

# World Journal of *Clinical Cases*

*World J Clin Cases* 2022 December 6; 10(34): 12462-12803



**FIELD OF VISION**

- 12462 Problematics of neurosurgical service during the COVID-19 pandemic in Slovenia  
*Munda M, Bosnjak R, Velnar T*

**MINIREVIEWS**

- 12470 Circulating angiotensin converting enzyme 2 and COVID-19  
*Leowattana W, Leowattana T, Leowattana P*
- 12484 Evaluation of gut dysbiosis using serum and fecal bile acid profiles  
*Monma T, Iwamoto J, Ueda H, Tamamushi M, Kakizaki F, Konishi N, Yara S, Miyazaki T, Hirayama T, Ikegami T, Honda A*
- 12494 Pediatric kidney transplantation during the COVID-19 pandemic  
*Tamura H*

**ORIGINAL ARTICLE****Clinical and Translational Research**

- 12500 *Coptis*, *Pinellia*, and *Scutellaria* as a promising new drug combination for treatment of *Helicobacter pylori* infection  
*Yu Z, Sheng WD, Yin X, Bin Y*

**Case Control Study**

- 12515 Effects of illness perception on negative emotions and fatigue in chronic rheumatic diseases: Rumination as a possible mediator  
*Lu Y, Jin X, Feng LW, Tang C, Neo M, Ho RC*

**Retrospective Study**

- 12532 Significance of incidental focal fluorine-18 fluorodeoxyglucose uptake in colon/rectum, thyroid, and prostate: With a brief literature review  
*Lee H, Hwang KH*
- 12543 Follow-up study on ThinPrep cytology test-positive patients in tropical regions  
*Chen YC, Liang CN, Wang XF, Wang MF, Huang XN, Hu JD*
- 12551 Effect of teach-back health education combined with structured psychological nursing on adverse emotion and patient cooperation during  $^{99m}\text{Tc}$ -3PRGD2.SPECT/CT  
*Gong WN, Zhang YH, Niu J, Li XB*
- 12559 Nosocomial infection and spread of SARS-CoV-2 infection among hospital staff, patients and caregivers  
*Cheng CC, Fann LY, Chou YC, Liu CC, Hu HY, Chu D*

**Observational Study**

- 12566** Effectiveness and safety of generic and brand direct acting antivirals for treatment of chronic hepatitis C  
*Abdulla M, Al Ghareeb AM, Husain HAHY, Mohammed N, Al Qamish J*
- 12578** Influence of group B streptococcus and vaginal cleanliness on the vaginal microbiome of pregnant women  
*Liao Q, Zhang XF, Mi X, Jin F, Sun HM, Wang QX*

**Randomized Controlled Trial**

- 12587** Clinical study on tri-tongue acupuncture combined with low-frequency electrical stimulation for treating post-stroke dysarthria  
*Man B, Li WW, Xu JF, Wang Q*

**META-ANALYSIS**

- 12594** Three-dimensional time-of-flight magnetic resonance angiography combined with high resolution T2-weighted imaging in preoperative evaluation of microvascular decompression  
*Liang C, Yang L, Zhang BB, Guo SW, Li RC*

**CASE REPORT**

- 12605** Acute cytomegalovirus hepatitis in an immunocompetent patient: A case report  
*Wang JP, Lin BZ, Lin CL, Chen KY, Lin TJ*
- 12610** Long-term results of extended Boari flap technique for management of complete ureteral avulsion: A case report  
*Zhong MZ, Huang WN, Huang GX, Zhang EP, Gan L*
- 12617** Amyloid  $\beta$ -related angiitis of the central nervous system occurring after COVID-19 vaccination: A case report  
*Kizawa M, Iwasaki Y*
- 12623** Pseudoileus caused by primary visceral myopathy in a Han Chinese patient with a rare MYH11 mutation: A case report  
*Li N, Song YM, Zhang XD, Zhao XS, He XY, Yu LF, Zou DW*
- 12631** Emergent use of tube tip in pharynx technique in "cannot intubate cannot oxygenate" situation: A case report  
*Lin TC, Lai YW, Wu SH*
- 12637** Inflammatory myofibroblastic tumor of the central nervous system: A case report  
*Su ZJ, Guo ZS, Wan HT, Hong XY*
- 12648** Atypical aggressive vertebral hemangioma of the sacrum with postoperative recurrence: A case report  
*Wang GX, Chen YQ, Wang Y, Gao CP*
- 12654** Closed reduction of hip dislocation associated with ipsilateral lower extremity fractures: A case report and review of the literature  
*Xu Y, Lv M, Yu SQ, Liu GP*

- 12665** Repair of a large patellar cartilage defect using human umbilical cord blood-derived mesenchymal stem cells: A case report  
*Song JS, Hong KT, Song KJ, Kim SJ*
- 12671** Abdominal bronchogenic cyst: A rare case report  
*Li C, Zhang XW, Zhao CA, Liu M*
- 12678** Malignant fibrous histiocytoma of the axilla with breast cancer: A case report  
*Gao N, Yang AQ, Xu HR, Li L*
- 12684** Rapid hemostasis of the residual inguinal access sites during endovascular procedures: A case report  
*Kim H, Lee K, Cho S, Joh JH*
- 12690** Formation of granulation tissue on bilateral vocal cords after double-lumen endotracheal intubation: A case report  
*Xiong XJ, Wang L, Li T*
- 12696** Giant cellular leiomyoma in the broad ligament of the uterus: A case report  
*Yan J, Li Y, Long XY, Li DC, Li SJ*
- 12703** Pomolidomide for relapsed/refractory light chain amyloidosis after resistance to both bortezomib and daratumumab: A case report  
*Li X, Pan XH, Fang Q, Liang Y*
- 12711** Ureteral- artificial iliac artery fistula: A case report  
*Feng T, Zhao X, Zhu L, Chen W, Gao YL, Wei JL*
- 12717** How to manage isolated tension non-surgical pneumoperitonium during bronchoscopy? A case report  
*Baima YJ, Shi DD, Shi XY, Yang L, Zhang YT, Xiao BS, Wang HY, He HY*
- 12726** Amiodarone-induced muscle tremor in an elderly patient: A case report  
*Zhu XY, Tang XH, Yu H*
- 12734** Surgical treatment of Pitt-Hopkins syndrome associated with strabismus and early-onset myopia: Two case reports  
*Huang Y, Di Y, Zhang XX, Li XY, Fang WY, Qiao T*
- 12742** Massive low-grade myxoid liposarcoma of the floor of the mouth: A case report and review of literature  
*Kugimoto T, Yamagata Y, Ohsako T, Hirai H, Nishii N, Kayamori K, Ikeda T, Harada H*
- 12750** Gingival enlargement induced by cyclosporine in Medullary aplasia: A case report  
*Victory Rodríguez G, Ruiz Gutiérrez ADC, Gómez Sandoval JR, Lomeli Martínez SM*
- 12761** Compound heterozygous mutations in PMFBP1 cause acephalic spermatozoa syndrome: A case report  
*Deng TQ, Xie YL, Pu JB, Xuan J, Li XM*
- 12768** Colonic tubular duplication combined with congenital megacolon: A case report  
*Zhang ZM, Kong S, Gao XX, Jia XH, Zheng CN*

- 12775** Perforated duodenal ulcer secondary to deferasirox use in a child successfully managed with laparoscopic drainage: A case report  
*Alshehri A, Alsinan TA*
- 12781** Complication after nipple-areolar complex tattooing performed by a non-medical person: A case report  
*Byeon JY, Kim TH, Choi HJ*
- 12787** Interventional urethral balloon dilatation before endoscopic visual internal urethrotomy for post-traumatic bulbous urethral stricture: A case report  
*Ha JY, Lee MS*
- 12793** Regression of gastric endoscopic submucosal dissection induced polypoid nodular scar after *Helicobacter pylori* eradication: A case report  
*Jin BC, Ahn AR, Kim SH, Seo SY*
- 12799** Congenital absence of the right coronary artery: A case report  
*Zhu XY, Tang XH*

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Si Zhao*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jin-Lei Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

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<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

December 6, 2022

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## Clinical and Translational Research

**Coptis, Pinellia, and Scutellaria as a promising new drug combination for treatment of *Helicobacter pylori* infection**

Zhang Yu, Wu-Dong Sheng, Xu Yin, Yu Bin

**Specialty type:** Medicine, research and experimental**Provenance and peer review:** Unsolicited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): D  
Grade E (Poor): 0**P-Reviewer:** Gupta L, Indonesia;  
Krzyzek P, Poland**Received:** July 23, 2022**Peer-review started:** July 23, 2022**First decision:** September 26, 2022**Revised:** October 9, 2022**Accepted:** November 7, 2022**Article in press:** November 7, 2022**Published online:** December 6, 2022**Zhang Yu, Xu Yin, Yu Bin**, Department of Internal Medicine, The First Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan Province, China**Wu-Dong Sheng**, Department of Surgery, The First Hospital of Hunan University of Chinese Medicine, Changsha 410007, Hunan Province, China**Corresponding author:** Yu Bin, MM, Chief Physician, Professor, Department of Internal Medicine, The First Hospital of Hunan University of Chinese Medicine, No. 95 Shaoshan Middle Road, Yuhua District, Changsha 410007, Hunan Province, China. [yubin410@163.com](mailto:yubin410@163.com)**Abstract****BACKGROUND**

*Helicobacter pylori* (*H. pylori*) is the most important infectious agent and plays an important role in the progression of chronic gastritis and the development of gastric cancer.

**AIM**

To identify efficient therapeutic agents or strategies that can treat *H. pylori* infection.

**METHODS**

We performed literature analysis, experimental validation, and network pharmacology. First, traditional Chinese medicine (TCM) prescriptions for the treatment of *H. pylori* infection were obtained from the China National Knowledge Infrastructure, China Biology Medicine, China Science and Technology Journal Database, and WanFang databases. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (<https://www.referencecitationanalysis.com>). Next, we used TCM Inheritance Support System V2.5 to identify core drug combinations in the TCM prescriptions. Then, an *H. pylori*-associated chronic mouse model of gastritis was established. The antibacterial properties and anti-inflammatory potential of the core drug combination were evaluated by the rapid urease test, modified Warthin-Starry silver staining, histopathological analysis, and enzyme linked immunosorbent assay. Finally, the active compounds, hub targets, and potential signaling pathways associated with the core drug combination were analyzed by network pharmacology.

**RESULTS**

The TCM treatment of *H. pylori* was mainly based on reinforcing the healthy Qi

and eliminating pathogenic factors by simultaneously applying pungent dispersing, bitter descending, cold and warm drugs. The combination of *Coptis*, *Pinellia*, and *Scutellaria* (CPS) was identified as the core drug combination from 207 prescriptions and 168 herbs. This drug combination eradicated *H. pylori*, alleviated the gastric pathology induced by *H. pylori* infection, and reduced the expression levels of tumor necrosis factor- $\alpha$  ( $P = 0.024$ ) and interleukin-1 $\beta$  ( $P = 0.001$ ). Moreover, a total of 35 compounds and 2807 targets of CPS were identified using online databases. Nine key compounds (tenaxin I, neobaicalein, norwogonin, skullcapflavone II, baicalein, 5,8,2'-trihydroxy-7-methoxyflavone, acacetin, panicolin, and wogonin) and nine hub target proteins (EGFR, PTGS2, STAT3, MAPK3, MAPK8, HSP90AA1, MAPK1, MMP9, and MTOR) were further explored. Seventy-seven signaling pathways were correlated with *H. pylori*-induced inflammation and carcinogenesis.

### CONCLUSION

In summary, we showed that CPS is the core drug combination for treating *H. pylori* infection. Animal experiments demonstrated that CPS has bacteriostatic properties and can reduce the release of inflammatory cytokines in the gastric mucosa. Network pharmacology predictions further revealed that CPS showed complex chemical compositions with multi-target and multi-pathway regulatory mechanisms. Although the results derived from network pharmacology are not necessarily comprehensive, they still expand our understanding of CPS for treating *H. pylori* infection.

**Key Words:** *Coptis*; *Pinellia*; *Scutellaria*; Anti-*Helicobacter pylori*; Drug combination; Traditional Chinese medicine

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**Core Tip:** Infection with *Helicobacter pylori* (*H. pylori*) is associated with severe digestive diseases, while successful eradication of this pathogen is known to prevent the occurrence of peptic ulcer disease and gastric cancer. Traditional Chinese medicine (TCM) has unique advantages for treating *H. pylori* infection, which can reduce drug resistance and increase the eradication rate of *H. pylori*. Here, we attempted to identify medication rules, effective materials, and the molecular mechanisms underlying the therapeutic effect of TCM against *H. pylori* using data mining, *in vivo* experiment, and network pharmacology. *Coptis*, *Pinellia*, and *Scutellaria* (CPS) were identified as the core drug combination for *H. pylori* eradication. We evidenced that CPS eradicated *H. pylori*, alleviated the gastric pathology, and reduced circulating tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  levels. Nine key compounds and nine hub target proteins were further determined as the key active ingredients and therapeutic targets of CPS against *H. pylori*, respectively. Altogether, our data strongly suggest that the efficacy of CPS in the treatment of *H. pylori* is worthy of affirmation.

**Citation:** Yu Z, Sheng WD, Yin X, Bin Y. *Coptis*, *Pinellia*, and *Scutellaria* as a promising new drug combination for treatment of *Helicobacter pylori* infection. *World J Clin Cases* 2022; 10(34): 12500-12514

**URL:** <https://www.wjgnet.com/2307-8960/full/v10/i34/12500.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v10.i34.12500>

### INTRODUCTION

Worldwide, the most common cause of chronic gastritis is infection with *Helicobacter pylori* (*H. pylori*)[1]. *H. pylori*-induced gastritis is considered an independent disease and is commonly referred to as *H. pylori*-associated gastritis (HAG)[2,3]. *H. pylori* infection leads to progressive damage to the gastric mucosa by its virulence factors, host proinflammatory cytokines release, and reactive oxygen species[4]. Mucosal damage can progress to gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and even gastric carcinoma[5]. According to cancer statistics provided by GLOBOCAN 2018, *H. pylori* is the most important infectious organism and has been responsible for 810000 new cancer cases in 2018 [6]. Considering that *H. pylori* is the major cause of gastric carcinoma, the World Health Organization classifies *H. pylori* as a class I carcinogen[7,8]. The discovery of *H. pylori* led to increased research to uncover the etiology, natural history, and prognosis of HAG[9,10]. The Kyoto Global Consensus Report on HAG recommended that all individuals with *H. pylori* infection should receive eradication therapy to prevent gastric cancer[1]. However, it has been well established that eradicating *H. pylori* is challenging [11]. The main treatment for *H. pylori* infection is antibiotics, usually the combination of two types of

antibiotics in conjunction with a proton pump inhibitor[12]. Antibiotic resistance of *H. pylori* is increasing due to the extensive use (or abuse) of antibiotics as the leading cause of treatment failure[13, 14]. Current treatments are not sufficiently effective; therefore, there are significant attempts to identify more effective drugs or substances that can stop or inhibit *H. pylori* infection.

Over the last few decades, there has been a significant increase in the use of traditional Chinese medicine (TCM) as a form of complementary and alternative medicine[15]. TCM has unique advantages for treating *H. pylori* infection and has been widely used due to its remarkable efficacy. Consequently, a large body of clinical and experimental literature has accumulated[16-18]. Therefore, it is possible to apply data mining techniques to the existing literature and analyze specific herbal prescriptions to identify potential associations and core herbs. Here, we attempted to identify medication rules, effective materials, and the molecular mechanisms underlying the therapeutic effect of TCM against *H. pylori* using data mining and network pharmacology. Our findings will provide a theoretical basis for further research.

## MATERIALS AND METHODS

### Data mining

**Data source and normalization:** We collated data by searching key databases, including the China National Knowledge Infrastructure, China Biology Medicine disc, China Science and Technology Journal Database, and WanFang databases for articles related to the use of TCM for *H. pylori* infection. We eliminated studies that did not meet our specific requirements, including reviews, proven reports, and animal experiments. Next, we extracted syndrome types, prescriptions, and herbs from the literature. Traditional Chinese Medicine Inheritance Support System V2.5 (TCMISS V2.5) was used to perform prescription analysis. This system was designed especially for data mining and integrates statistical methods such as association rules analysis and complex system entropy methods. Herbs were classified according to the standard name and Chinese medicine classification provided by People's Republic of China Pharmacopoeia (2015 Edition)[19]. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (<https://www.referencecitationanalysis.com>).

**Data processing and analysis:** Frequency analysis, association rules algorithms, and complex system entropy clustering analysis methods were integrated with TCMISS V2.5 and were applied for data analysis and mining. Details related to herbs and their characteristics, flavors, meridian tropisms, and medication modes were summarized. High-frequency herbs, along with the association rules method, were used to identify core drug combinations.

### Experimental validation

**Materials:** BALB/c mice of either sex (aged 5 wk;  $n = 40$ ) were purchased from Hunan SJA Laboratory Animal Co., Ltd. (Changsha, China; qualification certificate number: SCXK (XIANG) 2016-0002). Animals had free access to sterilized standard food and water and were kept in 12:12 h light to dark cycles and standard conditions. The *H. pylori* Sydney strain was provided by Dr. Wu Canrong of the Hunan University of Traditional Chinese Medicine (Changsha). CPS was prepared from three herbs (*Coptis* 6 g, *Pinellia* 10 g, and *Scutellaria* 10 g) and used in the following manner. CPS was extracted with water. The concentration of the water extract was 374.99 mg/mL. Quadruple therapy (QT) included esomeprazole (20 mg bid, Chongqing, China), amoxicillin (1000 mg bid, Shanxi, China), clarithromycin (500 mg bid, Guangdong, China), and colloidal bismuth pectin (300 mg bid, Hunan, China). The QT suspension was given by oral gavage, and the suspension concentration was 26.25 mg/mL.

***H. pylori* culture:** The *H. pylori* Sydney strain (SS1, a CagA<sup>+</sup> and VacA<sup>+</sup> strain) was inoculated on 10% sheep blood-containing Brucella agar (HOPEBIO, QingDao, China) plates and placed in a culture box (Zhejiang, China) with the following settings: 37°C, 5% O<sub>2</sub>, 10% CO<sub>2</sub>, and 85% N<sub>2</sub>. After 72 h of culture, *H. pylori* was identified by the unaided visualization of bacterial morphology[20].

### Induction of mouse infection and treatment protocol

Forty mice were randomly assigned to a negative control (NC) group ( $n = 10$ ) and an infection model group ( $n = 30$ ). All mice were fasted for 12 h before inoculation. On day 1, mice in the infection model group were intra-gastrically inoculated with a suspension of *H. pylori* containing  $1 \times 10^9$  CFUs/mL using gastric intubation needles. The NC group was given an equal volume (200  $\mu$ L) of normal saline. Inoculation was performed every 2 d and five times in total. *H. pylori* colonized for 2 wk after the last inoculation. On day 23, three mice from each group were randomly anesthetized with an intraperitoneal injection of pentobarbital and sacrificed by cervical dislocation. Stomach tissues from the greater curvature were harvested and washed in ice-cold normal saline. The rapid urease test (RUT) and Warthin-Starry silver staining were performed to identify infection and confirm the successful establishment of the infection. The animal experiment was approved by the Animal Ethics Committee of Hunan University of Traditional Chinese Medicine (ZYFY20190620). After induction, mice in the

infection model were randomly assigned to a vehicle-treated group, a QT-treated group, and a CPS-treated group ( $n = 9$ ). Treatment began on day 24, and mice ( $n = 7-9$ ) received a daily dose of CPS (3749.86 mg/kg), QT (262.49 mg/kg), or vehicle (0.9% normal saline) for 2 wk and were subsequently sacrificed.

**Measurements of serum cytokine levels:** Serum levels of key cytokines tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) were measured using enzyme linked immunosorbent assay (ELISA) kits for IL-1 $\beta$  (Boster Wuhan, China) and TNF- $\alpha$  (Boster Wuhan, China). Measurements were done according to the manufacturer's recommendations.

**Histopathological examinations:** Mice were sacrificed, and their stomachs were excised and kept in 10% phosphate buffered saline-buffered formalin. Fixed gastric tissues were embedded in paraffin, longitudinally cut into 3  $\mu$ m sections, and stained with hematoxylin and eosin (H&E).

### Network pharmacology analysis

**Active compounds and targets of CPS:** TCMISP (<http://Lsp.nwsuaf.edu.cn/tcmsp.pHp>) can be used to analyze the drug molecule-target network and drug-target-disease network. It can help unfold the underlying mechanisms of herbs[21]. The active compounds of CPS and their targets were obtained in TCMSP. The obtained two-dimensional structures of the bioactive compounds in the PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) database were then imported into Swiss Target Prediction (<http://www.swisstargetprediction.ch/>) to identify their targets.

**Identifying gene targets associated with HAG:** The term "*Helicobacter pylori*-associated gastritis" was used as a search term in the GeneCards database (<http://www.genecards.org/>) and OMIM database (<http://www.omim.org/>). Then genes, signaling pathways, and other items of key information related to HAG were identified. The targets generated by the intersection between HAG-related targets and the predicted targets of CPS were then identified as HAG targets of CPS.

**Construction of a protein-protein interaction network:** The HAG targets of CPS were submitted to the STRING database (<https://string-db.org/>), which has information related to protein interactions. Key protein information was then imported into Cytoscape to construct a protein-protein interaction (PPI) network and merge with an herbs-compounds-targets network[22]. The size of a node represents its degree value. The larger diameter of the node shows greater degrees.

**Gene ontology and pathway enrichment analysis:** To evaluate the role of targets by bioinformatics annotation, the HAG targets of CPS were imported into the DAVID database (<https://david.ncifcrf.gov/>), which contains a large collection of diverse gene set libraries available for analysis. The HAG targets of CPS were analyzed by DAVID high-throughput functional annotation bioinformatics to identify functional annotation, enrichment analysis, and gene ontology (GO) terms based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Terms and pathways were sorted based on combined scores, and a target-pathway network was constructed *via* Cytoscape to visualize the tight connections between targets and HAG-related pathways[23].

## RESULTS

### Data mining analysis

**Distribution of TCM syndrome types:** Of 178 articles identified in the first step, we identified 77 clear TCM syndrome types. Ten TCM syndrome types were evident in 77 articles; spleen-stomach damp-heat syndrome, spleen-stomach weakness syndrome, and liver-stomach discordance syndrome appeared more frequently, with a cumulative frequency of 69.05% (Figure 1A).

**Features and properties of herbs for HAG:** TCMISS V2.5 was employed to analyze the frequencies of all herbs. In total, 168 herbs with a total of 2139 using times were identified. *Glycyrrhizae Radix et Rhizoma*, *Coptidis Rhizoma*, and *Pinelliae Rhizoma* had the top three frequencies (Table 1). According to their properties for HAG, the herbs were classified into 19 categories, and their frequencies of use are shown in Figure 1B. The nature and flavor of the 168 herbs were mostly cold, warm, bitter, and spicy. Their meridian tropism into the spleen, stomach, and lungs accounted for the largest proportion of applications with a cumulative frequency of 57.06% (Figure 1C, E and F).

**Drug combinations and association rules:** The support degree was set to  $\geq 45$ [11]. We identified 21 drug combinations using this setting, as shown in Table 2. The top four drug combinations were {*Coptidis Rhizoma*, *Glycyrrhizae Radix et Rhizoma*}, {*Pinelliae Rhizoma*, *Coptidis Rhizoma*}, {*Pinelliae Rhizoma*, *Glycyrrhizae Radix et Rhizoma*}, and {*Scutellariae Radix*, *Coptidis Rhizoma*}. These 21 drug combinations were matched by 10 herbs: *Coptidis Rhizoma*, *Pinelliae Rhizoma*, *Scutellariae Radix*, *Glycyrrhizae Radix et Rhizoma*, *Pericarpium Citri Reticulatae*, *Atractylodis Macrocephalae Rhizoma*, *Codonopsis*, *Radix Poria*, *Taraxaci Herba*, and *Paeoniae Radix Alba*. Figure 1D shows a map of the drug combination relationships. The

**Table 1 Identified herbs and their frequency**

Herb	Frequency	Herb	Frequency	Herb	Frequency
<i>Glycyrrhizae Radix et Rhizoma</i>	154	<i>Aucklandiae Radix</i>	40	<i>Citri Sarcodactylis Fructus</i>	14
<i>Coptidis Rhizoma</i>	121	<i>Magnoliae Officinalis Cortex</i>	40	<i>Gardeniae Fructus</i>	14
<i>Pinelliae Rhizoma</i>	100	<i>Salviae Miltiorrhizae Radix et Rhizoma</i>	38	<i>Rehmanniae Radix</i>	13
<i>Paeoniae Radix Alba</i>	82	<i>Notoginseng Radix et Rhizoma</i>	36	<i>Hordei Fructus Germinatus</i>	13
<i>Scutellariae Radix</i>	79	<i>Bletillae Rhizoma</i>	35	<i>Perillae Fructus</i>	13
<i>Pericarpium Citri Reticulatae</i>	78	<i>Jujubae Fructus</i>	35	<i>Toosendan Fructus</i>	13
<i>Atractylodis Macrocephalae Rhizoma</i>	75	<i>Aurantii Fructus</i>	33	<i>Lilii Bulbus</i>	12
<i>Codonopsis Radix</i>	73	<i>Euodiae Fructus</i>	24	<i>Linderiae Radix</i>	12
<i>Poria</i>	73	<i>Aurantii Fructus Immaturus</i>	23	<i>Faeces Trogopterri</i>	12
<i>Taraxaci Herba</i>	65	<i>Cyperii Rhizoma</i>	22	<i>Atractylodis Rhizoma</i>	12
<i>Astragali Radix</i>	56	<i>Cinnamomi Ramulus</i>	19	<i>Angelicae Sinensis Radix</i>	11
<i>Sepiae Endoconcha</i>	54	<i>Coicis Semen</i>	18	<i>Crataegi Fructus</i>	11
<i>Zingiberis Rhizoma</i>	49	<i>Rhei Radix et Rhizoma</i>	16	<i>Typhae Pollen</i>	11
<i>Corydalis Rhizoma</i>	43	<i>Arcae Concha</i>	15	<i>Amomi Fructus Rotundus</i>	11
<i>Amomi Fructus</i>	41	<i>Hedyotis Diffusa</i>	14	<i>Pseudostellariae Radix</i>	11
<i>Bupleuri Radix</i>	41	<i>Fritillariae Thunbergii Bulbus</i>	14	<i>Ginseng Radix et Rhizoma</i>	10

**Table 2 Drug combinations with a support level of ≥ 45**

Drug combination	Frequency	Drug combination	Frequency
<i>Coptidis Rhizoma, Glycyrrhizae Radix et Rhizoma</i>	88	<i>Glycyrrhizae Radix et Rhizoma, Poria</i>	55
<i>Pinelliae Rhizoma, Glycyrrhizae Radix et Rhizoma</i>	76	<i>Scutellariae Radix, Coptidis Rhizoma, Glycyrrhizae Radix et Rhizoma</i>	54
<i>Pinelliae Rhizoma, Glycyrrhizae Radix et Rhizoma</i>	74	<i>Pinelliae Rhizoma, Scutellariae Radix and Coptidis Rhizoma</i>	52
<i>Scutellariae Radix, Coptidis Rhizoma</i>	69	<i>Pericarpium Citri Reticulatae, Poria</i>	47
<i>Glycyrrhizae Radix et Rhizoma, Paeoniae Radix Alba</i>	68	<i>Coptidis Rhizoma, Taraxaci Herba</i>	46
<i>Scutellariae Radix, Glycyrrhizae Radix et Rhizoma</i>	61	<i>Pinelliae Rhizoma, Pericarpium Citri Reticulatae</i>	46
<i>Codonopsis Radix, Glycyrrhizae Radix et Rhizoma</i>	60	<i>Pinelliae Rhizoma, Poria</i>	46
<i>Pinelliae Rhizoma, Coptidis Rhizoma and Glycyrrhizae Radix et Rhizoma</i>	57	<i>Pinelliae Rhizoma, Scutellariae Radix, Glycyrrhizae Radix et Rhizoma</i>	45
<i>Pinelliae Rhizoma, Scutellariae Radix</i>	57	<i>Atractylodis Macrocephalae Rhizoma, Poria</i>	45
<i>Pericarpium Citri Reticulatae, Glycyrrhizae Radix et Rhizoma</i>	56	<i>Coptidis Rhizoma, Codonopsis Radix</i>	45
<i>Atractylodis Macrocephalae Rhizoma, Glycyrrhizae Radix et Rhizoma</i>	56	-	-

confidence level was set to ≥ 70%. This led to the identification of 20 correlation rules (Table 3). Association rules are defined by the probability of the herb on the right when using the herb on the left of the symbol "→". The highest confidence association rules were as follows: (1) {*Pinelliae Rhizoma, Scutellariae Radix* → *Coptidis Rhizoma*}; (2) {*Scutellariae Radix, Glycyrrhizae Radix et Rhizoma* → *Coptidis Rhizoma*}; and (3) {*Scutellariae Radix* → *Coptidis Rhizoma*}.

These drug combinations and association rules were related to four herbs: *Coptidis Rhizoma*, *Glycyrrhizae Radix et Rhizoma*, *Pinelliae Rhizoma* zi, and *Scutellariae Radix*. Since *Glycyrrhizae Radix et Rhizoma* is used as a courier medicinal in prescriptions, we demonstrated that *Coptis*, *Pinellia*, and *Scutellaria* represented the core drug combination for HAG treatment.

**In vivo studies**

**Confirmation and analysis of the model:** The results of RUT showed that within 30 min, the colors of

Table 3 Association rules with a confidence level of &gt; 0.7

Association rules	Confidence	Association rules	Confidence
<i>Pinelliae Rhizoma - Scutellariae Radix</i> → <i>Coptidis Rhizoma</i>	0.9123	<i>Pinelliae Rhizoma - Glycyrrhizae Radix et Rhizoma</i> → <i>Coptidis Rhizoma</i>	0.7703
<i>Scutellariae Radix - Glycyrrhizae Radix et Rhizoma</i> → <i>Coptidis Rhizoma</i>	0.8852	<i>Atractylodis Macrocephalae Rhizoma</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7568
<i>Scutellariae Radix</i> → <i>Coptidis Rhizoma</i>	0.8734	<i>Pinelliae Rhizoma</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7551
<i>Codonopsis Radix</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.8219	<i>Scutellariae Radix - Coptidis Rhizoma</i> → <i>Pinelliae Rhizoma</i>	0.7536
<i>Paeoniae Radix Alba</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.8000	<i>Pinelliae Rhizoma - Coptidis Rhizoma</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7500
<i>Pinelliae Rhizoma - Scutellariae Radix</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7895	<i>Scutellariae Radix - Glycyrrhizae Radix et Rhizoma</i> → <i>Pinelliae Rhizoma</i>	0.7377
<i>Scutellariae Radix - Coptidis Rhizoma</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7826	<i>Coptidis Rhizoma</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7273
<i>Pinelliae Rhizoma</i> → <i>Coptidis Rhizoma</i>	0.7755	<i>Scutellariae Radix</i> → <i>Pinelliae Rhizoma</i>	0.7215
<i>Poria</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7746	<i>Pericarpium Citri Reticulatae</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7089
<i>Scutellariae Radix</i> → <i>Glycyrrhizae Radix et Rhizoma</i>	0.7722	<i>Taraxaci Herba</i> → <i>Coptidis Rhizoma</i>	0.7077

the reaction solution in the NC group were yellow. In contrast, the solutions in the infection model group all became red (Figure 2A). These results demonstrated that bacteria produced urease in the stomachs of infected mice. In addition, Warthin-Starry silver staining showed that silver ions had been adsorbed and reduced to arc or spiral black metallic silver by the argyrophilic bacterium in the gastric mucosa of infected mice (Figure 2A). Collectively, RUT and silver staining demonstrated that mice in the infection model group had been successfully infected with *H. pylori*.

**Eradication rate of *H. pylori*:** To understand the role of CPS in eradicating *H. pylori*, we assessed the eradication rate of *H. pylori* after 2 wk of treatment. RUT results showed that the *H. pylori* eradication rates for QT-treated mice and CPS-treated mice exceeded 80%. There was no statistical difference between the groups in this regard (Figure 2B). These data indicate that CPS had a positive eradication effect on *H. pylori*.

**CPS inhibits the inflammatory response induced by *H. pylori*:** CPS was administered after *H. pylori* infection. Then, the anti-inflammatory effects of CPS on HAG mice were investigated by H&E staining and ELISA. Pathological analysis showed that the gastric mucosa of the NC mice was intact, characterized by normal glands without inflammatory cell infiltration and congestion. The vehicle-treated mice showed crypt destruction, abnormal glands, and variable amounts of lymphocytic infiltration in the epithelium and lamina propria (Figure 2C). ELISA analysis further confirmed high expression levels of TNF- $\alpha$  and IL-1 $\beta$  after *H. pylori* infection. CPS significantly reduced TNF- $\alpha$  levels (Figure 2D-E). Collectively, these results demonstrate that CPS significantly inhibited the inflammatory response induced by *H. pylori*.

### Network pharmacology analysis

**Identification of CPS active compounds and predicted targets:** The 40 main active compounds (including 5 duplicates) and 2806 targets of CPS were predicted by TCMSP, SwissTarget Predicted, Gene Cards, and OMIM. We identified 7, 9, and 24 compounds, along with 399, 499, and 1908 predicted targets in *Coptis*, *Pinellia*, and *Scutellaria*, respectively (Table 4). To demonstrate the relationship between herbs, compounds, and targets, we constructed a network diagram showing CPS, nine compounds with a degree  $\geq 14$ , and their predicted targets (Figure 3).

**Identification of potential targets of CPS involved in HAG:** In total, we identified 277 proteins that may be closely related to the occurrence and development of HAG. A total of 37 potential targets of CPS acting on HAG were identified by intersection analysis (Figure 4A). Next, we used STRING to generate a PPI network diagram for interactions between 37 potential targets of CPS involved in HAG. The PPI network diagram contained 37 nodes, 262 edges, and 9 target proteins with a degree  $\geq 20$ : EGFR, PTGS2, STAT3, MAPK3, MAPK8, HSP90AA1, MAPK1, MMP9, and MTOR. Collectively, these results indicated that CPS might have a therapeutic effect on HAG by affecting these target proteins (Figure 4B).

**Functional analysis of predicted targets of CPS:** The 37 predicted targets of CPS were imported into the DAVID database. We set the significance to  $P < 0.05$  for analysis. In this study, 119 GO terms were obtained, including 58 biological processes, 25 cellular components, and 36 molecular functions. The top 10 GO enrichment analyses were performed individually and were ranked by a combined score

Table 4 Information on compounds in *Coptis*, *Pinellia*, and *Scutellaria*

Herb	Compounds
<i>Coptidis Rhizoma</i>	Berberine; Berberrubine; (R)-Canadine; Berlambine; Worenine; Coptisine; Epiberberine
<i>Pinelliae Rhizoma</i>	Coniferin; Cavidine; Cycloartenol; Gondoic acid; 24-Ethylcholest-4-en-3-one; 10,13-eicosadienoic; Baicalein; Beta-sitosterol; Stigmasterol
<i>Scutellariae Radix</i>	Acacetin; Wogonin; Rivularin; Salvigenin; Norwogonin; Panicolin; Sitosterol; Oroxylin; Skullcapflavone II; Neobaicalein; Moslosooflavone; 11,13-Eicosadienoic acid; Methyl ester; Dihydrooroxylin A; Dihydrobaicalin_qt; 5,2',6'-Trihydroxy-7,8-dimethoxyflavone; 5,8,2'-Trihydroxy-7-methoxyflavone; Dihydrooroxylin; (2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one; Tenaxin I; Coptisine; Epiberberine; Baicalein; Beta-sitosterol; Stigmasterol

(Figure 4C). The targets of CPS acting on HAG were distributed in various cellular components, mainly in the cytoplasm. They participated in biological processes by various binding methods, including peptidyl-serine phosphorylation, positive regulation of the nitric oxide biosynthesis, regulation of the stress-activated MAPK cascade, and negative regulation of apoptosis. In addition, 77 of the most representative gene enrichments were involved in signaling pathways, such as cancer-related pathways, HIF-1 signaling pathway, estrogen signaling pathway, TNF signaling pathway, FoxO signaling pathway, and central carbon metabolism. The top 20 KEGG pathways were then visualized as a bubble plot (Figure 4D).

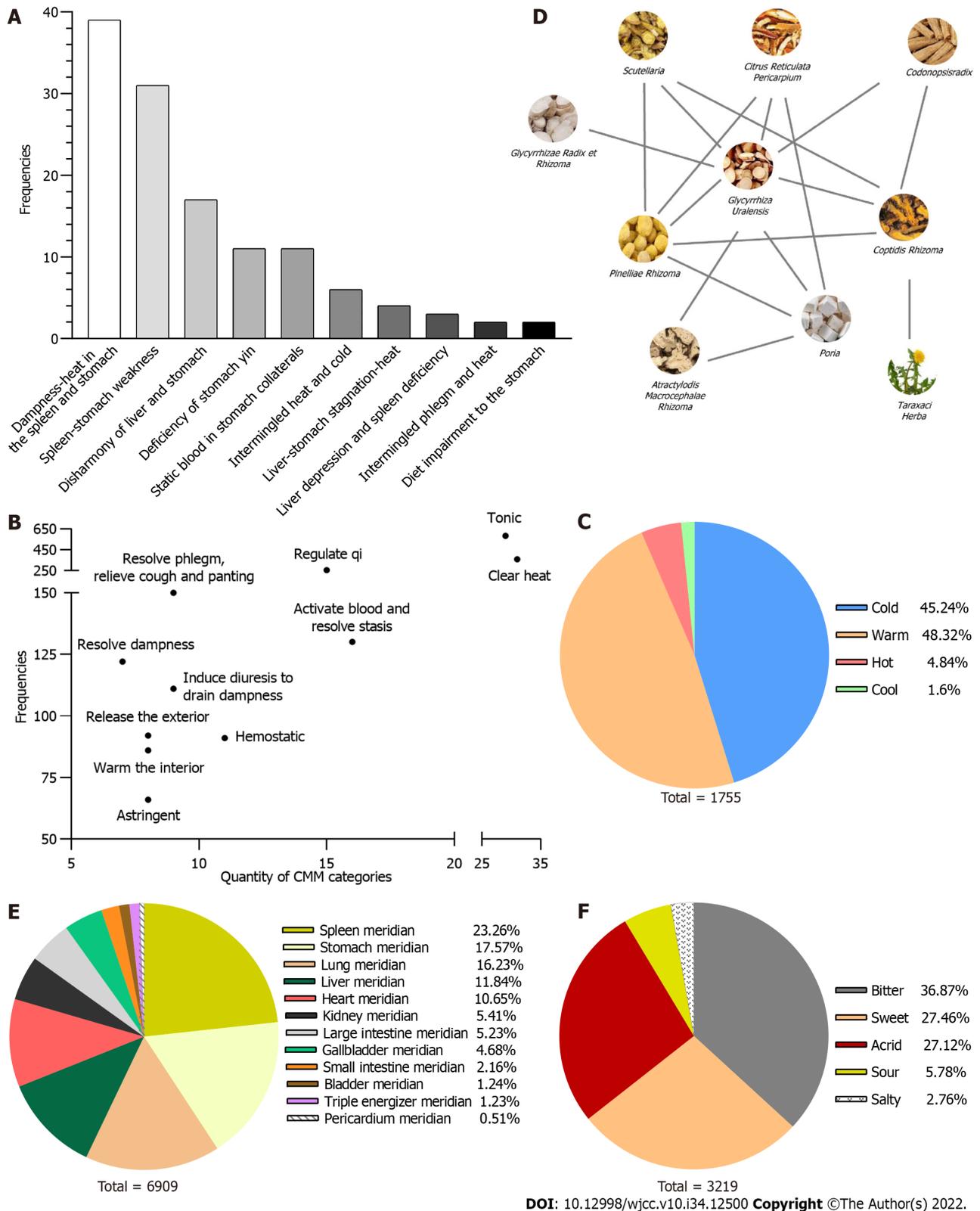
## DISCUSSION

*H. pylori* is a major driver of gastric cancer[24]. Over the last three decades, there has been a broad paradigm shift in our understanding of gastric cancer prevention. Efforts to identify agents or strategies capable of eradicating *H. pylori* remain a top priority in preventing gastric cancer.

TCM has potential advantages for treating *H. pylori* infection. TCM increases the eradication rate and reduces drug resistance[25]. According to statistics, the success rate of treatment with TCM for *H. pylori* infection can reach 95.45% [26]. According to TCM theory, *H. pylori* is caused by "damp-heat pathogenic Qi" or "toxins from pathogenic bacteria". Splenic and gastric dysfunction due to *H. pylori* infection often causes phlegm-turbidity, heat stagnation, and blood stasis. They can also lead to several pathological changes, including gastric atrophy and intestinal metaplasia. A previous cross-sectional study conducted in four hospitals in China found that phlegm turbidity and heat play a crucial role in the pathogenesis of chronic atrophic gastritis[27]. Using metabolomics technology, Xu *et al*[28] demonstrated that damp heat and blood stasis are the key factors in the transformation of gastritis into gastric cancer. Dampness-heat syndrome provides humidity and heat for bacterial growth in the stomach. Therefore, the treatment strategy for TCM herbal prescriptions should focus on clearing heat and dampness. Cold-natured herbs supplemented with a moderate amount of hot-natured drugs are often used as the main treatment for dampness-heat syndrome in the spleen and stomach[29]. Heat-clearing drugs include *Scutellaria*, *Coptis chinensis*, and *Rhubarb*[19]. Warm-natured herbs are *Pinelliae*, *Evodia rutaecarpa*, and *Clove*[19]. All of these drugs have been widely used in Chinese medicine for *H. pylori* eradication[30].

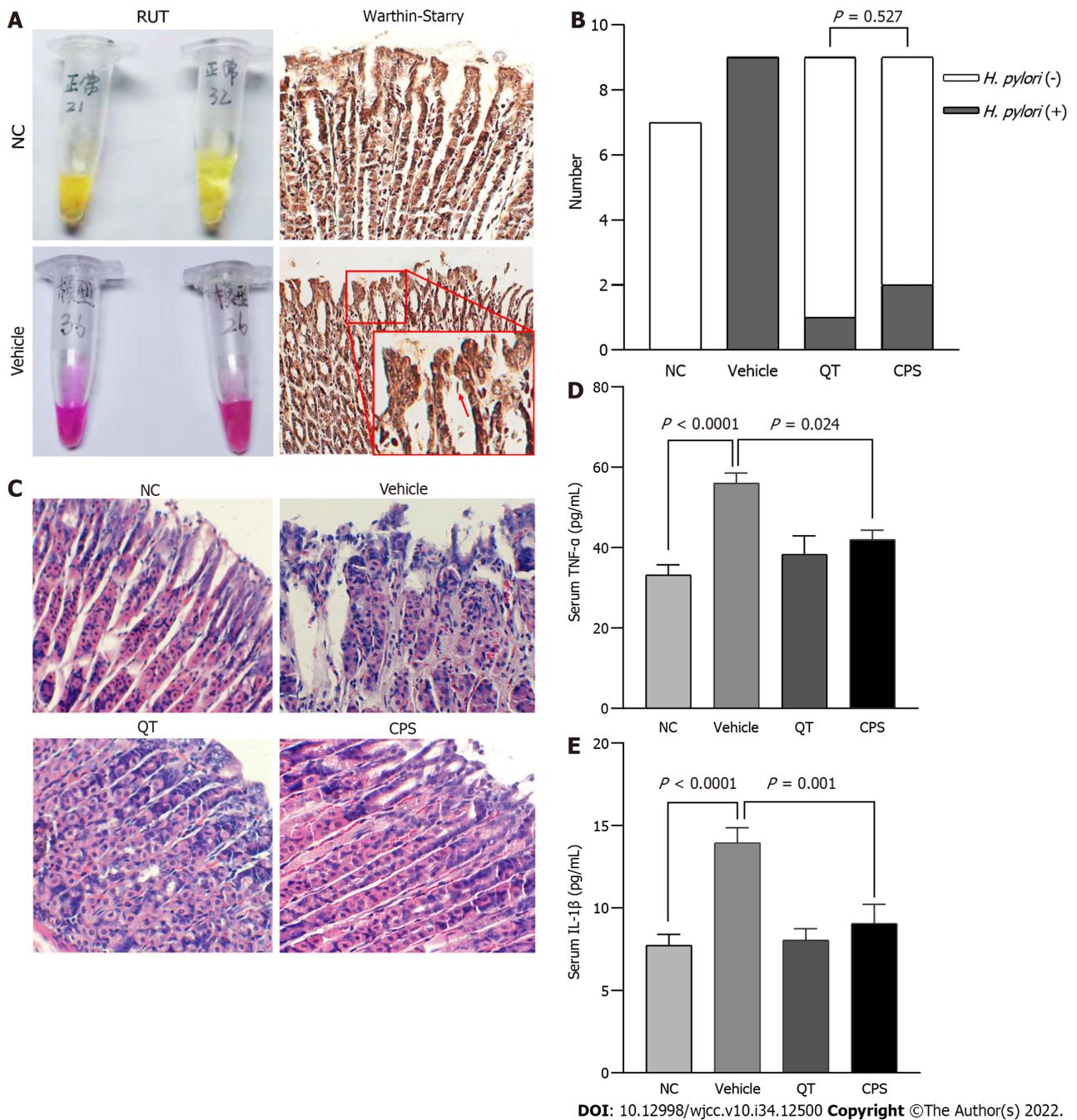
Based on the frequent use of herbs and association rules, the core drug combination was *Coptis*, *Pinellia*, and *Scutellaria* in this study. There are many examples of the remarkable therapeutic effects of *Coptis*, *Pinellia*, and *Scutellaria* supported by previous studies. Ma Feng *et al* conducted a susceptibility test for 50 selected traditional Chinese herbal medicines using a broth dilution method. They found that water extract from *Rhizoma Coptis* and *Scutellaria* could significantly inhibit the activity of *H. pylori*[31]. A recent meta-analysis showed that the Banxia Xiexin Decoction, using *Pinellia* as a monarch drug, had similar effects to standard therapy for eradicating *H. pylori*[32].

The active compounds of medicinal plants were extracted and analyzed using various analytical techniques to rationalize the use of TCM. Identifying the effective ingredients in these drugs may provide a basis for understanding their mechanisms of action and illuminate future research directions. *Coptis* contains several protoberberine alkaloids of berberine, palmatine, coptisine, epiberberine, and aporphinoid alkaloid of magnoflorine as the major pharmacologically active constituents[33,34]. These findings were consistent with the results of the present study. *In vitro*, Coptisine, epiberberine, and palmatine inhibited urease activity in a concentration-dependent manner, thereby effectively inhibiting *H. pylori* activity[35,36]. *In vivo*, berberine and palmatine exhibited *H. pylori*-inhibiting and antiulcerogenic properties by eliminating radical oxygen species[37]. Baicalin, baicalein, wogonin, and oroxylin were identified as the main active components of *Radix Scutellariae*[38,39]. However, only a few reports have been published discovering the active components of *Radix Scutellariae*. Lai *et al*[40] compared the metabolic pharmacokinetics of baicalin and baicalein in rats and found that baicalin absorption was slower and less efficient than baicalein absorption. Baicalin was not screened in this



**Figure 1** Medicinal characteristics of traditional Chinese medicine treatment in patients with *Helicobacter pylori*-associated gastritis. A: Traditional Chinese medicine syndromes of *Helicobacter pylori*-associated gastritis and their frequencies; B: Categories of herbs and their frequencies; C: Frequency of herbs' nature; D: Map showing drug combination relationships. E and F: Frequency of herbs' flavor and meridian tropism. TCM: Traditional Chinese medicine; HAG: *Helicobacter pylori*-associated gastritis.

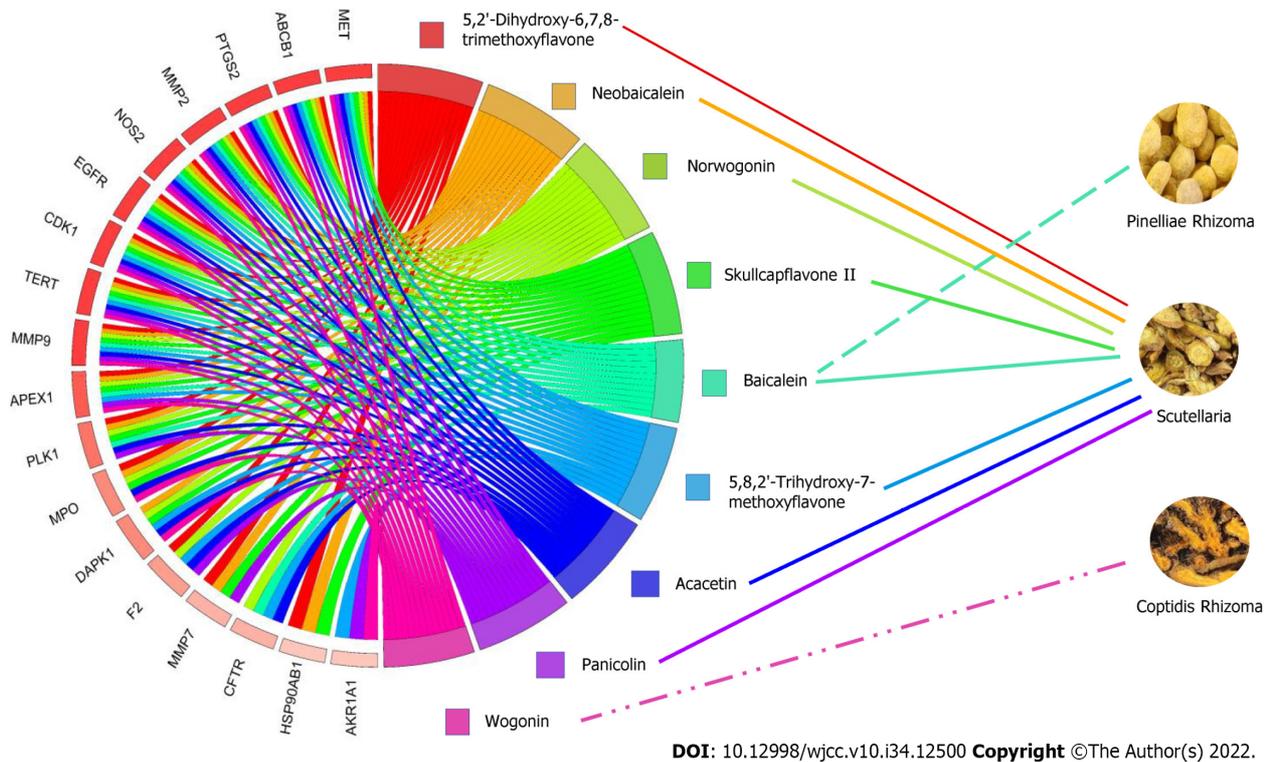
study. These results may be due to differences in study design. The flavonoid compounds (baicalin and baicalein) mainly found in medicinal plants have anti-inflammatory properties[41]. Chen *et al*[12] revealed that baicalin and baicalein both suppressed the expression of the *VacA* gene in *H. pylori* and interfered with the growth and virulence of *H. pylori*. These herbs also decreased *H. pylori*-induced expression of interleukin-8[42]. Pinellia is rich in flavonoids such as baicalin and baicalein[43]. An



**Figure 2** *Coptis*, *Pinellia*, and *Scutellaria* inhibit the inflammatory reaction. A: Rapid urease test (RUT) and Warthin-Starry staining in mouse models of *Helicobacter pylori* (*H. pylori*)-associated gastritis; B: Effect of *Coptis*, *Pinellia*, and *Scutellaria* (CPS) on *H. pylori* infection. RUTs confirmed that the efficacy in the CPS and quadruple therapy groups was equal; C: Hematoxylin and eosin staining (200 ×); D and E: Enzyme-Linked Immunosorbent Assay analysis of the serum levels of tumor necrosis factor-α and interleukin-1β in HAG mice. *n* = 7 per group or 9 per group (Vehicle, quadruple therapy, and CPS). Data are represented as the mean ± SD. RUT: Rapid urease test; HAG: *Helicobacter pylori*-associated gastritis; CPS: *Coptis*, *Pinellia*, and *Scutellaria*; NC: Negative control; QT: Quadruple therapy; IL-1β: Interleukin-1β; TNF-α: Tumor necrosis factor-α.

antimicrobial cerebroside, pinelloside, was previously isolated from *Pinellia*. This compound could inhibit the growth of *Bacillus subtilis*, *Staphylococcus aureus*, *Aspergillus niger*, and *Candida albicans*[44]. The present study demonstrated the inhibitory potential of the aqueous extract of CPS against *H. pylori*-induced gastric mucosal inflammation.

The constituents in the compound prescription showed delayed absorption and elimination and had a longer residence time in the body than a single herb decoction[45]. Therefore, compound prescriptions are more efficient and durable, making them promising candidates for *in vivo* studies. However, the multi-compound and multi-target approaches represent a significant obstacle to studying compound prescriptions. Network pharmacology provides a new research method for studying the network regulation effects of TCM[46].



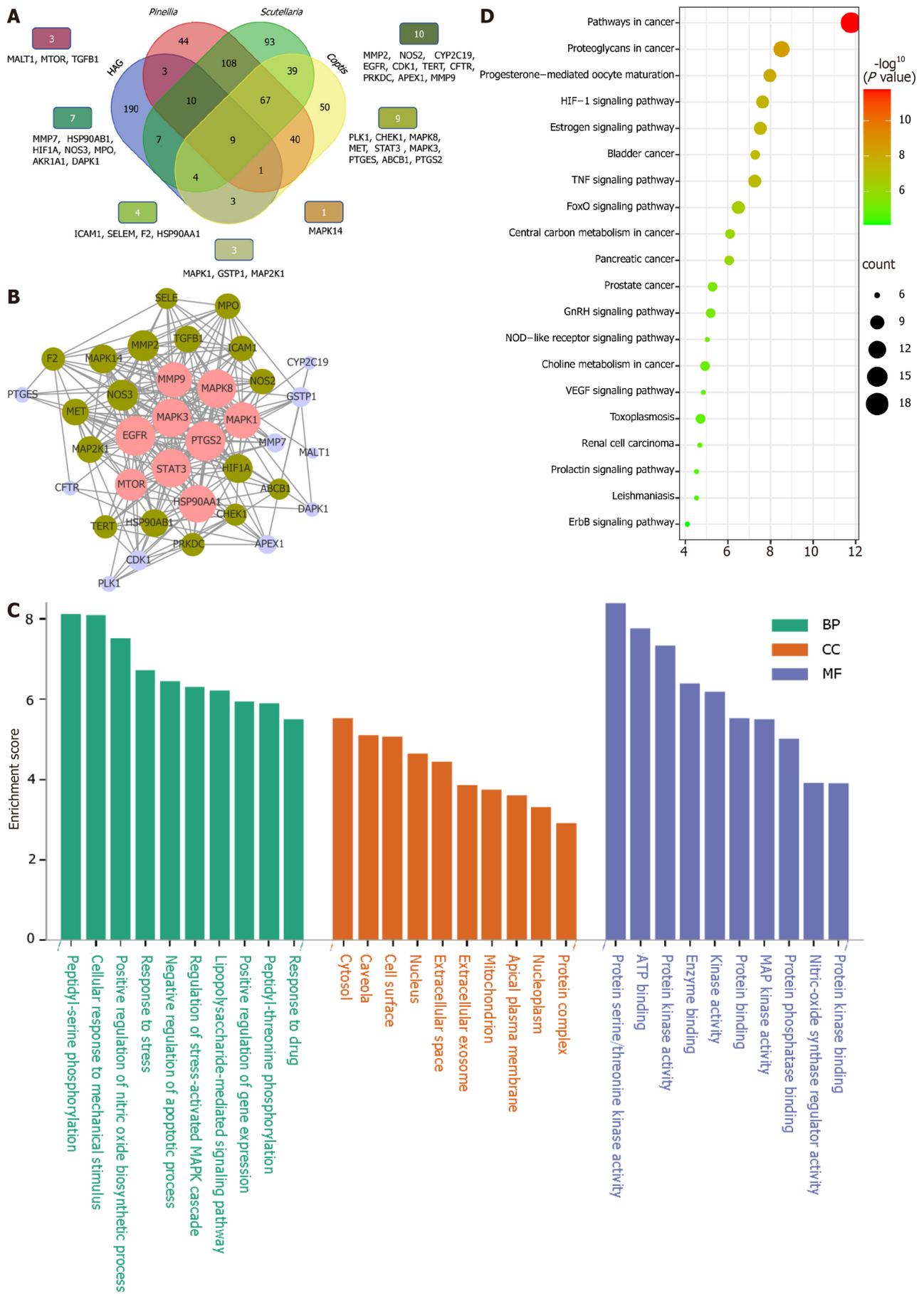
**Figure 3** Network diagram of *Coptis*, *Pinellia*, and *Scutellaria*, compounds, and targets.

EGFR, PTGS2, STAT3, MAPK3, MAPK8, HSP90AA1, MAPK1, MMP9, and MTOR were identified as the hub target proteins of CPS for HAG treatment. These targets mainly mediate *H. pylori*-induced inflammation and carcinogenesis. Multiple signaling pathways and receptors, including the ERK, JNK, JAK/STAT, and EGFR pathways, can be activated early post-infection and are involved in chemokine induction[47,48]. Matrix degradation by MMPs is critical for tumor cell invasion and metastasis. Pan *et al* indicated that *H. pylori* infection induces MMP9 expression by activating the ERK signaling pathway and increasing proliferation, growth, migration, and invasion of gastric cancer cells[49]. Aberrant activation of the PI3K/Akt/mTOR pathway modulates autophagy, epithelial-mesenchymal transition, apoptosis, chemoresistance, and metastasis in many human cancers and regulates the migration of gastric cancer cells[50].

In addition to identifying key inflammatory and oncogenic pathways, we also performed a KEGG pathway enrichment analysis. These analyses revealed that the CPS was related to pathways in cancer, proteoglycan synthesis in cancer, progesterone-mediated oocyte maturation, HIF-1 signaling pathway, estrogen signaling pathway, bladder cancer, and TNF signaling pathway. The antibacterial properties of estrogen and progesterone have been unfolded over recent years. A previous study found that feeding mice with estrogen alleviated *H. pylori*-induced gastric pathology[51]. In addition to estrogen, another steroid hormone, progesterone, was also found to exert bacteriolytic effects against *H. pylori*, stronger than those exhibited by estrogen[52]. In another study, Fong *et al* revealed the potential protective effect of oral contraceptives against *H. pylori* infection using the US National Health and Nutrition Examination Survey dataset[53]. A recent study found that the nuclear receptor estrogen-related receptor gamma (ESRRG) can affect *H. pylori* infection-driven gastric cancer. Mechanistically, activation of B cells (NF- $\kappa$ B) and p65 by *H. pylori* abrogates ESRRG-mediated activation of TFF1, a tumor suppressor[54]. Accumulating evidence links *H. pylori* infection with extra-gastric diseases, such as neurological, dermatological, hematological, ocular, cardiovascular, metabolic, and allergic diseases, although causal relationships must be considered[55,56]. The specific role of *H. pylori* in the pathogenesis of extra-gastric diseases may be related to the persistent chronic inflammatory state.

## CONCLUSION

The literature search shows that CPS was the core drug for treating *H. Pylori* infection. Using an *in vivo* model, we revealed that CPS has bacteriostatic properties and can reduce inflammatory cytokine release and inflammation in the gastric mucosa. Network pharmacology predictions showed that CPS has complex chemical compositions and multi-target, multi-pathway regulatory mechanisms. Although our network pharmacology results are not extensive, our results still highlight the role of CPS in treating *H.*



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Figure 4 Network analysis of predicted *Coptis*, *Pinellia*, and *Scutellaria* targets and differentially expressed *Helicobacter pylori* genes. A:

Venn diagram of *Coptis*, *Pinellia*, and *Scutellaria* (CPS) indicates targets and differentially expressed genes in *Helicobacter pylori*-associated gastritis (HAG); B: Protein-protein interaction diagram of CPS and HAG; C: Cellular component, biological process, and molecular function analysis of gene ontology pathway enrichment; D: Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis. CPS: *Coptis*, *Pinellia*, and *Scutellaria*; HAG: *Helicobacter pylori*-associated gastritis; GO: Gene ontology; BP: Biological process; CC: Cellular component; MF: Molecular function; KEGG: Kyoto Encyclopedia of Genes and Genomes.

*pylori*. We also described the close association between an *H. pylori*-induced persistent chronic inflammatory state and gastric cancer progression and extra-gastric diseases. These findings can provide a basis to investigate the mechanisms of action for CPS in the future.

## ARTICLE HIGHLIGHTS

### Research background

Infection with *Helicobacter pylori* (*H. pylori*) is associated with severe digestive diseases, while successful eradication of this pathogen is known to prevent the occurrence of peptic ulcer disease and gastric cancer.

### Research motivation

*H. pylori* eradication has become more challenging over the past decade due to increasing antimicrobial resistance. Traditional Chinese medicine (TCM) has unique advantages for treating *H. pylori* infection, which can reduce drug resistance and increase the eradication rate of *H. pylori*.

### Research objectives

To effectively treat *H. pylori* infection in the future, we need efficient therapeutic agents or strategies.

### Research methods

Here, we attempted to identify medication rules, effective materials, and the molecular mechanisms underlying the therapeutic effect of TCM against *H. pylori* using data mining, *in vivo* experiment, and network pharmacology.

### Research results

*Coptis*, *Pinellia*, and *Scutellaria* (CPS) were identified as the core drug combination for *H. pylori* eradication. We evidenced that CPS eradicated *H. pylori*, alleviated the gastric pathology, and reduced circulating tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  levels. Nine key compounds and nine hub target proteins were further determined as the key active ingredients and therapeutic targets of CPS against *H. pylori*, respectively.

### Research conclusions

Altogether, our data strongly suggest that the efficacy of CPS in the treatment of *H. pylori* is worthy of affirmation.

### Research perspectives

We will further explore the mechanism of CPS in treating *H. pylori* infection through *in vitro* and *in vivo* experiments based on the close association between an *H. pylori*-induced persistent chronic inflammatory state and gastric cancer progression and extra-gastric diseases.

## FOOTNOTES

**Author contributions:** Bin Y initiated the project; Yu Z and Sheng WD had the idea for this study and performed the experiments; Yu Z wrote the manuscript; Bin Y and Yin X performed the experiments and wrote the manuscript; all authors contributed to the final manuscript.

**Supported by** the Domestic First-class Construction Disciplines of the Hunan University of Chinese Medicine, No. 2018[03]; the Key Scientific Research Project of Hunan Provincial Education Board, No. 20A371; and the Key Programs of Administration of Traditional Chinese Medicine of Hunan Province, No. C2022016.

**Institutional review board statement:** The study was reviewed and approved by The First Hospital of Hunan University of Chinese Medicine Institutional Review Board (Approval No. ZYFY20190620).

**Conflict-of-interest statement:** None of the authors have any conflicts of interest to declare.

**Data sharing statement:** No additional data are available.

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**S-Editor:** Wang LL

**L-Editor:** Wang TQ

**P-Editor:** Zhao S

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