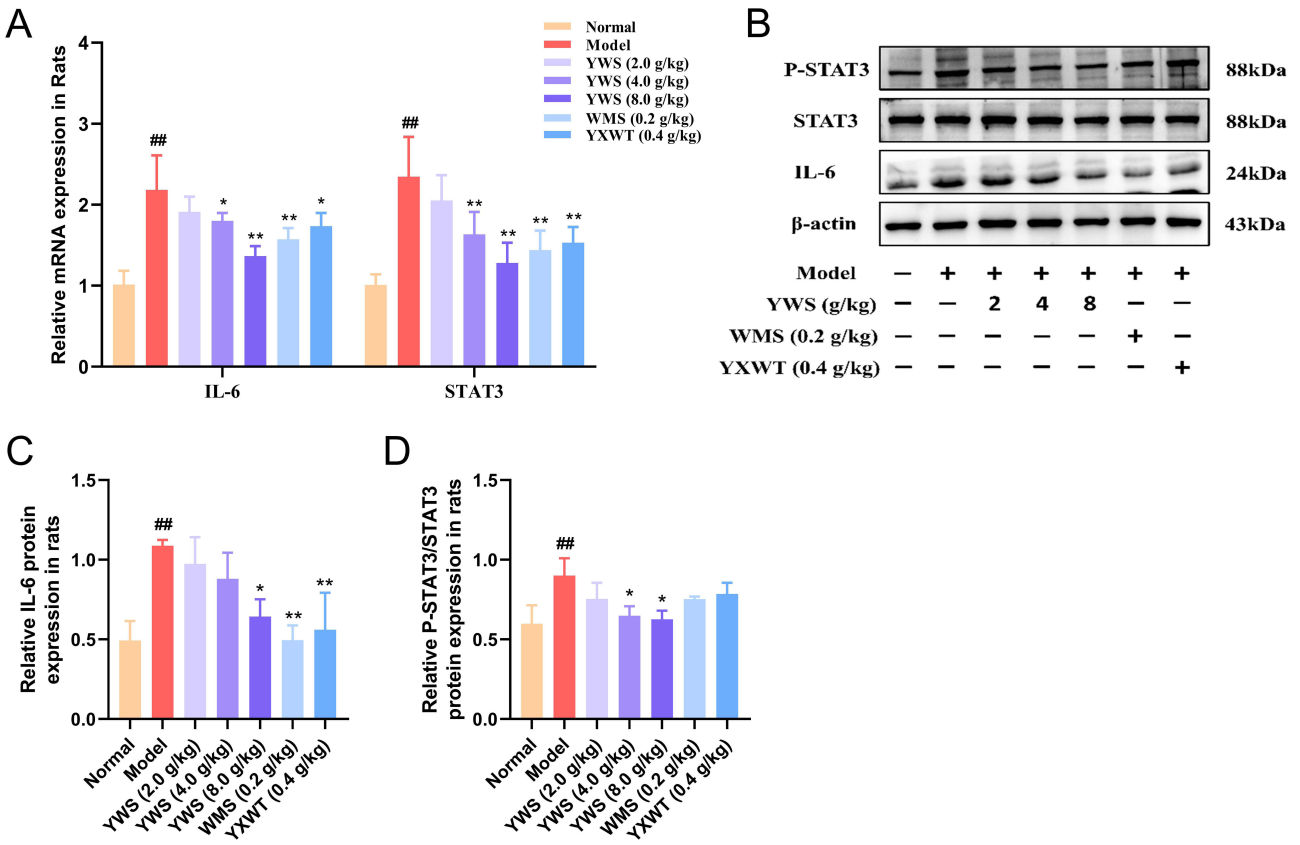

Figure 7 YWS inhibited IL-6 and STAT3 gene and protein levels in the gastric tissue of rats with YDCAG in vivo. (**A**) Expression of IL-6 and STAT3 genes in rats (n = 6). The data were expressed as the means ± SD (n = 6). (**B**–**D**) Western blotting of IL-6, STAT3, and P-STAT3 in gastric tissue (n = 3). The data were expressed as the means ± SD. $^{\#\#}p<0.01$, compared with the normal group; $^{*}p<0.05$, $^{**}p<0.01$, compared with the model group.

expression of Bcl-2 was significantly reduced, while Bax and Caspase-3 levels were elevated in the model group. YWS intervention effectively restored Bcl-2 expression and suppressed the levels of Bax and Caspase-3. Thus, these results suggest that YWS inhibits GES-1 cell apoptosis by modulating the IL-6/STAT3 signaling pathway.

Discussion

CAG is a common digestive system disease in clinical practice. Its characteristic is that the gastric mucosal epithelium is repeatedly damaged, resulting in a reduction in the number of intrinsic glands. CAG represents a critical stage of precancerous gastric lesions and serves as an important window for the potential onset of gastric cancer.[25–27] However, the pathogenesis of CAG has not been fully elucidated. The chronic infection of Hp is regarded as the most common cause of CAG. Hp secretes urease, which decomposes urea to produce ammonia, thereby causing damage to the gastric mucosa.[6] Furthermore, sodium deoxycholate, indomethacin, and long-term alcohol consumption will cause damage to the gastric mucosa and trigger a series of inflammatory responses.[28–30] YDCAG is classified as a common form of CAG.[31] CAG is usually caused by the combined effect of multiple factors. This study used a comprehensive modeling method (ginger, aconite, cinnamon, ammonia water, sodium deoxycholate, indomethacin, alcohol, irregular dietary habits) to establish the YDCAG rat model. This modeling method simulates the pathogenesis of YDCAG in the human body and has the clinical pathological characteristics of YDCAG, such as severe reduction and atrophy of glands, suggesting that the YDCAG model has been successfully established. After the YWS intervention, it was able to effectively alleviate the pathological changes in the gastric tissues of the YDCAGD rats.

According to TCM, the causes of YDCAG include emotional stress, poor diet, congenital deficiencies, and imbalances in spleen and stomach hormones. YDCAG is classified within TCM as “stomach duct pain” “fullness” and “stomach fullness”.[32] Clinically, patients may experience symptoms such as upper abdominal burning pain, feeling

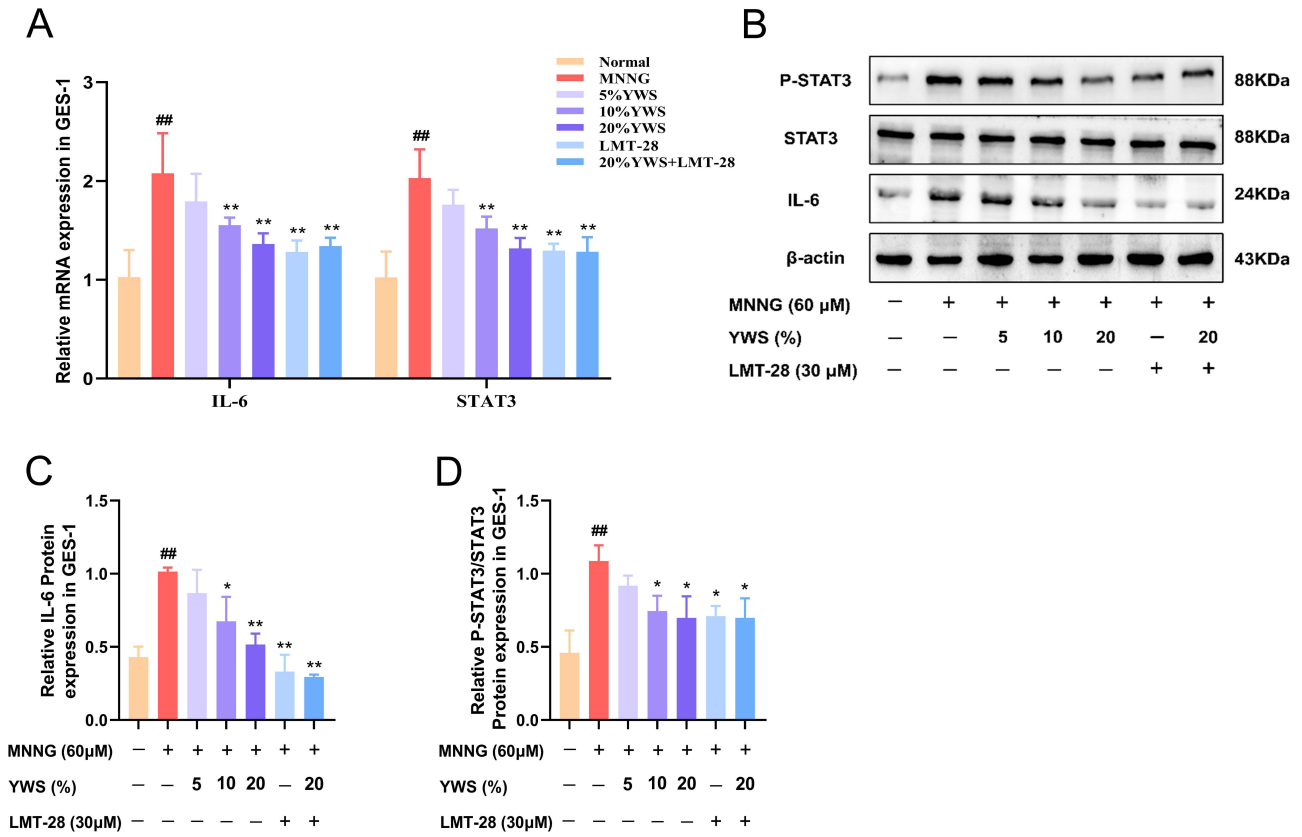

Figure 8 YWS exerted anti-apoptotic effect by inhibiting the IL-6/STAT3 signaling pathway of GES-1 cells. (**A**) Expression of IL-6 and STAT3 genes in GES-1 cells (n = 6). (**B–D**) Western blotting of IL-6, STAT3 and P-STAT3 in GES-1 cells (n = 3). The data were expressed as the means ± SD. ##p<0.01, compared with the normal group; *p<0.05, **p<0.01, compared with the model group.

hungry but lacking appetite, dry mouth, and dry stools. The main pathogenesis involves deficiency of yin and qi. The treatment principle focuses on nourishing yin and strengthening qi. YWS is a commonly used prescription drug, often used to treat gastrointestinal diseases. YWS has been demonstrated to have efficacy in promoting qi, nourishing yin, nourishing the stomach, regulating the middle jiao, promoting digestion and resolving food stagnation. It is used to relieve the gastric burning and distension pain caused by qi deficiency and yin deficiency. Among them, the single herbs *Codonopsis Radix*[33] and *Atractylodis Macrocephalae Rhizoma*[34,35] work together to have functions such as tonifying qi, strengthening the spleen, protecting the gastrointestinal mucosa, and regulating the body's immunity. *Dioscoreae Rhizoma*[36] and *Citri Reticulatae Pericarpium*[37] can enhance the activity of antioxidant enzymes and have anti-inflammatory pharmacological effects. The combined effect of *Scrophulariae Radix*[38] and *Glehniae Radix*[39] can enhance the antioxidant and anti-apoptotic functions. YWS has a mild pharmacological effect, a low incidence of adverse reactions, good safety, and significant clinical efficacy in treating gastrointestinal diseases. It demonstrates great potential for treating YDCAG. Compared with traditional Western medicines, its higher safety provides patients with a more sustainable and long-term effective treatment option.

The levels of gastrointestinal hormones are closely related to the gastric function of CAG rats. Among them, the level of GAS is often used to reflect the damage of gastric mucosa function, while PGI and PGII are secretory substances of gastric mucosal glands. The ratio of PGI/PGII can be used to determine whether gastric mucosa has atrophy.[40,41] It is well known that inflammatory cytokines coordinate the immune defense functions of neutrophils and lymphocytes under normal physiological conditions. However, excessive or persistent expression of inflammation can lead to dysfunction of immune cells, depletion of antioxidant enzymes, and continuous accumulation of oxidative stress. In YDCAG, inflammation and oxidative stress promote each other, forming a vicious cycle.[42] The results of this study indicate that YWS can improve gastric digestive function and enhance protection of the gastric mucosa by increasing the levels of GAS, PGI

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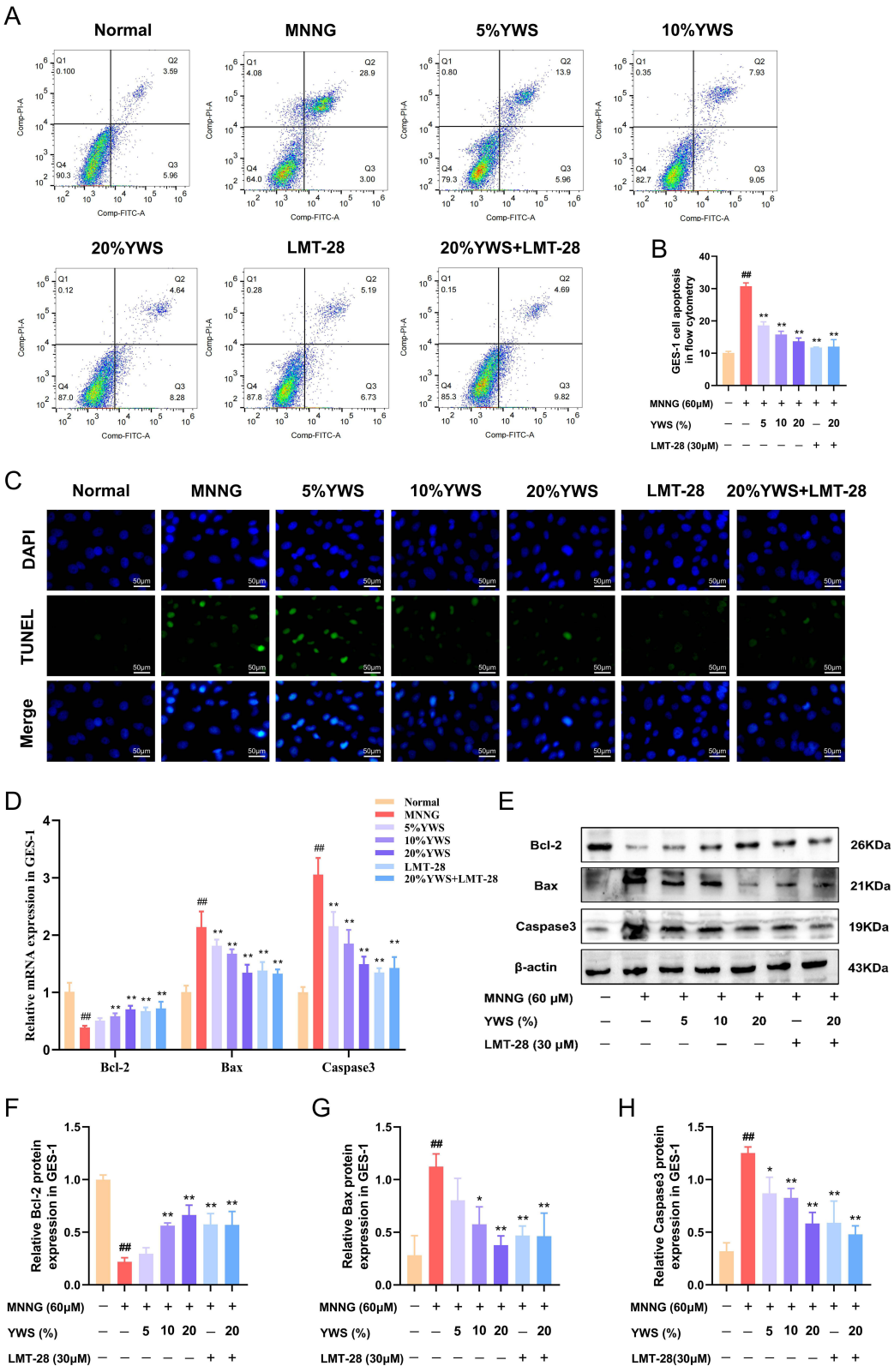

Figure 9 YWS exerted anti-apoptotic effect by inhibiting the IL-6/STAT3 signaling pathway of GES-1 cells. (**A** and **B**) GES-1 cell apoptosis was detected by Flow cytometry. (**C**) TUNEL staining is used to detect cell apoptosis. (scale = 50μm). (**D**) RT-PCR was used to analyze the relative expression levels of Bcl-2, Bax and Caspase3 genes (n = 6). (**E**–**H**) Western blotting of Bcl-2, Bax, and Caspase3 in GES-1 cells. The data were expressed as the means ± SD (n = 3). $^{\#\#}p<0.01$, compared with the normal group; $^{*}p<0.05$, $^{**}p<0.01$, compared with the model group.

and PGI/PGII. YWS can significantly reduce the levels of pro-inflammatory factors TNF-α, IL-1β, and IL-6 in both in vivo and in vitro conditions, effectively alleviate inflammatory responses, enhance antioxidant levels, improve the local microenvironment, and promote gastric mucosal injury and repair.

CAG plays a crucial role in the "inflammation-cancer transformation" hypothesis of gastric cancer, promoting the malignant progression from superficial inflammation to gastric adenocarcinoma. Its pathogenesis is closely related to inflammation and cell apoptosis.[43] It is widely believed that CAG is caused by repeated damage to the gastric mucosa, and inflammation is the main triggering factor. Inhibiting the inflammatory response can effectively prevent CAG from further developing into intestinal metaplasia or even gastric cancer. The inflammatory microenvironment is crucial for the transformation of gastritis to gastric cancer.[44] In this study, alcohol, sodium deoxycholate and indomethacin stimulated the gastric mucosa, causing gastric tissue damage and indirect chronic inflammatory stimulation, thereby inducing cell apoptosis.[45] The apoptotic program induced by inflammation will lead to the activation of caspases, subsequently causing tissue damage. Among them, the pro-inflammatory factor TNF-α can activate Caspase-8 by binding to death receptors, initiating the extrinsic apoptotic pathway; at the same time, it can induce the release of cytochrome C from mitochondria, activating the intrinsic pathway. IL-1β and IL-6 promote the amplification of inflammation, indirectly enhancing oxidative stress, resulting in DNA damage and apoptosis.[46,47] This study found that in the YDCAG model rats induced by the comprehensive modeling method, the apoptosis of the surface epithelial cells of the gastric mucosa increased, the expression of Bcl-2 decreased, and the expressions of Bax and Caspase-3 were upregulated. After YWS intervention, the ratio of Bax/Bcl-2 could be maintained, and the expression of Caspase-3 was reduced, thereby inhibiting the apoptosis of gastric mucosal cells. This suggests that inhibiting cell apoptosis may be the key to the protective effect of YWS on gastric mucosal barrier damage.

Network pharmacology, through interdisciplinary integration, provides a complete research framework for compound drugs, ranging from component identification to elucidation of the mechanism of action. It particularly demonstrates irreplaceable value in the modernization research of TCM.[48,49] In this study, we used the network pharmacology method to predict the potential target sites of YWS against YDCAG. The biological functions involved in YWS regulation of YDCAG were identified, and a network of GO biological processes and KEGG signaling pathways was constructed to elucidate the regulatory mechanisms. KEGG analysis suggested that the IL-6/STAT3 signaling pathway is a key participant in the anti-YDCAG effects of YWS. GO analysis revealed that YWS regulates biological modules involved in apoptosis, redox balance, inflammation/immunity, metabolism, and digestion in treating YDCAG. Experimental validation in a YDCAG model confirmed that YWS reduces inflammation, regulates oxidative stress, and inhibits apoptosis in vivo. These findings underscore the effectiveness of combining computational prediction with experimental validation in exploring the mechanisms of YWS action on YDCAG, with apoptosis inhibition likely being the primary mode of action.

The IL-6/STAT3 signaling pathway plays a central role in immune regulation, inflammatory responses, apoptosis regulation, and the occurrence and development of tumors.[50] Studies have shown that elevated levels of IL-6 were detected in the gastric tissues of patients with chronic atrophic gastritis as well as in the gastric tissues of experimental mice with atrophic gastritis.[51] Similarly, we found abnormal elevation of IL-6 in the gastric tissue of rats in the model group. IL-6, a multifunctional cytokine produced by various cells, including gastric mucosal epithelial cells, regulates cell proliferation, survival, and differentiation,[52,53] It binds to its receptor to form a complex that activates the glycoprotein 130 and triggers intracellular signal transduction. STAT3, a transcription factor activated by this pathway, enters the nucleus to regulate gene expression, influencing cell growth, differentiation, and apoptosis.[54] IL-6 promotes STAT3 phosphorylation, induces the anti-apoptotic regulator Bcl-2, and leads to an accumulation of neutrophils and lymphocytes in the gastric mucosa, disrupting the regulation of inflammatory factors.[55] The continuous activation of IL-6/STAT3 increases ROS production, leading to DNA damage and mitochondrial dysfunction.[56] In this study, inhibition of the IL-6/STAT3 pathway significantly reduced apoptosis in GES-1 cells, decreased the expression of Bax and Caspase-3, and increased Bcl-2 levels. When YWS was used in combination with LMT-28, it was also found that the number of GES-1 cell deaths decreased. This indicates that YWS inhibits cell apoptosis through the IL-6/STAT3 pathway. This mechanism may explain YWS's therapeutic effects in treating YDCAG.

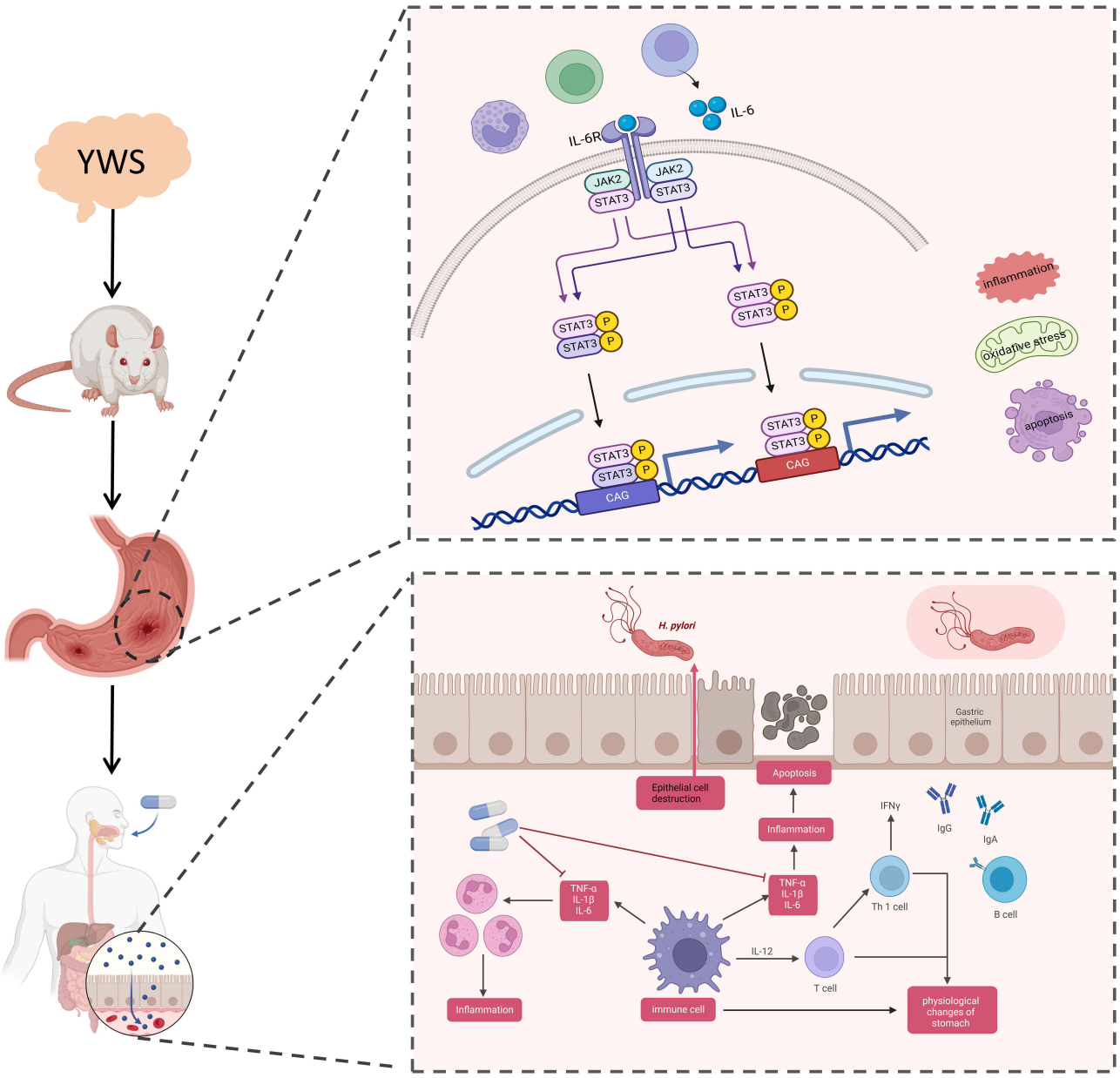

Figure 10 The mechanism of action of YWS in the treatment of YDCAG may be through IL-6/STAT3 signaling pathway, thereby inhibiting the apoptosis of gastric mucosal epithelial cells.

Conclusion

In summary, this study demonstrates that YWS has therapeutic effects on the YDCAG model induced by the comprehensive modeling method. Proteins such as IL-6 and STAT3 were found to play crucial roles in the YDCAG model by network pharmacology. Importantly, YWS inhibited inflammation, oxidative stress, and apoptosis thereby ameliorating YDCAG (Figure 10). In conclusion, our findings emphasize the efficacy of YWS in ameliorating YDCAG. These positive effects of YWS may portend its clinical potential in the treatment of YDCAG.

Abbreviations

CAG, chronic atrophic gastritis; ELISA, enzyme-linked immunosorbent assay; GES-1, human gastric epithelial cells; GSH-PX, glutathione peroxidase; HE, hematoxylin-eosin staining; Hp, helicobacter pylori; HPLC, high-performance liquid chromatography; MDA, malondialdehyde; PBS, phosphate-buffered saline; PPI, protein-protein interaction; RT-

PCR, real-time polymerase chain reaction; SOD, superoxide dismutase; TCM, traditional chinese medicine; WMS, vitacoenzyme tablets; YDCAG, chronic atrophic gastritis of stomach yin deficiency syndrome; YWS, yangweishu; YXWT, yin deficiency stomach pain capsules.

Data Sharing Statement

Data are available from the corresponding author upon a suitable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Zhiyong Jiao and Jia Zheng have contributed equally to this work and share first authorship.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential declaration of interest.

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