Evidence and Characteristics of Traditional Chinese Medicine for Coronary Heart Disease Patients With Anxiety or Depression: A Meta-Analysis and Systematic Review

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Aims: The objective of this study was to assess the efficacy and potential mechanisms of Chinese herbal medicine (CHM) for treating coronary heart disease (CHD) patients with anxiety or depression.

Methods: A systematic literature search was performed. Screening studies, extracting data, and assessing article quality were carried out independently by two researchers. The active ingredients of CHM for the treatment of CHD with anxiety or depression were analyzed by the network pharmacology, and the main potential mechanisms were summarized by the database of Web of Science.

Results: A total of 32 studies were included. The results showed that compared with the blank control groups, CHM was more beneficial in treating anxiety or depression in patients with CHD [anxiety: OR = 3.22, 95% CI (1.94, 5.35), \( p < 0.00001 \), \( I^2 = 0\% \); depression: OR = 3.27, 95% CI (1.67, 6.40), \( p = 0.0005 \), \( I^2 = 0\% \)], and the efficacy of CHM was not inferior to that of Western medicine (WM) [anxiety: OR = 1.58, 95%CI (0.39, 6.35), \( p = 0.52 \), \( I^2 = 67\% \); depression: OR = 1.97, 95%CI (0.73, 5.28), \( p = 0.18 \), \( I^2 = 33\% \)]. Additionally, CHM also showed a significant advantage in improving angina stability (AS) in CHD patients with anxiety or depression compared with blank groups [anxiety: SMD = 0.55, 95% CI (0.32, 0.79), \( p < 0.00001 \), \( I^2 = 0\% \); depression: \( p = 0.004 \) and WM groups [anxiety: SMD = 1.14, 95%CI (0.80, 1.47), \( p < 0.00001 \), \( I^2 = 0\% \); depression: SMD = 12.15, 95%CI (6.07, 18.23), \( p < 0.0001 \), \( I^2 = 0\% \)]. Angina frequency (AF) and electrocardiogram (ECG) analysis after using CHM demonstrated similar trends. Based on the network pharmacology, quercetin, kaempferol, luteolin, beta-sitosterol, puerarin, stigmasterol, isorhamnetin, baicalein, tanshinone IIa, and nobiletin were most closely and simultaneously related to the pathological targets of CHD, anxiety, and depression. The main underlying

Abbreviations: AF, angina frequency; AS, angina stability; CHD, coronary heart disease; CHM, Chinese herbal medicine; ECG, electrocardiogram; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; TCM, traditional Chinese medicine; WM, Western medicine.
mechanisms might involve anti-damage/apoptosis, anti-inflammation, antioxidative stress, and maintaining neurotransmitter homeostasis.

Conclusion: CHM exhibited an obvious efficacy in treating CHD patients with anxiety or depression, especially for improving the symptom of angina pectoris. The most active compounds of CHM could simultaneously act on the pathological targets of CHD, anxiety, and depression. Multiple effective components and multiple targets were the advantages of CHM compared with WM.

Keywords: coronary heart disease, anxiety, depression, Chinese herbal medicine, efficacy

INTRODUCTION

Anxiety and depression are commonly found in patients with coronary heart disease (CHD), and the prevalence of CHD complicated with anxiety or depression is 21 and 13%, respectively (Daniel et al., 2018). Percutaneous coronary intervention (PCI) treatment increases the prevalence of anxiety and depression symptoms in CHD patients (Gu et al., 2016). Accumulating evidence has demonstrated that anxiety and depression are associated with the increased risk of CHD (Roest et al., 2010; Lederbogen and Ströhle, 2012; Giannarelli et al., 2017), and the use of anxiolytics or antidepressants is necessary for CHD patients with anxiety or depression. However, current drugs for emotional disorders, such as serotonin-specific reuptake inhibitors (SSRIs) and benzodiazepines, usually exert their effects after several weeks of treatment, with some unwanted side effects (Lakhan and Vieira, 2010; Ko et al., 2020). Thus, a more optimized treatment option is needed.

As an important treatment strategy, Chinese herbal medicine (CHM) is characterized by multiple components, multiple targets, and multiple channels. It has been verified that CHM had a satisfactory efficacy and fewer adverse effects on CHD with anxiety or depression (Liu and Qin, 2016; Ma et al., 2019). However, due to poor methodological quality and limited sample size, the evidence to support the effect of CHM on CHD with anxiety or depression is still weak. Moreover, the possible underlying mechanisms via which CHM treats CHD patients with anxiety or depression is still needed to be clarified. Therefore, by comprehensively analyzing published studies, a meta-analysis and systematic review were performed to assess the efficacy of CHM and the underlying mechanisms in the treatment of CHD patients with anxiety or depression, which might provide an essential clinical value for the disease management in the future.

METHODS

This meta-analysis and systematic review were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (Moher et al., 2009).

Information Source and Search Strategy

Published articles were searched comprehensively in electronic databases (PubMed, Web of Science, Embase, Cochrane, China National Knowledge Infrastructure, WanFang Data, VIP Database, and SinoMed) up to October 2021. “Coronary disease OR coronary artery disease OR myocardial infarction OR acute coronary syndrome” AND “anxiety OR depression OR depressive disorder” AND “traditional Chinese medicine OR herbal medicine” AND “randomized controlled trial” and their common synonyms were used for the searching strategy. The detailed searching strategy was shown in supplementary material.

Inclusion and Exclusion Criteria

The inclusion criteria of the articles were as follows: 1) all participants met the diagnostic criteria of CHD with anxiety or depression; 2) the number of subjects in each group was not less than 30; 3) CHD patients in control and trial groups received basic treatments, with antianxiety or antidepressant Western medicine (WM) used (WM groups) or not (blank control groups) in control groups, and oral CHM was used in trial groups; 4) Hamilton anxiety scale (HAMA) and Hamilton depression scale (HAMD) were used to evaluate patients’ anxiety and depression, respectively; and 5) the efficacy index of CHD included one of the following: ① electrocardiogram (ECG); ② angina stability (AS) and angina frequency (AF) come from Seattle Angina Questionnaire; and ③ traditional Chinese medicine syndrome (TCMS) score.

The exclusion criteria of the studies were as follows: 1) Nonclinical study and irrelevant research; 2) CHM was used in control groups, antianxiety or antidepressant WM was used in trial groups; 3) articles with incomplete data; 4) articles more than one high-risk item; and 5) review, meta-analysis, and conference abstracts.

Study Selection and Data Extraction

Retrieved articles were assessed independently by two researchers (YT and SL) according to the inclusion and exclusion criteria. Data, including first authors’ name, year of publication, sample size, age, gender, diseases, therapeutic regimen, final duration of treatment, dosage form and compositions of TCM, and the outcome index, were extracted from the included studies. The CHM was reported in scientific name, not the Latin name in pharmacopeia to avoid confusion (Table 1) (Rivera et al., 2014). Any disagreements were resolved by discussing and consulting with corresponding authors (MZ and XW).

Study Quality Assessment

Two authors (YL and YT) independently assessed the methodological quality according to the Cochrane risk-of-bias tool (Zhang K. J. et al., 2019). Sufficient domain information in relevant studies was considered as low risk, inadequate
| Study (year) | Formulation or patented drugs | Source | Compositions | Quality control reported? | Chemical analysis reported? |
|-------------|------------------------------|--------|--------------|---------------------------|----------------------------|
| Anxiety     |                              |        |              |                           | N                          |
| Mo 2016 Mo et al. (2016) | Wuling capsule | Zhejiang Zoli Pharmaceutical Company | Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizeae radix et rhizoma] 15 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 15 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 15 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydis rhizoma] 15 g, Platycodon grandiflorus (Jacq.) A.DC. [Campanulaceae; Platycodon radix] 10 g, Curcumae aromaticae Salisb. [Zingiberaceae; Curcumae radix] 10 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 10 g, Paonia lactiflora Pall. [Paonieae; Paeniae radix alba] 20 g, Albiæ japonicae Durazz. [Fabaceae; Albiæ cortex] 15 g, Lilium lancifolium Thunb. [Liliaceae; Lilii bulb] 20 g, Reynoutriae multiflora [Thunb.] Moldenke [Polygonaceae; Polygonyi multiflori caulis] 20 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 10 g | Y—Prepared according to NMPA: Z199900—18 | N                          |
| Guo 2017 Guo (2017) | Shenchai Shuxin decoction | Pharmacy of The First Affiliated Hospital of Heilongjiang University of TCM | Xylaria nigripes (KL.) Sacc [Xylaria; Wuling mycelia] | N                          | N                          |
| Li 2017 Li G. Y. et al. (2017) | Tiaogan Jianpi decoction | — | Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizeae radix et rhizoma] 15 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Paonia anomala subsp. veitchii (Lynch) D.Y.Hong and K.Y.Pan [Paonieae; Paeniae radix rubra] 10 g, Atractylodes macrocephala Koehn. [Asteraceae; Atractylodis macrocephalae rhizoma] 20 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 20 g, Pseudostellaria heterophylla (Miq.) Pax [Caryophyllaceae; Pseudostellariae radix] 15 g, Neolitsea cassinia (L.) Kosterm. [Lauraceae; Cinnamomi ramulus] 10 g, Alliun chinensis G.Don [Amaryllidaceae; Alii macrostemonis bulb] 10 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 20 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 10 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydis rhizoma] 10 g, Phereutis asperlifolia (E. Perrier) [Megascolecidae; Phereutis] 10 g, Schisandrae chinensis (Turcz.) Baill. [Schisandraceae; Schisandraceae chinensis fructus] 5 g, Mentha canadensis L. [Lamiaceae; Menthae hapiocalycis herba] 10 g, Gardenia jasminoides J.Ellis [Rubiacae; Gardeniae fructus] 5 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 10 g | N                          | N                          |
| Qi 2017 Qi and Song (2017) | Jieyu Tongmai granule | — | Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizeae radix et rhizoma] 15 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Paonia anomala subsp. veitchii (Lynch) D.Y.Hong and K.Y.Pan [Paonieae; Paeniae radix rubra] 10 g, Atractylodes macrocephala Koehn. [Asteraceae; Atractylodis macrocephalae rhizoma] 20 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 20 g, Pseudostellaria heterophylla (Miq.) Pax [Caryophyllaceae; Pseudostellariae radix] 15 g, Neolitsea cassinia (L.) Kosterm. [Lauraceae; Cinnamomi ramulus] 10 g, Alliun chinensis G.Don [Amaryllidaceae; Alii macrostemonis bulb] 10 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 20 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 10 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydis rhizoma] 10 g, Phereutis asperlifolia (E. Perrier) [Megascolecidae; Phereutis] 10 g, Schisandrae chinensis (Turcz.) Baill. [Schisandraceae; Schisandraceae chinensis fructus] 5 g, Mentha canadensis L. [Lamiaceae; Menthae hapiocalycis herba] 10 g, Gardenia jasminoides J.Ellis [Rubiacae; Gardeniae fructus] 5 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 10 g | N                          | N                          |
| Zhang 2017 Zhang et al. (2017) | Wuling capsule | Zhejiang Zoli Pharmaceutical Company | Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizeae radix et rhizoma] 15 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Paonia anomala subsp. veitchii (Lynch) D.Y.Hong and K.Y.Pan [Paonieae; Paeniae radix rubra] 10 g, Atractylodes macrocephala Koehn. [Asteraceae; Atractylodis macrocephalae rhizoma] 20 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 20 g, Pseudostellaria heterophylla (Miq.) Pax [Caryophyllaceae; Pseudostellariae radix] 15 g, Neolitsea cassinia (L.) Kosterm. [Lauraceae; Cinnamomi ramulus] 10 g, Alliun chinensis G.Don [Amaryllidaceae; Alii macrostemonis bulb] 10 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 20 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 10 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydis rhizoma] 10 g, Phereutis asperlifolia (E. Perrier) [Megascolecidae; Phereutis] 10 g, Schisandrae chinensis (Turcz.) Baill. [Schisandraceae; Schisandraceae chinensis fructus] 5 g, Mentha canadensis L. [Lamiaceae; Menthae hapiocalycis herba] 10 g, Gardenia jasminoides J.Ellis [Rubiacae; Gardeniae fructus] 5 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 10 g | Y—Prepared according to NMPA: Z199900—18 | N                          |
| Qin 2018 Qin (2018) | Yuxin decoction | — | Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizeae radix et rhizoma] 15 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Paonia anomala subsp. veitchii (Lynch) D.Y.Hong and K.Y.Pan [Paonieae; Paeniae radix rubra] 10 g, Atractylodes macrocephala Koehn. [Asteraceae; Atractylodis macrocephalae rhizoma] 20 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 20 g, Pseudostellaria heterophylla (Miq.) Pax [Caryophyllaceae; Pseudostellariae radix] 15 g, Neolitsea cassinia (L.) Kosterm. [Lauraceae; Cinnamomi ramulus] 10 g, Alliun chinensis G.Don [Amaryllidaceae; Alii macrostemonis bulb] 10 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 20 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 10 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydis rhizoma] 10 g, Phereutis asperlifolia (E. Perrier) [Megascolecidae; Phereutis] 10 g, Schisandrae chinensis (Turcz.) Baill. [Schisandraceae; Schisandraceae chinensis fructus] 5 g, Mentha canadensis L. [Lamiaceae; Menthae hapiocalycis herba] 10 g, Gardenia jasminoides J.Ellis [Rubiacae; Gardeniae fructus] 5 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 10 g | N                          | N                          |

(Continued on following page)
TABLE 1 | (Continued) Compositions of formulation and patented drugs.

| Study (year) | Formulation or patented drugs | Source | Compositions | Quality control reported? | Chemical analysis reported? |
|--------------|-------------------------------|--------|--------------|---------------------------|-----------------------------|
| Wang 2018    | Chaihu Longgu Muli granule    | Beijing Kangrentang Pharmaceutical Co. LTD. | fructus] 12 g, Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosae semen] 12 g, Crataegus pinnatifida Bunge [Rosaceae; Crataegi fructus] 12 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Trichosanthis pericarpium] 12 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 9 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 12 g, Os Draconis 15 g, Ostraea gigas Thunberg [Ostraeae; Ostreae concha] 15 g, Scutellaria baicalensis Georgi [Lamiaceae; Scutellariae radix] 9 g, Zingiber officinale Roscoe [Zingiberaceae; Zingiberis rhizoma recens] 9 g, Codonopsis pilosula (Franch.) Nannf. [Campanulaceae; Codonopsis radix] 9 g, Neolitsea cassia (L.) Kosterm. [Lauraceae; Cinnamomum ramulus] 9 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 15 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 9 g, Rheum palmatum L. [Polygonaceae; Rhei radix et rhizoma] 9 g, Pteris multifida (Dunk.) Pteridieria; Margantia] 15 g, Ziziphus jujuba Mill. [Rhamnaceae; Jujubae fructus] 10 g | N | N |
| Chen 2019    | Chaihu Jieyu decoction       | —      | Citrus × aurantium L. [Rutaceae; Citri reticulatae pericarpium] 15 g, Ligusticum chinense Hort. [Apiaceae; Chuanxiong rhizoma] 15 g, Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma] 15 g, Citrus × aurantium L. [Rutaceae; Aurantii fructus] 10 g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 10 g, Angelica sinensis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix] 10 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] 15 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumae radix] 15 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydalis rhizoma] 15 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Trichosanthis fructus] 15 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 15 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma], Astragalus mongholicus Bunge [Fabaceae; Astragali radix], Angelica sinensis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], Rehmannia glutinosa (Gaertn.) DC. [Orobancheaeae; Rehmanniae radix praeparata], Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba], Ligusticum chinense Hort. [Apiaceae; Chuanxiong rhizoma], Codonopsis pilosula (Franch.) Nannf. [Campanulaceae; Codonopsis radix], Os Draconis, Ostraea gigas Thunberg [Ostraeae; Ostreae concha], Bupleurum chinense DC. [Apiaceae; Bupleuri radix], Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma], Albizia julibrissin Durazz. [Fabaceae; Albiziae flos], Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] | N | N |
| Dong 2019    | Danqi Anshen decoction       | Heilongjiang University of TCM | — | — | — |
| Yang 2019    | Chaihu Longgu Muli granule   | Beijing Kangrentang Pharmaceutical Co. LTD. | Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Os Draconis 15 g, Ostraea gigas Thunberg [Ostraeae; Ostreae concha] 15 g, Scutellaria baicalensis Georgi [Lamiaceae; Scutellariae radix] 10 g, Zingiber officinale Roscoe [Zingiberaceae; Zingiberis rhizoma recens] 10 g, Codonopsis pilosula (Franch.) Nannf. [Campanulaceae; Codonopsis radix] 10 g, Neolitsea cassia (L.) Kosterm. [Lauraceae; Cinnamomum ramulus] 10 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 15 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 10 g, Rheum palmatum L. [Polygonaceae; Rhei radix et rhizoma] 10 g, Pteris multifida (Dunk.) Pteridieria; Margantia] 15 g, Ziziphus jujuba Mill. [Rhamnaceae; Jujubae fructus] 10 g | N | N |

(Continued on following page)
TABLE 1 | (Continued) Compositions of formulation and patented drugs.

| Study (year) | Source | Compositions | Quality control reported? | Chemical analysis reported? |
|--------------|--------|--------------|---------------------------|-----------------------------|
| Zhang 2019   | Pharmacy of Affiliated Hospital of Liaoning University of TCM | Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 15 g, Dromaeae costus (Falci.) Kasana and A.K.Pandey [Asteraceae; eckloniades radii] 15 g, Citrus × aurantium L. [Rutaceae; Auranti fructus], 15 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumae radix] 15 g, Alibizia julibrissin Durazz. [Fabaceae; Albiziae flos] 15 g, Reynoutria multiflora (Thum.) Moldenke [Polygonaceae; Polygoni multiflori caulis] 20 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 10 g | N                         | N                         |
| Zhao 2019    | Xining pill | — | N                         | N                         |
| Jin 2021     | Pharmacy of Dalian Municipal Hospital and The Second Affiliated Hospital of Liaoning University of TCM | Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma praeparata cum melle] 20 g, Triticum aestivum L. [Poaceae; Triticum aestivum] 100 g, Poria cocos (Schw.) Wolf [Polyporaceae; Poria] 20 g, Citrus × aurantium L. [Rutaceae; Citri reticulatae pericarpium] 15 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 15 g, Citrus × aurantium L. [Rutaceae; Aurantii fructus immaturus] 15 g, Allium sativum L. [Liliaceae; Allii sativi bulb] 15 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Trichosanthis fructus] 20 g, Ziziphus jujuba Mill. [Rhamnaceae; Jujubae fructus] 15 g, Zingiber officinale Rosc [Zingiberaceae; Zingiberis rhizoma recens] 10 g | Y—Prepared according to NMPA: Z10900011 | N                         |
| Wang 2021    | Shuxin oral liquid | Codonopsis pilosula (Franch.) Namf. [Campanulaceae; Codonopsis radix], Astragalus mongholicus Bunge [Fabaceae; Astragali radix], Carthamus tinctorius L. [Asteraceae; Carthami flos], Angelica sinensis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma], Sparganium stoloniferum (Buch.-Ham. ex Grah.) Buch.-Ham. ex Juz. [Typhaceae; Spargani rhizoma], Typha angustifolia L. [Typhaceae; Typhae pollen] | Y—Prepared according to NMPA: Z10900011 | N                         |
| Zhang 2021   | Xuefu Zhuyu decoction and Yueju pill | — | N                         | N                         |

(Continued on following page)
| Study (year) | Formulation or patented drugs | Source | Compositions | Quality control reported? | Chemical analysis reported? |
|-------------|--------------------------------|--------|--------------|---------------------------|-----------------------------|
| Sun 2011 Sun (2011) | Jieyu Anshen decoction | — | Bupleurum chinense DC, [Apiaceae; Bupleuri radix] 12 g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 30 g, Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma] 12 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 12 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumae radix] 12 g, Albizia julibrissin Durazz. [Fabaceae; Albiiae flos] 12 g, Angelica sinesis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix] 12 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 12 g, Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosae semen] 30 g, Citrus × aurantium L. [Rutaceae; Citri reticulatae pericarpium] 12 g, Wurfbainia villosa (Lour.) Skrmick. and A.D.Poulset [Zingiberaceae; Amomi fructus] 6 g, Glycyrrhiza uralensis Fisch, ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 6 g, Angelica sinesis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba], Bupleurum chinense DC, [Apiaceae; Bupleuri radix], Salviae miltiorrhizae radix et rhizoma® 30 g, Ophiopogonis radix, Ligustici chuanxiong radix et rhizoma® 30 g, Liquorice root, Su Hui Qian Zhong® 20 g, Panax ginseng extract, Longezi Zhi Lu® 15 g, Lycium barbarum extract, Dong Quai extract, and Pinellia extract. | N | N |
| Lin 2012 Lin (2012) | Xiaoyao pill | Lanzhou Tabao Pharmaceutical Co. LTD. | Codonopsis pilosula (Franch.), Nanf. [Campanulaceae; Codonopsis radix] 12 g, Ophiopogon japonicus (Thunb.), Ker Gawl. [Asparagaceae; Ophiopogonis radix] 9 g, Schisandra chinensis (Turcz.) Ball. [Schisandraceae; Schisandraceae chinensis fructus] 6 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] 50 g, Santalum album L. [Santalaceae; Santalum album L.] 50 g, Wurfbainia villosa (Lour.) Skrmick. and A.D.Poulset [Zingiberaceae; Amomi fructus] 3 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Trichosanthes kirilowii fructus] 12 g, Allium chinense G.Don [Amaryllidaceae; Allium macrostemon bulbosus] 10 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 9 g, Bupleurum chinense DC, [Apiaceae; Bupleuri radix] 12 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 9 g, Paeonia anomala subsp. veitchii (Lynch) D.Y.Hong and K.Y.Pan [Paeoniaceae; Paeoniae radix rubra] 9 g, Glycyrrhiza uralensis Fisch, ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 6 g, Angelica sinesis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], and Panax ginseng extract. | Y—Prepared according to NMPA: ZB2001225 | N |
| Zhang 2012 Zhang et al. (2012) | Jiawei Shengdan Louie Sini granule | Pharmacy of Xyuan Hospital, China Academy of Chinese Medical Sciences | Panax ginseng C.A.Meyer, Angelicae sinensis radix, Ophiopogon japonicus (Thunb.), Ker Gawl. [Asparagaceae; Ophiopogonis radix] 9 g, Schisandra chinensis (Turcz.) Ball. [Schisandraceae; Schisandraceae chinensis fructus] 6 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] 50 g, Santalum album L. [Santalaceae; Santalum album L.] 50 g, Wurfbainia villosa (Lour.) Skrmick. and A.D.Poulset [Zingiberaceae; Amomi fructus] 3 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Trichosanthes kirilowii fructus] 12 g, Allium chinense G.Don [Amaryllidaceae; Allium macrostemon bulbosus] 10 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 9 g, Bupleurum chinense DC, [Apiaceae; Bupleuri radix] 12 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 9 g, Paeonia anomala subsp. veitchii (Lynch) D.Y.Hong and K.Y.Pan [Paeoniaceae; Paeoniae radix rubra] 9 g, Glycyrrhiza uralensis Fisch, ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 6 g, Angelica sinesis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], and Panax ginseng extract. | N | N |
| Qin 2013 Qin and Liu (2013) | Tongxin Jieyu granule | Pharmacy of Longhua Hospital affiliated to Shanghai University of TCM | Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 30 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Trichosanthes kirilowii fructus] 15 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] 12 g, Bupleurum chinense DC, [Apiaceae; Bupleuri radix] 15 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydalis rhizoma] 15 g, Poria cocos (Schw.) Wolf [Polyoporaceae; Poria] 20 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumae radix] 15 g, Citrus medica L. [Rutaceae; Citri reticulatae pericarpium] 10 g, Dolomiaea costus (Falc.) Kasana and A.K.Pande [Asteraceae; aucklandiae radix] 10 g, Bupleurum chinense DC, [Apiaceae; Bupleuri radix], Angelica sinesis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], and Panax ginseng extract. | N | N |
| Zhu 2013 Zhu (2013) | Jieyu granule | Weifang Hospital of TCM | Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba], Murraya paniculata L. [Rutaceae; Muriacyci folium] 10 g, Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosae semen] 30 g, Mentha arvensis L. [Lamiaceae; Menthae arvensis herba], Angelicae sinensis radix, Ophiopogon japonicus (Thunb.), Ker Gawl. [Asparagaceae; Ophiopogonis radix] 9 g, Schisandra chinensis (Turcz.) Ball. [Schisandraceae; Schisandraceae chinensis fructus] 6 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] 50 g, Santalum album L. [Santalaceae; Santalum album L.] 50 g, Wurfbainia villosa (Lour.) Skrmick. and A.D.Poulset [Zingiberaceae; Amomi fructus] 3 g, Trichosanthes kirilowii Maxim. [Cucurbitaceae; Trichosanthes kirilowii fructus] 12 g, Allium chinense G.Don [Amaryllidaceae; Allium macrostemon bulbosus] 10 g, Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] 9 g, Bupleurum chinense DC, [Apiaceae; Bupleuri radix] 12 g, Citrus × aurantium L. [Rutaceae; Auranti fructus] 9 g, Paeonia anomala subsp. veitchii (Lynch) D.Y.Hong and K.Y.Pan [Paeoniaceae; Paeoniae radix rubra] 9 g, Glycyrrhiza uralensis Fisch, ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma] 6 g, Angelica sinesis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], and Panax ginseng extract. | (Continued on following page) | (Continued on following page) |
| Study (year) | Formulation or patented drugs | Source | Compositions | Quality control reported? | Chemical analysis reported? |
|--------------|-------------------------------|--------|--------------|--------------------------|---------------------------|
| Gu 2014      | Shugan Jieyu decoction        | —      | Citrus medica L. [Rutaceae; Citri fructus], Dalbergia odorifera T.C.Chen [Fabaceae; Dalbergiæ odoriferae lignum], Gardenia jasminoides J.Ellis [Rubiaeæ; Gardeniæ fructus], Scutellaria baicalensis Georgi [Lamiææ; Scutellarialæ radix], Acorus calamus var. angustatus Beisser [Acoraceae; Acori tatarinowii rhizoma], Abietis julibrissin Durazz. [Fabaceae; Albidiae cortex], Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosæ semen], succinum Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 15 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 10 g, Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma] 10 g, Citrus x aurantium L. [Rutaceae; Auranti fructus] 12 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumææ radix] 12 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydaliæ rhizoma] 15 g, Paonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 12 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizæ radix et rhizoma] 6 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 30 g, Scutellaria baicalensis Georgi [Lamiææ; Scutellarialæ radix] 10 g, Pinellia ternata (Thurb.) Makino [Araeæ; Pinelliae rhizoma praeparatum cum alamine] 10 g, Zingiber officinale Roscoe [Zingiberaceae; Zingiberis rhizoma recens] 10 g, Neolitsea cassia (L.) Kosterm. [Laureææ; Cinnamomomi ramulus] 10 g, Porzia cocos (Schw.) Wolf [Polyoreææ; Poria] 20 g, Magnellatum 10 g, Rheum palmatum L. [Polygonaceae; Rhei radix et rhizoma] 10 g, Gardenia jasminoides J.Ellis [Rubiaeæ; Gardeniæ fructus] 10 g, Polygala tenuifolia Wild. [Polygalææ; Polygalæ radix] 10 g, Forsythia suspensa (Thurb.) Vahl [Oleææ; Forsythiæ fructus] 10 g, Ziziphus jujuba Mill. [Rhamnaceae; Jujubæ fructus] 3 pieces, Citrus × aurantium L. [Rutaceae; Citri reticulatae pericarpium] 10 g, Os Draconis 30 g, Ostrea gigas Thunberg [Ostreææ; Ostreae concha] 30 g, | N   | N   |
| Shang 2014    | Chahu Longgu Mali decoction  | —      |  |  |  |
| Mu 2015       | Yangxin Jieyu decoction      | Pharmacy of Shandong Hospital of TCM | Citrus medica L. [Rutaceae; Citri fructus], Dalbergia odorifera T.C.Chen [Fabaceae; Dalbergiæ odoriferae lignum], Gardenia jasminoides J.Ellis [Rubiaeæ; Gardeniæ fructus], Scutellaria baicalensis Georgi [Lamiææ; Scutellarialæ radix], Acorus calamus var. angustatus Beisser [Acoraceae; Acori tatarinowii rhizoma], Abietis julibrissin Durazz. [Fabaceae; Albidiae cortex], Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosæ semen], succinum Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 15 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 10 g, Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma] 10 g, Citrus x aurantium L. [Rutaceae; Auranti fructus] 12 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumææ radix] 12 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydaliæ rhizoma] 15 g, Paonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 12 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizæ radix et rhizoma] 6 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 30 g, Scutellaria baicalensis Georgi [Lamiææ; Scutellarialæ radix] 10 g, Pinellia ternata (Thurb.) Makino [Araeæ; Pinelliae rhizoma praeparatum cum alamine] 10 g, Zingiber officinale Roscoe [Zingiberaceae; Zingiberis rhizoma recens] 10 g, Neolitsea cassia (L.) Kosterm. [Laureææ; Cinnamomomi ramulus] 10 g, Porzia cocos (Schw.) Wolf [Polyoreææ; Poria] 20 g, Magnellatum 10 g, Rheum palmatum L. [Polygonaceae; Rhei radix et rhizoma] 10 g, Gardenia jasminoides J.Ellis [Rubiaeæ; Gardeniæ fructus] 10 g, Polygala tenuifolia Wild. [Polygalææ; Polygalæ radix] 10 g, Forsythia suspensa (Thurb.) Vahl [Oleææ; Forsythiæ fructus] 10 g, Ziziphus jujuba Mill. [Rhamnaceae; Jujubæ fructus] 3 pieces, Citrus × aurantium L. [Rutaceae; Citri reticulatae pericarpium] 10 g, Os Draconis 30 g, Ostrea gigas Thunberg [Ostreææ; Ostreae concha] 30 g, | N   | N   |
| Shi 2016      | Jieyu Tongmai decoction      | Pharmacy of the First Affiliated Hospital of Tianjin University of Chinese Medicine | Citrus medica L. [Rutaceae; Citri fructus], Dalbergia odorifera T.C.Chen [Fabaceae; Dalbergiæ odoriferae lignum], Gardenia jasminoides J.Ellis [Rubiaeæ; Gardeniæ fructus], Scutellaria baicalensis Georgi [Lamiææ; Scutellarialæ radix], Acorus calamus var. angustatus Beisser [Acoraceae; Acori tatarinowii rhizoma], Abietis julibrissin Durazz. [Fabaceae; Albidiae cortex], Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosæ semen], succinum Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 15 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 10 g, Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma] 10 g, Citrus x aurantium L. [Rutaceae; Auranti fructus] 12 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumææ radix] 12 g, Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydaliæ rhizoma] 15 g, Paonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 12 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizæ radix et rhizoma] 6 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Astragalus mongholicus Bunge [Fabaceae; Astragali radix] 30 g, Scutellaria baicalensis Georgi [Lamiææ; Scutellarialæ radix] 10 g, Pinellia ternata (Thurb.) Makino [Araeæ; Pinelliae rhizoma praeparatum cum alamine] 10 g, Zingiber officinale Roscoe [Zingiberaceae; Zingiberis rhizoma recens] 10 g, Neolitsea cassia (L.) Kosterm. [Laureææ; Cinnamomomi ramulus] 10 g, Porzia cocos (Schw.) Wolf [Polyoreææ; Poria] 20 g, Magnellatum 10 g, Rheum palmatum L. [Polygonaceae; Rhei radix et rhizoma] 10 g, Gardenia jasminoides J.Ellis [Rubiaeæ; Gardeniæ fructus] 10 g, Polygala tenuifolia Wild. [Polygalææ; Polygalæ radix] 10 g, Forsythia suspensa (Thurb.) Vahl [Oleææ; Forsythiæ fructus] 10 g, Ziziphus jujuba Mill. [Rhamnaceae; Jujubæ fructus] 3 pieces, Citrus × aurantium L. [Rutaceae; Citri reticulatae pericarpium] 10 g, Os Draconis 30 g, Ostrea gigas Thunberg [Ostreææ; Ostreae concha] 30 g, | N   | N   |
| Study (year) | Formulation or patented drugs | Source | Compositions | Quality control reported? | Chemical analysis reported? |
|--------------|-------------------------------|--------|--------------|---------------------------|-----------------------------|
| Li 2017 U F. E. et al. (2017) | Jiawei Wendan decoction | — | miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhize radix et rhizoma] 30 g, Spatholobus suberectus Dunn [Fabaceae; Spatholobi caulis] 30 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 10 g, Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma] 10 g, Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosae semen] 15 g, Platycladus orientalis (L.) Franco [Cupressaceae; Platycladi semen] 15 g, Lilium lancifolium Thunb. [Liliaceae; Lilii bulbus] 30 g, Abizia julibrissin Durazz. [Fabaceae; Alibiziae cortex] 30 g, Curcuma aromatica Salisb. [Zingiberaceae; Curcumae radix] 10 g | N | N |
| Su 2017 Su (2017) | Suanzaoren decoction | Pharmacy of Shandong Hospital of TCM | Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi spinosae semen] 30 g, Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma] 12 g, Poria cocos (Schw.)Wolf [Polyporaceae; Poria] 15 g, Anemarrhena asphodeloides Bunge [Asparagaceae; Anemarrhenae rhizoma] 12 g, Pseudostellaria heterophylla (Mtq.) Pax [Caryophyllaceae; Pseudostellariae radix] 15 g, Ophiopogon japonicus (Thunb.) Ker Gawl. [Asparagaceae; Ophiopogonis radix] 15 g, Schisandra chinensis (Turcz.) Baitl. [Schisandraceae; Schisandraceae chinensis fructus] 9 g, Eclipta prostrata (L.) L. [Asteraceae; Ecliptae herba] 15 g, Ligusticum lucidum W.T.Aiton [Lamiaceae; Ligustri lucidi fructus] 15 g, Neolitsea cassia (L.) Kosterm. [Lauraceae; Cinnamomum cassia] 9 g, Glycyrrhiza uralensis Fisch. [Fabaceae; Glycyrrhizae radix et rhizoma] 3 g | N | N |
| Wang 2018 Wang D. D. (2018) | Dachaihu decoction | — | Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 18 g, Scutellaria baicalensis Georgi [Lamiaceae; Scutellariae radix] 12 g, Pinella ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma praeparatum cum albumine] 12 g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 15 g, Zingiber officinale Roscoe [Zingiberaceae; Zingiberis rhizoma recens] 9 g, Citrus × aurantium L. [Rutaceae; Aurantii fructus] 10 g, Ziziphus jujuba Mill. [Rhamnaceae; Ziziphi fructus] 3 pieces, Rheum palmatum L. [Polygonaceae; Rhei radix et rhizoma] 3 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhize radix et rhizoma] 20 g, Bombyx mori Linnaeus [Silkworm pilgrimaging; Bombyx batryticatus] 8 g, Cryptotympana postulata Fabricius | N | N |

(Continued on following page)
TABLE 1 | (Continued) Compositions of formulation and patented drugs.

| Study (year) | Formulation or patented drugs | Source | Compositions | Quality control reported? | Chemical analysis reported? |
|--------------|-------------------------------|--------|--------------|----------------------------|------------------------------|
| Wang 2018    | Buxing decoction              |        | [Cicadae; Cicadae periostracum] 8 g, Curcuma longa L. [Zingiberaeae; Curcumae longae rhizoma] 12 g Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhiza], Poria cocos [Schw.]Wolf [Polyporaceae; Poria], Atractylodes macrocephala Koidz. [Asteraceae; Atractylodis macrocephalae rhizoma], Astragalus mongholicus Bunge [Fabaceae; Astragali radix], Angelica sinensis (Oliv.) Diels [Araliaceae; Angelicae sinensis radix], Neolitsea cassia (L.) Kosterm. [Lauraceae; Cinnamomi ramulus], Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhiza] | Y—Prepared according to 2010 Chinese pharmacopeia | N |
| Shi 2018     | Tongmai Sanyu granule         | Beijing Kangrentang Pharmaceutical Co. LTD. | Angelica sinensis (Oliv.) Diels [Araliaceae; Angelicae sinensis radix] 10 g, Paeonia anomaalis subsp. veitchii (Lynch) D.Y. Hong and K.Y. Pan [Paeoniaceae; Paeoniae radix rubra] 10 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhiza] 10 g, Carthamus tinctorius L. [Asteraceae; Carthami flos] 10 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhiza] 10 g, Citrus × aurantium L. [ Rutaceae; Aurantii fructus] 10 g, Alba ụlọjụ ụrunọ Durazz. [Fabaceae; Albiae cortex] 15 g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 15 g, Cordyceps yanhusuo (Y.H. Chou & Chun C. Hsu) W.T. Wang ex Z.Y. Su and C.Y. Wu [Papaveraceae; Corydalis rhizoma] 15 g, Wurtzania villosa (Lour.) Skornick. and A.D. Poulsen [Zingiberaeae; Amomi fructus] 15 g, Curcuma aromatica Salisb. [Zingiberaeae; Curcumae radix] 20 g | N | N |
| Lu 2019      | Jieyu Shugan Tongmai decoction | Department of TCM, Shenyang Hospital of TCM | Angelica sinensis (Oliv.) Diels [Araliaceae; Angelicae sinensis radix] 10 g, Paeonia anomaalis subsp. veitchii (Lynch) D.Y. Hong and K.Y. Pan [Paeoniaceae; Paeoniae radix rubra] 10 g, Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhiza] 10 g, Carthamus tinctorius L. [Asteraceae; Carthami flos] 10 g, Bupleurum chinense DC. [Apiaceae; Bupleuri radix] 10 g, Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhiza] 10 g, Citrus × aurantium L. [ Rutaceae; Aurantii fructus] 10 g, Alba ụlọjụ ụrunọ Durazz. [Fabaceae; Albiae cortex] 15 g, Lilium lancifolium Thunb. [Liliaceae; Lili bulbus] 15 g, Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba] 15 g, Cordyceps yanhusuo (Y.H. Chou & Chun C. Hsu) W.T. Wang ex Z.Y. Su and C.Y. Wu [Papaveraceae; Corydalis rhizoma] 15 g, Wurtzania villosa (Lour.) Skornick. and A.D. Poulsen [Zingiberaeae; Amomi fructus] 15 g, Curcuma aromatica Salisb. [Zingiberaeae; Curcumae radix] 20 g | N | N |
| Huang 2020   | Guanxinming tablet            | Chia tai Qing Chun Bao pharmaceutical Co. LTD. | Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhiza], Ligusticum chuanxiong Hort. [Araliaceae; Chuanxiong rhizoma] Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma] 12 g, Atractylodes lancea (Thunb.) DC. [Asteraceae; Atractylodis rhizoma] 10 g, Gardenia jasminoides J.Ellis [Rubiaceae; Gardeniae fructus] 10 g, Ligusticum chuanxiong Hort. [Araliaceae; Chuanxiong rhizoma] 12 g, Citrus × aurantium L. [ Rutaceae; Citri reticulatae pericarpium] 10 g, Curcuma aromatica Salisb. [Zingiberaeae; Curcumae radix] 10 g, Pinellia ternata (Thunb.) Makino [Araliaceae; Pinelliae rhizoma] 10 g, Wurtzania villosa (Lour.) Skornick. and A.D. Poulsen [Zingiberaeae; Amomi fructus] 3 g, Prunus persica (L.) Batsch [Rosaceae; Persicae semen] 10 g, Carthamus tinctorius L. [Asteraceae; Carthami flos] 10 g | Y—Prepared according to NMPA: Z20150028 | N |

Note: Co. LTD.: company limited; NMPA: China of National Medical Products Administration; N: NO; Y: YES.
information was regarded as unclear risk, and no related information was regarded as high risk.

**Data Analysis and Synthesis**
RevMan 5.3 software provided by the Cochrane Collaboration was used for meta-analysis. The odds ratio (OR) and standard mean difference (SMD) were used to analyze the pooled effects of dichotomous outcomes and continuous variable, respectively. When the heterogeneity of included studies was low ($I^2 < 50\%$), the fixed effect model was selected to analyze the data; otherwise, a random-effects model was applied. The subgroups analysis was based on whether control groups used WM or not. Sensitivity analysis was performed to explore potential effect modification. Also, funnel plots were used to assess publication bias. $p < 0.05$ was considered statistically significant.

**Chinese Herbal Medicine Compositions and Potential Mechanisms**
The frequency statistics of single CHM was performed to identify the commonly used drugs, and CHM with frequency not less than three were selected for network pharmacology to find the primary active ingredients and the disease targets. The targets of the active ingredient of CHM were extracted from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, while the targets of CHD, anxiety, and depression were collected from the GeneCards database. The networks of active ingredients-disease targets were acquired according to the Cytoscape 3.6.1. The active ingredients that most related with CHD, anxiety, and depression simultaneously were acquired by matching ingredients-disease targets. Also, the main potential mechanisms of the primary active compounds (top 10) were summarized by the database of Web of Science.

**RESULTS**

**Literature Search Results**
A total of 2,102 records were identified from eight electronic databases. Thirty-two studies met the inclusion criteria, and 2070 studies were excluded due to 1) irrelevant studies; 2) nonclinical studies; 3) review, meta-analysis, and conference abstracts; 4) sample size was less than 30; 5) using WM in trial groups; 6) non-HAMA or HAMD for evaluating the efficacy of anxiety or depression; 7) non-ECG or AS or AF or TCMS score for evaluating the efficacy of CHD; and 8) articles with
| Study (year) | Disease | N (male/female), Mean age (years) | Basic treatment | Interventions | Duration of treatment | Outcome index | Intergroup difference |
|-------------|---------|----------------------------------|-----------------|---------------|----------------------|--------------|-----------------------|
|             | CHD     | Anxiety                          | Control group   | Trial group    |                       |              |                       |
| Mo 2016     | Post-PCI| HAMA ≥ 14                        | 32 (17/15) 60   | 33 (19/14) 58 | Unspecified          | N            | Wuling capsule        | 8 weeks | 1. HAMA score        | 1. <0.05       |
|             |         |                                  |                 |               |                      |              | 2. ECG efficacy      |         |                       | 2. <0.05       |
| Guo 2017    | SA      | HAMA < 29                        | 30 (8/22) 56.97 | 30 (9/21) 58  | A1, A3, E           | N            | Shenchai Shuxin decoction | 4 weeks | 1. HAMA score & efficacy | 1. <0.05 |
|             |         |                                  |                 |               |                      |              | 2. ECG efficacy      |         |                       | 2. >0.05       |
| Jin 2021    | SA      | HAMA ≥ 7                         | 40 (19/21) 54.67| 40 (18/22) 55.24| A1, A3, C1         | N            | Diazepam Shuxin decoction | 4 weeks | 1. HAMA score & efficacy | 1. <0.05 |
|             |         |                                  |                 |               |                      |              | 2. ECG efficacy      |         |                       | 2. >0.05       |
| Qin 2018    | Post-PCI| HAMA > 14                        | 31 (22/9) 68.87 | 31 (23/8) 70.74| A1, B, C1, M       | Fupentixol and meltracen tablets | 30 days | 1. HAMA score & efficacy | 1. <0.05       |
|             |         |                                  |                 |               |                      |              | 2. ECG efficacy      |         |                       | 2. <0.05       |
| Wang 2018   | SA      | HAMA ≤ 14                        | 30 (13/17) 80.80| 30 (11/19) 80.27| A1, A2, A3, B, C1, C2, M | N            | Chaihu Longgu Muli granule | 4 weeks | 1. HAMA score & efficacy | 1. <0.05       |
|             |         |                                  |                 |               |                      |              | 2. ECG efficacy      |         |                       | 2. <0.05       |
| Zhao 2019   | Post-PCI| HAMA ≥ 7                         | 40 (14/26) 75.23| 40 (18/22) 76.75| A1, A2, A3, B, C1, C2, E | N            | Xinling pill         | 3 months | 1. HAMA score & efficacy | 1. <0.05 |
|             |         |                                  |                 |               |                      |              | 2. ECG efficacy      |         |                       | 2. <0.05       |

(Continued on following page)
incomplete data or more than one high-risk item. The specific screening process is illustrated in Figure 1.

**Study and Patient Characteristics**

Thirty-two studies included 15 studies on CHD with anxiety (Mo et al., 2016; Li G. Y. et al., 2017; Guo, 2017; Qi and Song, 2017; Zhang et al., 2017; Qin, 2018; Wang C., 2018; Chen, 2019; Dong, 2019; Yang, 2019; Zhang, 2019; Zhao et al., 2019; Jin et al., 2021; Wang et al., 2021; Zhang and Jin, 2021) and 17 studies on CHD with depression (Sun, 2011; Lin, 2012; Zhang et al., 2012; Qin and Liu, 2013; Zhu, 2013; Gu et al., 2014; Shang et al., 2014; Mu, 2015; Shi et al., 2016; Li F. E. et al., 2017; Su, 2017; Shi, 2018; Wang Y. et al., 2018; Wang D. D., 2018; Lu, 2019; Huang et al., 2020; Zhang et al., 2020). All studies accounted for baseline comparability, and the patients’ overall characteristics are summarized in Tables 2A.B. Subjects of CHD who were diagnosed as stable angina (SA), unstable angina (UA), acute myocardial infarction (AMI), non-ST segment elevation myocardial infarction (NSTEMI), or post-percutaneous coronary intervention (post-PCI) were also evaluated by HAMA (Qi and Song, 2017; Qin, 2018; Wang et al., 2021; Zhang and Jin, 2021) and HAMD (Sun, 2011; Lin, 2012; Zhang et al., 2012; Qin and Liu, 2013; Shang et al., 2014; Mu, 2015; Shi et al., 2016; Li F. E. et al., 2017; Su, 2017; Shi, 2018; Wang Y. et al., 2018; Wang D. D., 2018; Lu, 2019; Huang et al., 2020; Zhang et al., 2020). Secondary prevention drugs for CHD were used in all studies.

For control groups of CHD with anxiety, four studies used flupentixol and melitracen tablets (Qi and Song, 2017; Qin, 2018), diazepam (Jin et al., 2021), and lorazepam (Zhang and Jin, 2021), while nine studies used fluoxetine hydrochloride (Zhang et al., 2012; Qiu and Liu, 2013; Shang et al., 2014), flupentixol and melitracen tablets (Zhu, 2013; Li F. E. et al., 2017; Wang D. D., 2018; Lu, 2019), and escitalopram (Shi et al., 2016; Wang Y. et al., 2018) in the CHD with depression. No WM were used in control groups in the remaining researches except for the study by Lin et al. who used a placebo (Lin, 2012). CHM was used in trial groups and the details are shown in Table 2. The treatment course in all studies varied from 2 weeks to 3 months. The primary efficacy endpoints, including the score and efficacy of HAMA and HAMD, ECG efficacy, AS score, and AF score, were extracted for this meta-analysis and systematic review. The score and efficacy of TCMS were also extracted for the evaluation as the secondary efficacy endpoint.

**Quality Assessment of Included Studies**

The study methodological quality is concluded in Supplementary Table S1. Random allocation was used in all included studies. Five studies performed blind method (Lin, 2012; Mo et al., 2016; Li G. Y. et al., 2017; Wang C., 2018; Su, 2017), and blinded outcome assessment was conducted in two studies (Qi and Song, 2017; Zhang and Jin, 2021). Additionally, allocation concealment was used in three studies (Sun, 2011; Mo et al., 2016; Wang C., 2018).

**Efficacy of Chinese Herbal Medicine in Coronary Heart Disease With Anxiety**

As shown in Table 2A, the score and efficacy of HAMA, ECG, AS, AF, and TCMS in trial groups in most studies possessed a significant improvement. However, there were also some different results. Two studies showed that there was no significant difference in the score or efficacy of HAMA between trial groups and control groups (Qi and Song, 2017; Qin and Liu, 2013; Shang et al., 2014). Three studies reported that the efficacy of ECG in trial groups was not significantly different compared with blank control groups (Mo et al., 2016; Chen, 2019; Zhang, 2019). Thus, the primary endpoint results were pooled to further confirm the efficacy of CHM.

**Efficacy of Chinese Herbal Medicine in Anxiety**

In Supplementary Figure S1, the HAMA score displayed significant heterogeneity due to scoring bias in different studies. Therefore, the

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**TABLE 2A (Continued) Research characteristics of the CHD with anxiety.**

| Study (year) | Disease | N (male/female), Mean age (years) | Basic treatment | Interventions | Duration of treatment | Outcome index | Intergroup difference |
|--------------|---------|----------------------------------|----------------|--------------|----------------------|---------------|-----------------------|
|              | CHD Anxiety |                                   |                | Control group | Trial group |                  |                      |                       |
| Wang et al. 2021 | SA HAMA ≥14 | 43 (31/12) | A1, A3, B, C1, D, M | Shuxin oral liquid | 12 weeks | 1. HAMA score | 1. <0.05 |
| Wang et al. (2021) | SA < 29 | 42 (22/19) | A1, A3, B, C1, D, M | Lorazepam | 4 weeks | 1. HAMA score | 1. <0.05 |
| Zhang et al. 2021 | SA HAMA ≥29 | 66.8 ± 6.6 | Xuefu Zhuyu decoction and Yueju pill | 2. ECG efficacy | 4.03 ± 0.05 | 2. <0.05 |
| Zhang and Jin (2021) | SA HAMA ≤14 | 59.11 | Yueju pill | 4. TCMS score | 4.03 ± 0.05 | 4. <0.05 |

Note: A1, antiplatelets; A2, ACEI/ARB; A3, nitrate esters drugs; A4, anticoagulants; B, β-blocker; C1, statins; C2, Ca antagonists; CHD, coronary heart disease; D, antidiabetic drugs; E, regulate emotion; M, improve the metabolism; N, without intervention; PCI, percutaneous coronary intervention; SA, stable angina; TCMS, traditional Chinese medicine syndrome; UA, unstable angina.

*The evaluation criteria refer to the guiding principles for clinical research of Chinese medicine from China.

*The evaluation criteria refer to other acceptable evaluation methods.
TABLE 2B | Research characteristics of the CHD with depression.

| Study (year) | Disease | N (male/female), Mean age (years) | Basic treatment | Interventions | Duration of treatment | Outcome index | Intergroup difference |
|--------------|---------|----------------------------------|----------------|--------------|----------------------|--------------|-----------------------|
| Sun (2011)   | CHD     | 18 ≤ HAMD ≤ 34                  | 30 (12/18)     | A1, A3, A4, C1, E | Jieyu Anshen decoction | 4 weeks     | 1. <0.01 <0.05        |
|              |         | 61.80 ± 6.33                   | 30 (10/20)     |             |                      |              |                       |
|              |         | ± 6.34                         | 60.80 ± 6.34   |             |                      |              |                       |
| Lin (2012)   | CHD     | HAMD217                         | 30 (16/14)     | Unspecified  | Placebo Xiaoyao pill | 1 month     | 1. <0.05 <0.01        |
|              |         | 61.83 ± 7.95                   | 30 (15/15)     |             |                      |              |                       |
|              |         | ± 8.00                         | 61.77 ± 8.00   |             |                      |              |                       |
| Zhang et al. (2012) | CHD     | HAMD24                         | 35 (11/24)     | A3           | Fluoxetine hydrochloride | 4 weeks     | 1. <0.01 <0.01        |
|              |         | 68.67 ± 9.89                   | 36 (12/24)     |             |                      |              |                       |
|              |         | ± 8.41                         | 68.63 ± 8.41   |             |                      |              |                       |
| Qin and Liu (2013) | CHD     | HAMD-24                         | 30              | A3           | Fluoxetine hydrochloride | 8 weeks     | 1. <0.05 <0.01        |
|              |         | 61.4 ± 8.2                     | 31              |             |                      |              |                       |
| Zhu 2013     | CHD     | HAMD24                          | 30 (18/14)     | A1, A3, A4, B, C1 | Shugan Jieyu granule | 4 weeks     | 1. <0.05 <0.01        |
| Zhu 2013     |         | 61.4 ± 8.2                     | 30 (18/12)     |             |                      |              |                       |
|              |         | ± 9.5                          | 62.8 ± 9.5     |             |                      |              |                       |
| Gu et al. (2014) | CHD     | HAMD24                          | 30 (18/12)     | A1, A3, B, C1 | Shugan Jieyu granule | 4 weeks     | 1. <0.05 <0.01        |
|              |         | 64.12 ± 7.33                   | 30 (19/11)     |             |                      |              |                       |
|              |         | ± 7.33                         | 63.32 ± 8.16   |             |                      |              |                       |
| Gu et al. (2014) | CHD     | HAMD24                          | 30 (16/18)     | A1, A3, B, C1 | Shugan Jieyu granule | 4 weeks     | 1. <0.05 <0.01        |
|              |         | 65.0 ± 5.8                     | 30 (16/18)     |             |                      |              |                       |
|              |         | ± 5.8                          | 65.0 ± 5.8     |             |                      |              |                       |
| Shang 2014   | CHD     | HAMD-17                         | 30 (12/10)     | Unspecified  | Fluoxetine hydrochloride | 4 weeks     | 1. <0.05 <0.01        |
| Shang et al. (2014) | CHD     | HAMD-17                         | 30 (12/10)     |             |                      |              |                       |
|              |         | 58.0 ± 7.3                      | 30 (14/10)     |             |                      |              |                       |
|              |         | ± 6.5                          | 56.5 ± 6.5     |             |                      |              |                       |
| Mu 2015      | CHD     | HAMD-24                         | 30 (22/8)      | A1, A3, A4, C1, E | Yangxin Jieyu decoction | 4 weeks     | 1. <0.01 <0.01        |
| Mu. (2015)   |         | 70.9 ± 12.3                    | 30 (23/7)      |             |                      |              |                       |
|              |         | ± 11.4                         | 72.8 ± 11.4    |             |                      |              |                       |
| Shi 2016     | CHD     | 8 < HAMD-24 ≤ 34                | 31              | A1           | Escitalopram Jieyu Yongmai recipe | 8 weeks     | 1. <0.01 <0.01        |
| Shi et al. (2016) | CHD     | 8 < HAMD-24 ≤ 34                | 31              |             |                      |              |                       |
| Li (2017)    | CHD     | HAMD-20                         | 40 (17/23)     | Unspecified  | Rupentixol and meltracen tablets | Jiewei Wanda decoction | 12 weeks     | 1. <0.05 <0.01        |
| Li et al. (2017) | CHD     | HAMD-20                         | 40 (17/23)     |             |                      |              |                       |
|              |         | 64.1 ± 9.3                     | 40 (21/19)     |             |                      |              |                       |
|              |         | ± 6.3                          | 62.3 ± 5.3     |             |                      |              |                       |
| Su (2017)    | CHD     | HAMD-24                         | 30 (15/15)     | A1, A3, C1, E | Suanzhaoren decoction | 8 weeks     | 1. <0.01 <0.01        |
| Su (2017)    |         | 73.17 ± 8.4                    | 30 (16/14)     |             |                      |              |                       |
|              |         | ± 8.4                          | 70.77 ± 8.3    |             |                      |              |                       |

(Continued on following page)
TABLE 2B | (Continued) Research characteristics of the CHD with depression.

| Study (year) | Disease (male/female), Mean age (years) | Basic treatment | Interventions | Duration of treatment | Outcome index | Intergroup difference |
|-------------|----------------------------------------|-----------------|---------------|----------------------|--------------|-----------------------|
|             | CHD Depression                          | Control group   | Trial group   | Control group        | Trial group  |                       |
| Wang1       | SA 20±HAMD-24 ≤ 35                     | 34 (18/16)      | 36 (16/20)   | A1, A3, B, C1       | Dachaihu decoction | 4 weeks             | 1. HAMD-24 score & efficacy |
| Wang D. D.  |                                         | ± 7.20         | ± 6.44       |                      |              | 1. <0.05              | and <0.05 |
|             |                                        | ± 9.45         | ± 61.44      |                      |              |                       | <0.05                |
| Wang2       | SA, UA HAMD>20                          | 140 (84/76)    | 140 (61/79)  | A1, A2, A3, B, C1, C2 | Escitalopram | 8 weeks             | 1. HAMD score |
| Wang Y. et al. 2018 |                           | ± 56.3         | ± 55.2       |                      | Buxinji decoction |              | 2. Episodes of angina |
| Shı 2018 | UA HAMD-17                              | 34 (14/20)     | 34 (13/21)   | A1, A3, B, C1       | Tongmai Sanyu granule | 2 weeks          | 1. HAMD-17 score |
| Shı (2018) |                                         | ± 62.77        | ± 61.59      |                      |              | 1. <0.05             | and <0.05 |
|             |                                        | ± 7.79         | ± 7.79       |                      |              |                       | <0.05                |
| Lu 2019     | Post-PCI HAMD                           | 41 (27/14)     | 38 (21/17)  | A1, C1               | Rupentinol and melitracen tablets | 2 weeks | 1. HAMD-24 score & efficacy |
| Lu (2019)   |                                         | ± 63.12        | ± 64.13      |                      | Jieyu Shugan Tongmai recipe |              | 1. >0.05             | and >0.05 |
| Huang 2020  | IHD HAMD                                | 50 (32/18)     | 50 (36/14)   | A1, A3, B, C1, C2, E | Guaxrawing tablet | 1 month          | 1. HAMD-17 score & efficacy |
| Huang et al. (2020) |                            | ± 67.38        | ± 68.68      |                      |              | 1. <0.05             | and <0.05 |
| Zhang 2020  | SA &HAMD-17 < 24                        | 30 (17/10)     | 30 (15/15)  | A1, A3, B, C1       | Huatan Quyu recipe | 4 weeks | 1. HAMD-17 score & efficacy |
| Zhang et al. (2020) |                      | ± 62.73        | ± 60.77      |                      |                | 1. <0.05             | and <0.05 |
|             |                                        | ± 7.55         | ± 7.55       |                      |                | 2. HAMD-17 score & efficacy |
|             |                                        | ± 6.72         | ± 6.72       |                      |                | 2. TCMS score & efficacy |
|             |                                        | ± 7.27         | ± 7.27       |                      |                | 3. >0.05             | and >0.05 |

Note: A1, antiplatelets; A2, ACEI/ARB; A3, nitrate esters drugs; A4, anticoagulants; AMI, acute myocardial infarction; B, β-blocker; C1, statins; C2, Ca antagonists; CABG, coronary artery bypass grafting; CHD, coronary heart disease; E, regulate emotion; IHD, ischemic heart disease; N, without intervention; HSTEMI, non-ST, segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; TCMS, traditional Chinese medicine syndrome; UA, unstable angina

*The evaluation criteria refer to the guiding principles for clinical research of Chinese medicine from China.
**The evaluation criteria refer to other acceptable evaluation methods.

Efficacy of Chinese Herbal Medicine in Coronary Heart Disease

Meta-analysis of nine studies showed a significant efficacy of CHM for improving anxiety [OR = 2.73, 95%CI (1.78, 4.18), p < 0.00001, I² = 0%] (Figure 2), and the subgroup analysis based on whether the control group used WM or not was also performed. As shown in Figure 2, the results of subgroup analysis showed a favor for CHM in curing anxiety in CHD patients compared with blank control groups [OR = 3.22, 95%CI (1.94, 5.35), p < 0.00001, I² = 0%], whereas the efficacy of CHM in treating anxiety was not inferior to that of WM [OR = 1.58, 95%CI (0.39, 6.35), p = 0.52, I² = 67%]. Moreover, a repetitive meta-analysis by consecutively excluding each study in WM groups was performed. The study by Qi et al. was the main source of heterogeneous, but it was not removed because of reasonable research design.

Efficacy of Traditional Chinese Medicine in Coronary Heart Disease With Depression

As shown in Table 2B, most included studies showed a significant improvement in the score and efficacy of HAMD, ECG, AS, AF, and TCMS in treatment groups. However, some studies showed different results. Three studies reported that the score or efficacy of HAMD in CHM groups was no statistical difference between...
Wang et al. TCM for CHD With Anxiety or Depression

FIGURE 2 | Forest plot: CHM improved HAMA efficacy in CHD with anxiety compared with control groups.

FIGURE 3 | Forest plot: CHM improved ECG in CHD with anxiety compared with control groups.
treatment and control groups using antidepressants (Zhu, 2013; Shi et al., 2016; Lu, 2019). Similarly, for the score of efficacy of ECG, angina, and TCMS, there were also no statistical differences between treatment and control groups (Zhu, 2013; Gu et al., 2014; Shang et al., 2014; Li F. E. et al., 2017; Zhang et al., 2020).

Additionally, the study by Lin et al. was the only study that used placebo (Lin, 2012). The scores of AS and AF were not significantly different between the CHM and placebo group, but the result of the 36-item short form survey showed a superior benefit of CHM compared with placebo. In the study by Wang Y. et al. (2018), antidepressants and CHM both possessed obvious efficacy for treating CHD with depression, and antidepressants exhibited even more efficiency. Therefore, the primary endpoint results were pooled to further confirm the efficacy of CHM.

**Efficacy of Chinese Herbal Medicine in Depression**

Meta-analysis of seven studies showed that CHM had a significant effect on treating depression compared with control groups [OR = 2.79, 95%CI (1.61, 4.86), p = 0.0003, I² = 0%] (Figure 6). The results of subgroup analysis also revealed that the antidepressive effect was improved significantly compared with blank control groups [OR = 3.27, 95%CI (1.67, 6.40), p = 0.0005, I² = 0%] but was the same as WM groups [OR = 1.97, 95%CI (0.73, 5.28), p = 0.18, I² = 33%] (Figure 6).
FIGURE 6 | Forest plot: CHM improved HAMD efficacy in CHD with depression compared with control groups.

FIGURE 7 | Forest plot: CHM improved ECG in CHD with depression compared with control groups.
Efficacy of Chinese Herbal Medicine in Coronary Heart Disease

Eight studies reported that CHM significantly improved ECG in CHD patients [OR = 1.89, 95%CI (1.23, 2.89), p = 0.004, I² = 0%] (Figure 7). In addition, subgroup analysis showed a similar result favoring CHM in improving CHD compared with blank groups [OR = 1.96, 95%CI (1.14, 3.37), p = 0.02, I² = 0%], but no statistical difference was found when comparing CHM with WM groups [OR = 1.78, 95%CI (0.89, 3.55), p = 0.10, I² = 0%] (Figure 7).

Regarding the efficacy of CHM in AS and AF, CHM also provided a more significant advantage compared with control groups [AS: SMD = 11.62, 95%CI (6.92, 16.33), p < 0.00001, I² = 0%; AF: SMD = 11.13, 95%CI (7.46, 14.80), p < 0.00001, I² = 6%] (Figures 8, 9), blank groups [AS: p = 0.004; AF: p < 0.00001], and WM [AS: SMD = 12.15, 95%CI (6.07, 18.23), p < 0.00001, I² = 0%; AF: SMD = 10.34, 95%CI (5.26, 15.41), p < 0.00001, I² = 48%] (Figures 8, 9).

Comparisons of the Characteristics of Chinese Herbal Medicine in Coronary Heart Disease With Anxiety or Depression

Due to the promising results of CHM treatment observed in most included studies, the frequency statistics of CHM was analyzed to identify the commonly used drugs among different groups. The results showed that *Bupleurum chinense* DC. [Apiaceae; Bupleuri radix], *Glycyrrhiza uralensis* Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma], *Ligusticum chuanxiong* Hort. [Apiaceae; Chuanxiong rhizoma], *Salvia miltiorrhiza* Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma], *Angelica sinensis* (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], *Paonia lactiflora* Pall. [Paeoniaceae; Paeoniae radix alba], *Pinellia ternata* (Thunb.) Makino [Araceae; Pinelliae rhizoma], *Curcuma aromatica* Salisb. [Zingiberaceae; Curcumae radix], and *Citrus×aurantium* L. [Rutaceae; Aurantii fructus] were commonly used for treating CHD with anxiety or depression (Supplementary Table S2). Also, the CHM with a frequency not
### TABLE 3 | Mechanisms of main active components of CHM on CHD with anxiety or depression.

| Active ingredient | Source | Structure | Models | Related mechanisms | References |
|-------------------|--------|-----------|--------|-------------------|------------|
| **Quercetin**     | Bupleurum chinense DC. [ Apiaceae; Bupleuri radix], Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma], Ziziphus jujuba Mill. [Rhamnaceae; Jujubae fructus], Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu [Papaveraceae; Corydalis rhizoma], Carthamus tinctorius L. [Asteraceae; Carthami flos], and Bupleuri radix | CHD: M1 rat TNF-α-HUVEC | 1. Anti-damage/apoptosis (LDH, CK-MB, cTnl, Bax, cleaved caspase-3/9) | Albadrani et al. (2020), Chen T. et al. (2020), Gma et al. (2021) |
| **Kaempferol**    | Bupleurum chinense DC. [Apiaceae; Bupleuri radix], Paeonia lacti [Paeoniaceae; Paeoniae radix alba], Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma], Gardenia jasminoides J.Ellis [Rubiaceae; Gardeniae fructus], Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma], Astragalus mongholicus Bunge [Fabaceae; Astragali radix] | CHD: t/R DM rat ox-LDL-HUVECs | 1. Anti-damage/apoptosis (Bax, cleaved-caspase-3, TUNEL, p38; Bcl-2) | Suchal et al. (2017), Li et al. (2021) |
| **Luteolin**      | Codonopsis pilosula (Franch.) Nannf. [Campanulaceae; Codonopsis radix], Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma], Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma], Platycodon grandiflorus (Jacq.) A.D.C. [Campanulaceae; Platycodonis radix], Carthamus tinctorius L. [Asteraceae; Carthami flos] | CHD: I/R-rats/ mouse H$_2$O$_2$-H9C2 H/R-H9C2 | 1. Anti-damage/apoptosis (LDH, CK-MB, cTnl, Bax, caspase-1/3/9, cleaved caspase-3, TUNEL, Bcl-2) | Yu et al. (2015), Hu et al. (2018), Wei et al. (2018), Hu et al. (2020), Zhao et al. (2020) |

(Continued on following page)
| Active ingredient | Source | Structure | Models | Related mechanisms | References |
|-------------------|--------|-----------|--------|--------------------|------------|
| Beta-sitosterol    | Citrus×aurantium L. [ Rutaceae; Citrus aurantium L., Citrus reticulata Blanco, Citrus paradisi Macf., Citrus x sinensis (L.) Osbeck ] | ![Structure](image) | Depression: OID rat + HNC male ICR mouse | 1. Maintaining neurotransmitters homeostasis (BDNF, 5-HTs, PMATs, GABAergic receptor-Cl ion channel complexes) | de la Peña et al. (2014), Zhu et al. (2019) |
|                   |        |           |        |                   | Lin et al. (2020) |
|                   |        |           |        |                   |            |
|                   |        |           |        |                   |            |
| Puerarin          | Bupleurum chinense DC. [ Apiaceae; Bupleurum chinense DC. ] | ![Structure](image) | Depression: Adult male ICR mouse | 1. Maintaining neurotransmitters homeostasis (5-HT, 5-HIAA, NE, DA, GABAergic) | Zhao et al. (2016), Yin et al. (2018) |

(Continued on following page)
TABLE 3 | (Continued) Mechanisms of main active components of CHM on CHD with anxiety or depression.

| Active ingredient | Source | Structure Models | Related mechanisms | References |
|-------------------|--------|-----------------|--------------------|------------|
| stigmasterol      | Bupleurum chinense DC. [Apiaceae; Bupleuri radix], Angelica sinensis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], Codonopsis pilosula (Franch.) Nanfr. [Campanulaceae; Codonopisis radix], Pinella ternata (Thunb.) Makino [Araliaceae; Pinelliae rhizoma], Wurfbainia villosa (Lour.) Skornick. and A.D.Poulsen [Zingiberaceae; Amomi fructus], Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma], Ziziphus jujuba Mill. [Rhamnaceae; Jujubae fructus], Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae rhizoma] | Anxiety: male Swiss mouse | 1. Maintaining neurotransmitters homeostasis (positive modulation of GABAA receptors [GABAergic mechanism]) | Karim et al. (2021) |
| Isorhamnatin      | Bupleurum chinense DC. [Apiaceae; Bupleuri radix], Cyperus rotundus L. [Cyperaceae; Cyperi rhizoma], Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhize radix et rhizoma], Astragalus mongholicus Bunge [Fabaceae; Astragali radix] | 1. Anti-damage/apoptosis (CK, LDH, Bax, cleaved-caspase-3; Bcl-2) | CHD: I/R rat H/R | Chen et al. (2015), Zhao et al. (2018), Xu et al. (2020) |
| Baicalein         | Pinella ternata (Thunb.) Makino [Araliaceae; Pinelliae rhizoma], Astragalus mongholicus Bunge [Fabaceae; Astragali radix], Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba], Carthamus tinctorius L. [Asteraceae; Carthami flos], Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba], Carthamus tinctorius L. [Asteraceae; Carthami flos] | Depression: starved PC12 cells, CHD: I/R-mouse/ rat AMI rat | 1. Inducing neuronal differentiation (NF68, NF160) | Xu et al. (2012) |
|                   |        | CHD: I/R-mouse/ rat AMI rat | 1. Anti-damage/apoptosis (OK, LDH, cTnI, CK-MB, Bax:Bcl-2, p53) | Song et al. (2014), Kumar et al. (2016), Jie et al. (2019) |
|                   |        | Anxiety: adult female Swiss mouse | 1. Maintaining neurotransmitters homeostasis (dependent on GABAergic non-benzodiazepine sites but not on the 5-HT system) | de Carvalho et al. (2011) |
|                   |        | CHD: RRSD rat PDRD mouse | 1. Anti-inflammation (IL-1β/5/6/12, IFN-y) | Lee et al. (2013), Zhao X. et al. (2021) |

(Continued on following page)
TABLE 3 (Continued) Mechanisms of main active components of CHM on CHD with anxiety or depression.

| Active ingredient | Source | Structure | Models | Related mechanisms | References |
|-------------------|--------|-----------|--------|-------------------|------------|
| Tanshinone Ila  | Salvia miltiorrhiza Bunge [Lamiaceae; Salvia miltiorrhiza radix et rhizoma] | CHD: MI-rats/ mouse I/R mouse H/R-H9C2 Ang II-CFs | 1. Anti-damage/apoptosis (CK, CK-MB, LDH, Bax, cleaved-caspase-3a, Bcl-2) 2. Anti-inflammation (IL-1β, TNF-α, TGF-β) | 1. Anti-damage/apoptosis (CK, CK-MB, LDH, Bax, cleaved-caspase-3a, Bcl-2) 2. Anti-inflammation (IL-1β, TNF-α, TGF-β) | Gao S. et al. (2019), Chen L. et al. (2020), Chen et al. (2021) |
| Nobiletin | Citrus x aurantium L. [Rutaceae; Aurantii fructus immaturus], Citrus x aurantium L. [Rutaceae; Citri reticulatae pericarpium] | CHD: AMI-mouse/ rat + NRVM mouse I/R rat OGD-H9C2 | 1. Anti-damage/apoptosis (LDH, CK-MB, Bax/Bcl2, cleaved caspase-3, caspase-12, ANP, BNPs) 2. Anti-inflammation (α-SMA, collagen I/III) | 1. Anti-damage/apoptosis (LDH, CK-MB, Bax/Bcl2, cleaved caspase-3, caspase-12, ANP, BNPs) 2. Anti-inflammation (α-SMA, collagen I/III) | Wu et al. (2017), Zhang B. F. et al. (2019), Liu et al. (2021), Zhou et al. (2021) |

Note: Examples of CHM in Source are derived from the results of network pharmacology analysis. ACh: acetylcholine; ACTH: adrenocorticotropic hormone; AGE: advanced glycation end product; AKT: protein kinase B; AMPAR: AMPA-type glutamate receptor; Ang II: angiotensin II; AP-1: activator protein 1; ASC: apoptosis-associated speck-like protein; ATP: adenosine triphosphate; Bax: Bcl-2 associated X protein; Bcl-2: B-cell lymphoma/leukemia-2; BDNF: brain-derived neurotrophic factor; Bim: Bcl-2-interacting mediator of cell death; BMP: bone morphogenetic protein; CaMK-II: members of the Ca(2+)/calmodulin-dependent protein kinase II; CAT: catalase; CaM: calmodulin; CK: creatine kinase MB; COL1A1: Collagen 1A1; Cort: corticosterone; Cox-2: cyclooxygenase-2; CREB: cAMP response element-binding protein; CRH: corticotropin-releasing hormone; CRP: C-reactive protein; CSRS: CUMS: chronic unpredictable mild stress; CT: coronary thrombosis; eNOS: endothelial nitric oxide synthase; ERK: extracellular signal-regulated kinase; ES: endoplasmic reticulum stress; FGF-2: fibroblast growth factor-2; FGR: fibroblast growth factor receptor; FAK: focal adhesion kinase; GAPA: gamma-aminobutyric acid; GPR77: Glucose-Regulated Protein 77; GSH-P: glutathione-Peroxidase; GSK-3β: glycogen synthase kinase-3β; GST: glutathione S-transferase; GSSG: glutathione disulfide; HDAC: histone deacetylase; HIF: hypoxia-inducible factor; HMOX: heme oxygenase-1; iNOS: inducible nitric oxide synthase; IRE-1: endoplasmic reticulum stress; JAK: janus kinase; JNK: Jun N-terminal kinase; NLRP3: NOD-like receptor, pyrin domain-containing 3; M1: macrophage (pro-inflammatory); M2: macrophage (anti-inflammatory); mTOR: mammalian target of rapamycin; miRNA: microRNA; MR: mannitol; MUP: multi-organ perfusion; NLRP3: NOD-like receptor, pyrin domain-containing 3; NOS: nitric oxide synthase; OGD: oxygen-glucose deprivation; OA: osteoarthritis; ORP150: organ perfusion; PPAR: peroxisome proliferator-activated receptor; PI3K: phosphatidylinositol 3-kinase; PI4PK: phosphatidylinositol 4,5-bisphosphate 3-kinase; PI3K: phosphatidylinositol 3-kinase; PGC1α: peroxisome proliferator-activated receptor-α; PDGF: platelet-derived growth factor; PKC: protein kinase C; PPAR: peroxisome proliferator-activated receptor; RAGE: receptor for advanced glycation end products; RAS: renin-angiotensin system; RANK: receptor activator of nuclear factor-κB; RAGE: receptor for advanced glycation end products; SOD: superoxide dismutase; SP: specific protein; STAT3: signal transducers and activators of transcription 3; TGF: transforming growth factor-β; TNF: tumor necrosis factor-α; TRPV1: transient receptor potential vanilloid 1; TRPV2: transient receptor potential vanilloid 2; TUNEL: terminal deoxyuridine triphosphate nick-end labeling; US: unconditioned stimulus; VEGF: vascular endothelial growth factor; Wnt: wingless-related integration site; Y1: dopamine D1 receptors; Y2: dopamine D2 receptors; Y3: dopamine D3 receptors; Y4: dopamine D4 receptors; Y5: dopamine D5 receptors; Y6: dopamine D6 receptors.
less than three were selected for the networks of active ingredients-disease targets, and the results demonstrated the efficacy of CHM for CHD with anxiety or depression (Supplementary Figure S2). Furthermore, the primary active ingredients of these CHM that could act on the targets of CHD, anxiety, and depression simultaneously were analyzed by matching ingredients disease targets. The results showed the active ingredients including quercetin, kaempferol, luteolin, beta-sitosterol, puerarin, stigmasterol, isorhamnetin, baicalein, tanshinone IIa, and nobiletin. These phytochemicals were also reported to exert antioxidant stress, anti-inflammatory role of quercetin, beta-sitosterol, puerarin, or nobiletin was reported in anxiety or depression. However, the efficacy and benefit of CHM in treating CHD with anxiety or depression still need to be further verified due to poor methodological quality and potential confounding factors. This meta-analysis and systematic review was performed to provide the evidence for the application of CHM in CHD patients with anxiety or depression. Thirty-two studies (15 CHD with anxiety, and 17 CHD with depression) were included for the evaluation of the efficacy of CHM. The results showed that CHM had a significant benefit on anxiety and depression in CHD patients, and its efficacy was not inferior to that of WM. Importantly, CHM also had a significant advantage to alleviate the angina symptom compared with blank control and WM groups. Besides that, there were no obvious adverse effects of CHM in the included studies (Zhang et al., 2012; Qin and Liu, 2013; Zhu, 2013; Mo et al., 2016; Shi et al., 2016; Guo, 2017; Wang Y. et al., 2018; Wang C., 2018; Wang D. D., 2018; Chen, 2019; Lu, 2019; Yang, 2019; Huang et al., 2020).

Furthermore, the frequency of CHM used in the included studies was analyzed, and the commonly used drugs were analyzed by network pharmacology. The results concluded that the CHM regulating Qi and promoting blood circulation, including Bupleurum chinense DC. [Apiaceae; Bupleuri radix], Glycyrrhiza uralensis Fisch. ex DC. [Fabaceae; Glycyrrhizae radix et rhizoma], Ligusticum chuanxiong Hort. [Apiaceae; Chuanxiong rhizoma], Salvia miltiorrhiza Bunge [Lamiaceae; Salvia miltiorrhizae radix et rhizoma], Angelica sinensis (Oliv.) Diels [Apiaceae; Angelicae sinensis radix], Paeonia lactiflora Pall. [Paeoniaceae; Paeoniae radix alba], Pinellia ternata (Thunb.) Makino [Araceae; Pinelliae

Potential Relevant Mechanisms
The effects and mechanisms of the primary active compounds (top 10) were searched in the Web of Science database. As shown in Table 3, the experimental research of quercetin, kaempferol, luteolin, beta-sitosterol, puerarin, and baicalein covered CHD, anxiety, and depression. Models of myocardial infarction or ischemia reperfusion were commonly used in the study of CHD, while the ICR mice and multiple stress-stimulated rats were selected for anxiety and depression research.

The related mechanisms of these top 10 active ingredients in CHD, anxiety, and depression are summarized in Table 3, which mainly includes anti damage/apoptosis, anti-inflammation, antioxidative stress, anti-fibrosis, maintaining neurotransmitters homeostasis, and regulating autophagy. In addition, myocardial injure biomarkers (lactate dehydrogenase, creatine kinase MB, cardiac troponin I) and the damage/apoptosis biomarkers (Bcl-2 associated X protein, cleaved caspase-3, p53, B-cell lymphoma/leukemis-2) could be regulated by quercetin, kaempferol, luteolin, beta-sitosterol, puerarin, and baicalein. These phytochemicals were also reported to exert an anti-inflammatory effect by reducing the levels of interleukin (IL) -1β, tumor necrosis factor-α, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, or elevating the IL-10 level in CHD patients. The anti-inflammatory role of quercetin, puerarin, or nobiletin was reported in anxiety or depression. Additionally, almost all active ingredients except stigmasterol and nobiletin possessed the functions of antioxidative stress and balancing level of reactive oxygen species, malondialdehyde, myeloperoxidase, and catalase, superoxide dismutase, glutathione. Quercetin, tanshinone IIa, and nobiletin were reported to reduce the levels of α-smooth muscle actin, angiotensin II, collagen I/III, matrix metalloproteinases 2/9, transforming growth factor (TGF)-β, and Smad7 to prevent myocardial fibrosis, which was one of the complications associated with myocardial infarction. Besides, the imbalance of adrenocorticotropic hormone, 5-hydroxytryptamine, brain-derived neurotrophic factor (BDNF), acetylcholine, noradrenaline, dopamine, and gamma-aminobutyric acid, which caused anxiety or depression, could be regulated by quercetin, kaempferol, luteolin, beta-sitosterol, puerarin, stigmasterol, baicalein, tanshinone IIa, or nobiletin. Isoflavonoids and baicalein could improve the depression by inducing neuronal differentiation and protecting synaptic plasticity, respectively. The roles of active compounds in regulating autophagy and improving mitochondria were also reported. Overall, the related mechanisms of TCM-active compounds in treating CHD with anxiety or depression contained a variety of signaling pathways, such as nuclear factor-kappa B, mitogen-activated protein kinase, Jun N-terminal kinase, extracellular signal-regulated kinase1/2, signal transducers and activators of transcription3, TGF-β1/Smad3, phosphatidylinositol 3-kinase/protein kinase B, and BDNF.

DISCUSSION
There is accumulating evidence showing high prevalence of anxiety and depression comorbidities in patients with CHD. SSRIs and benzodiazepines are frequently used for treating depression or anxiety disorders, and the effectiveness of these drugs on psychiatric disorders has also been acknowledged (Davies et al., 2004). However, the side effects, such as suicidal ideation, sexual dysfunction, and dependency, have not been resolved (Lakhan and Vieira, 2010; Ko et al., 2020). In addition, it is a common clinical phenomenon that CHD patients show subsyndromal anxiety or depression-like symptoms that do not meet the diagnostic criteria of anxiety or depression (Cohen et al., 2006; Kasckow et al., 2013). The issue of treatment for these patients still deserves much attention.

TCM has been reported to be effective in treating CHD, anxiety, and depression with a less adverse effect, and might be a potential therapeutic option for patients with subsyndromal anxiety or depression. However, the efficacy and benefit of CHM in treating CHD with anxiety or depression still need to be further verified.
rhizoma], Curcuma aromatica Salisb. [Zingiberaceae; Curcuma
radix], and Citrusaurantium L. [Rutaceae; Aurantii fructus] were
commonly used for CHD with anxiety and depression. The
phytochemicals identified in the CHM could act on the
pathological targets of CHD, anxiety, and depression simultaneously.

Inflammatory response to vascular injury participates in the
pathological processes of the atherosclerosis and CHD, and is
associated with the increased risk of cardiovascular events and
recurrent myocardial infarction (Fioranelli et al., 2018; Zhang K.
J. et al., 2019). Oxidative stress is also an important factor
involved in myocardial cell injury and apoptosis caused by
ischemia reperfusion, which is followed by heart failure and
myocardial fibrosis (Li et al., 2018; Yang et al., 2019). The
effectiveness of CHM ingredients including quercetin, kaempferol, luteolin, beta-sitosterol, puerarin, and baicalein
was reported in the experimental research on CHD. Puerarin,
quercetin, and tanshinone Il a were also shown to have a
satisfactory efficacy in improving clinical prognosis (Mao
et al., 2019; Zhang S. et al., 2019; Dehghani et al., 2021).
Additionally, inflammation and oxidative stress could cause
neuron damage and neurotransmitter disorder, leading to
anxiety and depression (Bankier et al., 2009; Liu et al., 2015;
van Dooren et al., 2016; Salim, 2017; Wang Y. L. et al., 2018).
Quercetin, kaempferol, luteolin, and puerarin also showed a
positive effect in curing anxiety and depression.

Overall, these findings reveal that the CHM has a
satisfactory efficacy for CHD with anxiety and depression, especially for improving the symptom of angina pectoris. Of
importance, CHM itself contains multiple components that
play critical functions in a large number of signaling pathways
involved in distinct biological processes of CHD with anxiety
or depression mainly including anti-damage/apoptosis, anti-
inflammation, antioxidative stress, and maintaining
neurotransmitters homeostasis. Compared with WM’s single
effect on the nervous system, CHM may extert its functions in
multiple places and systems by targeting distinct factors in
CHD with anxiety or depression to improve both CHD and
anxiety/depression syndromes.

LIMITATIONS

First, the sample size in each group of included studies was not
more than 50, except the study by Wang Y. L. et al. (2018), and the
sample size needs to be expanded in future studies. Second, it is
difficult to perform double blind due to the special smell and taste
of TCM decoction. Also, the characteristics of TCM treatment
affect the implementation of double blind. Additionally, the
blinding of outcome assessment was conducted in 2 of 32
studies (Qi and Song, 2017; Zhang and Jin, 2021). Therefore,
the strict trial design is also necessary to further verify the efficacy
of CHM.

CONCLUSION

CHM had a significant efficacy for the treatment of CHD patients
with anxiety or depression. Particularly, CHM could improve
the symptoms of angina pectoris while alleviating anxiety and
depression. The main mechanisms underlying the functions of
these CHM-active ingredients might involve anti-damage/
apoptosis, anti-inflammation, antioxidative stress, antifibrosis,
maintaining neurotransmitters homeostasis, and regulating
autophagy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in
the article/Supplementary Material, further inquiries can be
directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

BW, YT, and YL are co-first authors. Theme and design of the
research: BW, YT, and YL. Extract data: YL, YT, and SL. Network
pharmacology: YW. Statistical analysis: SC, YL, and XH. Data
handling of mechanisms: HZ, YW, ZL, HL, YD, and LM. Writing
of the manuscript: BW, YT, and YL. Critical revision of the
manuscript for intellectual content: MZ and XW. Obtaining
funding: MZ and XW.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at:
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full#supplementary-material

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