

RESEARCH ARTICLE



Medicine for chronic atrophic gastritis: a systematic review, meta- and network pharmacology analysis

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ABSTRACT

Purpose: The aim of this study is to determine the effectiveness and reliability of adding traditional Chinese medicine (TCM) in the clinical intervention and explore mechanisms of action for chronic atrophic gastritis (CAG) through meta- and network pharmacology analysis (NPAs).

Methods: A predefined search strategy was used to retrieve literature from PubMed, Embase database, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese BioMedical Literature Database (CBM), Wan Fang Data and China Science and Technology Journal Database (VIP). After applying inclusion and exclusion criteria, a total of 12 randomized controlled trials (RCTs) were included for meta-analysis to provide clinical evidence of the intervention effects. A network meta-analysis using Bayesian networks was conducted to observe the relative effects of different intervention measures and possible ranking of effects. The composition of the TCM formulation in the experimental group was analysed, and association rule mining was performed to identify hub herbal medicines. Target genes for CAG were searched in GeneCards, Online Mendelian Inheritance in Man, PharmGKB, Therapeutic Target Database and DrugBank. A regulatory network was constructed to connect the target genes with active ingredients of the hub herbal medicines. Enrichment analyses were performed using the Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) to examine the central targets from a comprehensive viewpoint. Protein–protein interaction networks (PPINs) were constructed to identify hub genes and conduct molecular docking with differentially expressed genes (DEGs) and corresponding active molecules.

Results: A total of 1140 participants from 12 RCTs were included in the statistical analysis, confirming that the experimental group receiving the addition of TCM intervention had better clinical efficacy. Seven hub TCMs (*Paeonia lactiflora*, *Atractylodes macrocephala*, *Pinellia ternata*, *Citrus reticulata*, *Codonopsis pilosula*, *Salvia miltiorrhiza* and *Coptis chinensis*) were identified through association rule analysis of all included TCMs. Thirteen hub genes (CDKN1A, CASP3, STAT1, TP53, JUN, MAPK1, STAT3, MAPK3, MYC, HIF1A, FOS, MAPK14 and AKT1) were obtained from 90 gene PPINs. Differential gene expression analysis between the disease and normal gastric tissue identified MAPK1 and MAPK3 as the significant genes. Molecular docking analysis revealed that naringenin, luteolin and quercetin were the main active compounds with good binding activities to the two hub targets. GO analysis demonstrated the function of the targets in protein binding, while KEGG analysis indicated their involvement in important pathways related to cancer.

Conclusions: The results of a meta-analysis of 12 RCTs indicate that TCM intervention can improve the clinical treatment efficacy of CAG. NPAs identified seven hub TCM and 13 target genes associated with their actions, while bioinformatics analysis identified two DEGs between normal and CAG gastric tissues. Finally, molecular docking was employed to reveal the mechanism of action of the active molecules in TCM on the DEGs. These findings not only reveal the mechanisms of action of the active components of the TCMs, but also provide support for the development of new drugs, ultimately blocking the progression from chronic gastritis to gastric cancer.

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1. Introduction

Chronic atrophic gastritis (CAG) refers to the reduction of gastric glands, including non-biochemical atrophy and biochemical atrophy [1]. CAG is often recognized as a precancerous lesion of gastric cancer (GC), which ranks the fifth most common cancer worldwide with the third highest cancer-related mortality rate [2]. The prevalence of CAG among research populations from 2010 to 2020 is approximately 25% [3]. In CAG patients, the annual probability of developing GC is 0.1%, and the incidence rates during 1, 5 and 10 years of follow-up are 0.3%, 0.6% and 0.8%, respectively [2]. CAG represents a significant progression from gastritis to GC [4], and effective interventions are crucial in reducing the occurrence of GC. In recent years, Chinese patent medicine and traditional Chinese medicine (TCM) have been proven to have a high clinical efficacy in treating CAG [5–8]. Therefore, obtaining evidence on the target effects of Chinese medicine through evidence-based medicine can provide novel ideas and approaches for intervening in CAG.

Meta-analysis has emerged as a pivotal statistical method in the field of medicine and health sciences [9], serving as the best available evidence to inform clinical practice [10]. This approach overcomes limitations posed by small sample sizes or rare outcomes by integrating the findings of numerous individual studies to produce a single, optimal estimate [11]. While meta-analysis provides an objective quantitative synthesis based on existing research, it cannot address the flaws or deficiencies within the included studies or data, necessitating the consideration of heterogeneity and potential biases in a comprehensive manner [12]. Network meta-analysis (NMA) studies, on the other hand, offer advantages over traditional meta-analysis in comparing and evaluating various interventions or treatment approaches, enabling direct evidence comparisons and indirect evidence predictions [13]. By combining these two techniques, it becomes possible to analyse and derive answers to specific questions based on reported research data.

Network pharmacology (NP) is an emerging field in systematic drug research that primarily focuses on analysing and establishing interactions between active drug molecules and multiple targets [14]. Network-based approaches offer the potential to enhance researchers' understanding of the multi-layered information regarding drug actions, while also providing support for drug design and mechanism elucidation through the construction of cellular or characterization networks and chemical networks [15]. NP has become the next paradigm in drug discovery [16]. Moreover, NP is

anticipated to unveil and visualize the underlying interaction networks of TCM in relation to multifactorial diseases [17], encompassing investigations into the pharmacological mechanisms of herbal formulas [18], compound synergistic effects [19], as well as advancements in new drug discovery and development [20].

2. Materials and methods

2.1. Database search strategy

Researchers conducted literature searches using a combination of medical subject headings and free keywords in seven databases, without language restrictions, up until May 2023. They also searched the Chinese Clinical Trial Registry and the US ClinicalTrials.gov for relevant registered experiments. The main subject headings used in the search were 'Gastritis, Atrophic', 'randomized controlled trial', 'Drugs, Chinese Herbal' and 'Traditional Chinese Medicine'. The primary databases searched included PubMed [21], Embase database [22], Cochrane Library [23], China National Knowledge Infrastructure (CNKI) [24], Chinese Biomedical Literature Database (CBM) [25], Wanfang Data [26] and China Science and Technology Journal Database (VIP) [27]. All search results were downloaded and imported into EndNote X9.1 for literature management.

2.2. Inclusion and exclusion criteria

Our literature exclusion criteria were established as follows: (1) studies not utilizing a randomized controlled trial (RCT) design, (2) studies not related to CAG, (3) animal experiments, (4) literature reviews and (5) studies without access to the original text. The included literature needed to meet the following criteria: (1) the experimental group received TCM in addition to omeprazole, amoxicillin and clarithromycin, while the control group only received Western medicine (omeprazole, amoxicillin and clarithromycin), (2) the treatment duration was no less than seven days, (3) all studies were original and had not been previously published, (4) all participants were aged 18 and above (adults are more suitable for clinical analyses and therapeutic observations due to their relatively stable body functions and physiological states) and (5) a minimum Jadad score of three was obtained. The first round of screening was performed by two researchers based on the titles and abstracts of the literature, while the second round of screening required a full-text review. This study included the intersection of literature selected by the two clinical researchers, and in cases of substantial controversy, the judgment was deferred to a third clinical physician.

2.3. Data extraction and quality assessment

Two researchers have been assigned to independently extract data for reporting, including the following information: primary author name, publication date, sample size (control/experimental group), gender (male/female), age (mean \pm standard deviation), disease duration (mean \pm standard deviation), intervention measures, treatment duration, formulation names, Chinese herbal prescriptions, outcome measures, efficacy indicators, adverse reactions and Jadad scores. Consistency in data collection was ensured, and any discrepancies have been resolved through verification of the original text or third-party adjudication. We utilized the Jadad scale [28] and the Cochrane Collaboration tool [29] to assess the risk of bias in the included literature. The Jadad score primarily evaluates random sequence production, allocation concealment, blinding method and withdrawals. The Cochrane Collaboration tool assesses randomization methods, allocation concealment, blinding, completeness of outcome data, selective reporting of study results, and other sources of bias.

2.4. Data synthesis and analysis

Statistical analysis has been conducted using Review Manager 5.3 and Stata 14.0 software. A p value less than .05 indicated statistical significance for differences. For dichotomous variables, the evaluation has been done using relative risk (RR) ratios and 95% confidence intervals (CIs). For continuous variables, standardized mean differences (SMDs) or mean differences (MDs) were used [30], along with their respective 95% CIs. The consistency of the literature has been assessed using the χ^2 test and the inconsistency index statistic (I^2) [31]. If significant heterogeneity is present ($I^2 > 50\%$ or $p < .05$), a random-effects model was used for pooling results; otherwise, a fixed-effects model has been employed. Sensitivity analysis was conducted to further evaluate the sources of heterogeneity and the stability of results. Funnel plots were used to assess potential publication bias.

2.5. Network construction and analysis

Network analysis of included studies was conducted using Stata 14.0 software and GeMTC software to predict the effects of different interventions. Network meta-analysis, also known as mixed treatment comparison (MTC), is a technique that allows for the simultaneous inclusion of two or more drugs in a meta-analysis. By utilizing a comprehensive Bayesian evidence

network, all indirect comparisons are considered, resulting in a single, integrated estimate of treatment effects for all included interventions. In the parameter settings of the model, the number of chains has been set to 4, initial values scaling to 2.5, tuning iterations to 20,000, simulation iterations to 50,000, and thinning interval to 10. Through this analysis, we were able to observe the relative effects of the experimental and control groups, as well as the possible rankings of the intervention effects.

2.6. Hub Chinese medicine mining and targeting

The Chinese herbal medicines included in the literature were standardized according to 'Chinese materia medica' [32] and 'Pharmacopoeia of the People's Republic' [33]. Then, IBM SPSS Modeler 18.0 software (Armonk, NY) was used to conduct association rule analysis to generate a network of herbal medicine correlations. The support, confidence and lift measures have been calculated for each frequent itemset, and the hub herbal medicines within all prescriptions were identified. Using the search terms 'Baishao' (*Paeonia lactiflora*), 'Baizhu' (*Atractylodes macrocephala*), 'Banxia' (*Pinellia ternata*), 'Chenpi' (*Citrus reticulata*), 'Dangshen' (*Codonopsis pilosula*), 'Danshen' (*Salvia miltiorrhiza*) and 'Huanglian' (*Coptis chinensis*), the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform [34] (TCMSP, <http://tcmssp.com/tcmssp.php>) was utilized to select active ingredients with an oral bioavailability (OB) $\geq 30\%$ and drug likeness (DL) ≥ 0.18 . The UniProt database [35] (<https://www.uniprot.org/>) has been used to annotate the gene targets of the drugs. The disease-associated genes were retrieved using 'Gastritis, Atrophic' as the search term from multiple databases, including GeneCards [36] (<http://www.genecards.org/>), Online Mendelian Inheritance in Man [37] (OMIM, <https://omim.org/>), PharmGKB [38] (<http://www.pharmgkb.org>), Therapeutic Target Database [39] (TTD, <http://db.idrblab.net/ttd/>) and DrugBank [40] (<http://www.drugbank.ca/>). The disease genes from these databases were merged, and the intersection of disease genes and drug target genes was identified. The Cytoscape software (v3.9.1) [41] was used to visualize the regulatory network of compound herbal formulations.

2.7. Network pharmacology analysis of the based on hub Chinese medicine

Got the intersection genes from Section 2.6 and input them into the DAVID database [42] (<https://david.ncicrf.gov/home.jsp>) to obtain results using Gene

Ontology (GO) analysis [43] and the Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis [44]. Utilize the 'ggplot2' package [45] in the R language (R-4.1.3) to perform count value filtering and visualize the graphs artistically. The protein-protein interaction networks (PPINs) result from the String database [46] (<https://cn.string-db.org/>). The PPINs results imported into Cytoscape and analyse the core of the network employing the CytoNCA plugin [47]. Retrieve the protein IDs of hub targets from the UniProt database and search for the 3D structure of protein receptors based on the IDs in the PDB database [48] (<https://www.rcsb.org/>). Access the PubChem database [49] (<https://pubchem.ncbi.nlm.nih.gov/>) to obtain the 2D chemical structures of small molecule ligands, then transform them into 3D structures using the ChemBio3D Ultra (14.0) software, followed by performing structure optimization calculations. Introduce hydrogen bonds to the protein receptors and identify the ligand binding sites with the Autodock Tools software [50]. Lastly, carry out molecular docking using the Autodock Vina software to determine the site with the highest binding energy, and visualize the outcomes utilizing the PyMol software [51].

3. Results

3.1. Description of studies

According to the predefined retrieval strategy, we searched a total of 16,777 studies from four Chinese databases (CNKI, CBM, Wang fang data and VIP) and three English databases (PubMed, EMBASE and Cochrane Library) since the establishment of our database. Combining all the literature retrieved from all the databases, 7014 studies were left after weight reduction of the literature. Following the initial screening, 214 studies were included. After careful examination of the full texts by two researchers, only 15 studies met our criteria. However, upon further comparison, we identified one study with duplicate publications and two studies with unclear baselines, resulting in the inclusion of 12 RCTs for meta-analysis [52–62]. The flowchart (Figure 1) of this study's database search and literature screening process is depicted.

Among the 12 RCT studies published between 2013 and 2022, a total of 1140 participants, including 631 males and 509 females, were included. The control group in these studies received interventions of omeprazole, amoxicillin and clarithromycin, while the experimental group received the addition of a TCM compound based on the control group. The intervention period ranged from a minimum of seven days to

a maximum of 90 days. Clinical efficacy was the primary outcome measure for all experiments, categorized as effective, significant or ineffective. The main characteristics of all included studies in this meta-analysis are summarized in Table 1.

3.2. Risk of bias assessment

The risk of bias assessment using the Cochrane Collaboration's risk of bias tool revealed that none of the included studies provided clear information regarding allocation concealment. The reason for the absence of blinding in the trials may be attributed to the significant cost differences in treatments between different groups. The quality assessment results (Figure 2) indicate that all studies were at high risk of bias due to lack of allocation concealment. As for the Jadad scores (Table 2), three studies [53,61,62] employed random number tables for randomization, two studies [55,56] randomized participants based on admission sequence, and one study [59] used simple randomization. The remaining studies did not mention the method of randomization. Allocation concealment and follow-up were not described. The included studies in the meta-analysis had Jadad scores ranging from 3 to 4. Overall, the literature quality was relatively balanced, and the included studies were of moderate quality.

3.3. Clinical outcomes

3.3.1. Comparison of all studies

The 12 included studies reported three levels of clinical efficacy (effective, significant, ineffective). The results of the heterogeneity test ($I^2 = 0\% < 50\%$, and Q test $p = .64 > .1$) indicated that the heterogeneity among the selected literature was not statistically significant. Therefore, a fixed-effect model was chosen for the meta-analysis. The pooled RR value of the 12 studies was 4.87, with a 95% CI of (3.24, 7.30), indicating a statistically significant difference between the experimental and control groups. The overall effect ($Z = 7.64$, $p = .00001 < .05$) demonstrated that the clinical efficacy of combined Western medicine and TCM interventions was superior to the use of Western medicine alone. Further details can be found in the forest plot (Figure 3(A)). Sensitivity analysis (Figure 3(B)) was performed to assess the stability of the clinical efficacy. Additionally, a radial plot (Figure 3(C)) and L'Abbé plot (Figure 3(D)) were used for supplementary illustrations. The results showed that none of the studies significantly influenced the meta-analysis results, indicating good stability of the research findings. A funnel plot (Figure 3(E)) was

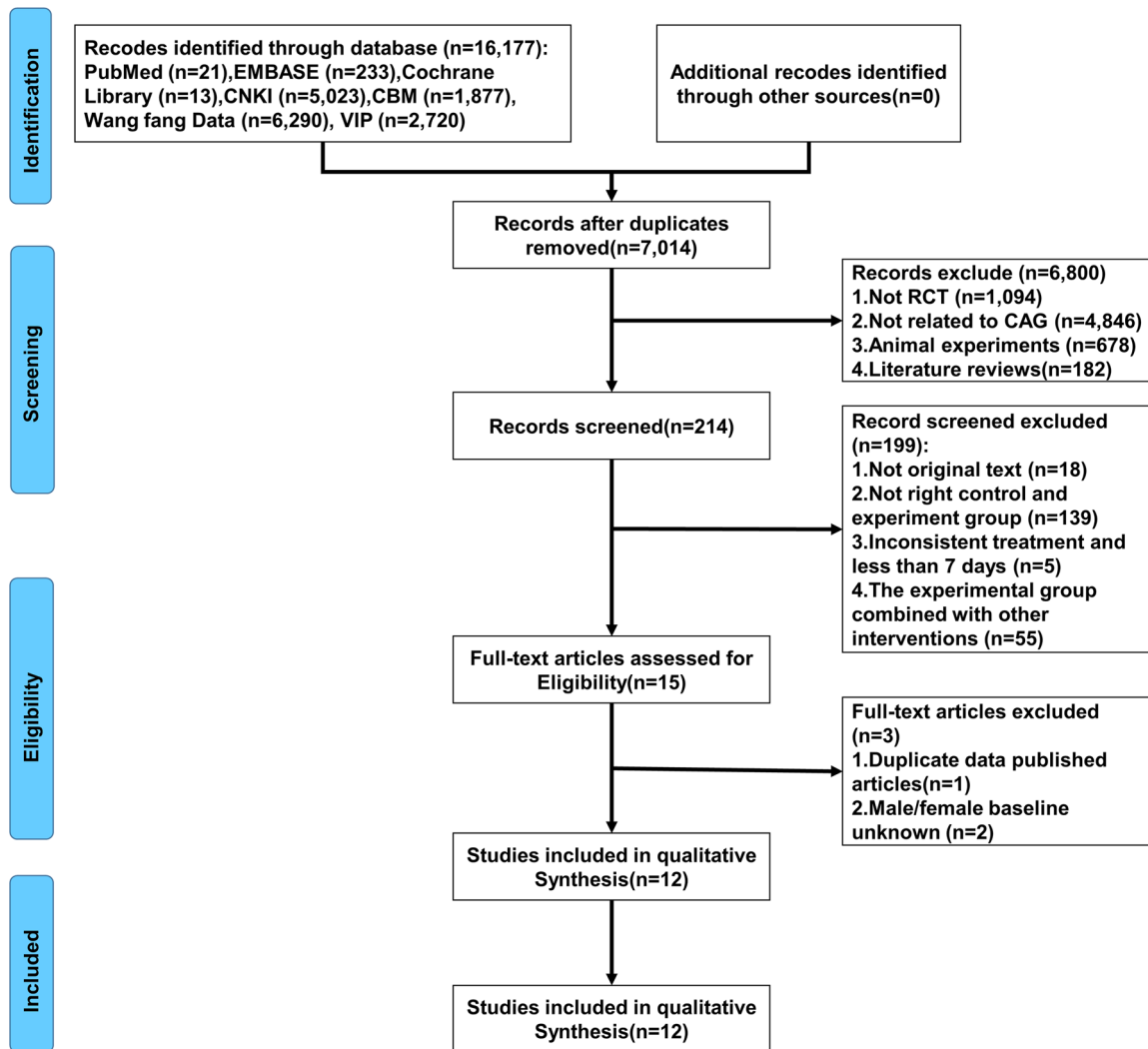


Figure 1. Flowchart of database searching and study identification.

generated to observe publication bias. Begg's test yielded $p = .244 > .05$, and Egger's test yielded $p = .282 > .05$, suggesting that the funnel plot was symmetric, and no publication bias was present in the studies.

3.3.2. Comparison of subgroup studies

In our investigation of the characteristic statistics, we have identified that the clinical efficacy of the six studies can be further categorized into four levels: cure, significant improvement, effectiveness and ineffectiveness. The results of the heterogeneity test ($I^2 = 0\% < 50\%$, and Q test $p = .866 > .1$) indicate that there is no heterogeneity among the subgroups of studies categorized into these four levels. The fixed-effect meta-analysis of the six articles yielded a RR value of 2.2, with a 95% CI of (1.65, 2.93) (Figure 4(A)), revealing a statistically significant overall effect ($Z = 5.41$, $p = .000 < .05$). The sensitivity analysis results (Figure 4(B)) demonstrate that Wang [60] has a significant impact. To examine

publication bias, a funnel plot was generated (Figure 4(C)). Begg's test yielded a p value of $.024 < .05$, and Egger's test yielded $p = .028 < .05$, indicating clear asymmetry in the funnel plot. After removing the influential study, publication bias was assessed again. The funnel plot (Figure 4(D)) exhibited a considerably symmetric shape. Begg's test yielded $p = .086 > .05$, and Egger's test yielded $p = .1 > .05$. These results suggest that there is no publication bias among the four subgroup analyses of the remaining five studies. The substantial influence of Wang [60] may be attributed to reporting bias or an exaggeration of the experimental group's clinical cure level effect.

3.4. Network meta-analysis of drugs

We constructed a Bayesian network comparing the intervention measures of the control group and the 12 experimental groups (Figure 5(A)) and compute the

Table 1. Principal characteristics of all included studies in meta-analysis.

Study ID	Intervention		Sex		Age (years)	Course of disease (years)	Duration (days)	Methodological characteristics	Outcome measures
	Experiment group	Control group	Male (E/C)	Female (E/C)					
Chen [52]	Fu Wei Tang + O + A + C	O + A + C	23/24	22/21	EG:46.2 ± 5.3 CG:45.8 ± 5.6	NR	14	RCT	AB
Dai [53]	Jia Wei Xiang Sha Liu Jun Zi Tang and O + A + C	O + A + C	27/28	23/22	EG:45.46 ± 2.65 CG:45.37 ± 2.65	NR	90	RCT	ABDE
Fu [54]	Fu's Formulas and O + A + C	O + A + C	10/9	15/16	EG:52.5 ± 2.2 CG:51.7 ± 2.1	EG:6.1 ± 1.5 CG:6.2 ± 1.3	90	RCT	ABC
Gao [55]	Wei Tong Ling Tang and O + A + C	O + A + C	12/19	24/17	EG:41.6 ± 3.6 CG:43.6 ± 4.7	EG:11.06 ± 7.56 CG:10.98 ± 6.54	60	RCT	ABC
Lü and Jia [56]	Yi Wei Tang and O + A + C	O + A + C	21/22	13/12	EG:52.2 ± 4.6 CG:53.1 ± 4.5	EG:8.2 ± 5.0 CG:8.5 ± 4.6	7	RCT	ABH
Liu [57]	Yi Wei Tang and O + A + C	O + A + C	40/39	20/21	EG:45.89 ± 2.79 CG:45.68 ± 2.68	EG:1.78 ± 0.79 CG:1.79 ± 0.68	90	RCT	FGI
Liu et al. [58]	Jian Pi Yi Wei Fu Fang Tang Ji and O + A + C	O + A + C	18/14	12/16	EG:56.4 ± 6.52 CG:55.6 ± 6.23	EG:16.8 ± 3.84 CG:17.2 ± 3.68	14	RCT	ABCJ
Lu et al. [63]	Wen Zhong Fu Yuan Cu Yu Tang and O + A + C	O + A + C	29/27	33/35	EG:46.7 ± 2.05 CG:46.9 ± 2.02	EG:9.07 ± 2.11 CG:9.13 ± 2.06	90	RCT	ABCDK
Wang et al. [64]	Hua Zhuo Jie Du Fang and O + A + C	O + A + C	29/30	24/23	EG:42.16 ± 5.13 CG:42.29 ± 5.06	EG:7.36 ± 2.25 CG:7.30 ± 2.32	14	RCT	ABF
Wang [60]	Yi Wei Huo Luo Jing Yan Fang and O + A + C	O + A + C	54/52	36/38	EG:50.4 ± 4.5 CG:49.3 ± 5.2	EG:3.5 ± 1.37 CG:3.7 ± 1.5	30	RCT	BCEF
Wang et al. [65]	Hui Chun Jian Wei Tang and O + A + C	O + A + C	27/26	17/18	EG:55.44 ± 4.04 CG:55.12 ± 4.32	EG:4.39 ± 1.24 CG:4.25 ± 1.51	60	RCT	ADGMN
Yan [62]	Ban Xia Xie Xin Tang Jia Jian and O + A + C	O + A + C	26/25	15/16	EG:46.54 ± 5.31 CG:46.33 ± 5.42	EG:2.37 ± 0.78 CG:2.46 ± 0.81	60	RCT	ADGO

O + A + C: omeprazole, amoxicillin and clarithromycin; EG: experiment group; CG: control group; NR: not reported; RCT: randomized controlled trial; A: clinical outcomes; B: gastroscopy; C: pathological examination; D: Chinese medical evidence; E: inflammatory factor testing; F: traditional Chinese medicine symptoms; G: adverse reactions; H: *Helicobacter pylori*; I: SF-36 scale score; J: gastric mucosal EGF assay; K: gastrointestinal hormones; L: cytokines; M: gastrointestinal function; N: oxidative stress indicators; O: immunoglobulins.

indirect comparisons of all intervention measures. During the computation, it was found that the intervention measures in the Liu [57] study had a significant effect on all patients, resulting in data bias in the prediction results. Therefore, the decision was made to exclude this reference. The possible relative effects of the experimental and control groups in the literature study were calculated (Table 3), including effect size and 95% CI. The effects of different intervention drugs in the different groups were ranked (Table 4), and a histogram was plotted (Figure 5(B)). The results indicate that the experimental groups have higher cumulative probability rankings compared to the control group, with the experimental group in the Wang study [61] having the highest ranking, this may be due to the fact that the study's follow-up period was longer than 2 months and the addition of the TCM symptom score to the observational indicators.

3.5. Hub Chinese medicine mining

The composition of TCM formulations (Table 5) in the 12 studies was collected and standardized (Table 6),

resulting in a total of 56 different medicinal herbs. Among them, the six most frequently used medicinal herbs were *Codonopsis pilosula* (eight times), *Paeonia lactiflora* (six times), *PORIA* (six times), *Coptis chinensis* (six times), *Pinellia ternata* (six times), *Citrus reticulata* (six times) and *Salvia miltiorrhiza* (five times). Inputting all the medicinal herbs into the association analysis network (Figure 6), the significant associations were identified based on support, confidence and lift. The association analysis (Table 7) results were ranked in descending order of support count (support count >3), with *Codonopsis pilosula* -> *Atractylodes macrocephala* having six association support counts. By conducting statistical analysis on the antecedents and consequents involved in Table 7, a total of seven hub medicinal herbs were identified.

3.6. Hub Chinese medicine genes target analysis

In the TCMSD database, 'Baishao' (*Paeonia lactiflora*) was found to have 13 active ingredients and 960 drug targets, 'Baizhu' (*Atractylodes macrocephala*) has seven active ingredients and 774 drug targets, 'Banxia'

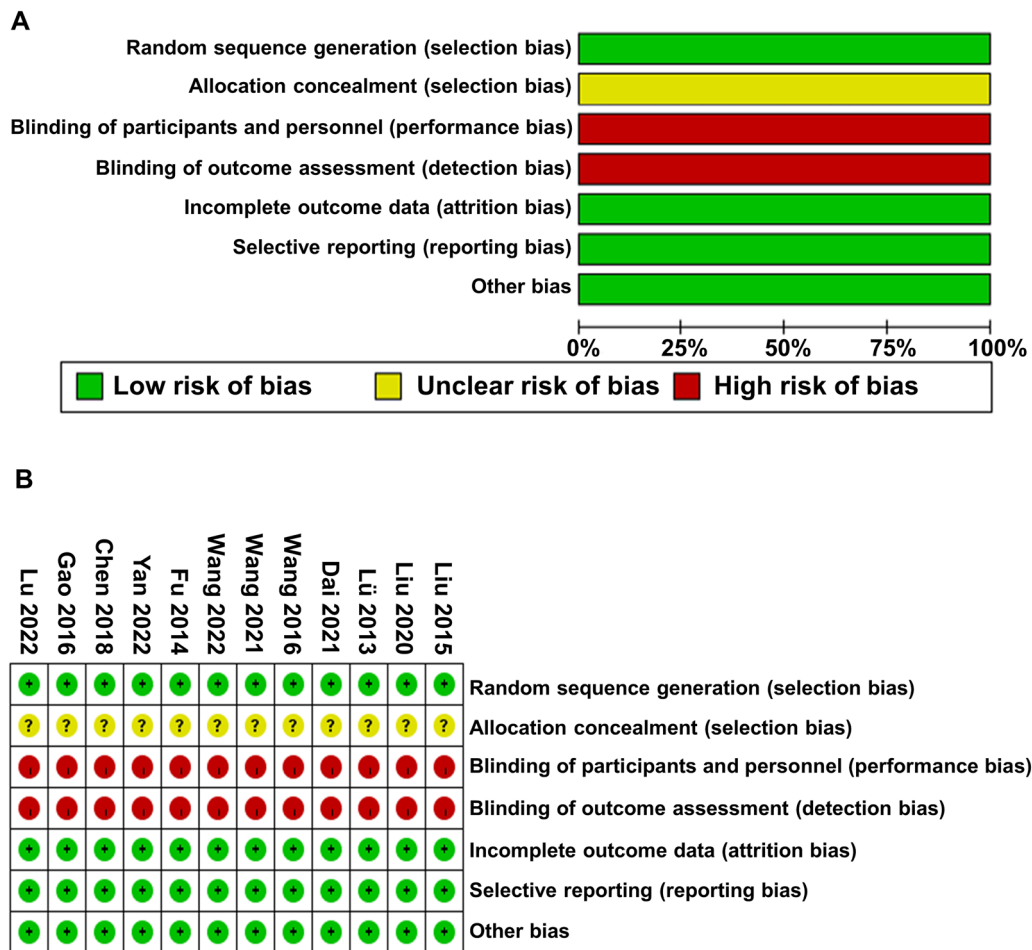


Figure 2. Evaluation of the quality of the included research literature. (A) Risk of bias summary. (B) Risk of bias graph.

Table 2. Evaluation of methodologic quality of the included studies based on the Cochrane handbook.

Study ID	Baseline	Randomization	Blinding	Allocation concealment	Follow-up	Withdrawals or dropouts	Jadad score
Chen [52]	Comparability	Mention not described	Inadequate	Unclear (NR)	Unclear (NR)	Described	3
Dai [53]	Comparability	Random number table	Inadequate	Unclear (NR)	Unclear (NR)	Described	4
Fu [54]	Comparability	Mention not described	Inadequate	Unclear (NR)	Unclear (NR)	Described	3
Gao [55]	Comparability	Admission order randomized	Inadequate	Unclear (NR)	Unclear (NR)	Described	4
Lü and Jia [56]	Comparability	Admission order randomized	Inadequate	Unclear (NR)	Unclear (NR)	Described	4
Liu [57]	Comparability	Mention not described	Inadequate	Unclear (NR)	Unclear (NR)	Described	3
Liu et al. [58]	Comparability	Mention not described	Inadequate	Unclear (NR)	Unclear (NR)	Described	3
Lu et al. [63]	Comparability	Mention not described	Inadequate	Unclear (NR)	Unclear (NR)	Described	3
Wang et al. [64]	Comparability	Simple random method	Inadequate	Unclear (NR)	Unclear (NR)	Described	3
Wang [60]	Comparability	Mention not described	Inadequate	Unclear (NR)	Unclear (NR)	Described	3
Wang et al. [65]	Comparability	Random number table	Inadequate	Unclear (NR)	Unclear (NR)	Described	4
Yan [62]	Comparability	Random number table	Inadequate	Unclear (NR)	Unclear (NR)	Described	4

NR: not reported.

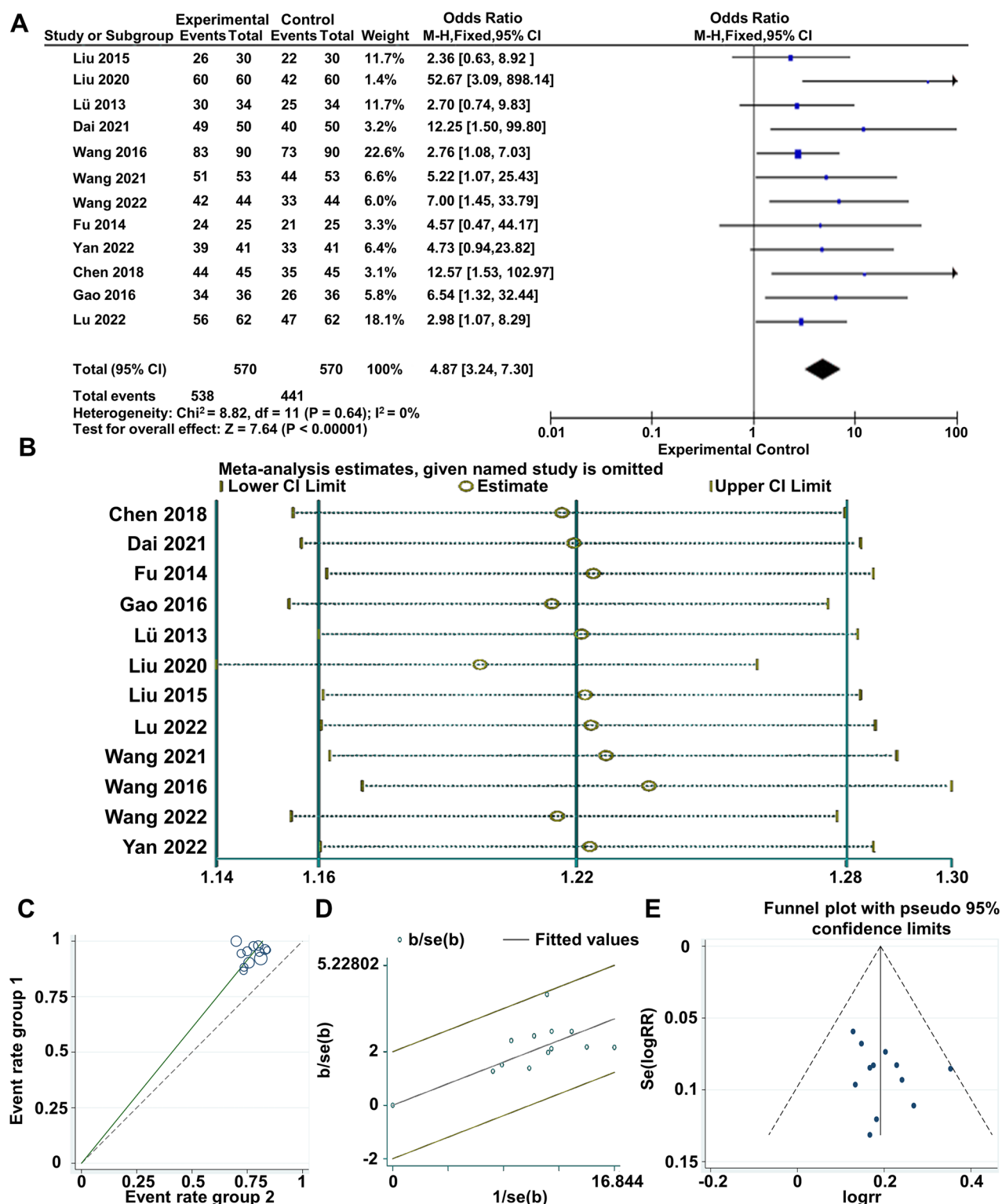


Figure 3. Meta-analysis of clinical efficacy of all included studies. (A) Meta-analysis Forest plot of clinical efficacy. (B) Sensitivity analysis of studies included in the literature. (C) Label diagram for heterogeneity test. (D) Star chart for heterogeneity test. (E) Funnel plot of total effectiveness rate.

(*Pinellia ternata*) has 13 active ingredients and 1287 drug targets, 'Chenpi' (*Citrus reticulata*) has five active ingredients and 479 drug targets, 'Dangshen' (*Codonopsis pilosula*) has 21 active ingredients and

911 drug targets and 'Danshen' (*Salvia miltiorrhiza*) has 65 active ingredients and 2536 drug targets. Additionally, 'Huanglian' (*Coptis chinensis*) has 14 active ingredients and 597 drug targets. By searching

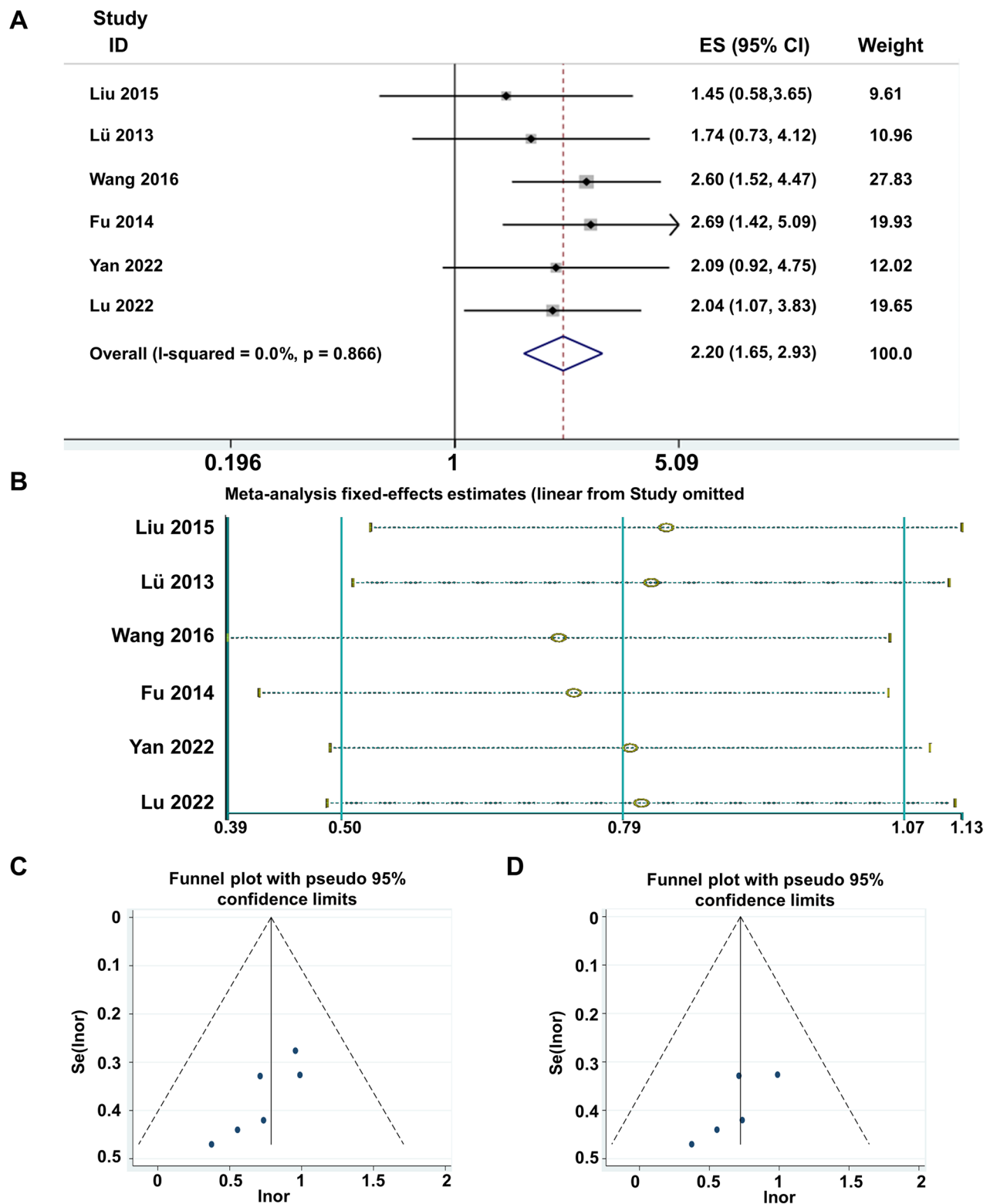


Figure 4. Meta-analysis of clinical efficacy of subgroup studies. (A) Meta-analysis Forest plot of clinical efficacy. (B) Sensitivity analysis of studies included in the subgroup literature. (C) Funnel plot of total effectiveness rate. (D) Funnel plot of total effectiveness rate (exclusion of publication bias literature).

in five online databases, 905 disease-related genes were identified. After organizing the drug target genes for the hub medicinal herbs, a total of 248

genes were obtained. Among these, 90 genes were found to be common to both the hub medicinal herbs and the disease-related genes. The medicinal

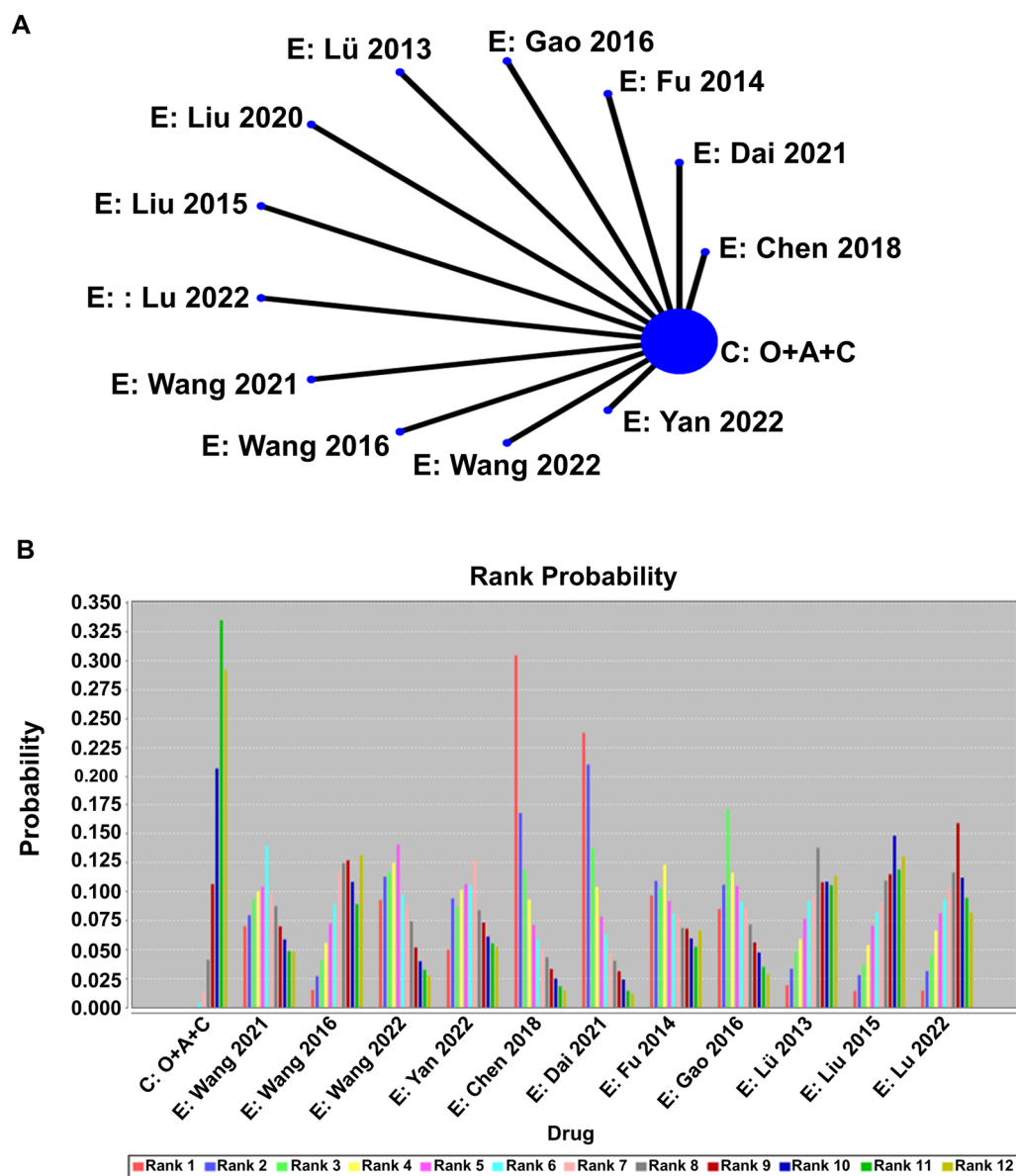


Figure 5. A network meta-analysis on the clinical efficacy of the experimental groups included in the literature. (A) Network plots for the drug efficacy considered in the review. (B) "Drug-Rank probability" histogram of effectiveness treatment for chronic atrophic gastritis.

herb compound regulation network (Figure 7) was constructed in Cytoscape software based on the properties of nodes and the connections between them.

3.7. Results of GO and KEGG analysis

Utilizing the DAVID database, we conducted GO and KEGG enrichment analyses for 90 drug targets and disease-related genes. The results were visualized using R programming language. Regarding GO enrichment analysis, only the top 10 enriched results were displayed for biological process (BP), cellular

component (CC) and molecular function (MF) (Figure 8(A)). In the MF category, genes were primarily enriched in the functionality of protein binding. Within the CC category, the functionalities of cytosol, nucleus and cytoplasm exhibited the highest enrichment. As for BP, the most enriched genes were involved in the positive regulation of transcription from RNA polymerase II promoter, negative regulation of apoptotic process, and positive regulation of gene expression. The top 30 enriched pathways from KEGG analysis were visualized (Figure 8(B)). Among the positively regulated pathways, pathways in cancer and lipid and atherosclerosis showed

Table 3. Standardized mean differences (SMDs; 95% CI) of direct and overall network estimates of efficacy.

CG	O	A	+ C	6.34 (0.29, 153.26)	2.77 (0.16, 51.19)	8.67 (0.41, 212.14)	5.34 (0.24, 134.99)	22.66 (0.69, 1815.66)	18.87 (0.74, 897.81)	7.57 (0.20, 357.31)	8.65 (0.37, 207.05)	2.73 (0.16, 63.61)	2.35 (0.13, 51.68)	2.84 (0.17, 53.35)
0.16 (0.01, 3.43)	EG Wang et al. [64]	0.44 (0.01, 28.89)	1.33 (0.02, 118.66)	0.85 (0.01, 71.95)	3.83 (0.03, 500.92)	3.51 (0.03, 411.45)	1.23 (0.01, 157.75)	1.47 (0.02, 127.26)	0.43 (0.01, 37.49)	0.37 (0.01, 31.10)	0.37 (0.01, 31.10)	0.45 (0.01, 35.19)	0.37 (0.01, 31.10)	0.45 (0.01, 35.19)
0.36 (0.02, 6.19)	EG Wang [60]	2.25 (0.03, 140.79)	3.13 (0.04, 220.96)	2.22 (0.03, 117.77)	7.94 (0.08, 1909.01)	7.14 (0.09, 695.64)	2.72 (0.03, 288.80)	3.11 (0.04, 202.05)	1.04 (0.02, 77.41)	0.90 (0.01, 51.08)	0.90 (0.01, 51.08)	1.13 (0.02, 60.96)	0.90 (0.01, 51.08)	1.13 (0.02, 60.96)
0.12 (0.00, 2.42)	0.75 (0.01, 60.30)	0.32 (0.00, 22.61)	EG Wang et al. [65]	0.60 (0.01, 53.17)	2.63 (0.02, 359.86)	2.45 (0.02, 264.19)	0.89 (0.01, 120.99)	1.06 (0.01, 80.89)	0.32 (0.00, 22.93)	0.27 (0.00, 19.43)	0.27 (0.00, 19.43)	0.34 (0.00, 23.26)	0.27 (0.00, 19.43)	0.34 (0.00, 23.26)
0.19 (0.01, 4.21)	1.17 (0.01, 93.94)	0.45 (0.01, 36.61)	1.67 (0.02, 130.63)	EG Yan [62]	4.19 (0.03, 545.16)	3.74 (0.04, 495.17)	1.29 (0.01, 209.79)	1.49 (0.02, 137.31)	0.47 (0.01, 41.36)	0.40 (0.01, 35.87)	0.40 (0.01, 35.87)	0.49 (0.01, 42.98)	0.40 (0.01, 35.87)	0.49 (0.01, 42.98)
0.04 (0.00, 1.44)	0.26 (0.00, 29.48)	0.13 (0.00, 12.00)	0.38 (0.00, 42.73)	EG Chen [52]	0.24 (0.00, 32.10)	0.85 (0.01, 167.39)	0.29 (0.00, 67.27)	0.35 (0.00, 41.16)	0.12 (0.00, 12.59)	0.11 (0.00, 11.61)	0.11 (0.00, 11.61)	0.14 (0.00, 13.81)	0.11 (0.00, 12.59)	0.14 (0.00, 13.81)
0.05 (0.00, 1.34)	0.28 (0.00, 30.80)	0.14 (0.00, 11.27)	0.41 (0.00, 46.96)	0.27 (0.00, 28.20)	1.17 (0.01, 198.17)	EG Dai [53]	0.34 (0.00, 69.20)	0.44 (0.00, 42.27)	0.13 (0.00, 13.99)	0.12 (0.00, 10.40)	0.12 (0.00, 10.40)	0.15 (0.00, 12.01)	0.12 (0.00, 13.99)	0.15 (0.00, 12.01)
0.13 (0.00, 4.94)	0.82 (0.01, 98.91)	0.37 (0.00, 38.33)	1.12 (0.01, 166.04)	0.77 (0.00, 85.43)	3.39 (0.01, 688.22)	2.94 (0.01, 507.22)	EG Fu [54]	1.41 (0.01, 133.50)	0.36 (0.00, 42.09)	0.32 (0.00, 31.52)	0.32 (0.00, 31.52)	0.38 (0.00, 40.27)	0.36 (0.00, 42.09)	0.38 (0.00, 40.27)
0.12 (0.00, 2.71)	0.68 (0.01, 63.76)	0.32 (0.00, 22.77)	0.95 (0.01, 84.39)	0.67 (0.01, 51.13)	2.89 (0.02, 379.71)	2.27 (0.02, 300.03)	0.71 (0.01, 139.01)	EG Gao [55]	0.31 (0.00, 26.31)	0.27 (0.00, 23.03)	0.27 (0.00, 23.03)	0.33 (0.01, 24.44)	0.31 (0.00, 26.31)	0.33 (0.01, 24.44)
0.37 (0.02, 6.10)	2.30 (0.03, 168.10)	0.96 (0.01, 58.35)	3.16 (0.04, 210.65)	2.13 (0.02, 134.58)	8.19 (0.08, 1324.03)	7.42 (0.07, 730.97)	2.78 (0.02, 362.20)	3.22 (0.04, 223.09)	EG Lü and Jia [56]	0.87 (0.01, 56.55)	0.87 (0.01, 56.55)	0.99 (0.02, 63.01)	0.87 (0.01, 56.55)	0.99 (0.02, 63.01)
0.43 (0.02, 7.67)	2.71 (0.03, 181.21)	1.12 (0.02, 67.76)	3.77 (0.05, 269.30)	2.49 (0.03, 161.75)	8.87 (0.09, 1753.67)	8.18 (0.10, 963.09)	3.11 (0.03, 394.39)	3.77 (0.04, 247.33)	EG Liu et al. [58]	1.15 (0.02, 84.65)	1.15 (0.02, 84.65)	1.17 (0.02, 80.00)	1.15 (0.02, 84.65)	1.17 (0.02, 80.00)
0.35 (0.02, 5.94)	2.22 (0.03, 139.80)	0.89 (0.02, 53.10)	2.95 (0.04, 206.48)	2.06 (0.02, 129.49)	7.32 (0.07, 1383.51)	6.59 (0.08, 760.11)	2.61 (0.02, 316.08)	3.00 (0.04, 184.68)	EG Lu et al. [63]	0.85 (0.01, 48.92)	0.85 (0.01, 48.92)	0.85 (0.01, 48.92)	0.85 (0.01, 48.92)	0.85 (0.01, 48.92)

EG: experiment group; CG: control group; NR: not reported.

significant enrichment, while the pathways of neurodegeneration–multiple diseases pathway had the highest number of enriched genes among negatively regulated pathways.

3.8. PPINs construction and hub node analysis

By importing 90 drug-disease targets and genes into the STRING database with a parameter set at a highest confidence level of 0.9 and hiding disconnected nodes in the network, we eliminated seven nodes, resulting in PPINs of 83 genes (Figure 9). This PPINs result was then imported into Cytoscape software, generating a primary PPIN (Figure 10(A)). Using the CytoNCA plugin, we calculated the topological parameters and applied the first filtering, resulting in a core sub-network structure consisting of 31 nodes and 946 edges (Figure 10(B)). The median values for these parameters were as follows: Closeness: 0.39047619, Degree: 12, Eigenvector: 0.056804042, LAC: 5.714285714 and Network: 7.111111111. After the second round of filtering, the core sub-network structure was reduced to 13 nodes and 428 edges (Figure 10(C)), with the following parameter values: Closeness: 0.6, Degree: 20, Eigenvector: 0.152755275, LAC: 11.6 and Network: 12.97607656. The 13 hub genes in this final sub-network are CDKN1A, CASP3, STAT1, TP53, JUN, MAPK1, STAT3, MAPK3, MYC, HIF1A, FOS, MAPK14 and AKT1.

3.9. Results of molecular docking

We obtained three datasets from the Gene Expression Omnibus (GEO) database [66]. There were GSE116312, GSE27411 [67] and GSE54129. Differentially expressed genes (DEGs) were screened for normal gastric tissue and CAG using p value $< .05$, $|\text{fold change}| \geq 2$ [68] as the threshold (Figure 11(A)). One thousand and twenty-four DEGs were taken and intersected with 13 hub genes of the PPI network to obtain MAPK1 and MAPK3 (Figure 11(B)). The protein corresponding to the MAPK1 gene target was found to have the identifier P28482 in the UniProt database, while the MAPK3 gene corresponds to Q16644.

We have downloaded the 3D structures of both proteins from the PDB database and the 2D structures of the small molecule probes (naringenin, luteolin and quercetin) for three drugs from the PubChem database. Finally, we utilized software to perform molecular docking and visualization, resulting in four protein receptor-ligand docking results as presented in Table 8. The positions of residues with hydrogen bonds were

Table 4. Possible ranking of the effects of drug use in literature studies.

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Rank 12
CG: O + A + C	0	0	0	0	0	0	0.01	0.04	0.11	0.21	0.34	0.29
EG: Wang et al. [64]	0.07	0.08	0.09	0.1	0.1	0.14	0.1	0.09	0.07	0.06	0.05	0.05
EG: Wang [60]	0.01	0.03	0.04	0.06	0.07	0.09	0.12	0.12	0.13	0.11	0.09	0.13
EG: Wang et al. [65]	0.09	0.11	0.12	0.13	0.14	0.1	0.09	0.07	0.05	0.04	0.03	0.03
EG: Yan [62]	0.05	0.09	0.09	0.1	0.11	0.11	0.13	0.08	0.07	0.06	0.06	0.05
EG: Chen [52]	0.3	0.17	0.12	0.09	0.07	0.06	0.05	0.04	0.03	0.02	0.02	0.01
EG: Dai [53]	0.24	0.21	0.14	0.1	0.08	0.06	0.05	0.04	0.03	0.02	0.01	0.01
EG: Fu [54]	0.1	0.11	0.1	0.12	0.09	0.08	0.08	0.07	0.07	0.06	0.05	0.07
EG: Gao [55]	0.09	0.11	0.17	0.12	0.11	0.09	0.09	0.07	0.06	0.05	0.03	0.03
EG: Lü and Jia [56]	0.02	0.03	0.05	0.06	0.08	0.09	0.1	0.14	0.11	0.11	0.11	0.11
EG: Liu et al. [58]	0.01	0.03	0.04	0.05	0.07	0.08	0.09	0.11	0.12	0.15	0.12	0.13
EG: Lu et al. [63]	0.01	0.03	0.05	0.07	0.08	0.09	0.1	0.12	0.16	0.11	0.09	0.08

EG: experiment group; CG: control group; NR: not reported.

Bold values represent the probability ranking of the therapies.

visualized by PyMOL. The results reveal that naringenin luteolin and forms hydrogen bonds with MET-108 positions (Figure 11(C,D)), quercetin forms hydrogen bonds at the ASP-106, MET-108, ASN-154 and SER-153 positions (Figure 11(E)). For the MAPK3 gene, naringenin forms hydrogen bonds at the ASP-149 positions (Figure 11(F)).

4. Discussion

The significance of CAG in the progression of GC necessitates the implementation of proactive and effective pharmacological interventions during the early stages of prevention and treatment. In this study, we employed a meta-analysis to examine whether the addition of TCM formula showed higher efficacy in treating CAG in the experimental group. Our research revealed the following findings: (1) among the three clinical outcome measures (effective, significant, ineffective), the clinical efficacy in the experimental group surpassed that of the control group; (2) in terms of the four clinical outcome grades (recovery, effective, significant, ineffective), the experimental group exhibited a higher recovery rate and demonstrated significantly better results compared to using western medicine alone; (3) the incidence rate of adverse events was lower statistically. Therefore, we believe that the intervention of TCM formula holds advantages in treating CAG. The results of the NMA indicated that the combined use of TCM formula showed higher cumulative probability compared to the use of western medicine alone. These studies unequivocally demonstrate the wisdom of incorporating TCM in the treatment plans for CAG. However, it must be acknowledged that the aforementioned meta-analyses have certain limitations: First, due to considerations of medication costs, the

inclusion of studies may have exhibited poor methodological quality, with few experiments mentioning double-blinding. Second, there may be reporting bias due to inconsistent age distribution and disease duration among patients. Finally, CAG falls within the realm of chronic diseases, yet the intervention duration of the studies included is less than three months, making the treatment and follow-up periods insufficient to observe long-term clinical effects of intervention.

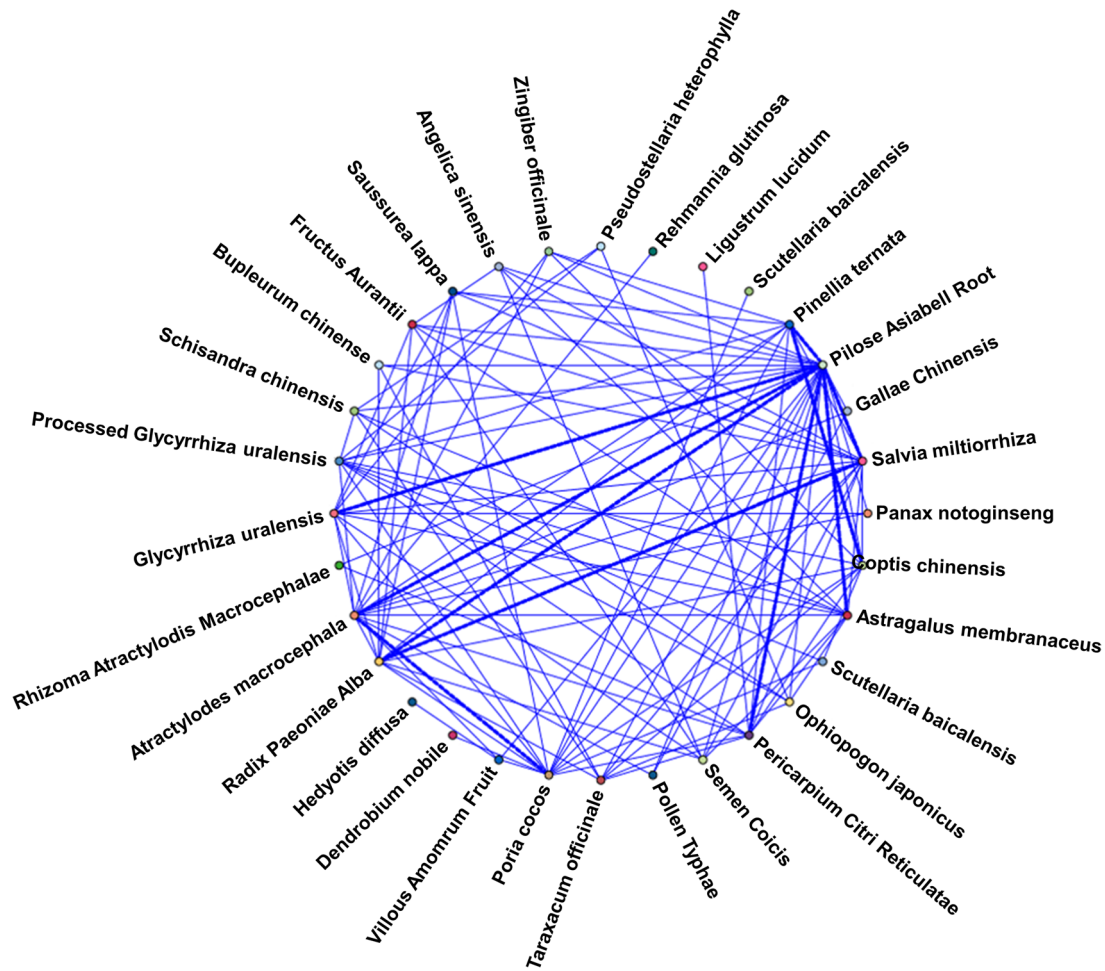
Utilizing association rule analysis, the following seven hub Chinese herbal medicines were identified: *Paeonia lactiflora*, *Atractylodes macrocephala*, *Pinellia ternata*, *Citrus reticulata*, *Codonopsis pilosula*, *Salvia miltiorrhiza* and *Coptis chinensis*. In TCM treatment, it is crucial to differentiate and treat diseases based on syndrome differentiation. For the spleen and stomach deficiency-cold type of CAG [52,63], *Salvia miltiorrhiza* has the effects of promoting blood circulation, removing blood stasis, regulating menstruation, alleviating pain and cooling the blood to resolve abscesses. *Coptis chinensis*, *Pinellia ternata* and *Codonopsis pilosula* have the effects of promoting blood circulation and invigorating Qi. *Atractylodes macrocephala* tonifies Qi, strengthens the spleen, and eliminates dampness. *Citrus reticulata* tonifies the spleen, warms the stomach, regulates Qi, and thereby relieves gastrointestinal symptoms, improves gastric mucosal circulation and enhances the body's immune system. For patients with blood stasis in stomach collaterals syndrome [60], *Codonopsis pilosula* and *Atractylodes macrocephala* are skilled at strengthening the spleen and consolidating the foundation, with the effects of invigorating Qi and promoting its smooth flow. *Pinellia ternata* can eliminate dampness, transform phlegm, reduce Rebellious Qi, stop vomiting and disperse masses. *Salvia miltiorrhiza* nourishes the blood, promotes blood circulation, removes blood stasis and generates

Table 5. The ingredients of each formula.

Study ID	Formulation name	Ingredients of each formula			
Chen [52]	Fu Wei Tang	<i>Astragalus membranaceus</i> (15 g) <i>Pinellia ternata</i> (15 g) Semen Coicis (20 g)	<i>Angelica sinensis</i> (15 g) <i>Salvia miltiorrhiza</i> (30 g) Fried <i>Phaseolus angularis</i> (10 g)	Fructus aurantii (15 g) <i>Coptis chinensis</i> (5 g) <i>Citrus reticulata</i> (15 g)	Prepared <i>Glycyrrhiza uralensis</i> (10 g) <i>Codonopsis pilosula</i> (10 g)
Dai [53]	Jia Wei Xiang Sha Liu Jun Zi Tang	<i>Pinellia ternata</i> (15 g) <i>Citrus reticulata</i> (15 g)	Fried <i>Phaseolus angularis</i> (10 g) Villous <i>Amomum Fruit</i> (15 g)	PORIA COCOS (15 g) <i>Saussurea lappa</i> (10 g)	<i>Codonopsis pilosula</i> (20 g) Fried <i>Atractylodes macrocephala</i> (15 g)
Fu [54]	Fu's formulas	Gallae Chinensis (10 g) <i>Pseudostellaria heterophylla</i> (20 g) <i>Schisandra chinensis</i> (15 g)	Raw <i>Rehmannia glutinosa</i> (10 g) Prepared <i>Glycyrrhiza uralensis</i> (6 g) <i>Ophiopogon japonicus</i> (15 g)	Pollen Typhae (10 g) Raw <i>Astragalus membranaceus</i> (30 g)	<i>Codonopsis pilosula</i> (10 g) Fried <i>Atractylodes macrocephala</i> (12 g)
Gao [55]	Wei Tong Ling Tang	<i>Ophiopogon japonicus</i> (10 g) <i>Angelica sinensis</i> (10 g) <i>Bupleurum chinense</i> (10 g) <i>Curcuma zedoaria</i> (9 g)	<i>Paeonia lactiflora</i> (10 g) Fructus aurantii (10 g) Villous <i>Amomum Fruit</i> (10 g) Trilliaceae (9 g)	<i>Schisandra chinensis</i> (10 g) Raw <i>Astragalus membranaceus</i> (10 g) <i>Hedyotis diffusa</i> (10 g) <i>Codonopsis pilosula</i> (15 g)	<i>Salvia miltiorrhiza</i> (10 g) <i>Taraxacum officinale</i> (10 g) Semen Coicis (9 g) <i>Glycyrrhiza uralensis</i> (10 g)
Lü and Jia [56]	Yi Wei Tang	<i>Paeonia lactiflora</i> (25 g) Squid bones (20 g) Rhizoma <i>Atractylodes Macrocephalae</i> (20 g)	<i>Taraxacum officinale</i> (15 g) <i>Gardenia jasminoides</i> (15 g) <i>Coptis chinensis</i> (20 g)	<i>Salvia miltiorrhiza</i> (20 g) <i>Corydalis yanhusuo</i> (10 g) Processed <i>Pinellia ternata</i> (10 g)	<i>Codonopsis pilosula</i> (15 g) <i>Bupleurum chinense</i> (10 g) <i>Citrus reticulata</i> (10 g)
Liu [57]	Yi Wei Tang	<i>Ophiopogon japonicus</i> (10 g) <i>Taraxacum officinale</i> (15 g) <i>Pseudostellaria heterophylla</i> (15 g)	<i>Scutellaria baicalensis</i> (10 g) Prepared <i>Glycyrrhiza uralensis</i> (6 g) <i>Ligustrum lucidum</i> (4 g)	<i>Schisandra chinensis</i> (15 g) <i>Coptis chinensis</i> (6 g) PORIA COCOS (15 g)	<i>Dendrobium nobile</i> (15 g) <i>Citrus reticulata</i> (20 g)
Liu et al. [58]	Jian Pi Yi Wei Fu Fang Tang Ji	<i>Codonopsis pilosula</i> (15 g) Processed <i>Pinellia ternata</i> (10 g) <i>Salvia miltiorrhiza</i> (8 g)	PORIA COCOS (12 g) <i>Saussurea lappa</i> (10 g) <i>Zingiber officinale</i> (8 g)	<i>Paeonia lactiflora</i> (10 g) <i>Coptis chinensis</i> (6 g) <i>Glycyrrhiza uralensis</i> (8 g)	<i>Atractylodes macrocephala</i> (12 g) <i>Centella asiatica</i> (10 g)
Lu et al. [63]	Wen Zhong Fu Yuan Cu Yu Tang	<i>Citrus reticulata</i> (10 g) <i>Astragalus membranaceus</i> (15 g) NotoPanax ginseng Powder (3 g)	<i>Cinnamomum cassia</i> (10 g) <i>Codonopsis pilosula</i> (10 g) Prepared <i>Glycyrrhiza uralensis</i> (6 g)	<i>Zingiber officinale</i> (15 g) <i>Ligustrum lucidum</i> (10 g)	Rhizoma <i>Atractylodes Macrocephalae</i> (10 g) <i>Atractylodes macrocephala</i> (10 g)
Study ID	Formulation name	Ingredients of each formula			
Wang et al. [64]	Hua Zhuo Jie Du Fang	PORIA COCOS (15 g) <i>Hedyotis diffusa</i> (15 g) <i>Scutellaria baicalensis</i> (12 g)	Villous <i>Amomum Fruit</i> (15 g) <i>Cyperus rotundus</i> (15 g) <i>Coptis chinensis</i> (12 g)	<i>Elettaria cardamomum</i> (15 g) <i>Agastache rugosa</i> (12 g)	<i>Scutellaria baicalensis</i> (15 g) <i>Elettaria cardamomum</i> (12 g)
Wang [60]	Yi Wei Huo Luo Jing Yan Fang	Fried <i>Codonopsis pilosula</i> (20 g) <i>Curcuma zedoaria</i> (15 g) <i>Paeonia lactiflora</i> (30 g) <i>Salvia miltiorrhiza</i> (10 g) NotoPanax Ginseng Powder (6 g)	Fried <i>Atractylodes macrocephala</i> (15 g) Persicae Semen (15 g) Pollen Typhae (10 g) <i>Saussurea lappa</i> (10 g) <i>Carthamus tinctorius</i> (5 g)	Fructus aurantii (15 g) Semen Coicis (15 g) Gallae Chinensis (10 g) <i>Nelumbo nucifera</i> (10 g)	<i>Scutellaria baicalensis</i> (15 g) White PORIA COCOS (30 g) Ginger Processed <i>Pinellia</i> (10 g) <i>Glycyrrhiza uralensis</i> (10 g)
Wang et al. [65]	Hui Chun Jian Wei Tang	PORIA COCOS (15 g) Raw <i>Rehmannia glutinosa</i> (15 g) <i>Scrophularia ningpoensis</i> (10 g)	<i>Polygonatum odoratum</i> (15 g) <i>Dendrobium nobile</i> (15 g) Radix <i>Rehmanniae</i> Glutinosae (10 g)	<i>Glehnia littoralis</i> (15 g) Villous <i>Amomum Fruit</i> (10 g)	Fried <i>Atractylodes macrocephala</i> (15 g) Rhizoma <i>Atractylodes</i> (10 g)
Yan [62]	Ban Xia Xie Xin Tang Jia Jian	<i>Pinellia ternata</i> (12 g) Prepared <i>Glycyrrhiza uralensis</i> (9 g)	<i>Scutellaria baicalensis</i> (9 g) <i>Coptis chinensis</i> (3 g)	<i>Zingiber officinale</i> (9 g) Fructus <i>Jujubae</i> (4)	<i>Panax ginseng</i> (9 g) Semen Coicis (9 g)

Table 6. Standardization of Chinese medicine.

Original name	Standard name	Original name	Standard name	Original name	Standard name
Raw <i>Rehmannia glutinosa</i>	<i>Rehmannia glutinosa</i>	Squid bones	<i>Sepia esculenta</i>	NotoPanax ginseng Powder	NotoPanax ginseng
Fried <i>Atractylodes macrocephala</i>	<i>Atractylodes macrocephala</i>	White Poria Cocos	Poria Cocos	Raw <i>Astragalus membranaceus</i>	<i>Astragalus membranaceus</i>
Fried <i>Phaseolus angularis</i>	<i>Phaseolus angularis</i>	Processed <i>Pinellia ternata</i>	<i>Pinellia ternata</i>	<i>Corydalis yanhussuo</i>	<i>Corydalis yanhussuo</i>
Fried <i>Codonopsis pilosula</i>	<i>Codonopsis pilosula</i>	Ginger Processed <i>Pinellia</i>	<i>Pinellia ternata</i>		

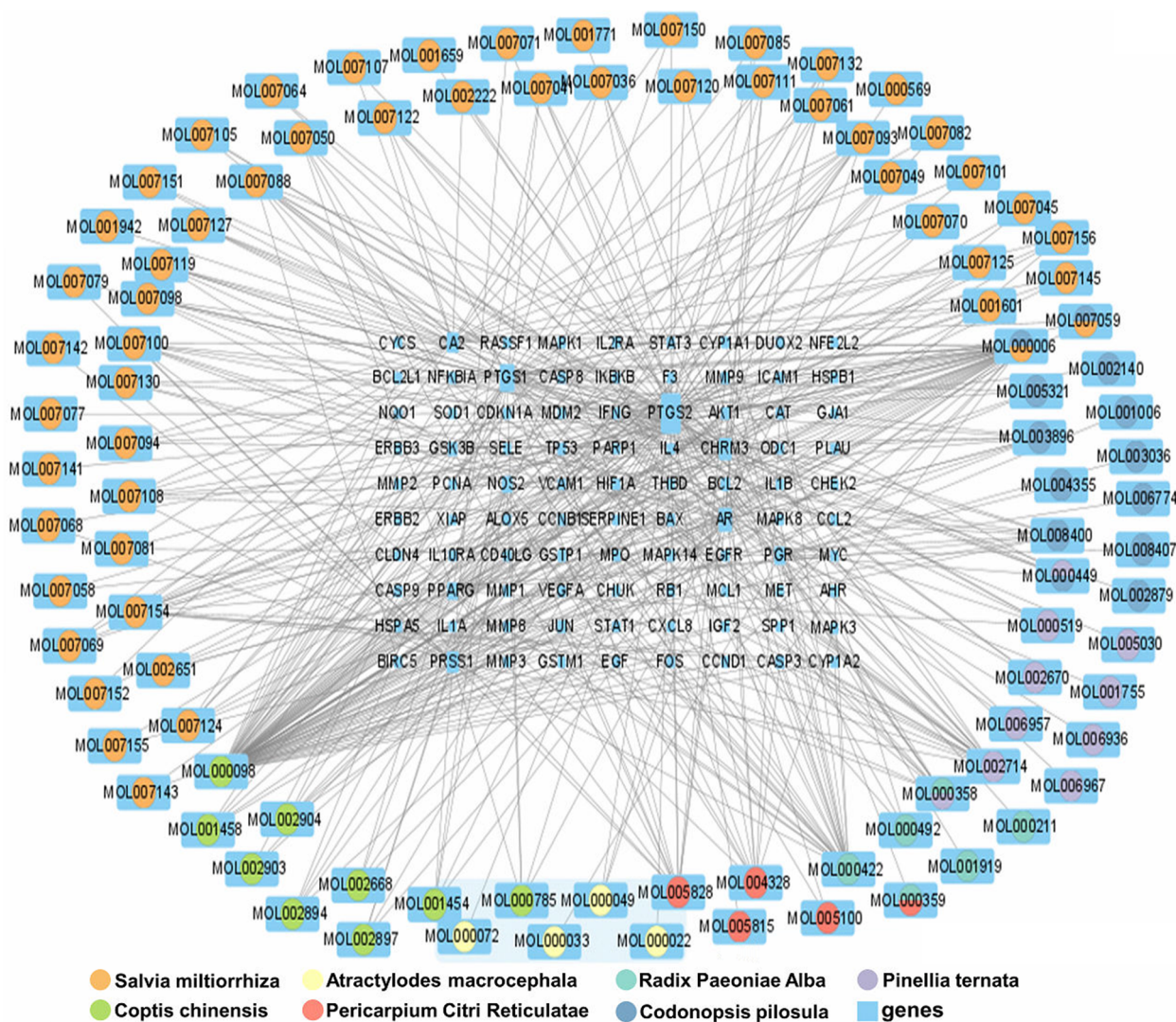
**Figure 6.** Associated network of hub Chinese medicines.

new blood. *Paeonia lactiflora* has the function of soothing the liver, nourishing the blood, and restraining Yin. For patients with both Qi and Yin deficiency [61], *Atractylodes macrocephala* can tonify the spleen, replenish Qi and eliminate dampness. By docking the active ingredients of Chinese herbs with the disease gene targets of CAG, the regulatory network of Chinese herbal compound can be observed for their interactions.

We have identified 13 hub genes through the exploration of the PPINs of drug targets and genes. In addition, we have selected the DEGs MAPK1 and MAPK3 in normal and CAG tissues. MAPK1 is a factor that is important in the value-added and metastasis of GC [69], MAPK3 expression is an independent prognostic marker in GC patients [70], which aligns with the findings of our KEGG analysis, where the most enriched pathways are associated with cancer.

Table 7. Chinese medicine association rule analysis.

Previous items	Back items	Support count	Support (%)	Confidence (%)	Lift
<i>Codonopsis pilosula</i>	<i>Atractylodes macrocephala</i>	6	50.00	83.33	1.25
<i>Coptis chinensis</i>	<i>Pinellia ternata</i>	5	41.67	80.00	1.60
<i>Codonopsis pilosula</i>	<i>Pinellia ternata</i>	5	41.67	80.00	1.20
<i>Codonopsis pilosula</i>	<i>Citrus reticulata</i>	5	41.67	80.00	1.20
<i>Paeonia lactiflora</i>	<i>Salvia miltiorrhiza</i>	5	41.67	80.00	2.40
<i>Codonopsis pilosula</i>	<i>Salvia miltiorrhiza</i>	5	41.67	100.00	1.50
<i>Paeonia lactiflora</i>	<i>Salvia miltiorrhiza</i> and <i>Codonopsis pilosula</i>	5	41.67	80.00	2.40
<i>Codonopsis pilosula</i>	<i>Astragalus membranaceus</i>	4	33.33	100.00	1.50
<i>Codonopsis pilosula</i>	<i>Glycyrrhiza uralensis</i>	4	33.33	100.00	1.50
<i>Salvia miltiorrhiza</i>	<i>Paeonia lactiflora</i>	4	33.33	100.00	2.40
<i>Codonopsis pilosula</i>	<i>Paeonia lactiflora</i>	4	33.33	100.00	1.50
<i>Codonopsis pilosula</i>	<i>Paeonia lactiflora</i> and <i>Salvia miltiorrhiza</i>	4	33.33	100.00	1.50
<i>Salvia miltiorrhiza</i>	<i>Paeonia lactiflora</i> and <i>Codonopsis pilosula</i>	4	33.33	100.00	2.40

**Figure 7.** Interaction network of hub Chinese medicines targets and genes.

The PI3K-Akt signalling pathway was shown to inhibit precancerous lesions of GC in *in vitro* experiments [64]. The MAPK signalling pathway also plays an

important role in the progression of GC [71,72]. Therefore, it is reasonable to hypothesize that targeting these two genes may impede the progression of

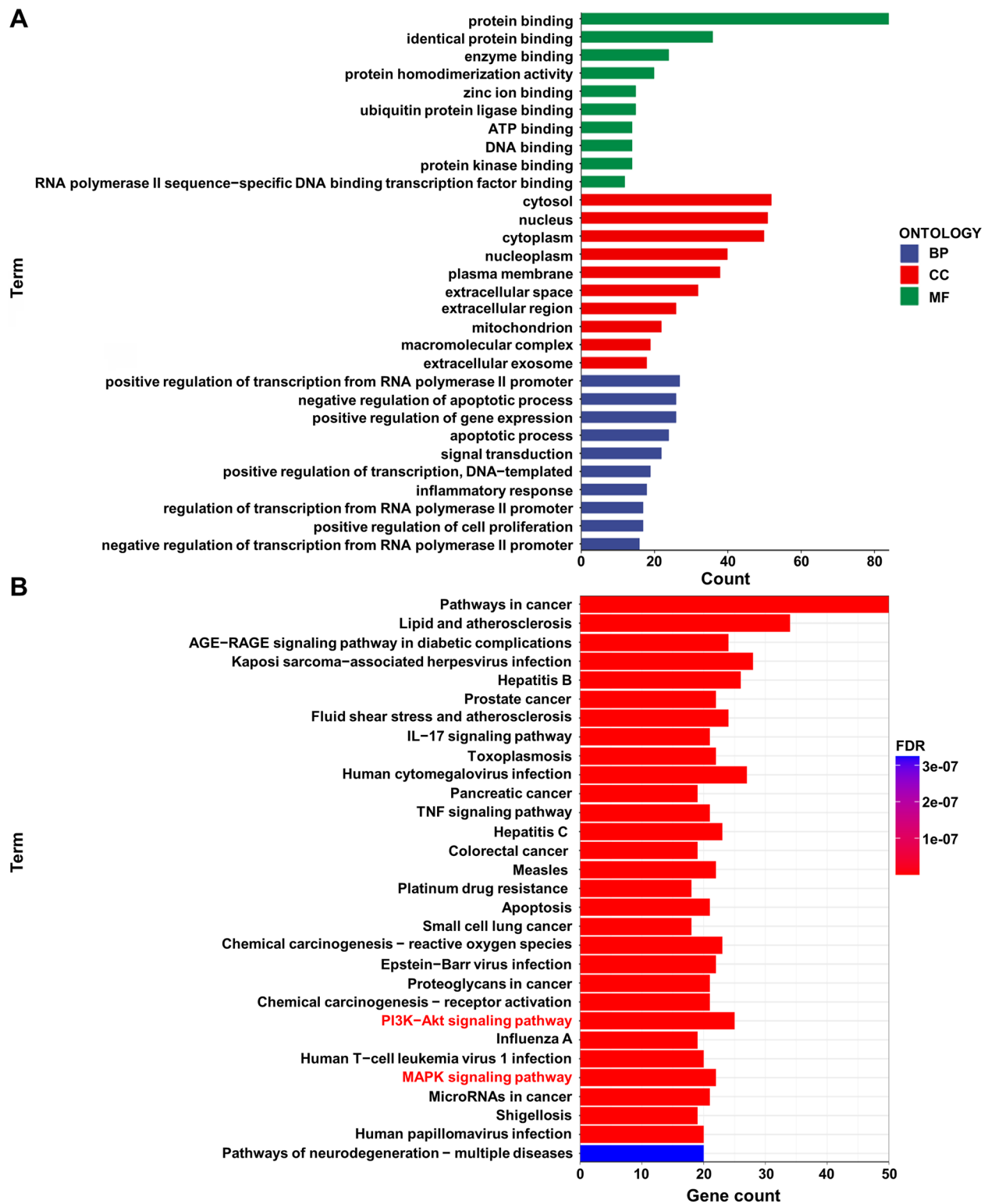


Figure 8. Enrichment analysis of 90 target genes for chronic atrophic gastritis (CAG). (A) Gene Ontology (GO) analysis. (B) Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. Red font indicates enriched pathways associated with CAG disease.

CAG to GC. In GO analysis, the targeted genes are predominantly enriched in protein binding, indicating the binding of drugs entering the bloodstream with plasma proteins.

Quercetin not only demonstrates significant anti-GC activity [65]. Additionally, it demonstrates anti-inflammatory properties by restraining the expression of matrix metalloproteinase-9, induced by tumour

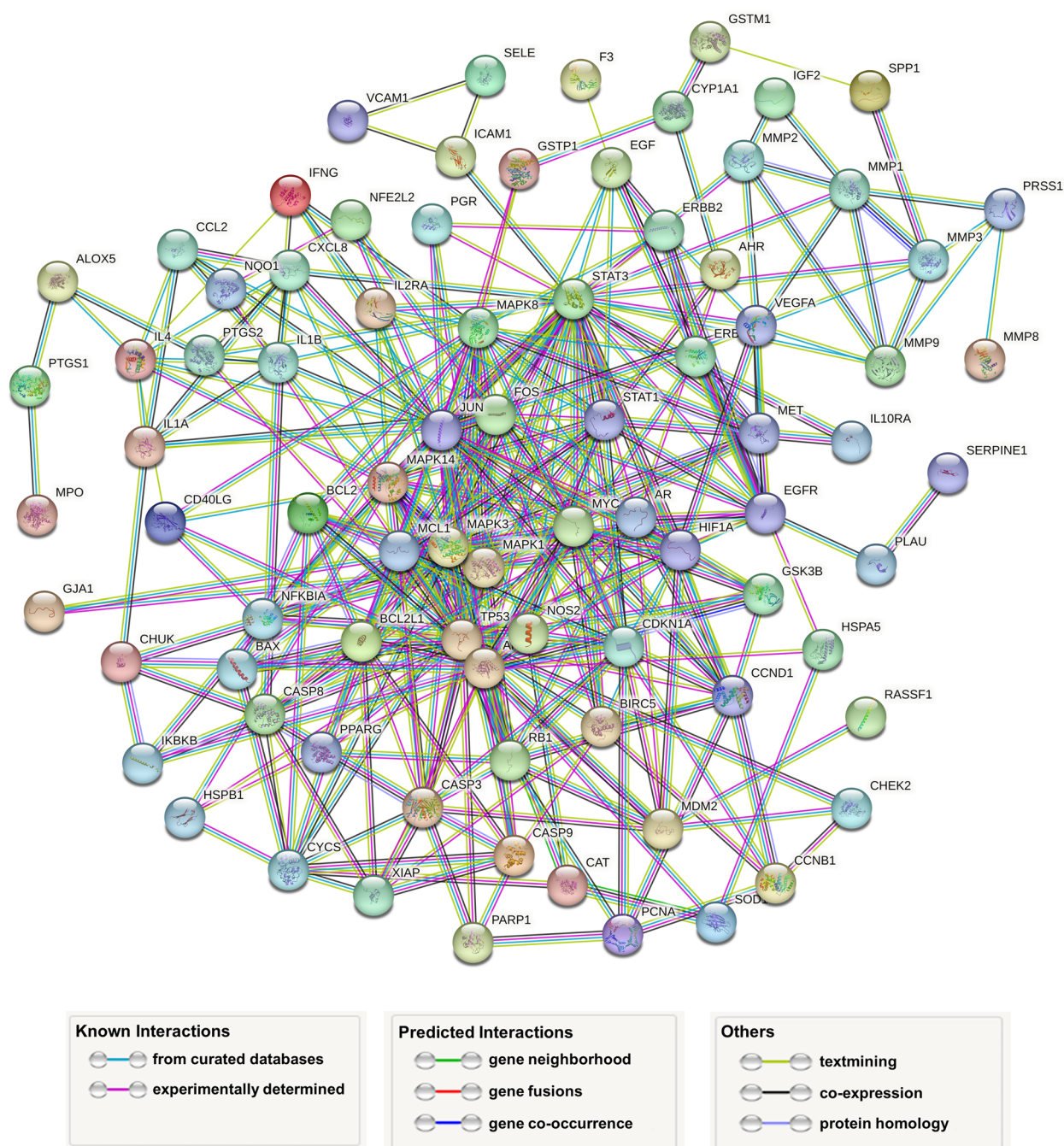


Figure 9. Protein-protein interaction networks (PPINs) of 83 target genes for CAG.

necrosis factor- α -induced, in normal human gastric epithelial cells [73]. Luteolin regulates GC cells through multiple signalling pathways [74], exhibiting anti-proliferative and chemo sensitizing effects [75]. Naringenin has been shown to have the potential to treat unused types of cancer [76]. Based on the summarized published studies, we have found that the drug activities revealed by our research exhibit

anti-proliferative effects in GC, which is a crucial process in the development of GC. Therefore, we boldly propose the hypothesis of incorporating active molecules into TCM formulations, particularly in the three herbs: *Coptis chinensis* (Huanglian), *Codonopsis pilosula* (Dangshen) and *Citrus reticulata* (Chenpi). Alternatively, these herbal plants can be utilized to extract effective components for new drug design and development.

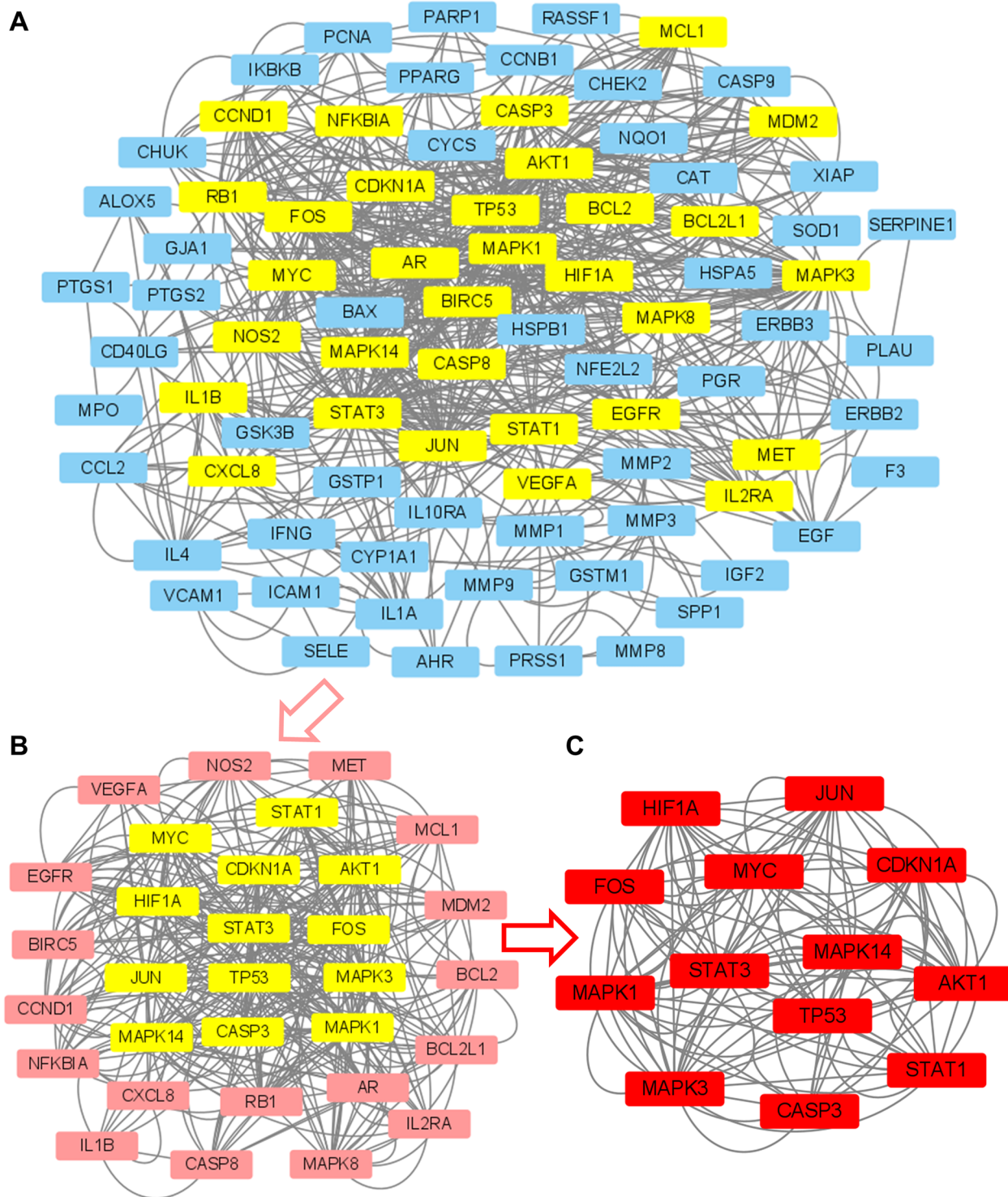


Figure 10. PPINs hub gene analysis. (A) PPINs of 83 target genes for chronic atrophic gastritis. (B) Results of the first analysis of PPINs hub genes. (C) Final analysis results of PPINs hub genes.

Of course, these ideas need to undergo a series of experiments, including cell, animal and clinical studies.

5. Conclusions

In conclusion, this research is based on meta-analysis studies and utilizes NP techniques to explore the

potential mechanisms of action of hub herbal formulae in treating CAG. The results demonstrate that incorporating herbal formulae into the clinical treatment regimen for CAG yields better clinical outcomes compared to using Western medicine alone. Furthermore, it is elucidated that the herbal formulae primarily exert their effects through the interaction of

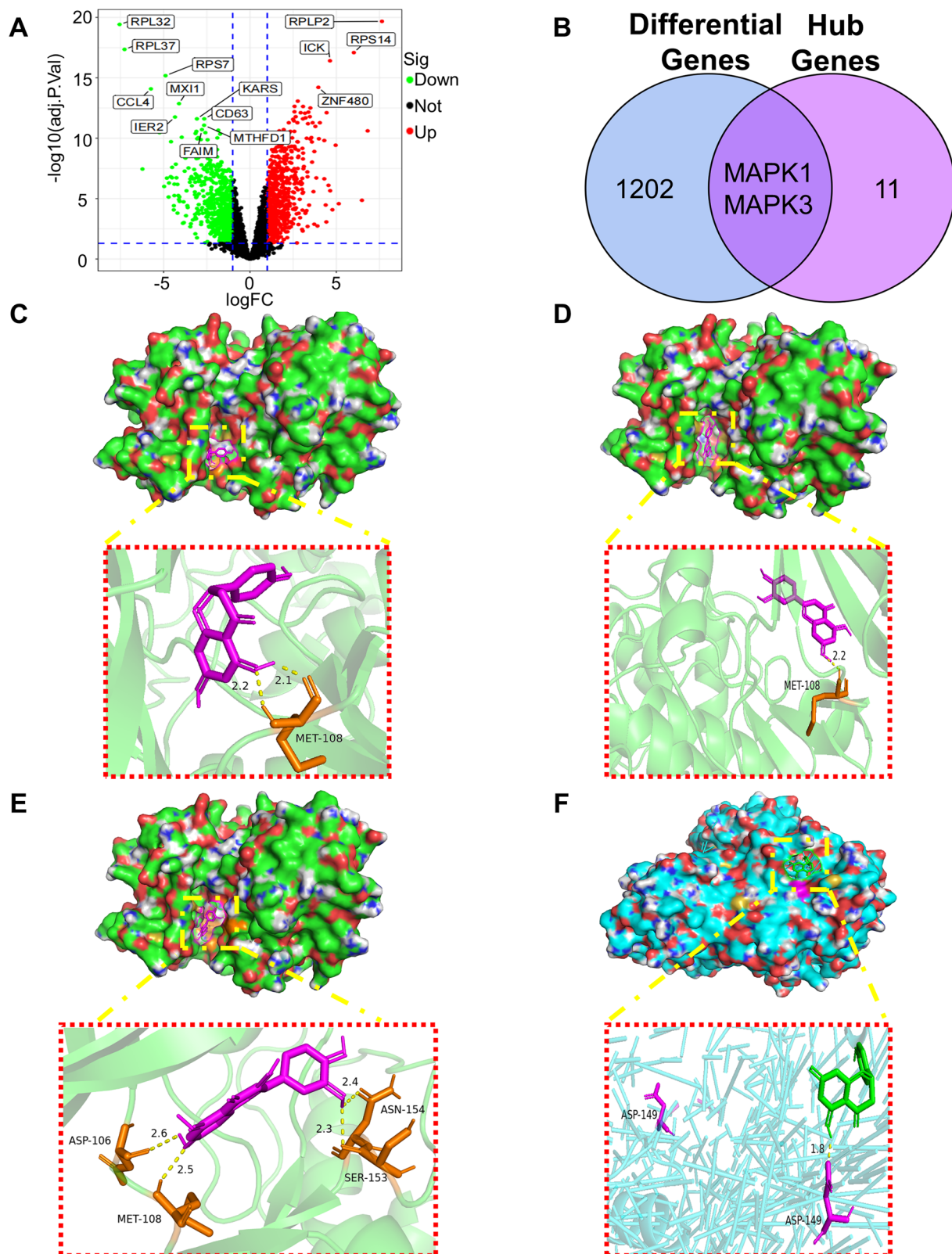


Figure 11. Protein receptor-small molecule ligand docking of two differentially expressed genes (DEGs). (A) Volcano plot with differentially expressed genes (DEGs) between normal stomach and chronic atrophic gastritis tissue. (B) Venn diagram showing the intersecting hub genes of 1204 DEGs and 13 hub genes. (C) MAPK1 (P28482) and naringenin. (D) MAPK1 (P28482) and luteolin. (E) MAPK1 (P28482) and quercetin. (F) MAPK3 (Q16644) and naringenin.

Table 8. Binding energy between main active components and key protein targets (kJ/mol).

Name of Chinese medicine	Number	Active ingredient	Protein name	Binding energy (kJ/mol)
<i>Citrus reticulata</i> (Chenpi)	MOL004328	Baicalein	MAPK1	−6.7
<i>Codonopsis pilosula</i> (Dangshen)	MOL000006	Quercetin	MAPK1	−10.2
<i>Coptis chinensis</i> (Huanglian)	MOL000098	Tanshinone Ila	MAPK1	−8.7
<i>Citrus reticulata</i> (Chenpi)	MOL004328	Kaempferol	MAPK3	−7.0

three active molecular components with two DEGs. Finally, several potential targets for CAG treatment and their non-covalent interactions are identified, offering insights into the pathogenesis and providing new strategies for clinical management.

Author contributions

The idea, formal analysis, methodology and writing – original draft from J.Weng. The data curation, validation and visualization from X.F. Wu, P. Shao and X.P. Liu. The supervision, project administration, funding acquisition and writing – review and editing from C.X. Wang. All authors reviewed the manuscript.

Ethical approval

The studies we searched were taken from publicly available databases. The patients involved in the studies have received ethical approval. Our studies are based on published research, so there are no ethical issues or other conflicts of interest.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The studies for meta-analysis were all searchable in the databases mentioned in the study.

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