Precision Medication 2 (2025) 100062

Contents lists available at ScienceDirect

Precision Medication

journal homepage: www.keaipublishing.com/en/journals/precision-medication/

Anti-platelet aggregation effect of Compound Danshen dripping pill: An integrated study of meta-analysis, network pharmacology, and *in vivo* and *vitro* experiments

Bo Pang[a,1], Haofan Xu[b,1], Zhouyi Xie[c], Yi Chen[d], Yu Wei[a], Mengying Zhang[a], Qian Zhao[a], Wenjia Wang[a], Jingbo Zhai[e,*], Yunhui Hu[a,*]

[a] *Tianjin Tasly Digital Intelligence Chinese Medicine Technology Co., Ltd., Tianjin 300400, China*
[b] *Keck School of Medicine, University of Southern California, Los angeles, CA 90089, USA*
[c] *School of Medicine, Nankai University, Tianjin 300000, China*
[d] *Department of Cell Biology and Genetics, School of Basic Medical Sciences, Hangzhou Normal University, Hangzhou 310000, China*
[e] *School of Public Health, Tianjin University of Traditional Chinese Medicine, Tianjin 301600, China*

ARTICLE INFO

Keywords:
Compound Danshen dripping pill
Platelet aggregation
Meta-analysis
Network pharmacology
Integrated study

ABSTRACT

Objective: Compound Danshen Dripping Pill (CDDP) is a marketed Chinese patent medicine, primarily efficacious in "promoting blood circulation to remove blood stasis, regulating Qi to relieve pain". CDDP, as an anti-platelet aggregation drug, has been applied in clinic. However, the evidence has not been critically assessed, and the underlying mechanism has still not been fully understood.

Methods: A meta-analysis was conducted to collect randomized controlled trials (RCTs) from PubMed, Embase, Cochrane library, Web of Science, CNKI, Wanfang and VIP, and assess the efficacy and safety of CDDP against platelet aggregation. A network pharmacology analysis was performed to predict the potential mechanisms of CDDP against platelet aggregation. A series of in vitro and vivo experiments were conducted to reveal the potential mechanisms of CDDP against platelet aggregation.

Results: The pooled result of the meta-analysis involving 20 RCTs showed a more significant reduction in platelet aggregation rate after CDDP plus anti-platelet drugs treatment than anti-platelet drugs alone (SMD = 1.27, 95 % CI: 0.97–1.57, $P < 0.0001$). The network pharmacology analysis found 86 overlapping target genes between CDDP and platelet aggregation that were closely related to lipid, atherosclerosis and inflammation signal pathways. The *in vitro* and *vivo* experiments found that CDDP inhibited carrageenan-induced thrombi in tissue vessels of mice. Especially, the combination of CDDP and aspirin/clopidogrel showed a better effect of inhibiting thrombus. CDDP also decreased the level of serum P-selectin and TXB2, and the expression of tumor necrosis factor α, P-selectin and activated matrix metalloproteinase 2 in tissues. CDDP protected human umbilical vein endothelial cells (HUVECs) against lipopolysaccharide (LPS)-induced cell death and reduced the expression of tumor necrosis factor-like cytokine 1 A and vascular endothelial growth factor-α. Meanwhile, CDDP reduced the adhesion of ox-LDL-induced platelets and LPS-induced THP-1 monocytes to HUVECs, and inhibited thrombin-induced human platelet clotting.

Conclusion: This integrated study suggests that CDDP have a potential anti-platelet aggregation effect. It may provide a new option for anti-platelet aggregation in clinical practice.

Introduction

Thrombosis refers to the formation of blood clots on the inner surface of vessels, and can occlude vessels, terminate tissue perfusion and lead to ischemia.[1] Thrombosis often appears in veins or arteries of different tissues. Many severe cardiovascular events are associated with thrombosis, such as pulmonary embolism, stroke and myocardial infarction.[2] Therefore, it is urgent to prevent and treat thrombosis.[3]

* Corresponding authors.
E-mail addresses: zhaijingbo@foxmail.com (J. Zhai), tsl-huyunhui@tasly.com (Y. Hu).
[1] Bo Pang and Haofan Xu contribute equally to this work

https://doi.org/10.1016/j.prmedi.2025.100062
Received 20 May 2025; Received in revised form 31 July 2025; Accepted 7 August 2025
Available online 9 December 2025

Occlusive clots are formed by activated platelets trapped by fibrin fibers that are produced by the blood coagulation system. Anti-thrombotic therapies that interfere with pathologic thrombus formation target either platelets or blood coagulation cascade.[1] However, traditional anti-thrombotic drugs often are accompanied with some side effects. For example, aspirin or clopidogrel can cause liver dysfunction, kidney dysfunction or gastrorrhagia.[1,4,5] Some patients taking aspirin may suffer from cardiovascular events, such as myocardial infarction, angina pectoris or stroke due to aspirin resistance.[6,7] It is reported that 10～20 % of aspirin users are resistant to aspirin.[8] Aspirin resistance usually occurs in patients taking anti-platelet drugs, which results in the high mortality and hospitalization rate in China.[9]

Some traditional Chinese medicine (TCM) has obvious anti-platelet effect, especially in patients with aspirin resistance.[10,11] Compound Danshen Dripping Pill (CDDP), a renowned commercial Chinese polyherbal preparation comprising *Salvia miltiorrhiza* Bunge (90 g), *Panax notoginseng* (Burkill) F.H. Chen (17.6 g), and Borneolum syntheticum (1 g), has been widely recognized and utilized for the prevention and treatment of ischemic heart diseases in numerous countries since its market launch in China in 1994.[12] In recent years, many clinical studies have revealed that CDDP can inhibit platelet activation and aggregation. However, the clinical evidence has not been critically assessed, and the underlying mechanism has been still not fully understood. Therefore, we conducted an integrated study of meta-analysis, network pharmacology and in vitro and vivo experiments to comprehensively assess the efficacy, safety and explore potential mechanism of CDDP against platelet aggregation.

Materials and methods

Meta-analysis

This meta-analysis was registered on PROSPERO (No. CRD42024583455). It was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement.

PubMed, Embase, Cochrane library, Web of Science CNKI, Wanfang and VIP databases were searched from inception to August, 2024 to identify eligible studies by two reviewers independently (J. Zhai and H. Xu). The search terms mainly included ("Compound danshen dripping pills" or "Fufang danshen diwan" or "Fufang danshen dripping pills") and "platelet aggregation". The detailed search strategies are available in Supplementary Material 1. Additionally, three clinical trial registry platforms (ClinicalTrials.gov, International Clinical Trials Registry Platform, and Chinese Clinical Trial Registry) and references of eligible studies were also searched to avoid missing potentially relevant studies.

This meta-analysis included randomized controlled trials (RCTs) comparing the efficacy of 'anti-platelet drugs plus CDDP' versus 'anti-platelet drugs alone or plus CDDP placebo' in the patients at risk of thrombosis. The publication date, language, disease, age, gender, race, nationality and anti-platelet drugs were unrestricted. Abstracts, letters, and comments were excluded. The primary outcome was the platelet aggregation rate. The secondary outcomes included thromboxane B_2 (TXB2), blood lipid and the incidence of adverse drug reaction.

The retrieved studies from the comprehensive literature search were imported into EndNote software to remove duplicates. Subsequently, two reviewers (J. Zhai and H. Xu) independently deleted irrelevant studies by checking titles and abstracts according to the above criteria. The full texts of the remaining studies were read to identify eligible studies. The process of screening eligible studies was presented by a PRISMA flow diagram. Disagreements were handled in consultation with a third reviewer (Y. Hu).

The important data was independently extracted and imported into Excel software by two authors (J. Zhai and H. Xu). This information involved characteristics of included studies (first author, publication year, country, sample size, design), patients (age, gender, race, nationality), interventions (type, dosage, frequency, duration) and reported outcomes.

The risk of bias was assessed using the Cochrane "Risk of Bias" tool. For continuous variables, effect size was expressed as mean difference (MD) with 95 % confidence intervals (CIs) when the same outcome was measured using the same tool across included studies. If different tools were used, standardized mean difference (SMD) was used. For the dichotomous variables, effect size was expressed as relative risk (RR). The meta-analysis with the random-effect model was conducted to acquire conservative results by Review Manager 5.4 software. $P < 0.05$ indicated a statistically significant difference. Subgroup analyses of the primary outcome were conducted based on control interventions (aspirin, clopidogrel, and aspirin plus clopidogrel), intervention duration and type of patients (with/without aspirin resistance).

Network pharmacology analysis

The underlying mechanisms of CDDP against platelet aggregation were analyzed by network pharmacology methods. The gene targets related with *Salvia miltiorrhiza* Bunge, *Panax notoginseng* (Burkill) F.H. Chen as the main active herbs of CDDP were obtained by searching keywords in HERB database (http://herb.ac.cn/). Human genes associated with platelet aggregation were acquired by searching GeneCards database (https://www.genecards.org/) with platelet aggregation as the keyword. Then, overlapping gene targets between CDDP and platelet aggregation were identified by inputting gene targets about CDDP and platelet aggregation into the STRING database (https://string-db.org/) to construct the protein-protein interaction (PPI) network. The PPI network was visualized by Cytoscape 3.7.0 software. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were conducted on the Matescape platform (https://metascape.org/gp/index.html). We inputted blood stasis symptoms into the SymMap database (http://www.symmap.org/) to identify herbs for treating blood stasis symptoms. We wanted to see if these herbs contained the main active herbs of CDDP.

Experimental study

Drug and reagents

Prostaglandin E1 (PGE1) was purchased from Cayman Chemical (Ann Arbor, MI, USA). 5, 6 Carboxyfluorescein diacetate succinimidyl ester (CFSE) was purchased from Santa Cruz Biotechnology (Dallas, TX, USA). Fibrinogen, thrombin, aspirin and carrageenan were purchased from Sigma-Aldrich (St Louis, MO, USA). Aspirin and clopidogrel sulfate were purchased from P212121 (Ypsilanti, MI, USA). Cell counting kit-8 (CCK-8) assay kit was purchased from ABclonal (Wuhan, Hubei, China). CDDP (batch number: 210612) was provided by Tasly Pharmaceutical Co., Ltd. (Tianjin, China).

Rabbit anti-protein kinase B (AKT, Cat# 17609–1-AP) polyclonal antibody, mouse anti-phosphorylated AKT (p-AKT, Ser473; Cat# 66444–1-Ig) monoclonal antibody and HRP-conjugated α-tubulin(Cat# HRP-66031) monoclonal antibody were purchased from Proteintech Group (Chicago, IL, USA). Rabbit anti-extracellular signal-regulated kinase 1/2 (ERK1/2, Cat# 9102S) and phosphorylated ERK1/2 (p-ERK1/2, Thr202/Tyr204; Cat# 9101S) polyclonal antibodies were purchased from Cell Signaling Technology (Danvers, MA, USA). Rabbit anti-cyclooxygenase 2 (COX-2, Cat# AF7003) polyclonal antibody was purchased from Affinity Biosciences Inc. (Cincinnati, OH, USA). Rabbit anti-purinergic receptor $P2Y_{12}$ (Cat# A1710) polyclonal antibody, protease-activated receptor 4 (PAR4, Cat# A4983) monoclonal antibody and cyclooxygenase 1 (COX-1, Cat# A4301) polyclonal antibody were purchased from ABclonal (Wuhan, Hubei, China).

Cell culture

Human umbilical vein endothelial cells (HUVECs) were purchased from A TCC (Manassas, VA, USA) and cultured in DMEM medium supplemented

with 10 % fetal bovine serum (FBS) and 50 mg/mL of penicillin/streptomycin in an incubator with a humidified atmosphere of 95 % air and 5 % CO_2 at 37°C. THP-1 monocytes (a human monocytic cell line) were purchased from ATCC and cultured in a RPMI 1640 medium containing 10 % FBS and 50 mg/mL of penicillin/streptomycin in an incubator with a humidified atmosphere of 95 % air and 5 % CO_2 at 37°C. Cells at ~90 % confluence received treatments in a serum-free medium.

Preparation of CDDP, Clopidogrel and Aspirin solution

For cell treatments, CDDP was dissolved in H_2O. The concentration of CDDP was 25 mg/mL. Clopidogrel was dissolved in DMSO. The concentration of clopidogrel was 1.8 mg/mL which equaled to the dose of 100 μM. Aspirin was dissolved in DMSO. The concentration of aspirin was 3.3 mg/mL which equaled to the dose of 80 μM. Solutions with different concentrations obtained by diluting the above solutions were used in subsequent experiments.

For the intragastric administration in mice, CDDP was dissolved in phosphate-buffered saline (PBS) at a clinical equivalent concentrations of 24.4 mg/mL which equaled to the dose of 166.5 mg/kg.[13] Clopidogrel was dissolved in PBS at a concentrations of 2.3 mg/mL, which equaled to the dose of 15.4 mg/kg. Aspirin was dissolved in PBS at a concentrations of 2.3 mg/mL which equaled to the dose of 15.4 mg/kg. The concentrations of all solutions were converted from human clinical doses to mouse doses.

Carrageenan-induced thrombosis experiment

BALB/c mice (male, ~7 weeks old and 22 g) were purchased from the Animal Center of Nanjing University (Nanjing, Jiangsu, China) and housed under specific pathogen-free conditions with free access to water and food in the Animal Center at the College of Life Sciences, Nankai University (Tianjin, China). The protocols for animal studies were granted by the Ethics Committee of Nankai University (Tianjin, China ; Approval number: 2023-SYDWLL-000638) and the studies were performed in compliance with the Guide for the Care and Use of Laboratory Animals (Publications No. 8023, revised 1978) published by the National Institutes of Health (NIH).

BALB/c mice were randomly divided into 5 groups (10 mice in each group) and received the treatments. In summary, mice in group 1 (Control group) and group 2 (Thrombosis group) received intragastric administration of PBS (150 μL/day) for 9 days; mice in group 3 (CDDP treatment group, 150 μL/day) received intragastric administration of CDDP solution for 9 days; mice in group 4 (clopidogrel plus aspirin group, 150 μL/day) received intragastric administration of clopidogrel solution and aspirin solution (15.4 mg/kg bodyweight) for 9 days; and mice in group 5 (CDDP plus clopidogrel and aspirin group, 150 μL/day) received intragastric administration of CDDP solution, clopidogrel solution and aspirin solution for 9 days. Mice in group 2, 3, 4 and 5 were injected intraperitoneally with 110 μL 1 % carrageenan solution (equals to 50 mg/kg bodyweight) on day 7. Two days after the carrageenan injection, all mice were anesthetized and euthanized in a CO_2 chamber. Thrombosis length and total tail length were measured by quickly photographing mouse tails. Blood, tail, liver and lung samples were collected separately.

Determination of serum P-selectin and Thromboxane B2 (TXB2) levels

Blood samples collected from the mice were kept for 2 h at room temperature, and then were centrifugated for 20 min at 2000 g. The serum was transferred into a new test tube, and the levels of P-selectin and TXB2 were measured by ELISA kit (Elabscience Biotechnology, Wuhan, Hubei, China) at 570 nm.

Hematoxylin-eosin (HE), Masson trichrome and immunohistochemical staining

To determine thrombus formation in mouse tissue vessels, samples from different locations of the mouse tail (defined as the distances from the tail tip), liver and lung were collected and fixed in 4 % paraformaldehyde overnight. The liver and lung samples received water deprivation using a standard procedure and were then embedded in paraffin. The 5-μm paraffin sections of liver and lung samples were prepared for HE staining. Mouse tail samples were incubated in a 30 % sucrose solution overnight and then embedded in OCT solution. Frozen 5-μm sections of mouse tail samples were prepared, of which some were used for HE staining, and the others were stained with Masson trichrome and immunohistochemistry to determine the collagen content and MMP-2 expression. The images of HE, Masson trichrome and immunohistochemical staining were photographed with a Leica DM3000 microscope (Wetzlar, Germany).

Cell viability assay

Cell viability was determined using the CCK-8 assay kit. HUVECs in 96-well plates were treated with lipopolysaccharide (LPS) and the prepared solutions of CDDP, clopidogrel and aspirin for the indicated times. After treatments, cells were added to the CCK-8 solution (10 μL/well) and incubated for 1 h, followed by determination of the absorbance at 450 nm.

Determination of the adhesion of monocytes or platelets to HUVECs

To determine the adhesion of THP-1 monocytes and platelets to HUVECs, HUVECs in 24-well plates were treated with LPS (1 μg/mL), CDDP (25 mg/mL) or LPS plus CDDP for 24 h; or treated with oxidized low-density lipoprotein (ox-LDL, 100 μg/mL), CDDP (25 mg/mL) or ox-LDL plus CDDP for 24 h. After treatments, CFSE-labeled THP-1 cells or platelets were added to HUVECs and incubated for 30 min at 37°C. The nonadherent cells or platelets were rinsed with PBS for 3 times. The bound cells or platelets were photographed by the Leica DMi8 Microscope (Wetzlar, Germany).

Platelet isolation and labeling

The human platelets research was prepared in accordance with the Code of Ethics of the World Medical Association. Briefly, human platelet-rich plasma was obtained from a healthy donor (Tianjin Blood Bank, Tianjin, China). At room temperature, it was added with PGE1 (1 μM) and incubated for 10 min, and then centrifuged for 10 min at 600 g. The platelet pellet was washed and resuspended in a resuspension buffer (10 mM HEPES, pH 7.4, 140 mM NaCl, 3 mM KCl, 0.5 mM $MgCl_2$, 5 mM $NaHCO_3$, 10 mM glucose), and warmed up to 37°C. To label human platelets or THP-1 cells, the suspension of platelets were added to CFSE solution (1 μM) and mixed. The mixture was incubated for 30 min at 37°C. Cells and platelets were washed with PBS for 3 times to remove free CFSE.

Clot retraction assay

The platelet suspension was added with 1 mM $CaCl_2$, PBS or the prepared solutions of CDDP, clopidogrel and aspirin, and incubated for 30 min at 37°C, followed by addition of fibrinogen (2 mg/mL). The mixture was transferred into a Sigmacote-coated glass tube (Sigma-Aldrich). The addition of human thrombin (1 U/mL) triggered the clot retraction at 37°C, and was then photographed at specified times.

Determination of mRNA expression by quantitative real-time PCR (qRT-PCR)

Total cellular RNA was extracted from mouse tissues or HUVECs, and cDNA was synthesized from 2 mg of total RNA using a reverse transcription kit (Vazyme, Nanjing, Jiangsu, China). After obtaining the cDNA, gene expression was quantified by qRT-PCR using SYBR Green Master Mix (Bio-Rad, Los Angeles, CA) and primers with the sequences listed in Table 1. The relative mRNA expression was normalized by β-actin mRNA with the corresponding samples.

Statistical analysis

Quantitative data are described as mean ± standard deviation. One-way analysis of variance (ANOVA) was used to compare the quantitative

Table 1
The sequences of primers for qRT-PCR analysis.

Gene	Forward	Backward
Homo VCAM-1	TGGGAAAAACAGAAAAGAGGTG	GTCTCCAATCTGAGCAGCAA
Homo ICAM-1	CCACAGTCACCTATGGCAACG	GGCCATACAGGACACGAAGCT
Homo TF	TGAAGGATGTGAAGCAGACG	GCCAGGATGATGACAAGGAT
Homo TFPI	AGCAGCAGGCATACAGAAGC	CCTGTCTTCAATACCTGGAAGG
Homo β-actin	CTGGAACGGTGAAGGTGACA	AAGGGACTTCCTGTAACAATGCA
Mus TNF-α	CGTCGTAGCAAACCACCAAG	TTGAAGAGAACCTGGGAGTAGACA
Mus MMP-2	TGGCAAGGTGTGGTGTGCGAC	TCGGGGCCATCAGAGCTCCAG
Mus P-selectin	GCATACTCATGGAATAACTCACG	GACGTCATTGAGGTGAGCG
Mus β-actin	ATGGAGGGGAATACAGCCC	TTCTTTGCAGCTCCTTCGTT

Homo, Homo sapiens; Mus, mouse sapiens; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TNF-α, tumor necrosis factor α; MMP-2, matrix metalloproteinase 2.

data across groups by SPSS 23.0 (IBM Corporation, Armonk, NY, USA). $P < 0.05$ indicated a statistically significant difference.

Results

Meta-analysis results

Literature search

A total of 1268 studies were identified in the initial search. Then, 432 duplicates were removed by EndNote software and 782 irrelevant studies were deleted by checking the titles and abstracts. After reading the full texts of the remaining studies, 19 studies were included in the final statistical analysis. The PRISMA flow diagram is presented in Fig. 1A.

Characteristic of included studies

The included 19 studies involved 20 RCTs published from 2008 to 2023. The sample size ranged from 10 to 160 in the experiment or control group. Fifteen RCTs compared CDDP + aspirin with aspirin alone. Two RCTs compared CDDP + clopidogrel with clopidogrel alone. The efficacy of CDDP + aspirin + clopidogrel versus aspirin + clopidogrel was assessed in 3 RCTs. The characteristics of the included studies are summarized in Table 2**.**

Assessment of risk of bias

The risk of bias assessment results of the 20 RCTs are shown in Fig. 1B. The bias for random sequence generation item in 8 RCTs and attrition bias in 16 RCTs was classified as low risk because of reported specific random sequence generation methods and complete outcome data separately. In addition, the risk of bias for allocation concealment, performance bias, detection bias and reporting bias was rated as unclear due to inadequate reported information in all RCTs.

Platelet aggregation rate, TXB2, Blood lipid, and Adverse drug reaction

Twenty RCTs reported the platelet aggregation rate. The pooled results showed a more significant reduction in platelet aggregation rate after 'CDDP plus anti-platelet drugs' treatment than 'anti-platelet drugs alone' (SMD = 1.27, 95 % CI: 0.97–1.57, $P < 0.00001$, Fig. 1C). Similar results were obtained in the subgroup analyses based on intervention duration, types of anti-platelet drugs, and patients with/without aspirin resistance (Table 3).

Eleven RCTs reported TXB2. The meta-analysis showed that TXB2 in the 'CDDP plus anti-platelet drugs' group was more significantly reduced compared with the 'anti-platelet drugs alone' group (SMD = 0.46, 95 % CI: 0.34–0.57, $P < 0.00001$).

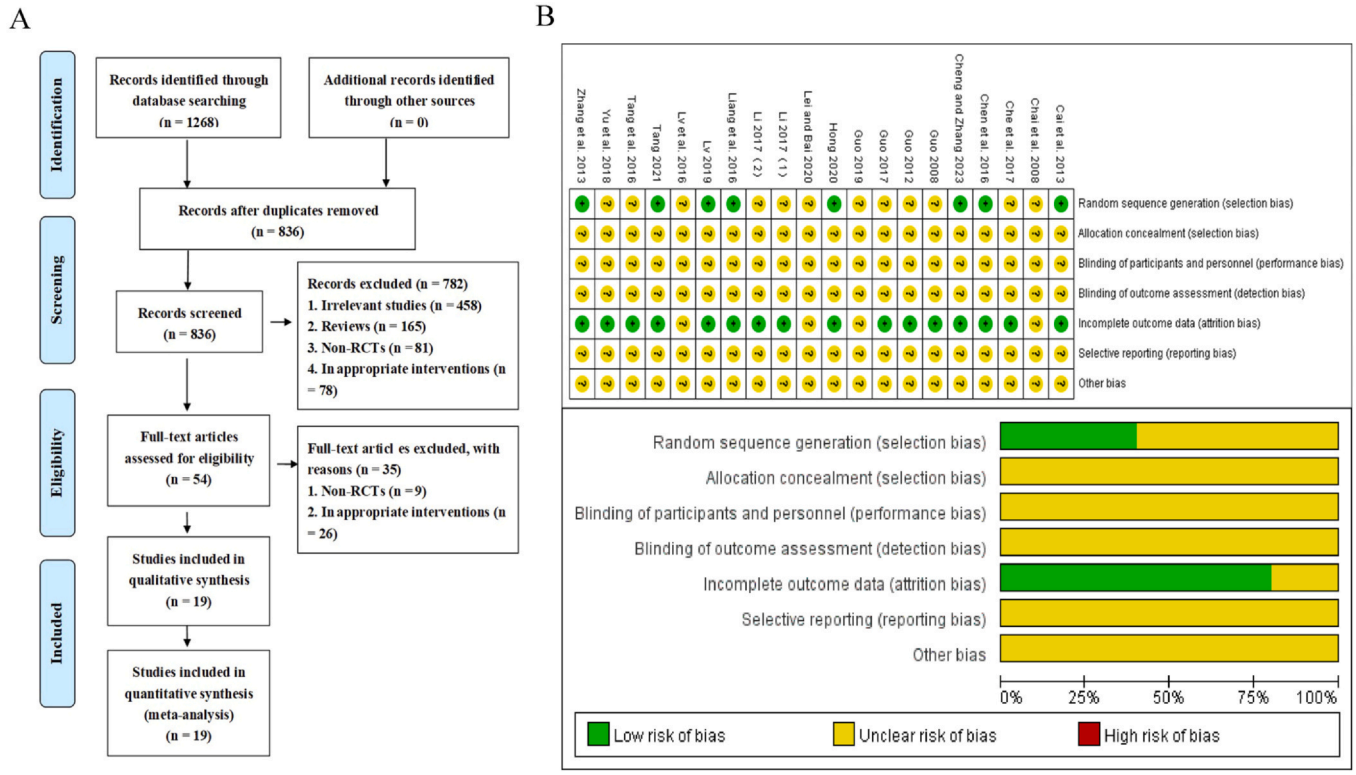
Seven RCTs reported blood lipid levels. The meta-analyses showed more significant improvements in blood lipid levels in the 'CDDP plus anti-platelet drugs' group than 'anti-platelet drugs alone' group [Total Cholesterol (TC), N = 6, MD = 1.23, 95 % CI: 0.60–1.86, $P = 0.0001$; Total Glyceride (TG), N = 7, MD = 0.97, 95 % CI: 0.53–1.42, $P < 0.0001$; High Density Lipoprotein (HDL), N = 6, MD = 0.51, 95 % CI: 0.16–0.86, $P = 0.004$; Low Density Lipoprotein (LDL), N = 6, MD = 1.13, 95 % CI: 0.48–1.77, $P = 0.0006$].

Five RCTs reported adverse drug reaction. The meta-analysis showed no statistically significant difference in the incidence of adverse drug reaction between the 'CDDP plus anti-platelet drugs' group and 'anti-platelet drugs alone' group (RR = 0.71, 95 % CI: 0.29–1.73, $P = 0.45$). In the 'CDDP plus anti-platelet drugs' group, adverse drug reactions included gastrointestinal tract burning sensation, nausea, vomiting, minor bleeding, abnormal glutamic oxalacetic transaminase, dizziness and allergy. In the 'anti-platelet drugs alone' group, adverse drug reactions included gastrointestinal tract burning sensation, nausea, vomiting, breathing difficulties, minor bleeding, abnormal glutamic oxalacetic transaminase, dizziness and allergy.

Network pharmacology analysis results

There were 156 gene targets associated with *Salvia miltiorrhiza* Bunge and 51 associated with *Panax notoginseng* (Burkill) F.H. Chen that were obtained from the HERB database. A total of 2391 target genes related to platelet aggregation were extracted from the GeneCards database. Eighty-six overlapping target genes between CDDP and platelet aggregation were identified (Fig. 2A) and the interactions among these genes were subsequently analyzed to elucidate their relationship (Fig. 2B). The network of CDDP-genes-pathways-platelet aggregation was shown in Fig. 2C. Then, the overlapping targets were imported into Metascape database to perform GO enrichment and KEGG enrichment analysis. The results of GO enrichment analysis showed that the effect of CDDP against platelet aggregation might be associated with "positive regulation of gene expression", "extracellular space", "extracellular region", "identical protein binding" and "enzyme bingding" (Fig. 2D). The KEGG enrichment analysis showed that the overlapping targets were enriched in pathways related to the cause or symptom of platelet aggregation, such as "lipid and atherosclerosis", "fluid shear stress and atherosclerosis", "TNF signaling pathway", "VEGF signaling pathway" PI3K-Akt signaling pathway and "platelet activation" (Fig. 2E).

Modern researches have showed that abnormal platelet function is a common clinical manifestation of blood stasis syndrome in TCM, and platelet aggregation hyperfunction is one of the clinical diagnostic criteria of blood stasis syndrome.[14] Many TCM and their effective components can promote blood circulation and remove blood stasis by depolymerizing platelet aggregation. For instance, panax notoginseng saponins can reduce the concentration of TXA2 and TXB2, as well as inhibit the activity of PLCγ2 enzyme. This protective effect helps to prevent endothelial cell damage and reduce platelet adhesion, ultimately improve anti-platelet aggregation and anti-thrombosis effects under pathological conditions.[15,16] Tanshinone A, B and C can inhibit platelet activation, dilate arterioles, speed up blood flow, protect vascular endothelium and inhibit platelet aggregation, and then change blood rheology and microcirculation.[17–20] After searching the SymMap database, the top 5 herbs (*Chuanxiong Rhizoma, Salviae miltiorrhizae Radix et Rhizoma, Notoginseng Radix Et Rhizoma, Carthami Flos and Curcumae Longae Rhizoma*) for treating blood stasis symptoms were obtained, which included the main active herbs of CDDP (Fig. 2**F**).



C

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Chai et al. 2008	10.36	7.1	10	-0.29	6.22	10	3.5%	1.53 [0.50, 2.55]	2008
Guo 2008	9.53	5.35	30	1.78	6.03	30	4.9%	1.34 [0.78, 1.91]	2008
Guo 2012	32.31	8.51	50	2.96	7.1	53	4.7%	3.73 [3.08, 4.37]	2012
Zhang et al. 2013	4.35	4.49	20	0.33	2.03	19	4.5%	1.12 [0.44, 1.80]	2013
Cai et al. 2013	40.55	3.73	34	37.99	3.67	35	5.1%	0.68 [0.20, 1.17]	2013
Chen et al. 2016	25	5.57	36	-1	5.29	36	3.8%	4.74 [3.82, 5.66]	2016
Liang et al. 2016	30.55	9.86	60	20.36	10.2	60	5.4%	1.01 [0.63, 1.39]	2016
Lv et al. 2016	24.72	7.81	64	16.94	6.97	64	5.5%	1.04 [0.67, 1.41]	2016
Tang et al. 2016	25	7	49	17	7.21	49	5.3%	1.12 [0.69, 1.54]	2016
Che et al. 2017	24.46	6.29	50	17.12	8.14	50	5.3%	1.00 [0.58, 1.42]	2017
Guo 2017	10.3	6.95	20	-0.32	5.92	20	4.4%	1.61 [0.89, 2.34]	2017
Li 2017 (1)	17.19	12.91	30	8.34	13.65	30	5.0%	0.66 [0.14, 1.18]	2017
Li 2017 (2)	18.56	16.07	30	9.86	16.47	30	5.1%	0.53 [0.01, 1.04]	2017
Yu et al. 2018	23.34	7.77	160	17.66	7.75	160	5.8%	0.73 [0.50, 0.96]	2018
Guo 2019	34.91	8.82	54	30.84	8.8	54	5.4%	0.46 [0.08, 0.84]	2019
Lv 2019	26.25	8.2	40	15.48	7.38	40	5.1%	1.37 [0.88, 1.86]	2019
Hong 2020	25.4	8.82	53	16.06	9.2	53	5.4%	1.03 [0.62, 1.43]	2020
Lei and Bai 2020	5.85	2.18	60	3.53	2.34	60	5.4%	1.02 [0.64, 1.40]	2020
Tang 2021	27.94	7.42	31	18.66	7.62	31	5.0%	1.22 [0.67, 1.76]	2021
Cheng and Zhang 2023	28.67	10.12	51	19.52	9.85	51	5.4%	0.91 [0.50, 1.32]	2023
Total (95% CI)			**932**			**935**	**100.0%**	**1.27 [0.97, 1.57]**	

Heterogeneity: Tau² = 0.39; Chi² = 159.40, df = 19 (P < 0.00001); I² = 88%
Test for overall effect: Z = 8.34 (P < 0.00001)

Fig. 1. PRISMA flow diagram, bias of risk assessment results and forest plot of meta-analysis on platelet aggregation rate. (A) The PRISMA flow diagram; (B) Risk of bias assessment results; (C) Forest plot of meta-analysis on platelet aggregation rate.

Experimental validation results

CDDP inhibits thrombosis in mouse tail vein, liver and lung

In order to preliminarily explore whether CDDP can inhibit thrombosis and also compare the efficacy of CDDP and aspirin/clopidogrel, BALB/c mice were treated as described in Fig. 3A. To summarize, mice received intragastric administration of vehicle (PBS), CDDP, aspirin/clopidogrel or CDDP plus aspirin/clopidogrel daily for 9 days. On day 7, the mice in groups 2, 3, 4 and 5 were intraperitoneally injected with 1 % carrageenan solution (equal to 50 mg/kg bodyweight). Two days after the carrageenan injection, severe thrombi were observed in the mice tails, especially in group 2. However, CDDP treatment substantially inhibited thrombosis progression, and the dark colored regions in the tails of mice receiving CDDP were shorter than group 2. The thrombosis rate (defined as the ratio of the tail length with thrombosis to whole tail length) significantly decreased, which indicated the thrombo-protective effects of CDDP. Its effectiveness was comparable to that of aspirin combined with clopidogrel, and the combination of all the three drugs showed the greater anti-thrombotic effect (Fig. 3B).

To further confirm the anti-thrombotic effects of CDDP, HE staining of tails sections at different locations (defined as the distances from mouse tail tip) was analyzed. In tail vessels of group 2 mice, severe thrombosis occurred at different locations. At 2 and 4 cm from the tail tip, thrombi were formed throughout the entire vessel. More than three-fifths of the vessel (~60 %) was still occluded by thrombi at the location of 6 cm from the tail tip. By contrast, CDDP inhibited thrombogenesis in the mouse tail vessel, although the vessel at the location of 2 cm from the tail tip was occluded by thrombi (~80 % in groups 3), the clots took up half the area of the vessel at the 4 cm position, while a

Table 2
Characteristics of included studies.

Author and Publication year	Disease	Sample size (E)	Sample size (C)	Intervention (E)	Intervention (C)	Dosage of CDDP	Duration of CDDP	Duration of (C)	Outcomes
Chai et al. 2008	AR	10	10	Aspirin + CDDP	Aspirin	10 pieces tid	2 weeks	2 weeks	PAR
Guo 2008	UAP	30	30	Aspirin + CDDP	Aspirin	10 pieces tid	1 month	1 month	PAGM, TXB2, ADR
Guo 2012	Hypertension	50	53	Aspirin + CDDP	Aspirin	270 mg tid	1 month	1 month	PAR
Zhang et al.2013	CHD	20	19	Aspirin + CDDP	Aspirin	10 pieces tid	1 month	1 month	PAR, SLL
Cai et al.2013	UAP	34	35	Aspirin + Clopidogrel + CDDP	Aspirin + Clopidogrel	270 mg bid	3 weeks	3 weeks	PAR, TXB2
Chen et al.2016	SAP with AR	36	36	Aspirin + CDDP	Aspirin	10 pieces tid	1 month	1 month	PAR
Liang et al.2016	CHD	60	60	Aspirin + CDDP	Aspirin	270 mg tid	6 months	6 months	PAGM, TXB2, ADR
Lv et al.2016	CHD	64	64	Aspirin + CDDP	Aspirin	10 pieces tid	2 months	2 months	PAGM, TXB2, SLL
Tang et al.2016	CHD	49	49	Aspirin + CDDP	Aspirin	10 pieces tid	3 months	3 months	PAGM, TXB2, SLL
Che et al.2017	CHD	50	50	Aspirin + CDDP	Aspirin	3 pieces tid	1 month	1 month	PAGM, TXB2
Guo 2017	AR	20	20	Aspirin + CDDP	Aspirin	10 pieces tid	2 weeks	2 weeks	PAR
Li 2017(1)	ACS	30	30	Aspirin + Clopidogrel + CDDP	Aspirin + Clopidogrel	10 pieces tid	1 month	1 month	PAR
Li 2017(2)	ACS	30	30	Aspirin + Clopidogrel + CDDP	Aspirin + Clopidogrel	10 pieces tid	1 month	1 month	PAR
Yu et al.2018	CHD	160	160	Aspirin + CDDP	Aspirin	10 pieces tid	6 months	6 months	PAGM, TXB2, SLL
Guo 2019	ACS	54	54	Clopidogrel + CDDP	Clopidogrel	10 pieces tid	2 months	2 months	PAR, ADR
Lv 2019	CHD	40	40	Aspirin + CDDP	Aspirin	10 pieces tid	3 months	3 months	PAGM, TXB2, SLL, ADR
Hong 2020	CHD	53	53	Aspirin + CDDP	Aspirin	10 pieces tid	3 months	3 months	PAGM, TXB2, SLL
Lei and Bai 2020	CHF with ventricular arrhythmia	60	60	Clopidogrel + CDDP	Clopidogrel	270 mg tid	2 months	2 months	PAR
Tang 2021	CHD with bone injury	31	31	Aspirin + CDDP	Aspirin	10 pieces tid	2 months	2 months	PAGM, TXB2
Cheng and Zhang 2023	CHD	51	51	Aspirin + CDDP	Aspirin	10 pieces tid	13 weeks	13 weeks	PAGM, TXB2, SLL, ADR

E: experimental group; C: control group; AR: aspirin resistance; SAP: stable angina; UAP: unstable angina; CHD: *coronary heart disease*; CHF: chronic heart failure; ACS: acute coronary syndrome; PAR: platelet aggregation rate; PAGM: maximum platelet aggregation rate; TXB2: thromboxane B2; ADR: adverse drug reaction; SLL: serum lipid levels

Table 3
Subgroup analyses of platelet aggregation rate.

Grouping methods	Number of included studies	Number of participants (E/C)	SMD (95 % CI)*
Subgroup analyses based on intervention duration			
2 weeks	2	30/30	1.58(0.99, 2.17)
3 weeks	1	34/35	0.68(0.20, 1.17)
1 month	7	246/248	1.84(0.85, 2.82)
2 months	4	209/209	0.92(0.59, 1.24)
13 weeks/3 months	4	193/193	1.08(0.87, 1.30)
6 months	2	220/220	0.83(0.57, 1.09)
Subgroup analyses based on patients with/without aspirin resistance			
Patients without aspirin resistance	15	796/797	0.92(0.79, 1.05)
Patients with aspirin resistance	5	136/138	2.54(1.18, 3.90)
Subgroup analyses based on types of anti-platelet drugs			
Aspirin	15	724/726	1.50(1.12, 1.88)
Clopidogrel	2	114/114	0.74(0.19, 1.29)
Aspirin + Clopidogrel	3	94/95	0.63(0.33, 0.92)

E: experimental group; C: control group; SMD: standardized mean difference; CI: confidence interval; *: Random-effect mode

low rate of thrombi (~10–20 %) was detected at the 6 cm position, which illustrated the protective effect of CDDP on the thrombosis in mice (Fig. 3**C**).

When endothelial damage occurs, collagen is exposed from the subendothelial matrix, resulting in platelet activation and subsequent thrombus formation. Therefore, intrathrombotic collagen contents can indicate thrombotic masses. By conducting Masson trichrome staining of tail cross sections at the 2 cm position, we found that compared with group 2, CDDP treatment reduced collagen content (Fig. 3D). MMP-2 is an important modulator for collagen degradation, associated with the collagen content. We observed the increase of MMP-2 expression after CDDP treatment (Fig. 3E).

Except for the tail vessels, carrageenan injection can induce the formation of thrombi in other tissues.[21,22] Consistent with the staining of the tails, we found multiple severe thrombi in mouse liver and lung vessels (Group 2, Fig. 3 F, G), while CDDP inhibited thrombi formation (Group 3, Fig. 3 F, G).

CDDP regulates the levels of coagulation molecule and inflammatory factor

P-selectin is a platelet activation dependent granule external membrane protein that mediates the interaction between activated platelets and endothelial cells. TXA2 is a bioactive substance that promotes vasoconstriction strongly and platelet aggregation synthesized and released by platelet microsomes and has a biological half-life of approximately 30 s before being rapidly metabolized into inactive TXB2. The circulating P-selectin and TXB2 are considered as biomarkers of thrombosis.[23] The results in Fig. 4**A** show that the circulating P-selectin level in serum was reduced by CDDP, compared to the high levels of P-selectin in group 2, which further confirmed the anti-thrombotic effects of CDDP.

The changes in the expression of some thrombosis-related genes were also seen. We found that MMP-2 mRNA expression was increased after CDDP treatment, while P-selectin was decreased in lung and liver tissues. TNF-α, an important inflammatory cytokine increasing thrombosis, was also down-regulated by CDDP treatment (Fig. 4 C, D). Therefore, CDDP largely inhibits thrombus formation. Aspirin in combination with clopidogrel also achieve similar results. Meanwhile, the combination of the three drugs could play a stronger effect.

3.3.2. CDDP protects HUVECs survival against LPS-induced cell injury

To determine whether CDDP can protect endothelial cells from inflammation, we treated HUVECs with LPS, or LPS plus CDDP at different concentrations to determine the cell viability. LPS significantly reduced HUVECs viability, which was improved by CDDP treatment in a dose-dependent manner (Fig. 5**A**). Aspirin combined with clopidogrel also caused cytotoxicity, whereas CDDP provided a certain protective role.

Both TL1A and VEGF can affect endothelial cells (ECs) survival. Therefore, we assessed the effects of CDDP on their expression. We found that LPS activated the expression of TL1A, while CDDP inhibited this activation. Correspondingly, LPS inhibited the expression of VEGF-α, while CDDP reversed this inhibition (Fig. 5B). They suggest the strong protective effect of CDDP against cell injury.

CDDP inhibits inflammation-activated adhesion of platelets or monocytes to HUVECs and attenuates platelet aggregation

To determine whether CDDP inhibits thrombosis by inhibiting platelet adhesion to HUVECs. HUVECs were pretreated with ox-LDL, which produces moderate inflammatory conditions and enhances platelet adhesion to HUVECs.[24,25] The results in Fig. 5C show that the adhesion of platelets to HUVECs was significantly increased by ox-LDL. However, after CDDP treatment, the increase was significantly reduced, which indicated that CDDP had a strong anti-platelet adhesion effect. The adhesion of monocytes to activated ECs is greatly involved in initiation of thrombus formation. LPS can induce inflammatory activation of ECs, which enhances monocytes adhesion to ECs. We observed that LPS treatment significantly increased the adhesion between THP-1 cells and HUVECs, while CDDP treatment significantly reduced this adhesion (Fig. 5D).

Tissue factor (TF) is related to thrombosis, while tissue factor pathway inhibitor (TFPI) inhibits platelet adhesion to HUVECs. Fig. 5E shows that TF was activated while TFPI was inhibited as ox-LDL increased platelet adhesion to HUVECs. However, CDDP not only reduced ox-LDL-activated TF expression, but also partially restored ox-LDL-inhibited TFPI expression. In addition, CDDP significantly restrained LPS-induced increases in the expression of ICAM-1 and VCAM-1 (Fig. 5F), which weakened the adhesion between monocytes and ECs.

Thrombin triggers the retraction of platelet clots, which is an important step in the process of thrombus consolidation. As shown in Fig. 5G, H, human platelet clots were clearly observed in the control group after the addition of thrombin. CDDP treatment significantly slowed thrombin-induced platelet clot retraction. The dose of 0.125 and 0.25 mg/mL of CDDP had the good anticoagulant effects.

Discussion

Platelets are important components in blood, responsible for adhesion, aggregation and release upon activation.[26] When the vascular wall is damaged, platelet activation is typically regulated and participates in the coagulation process. However, when platelets are excessively stimulated by inducers, such as collagen, thrombin, platelet activating factor or adenosine diphosphate, their adhesion, aggregation, release and metabolic capabilities are intensified.[27] This excessive aggregation results in thrombus formation and contributes to inflammatory reactions. During the process of platelet activation and thrombus formation,

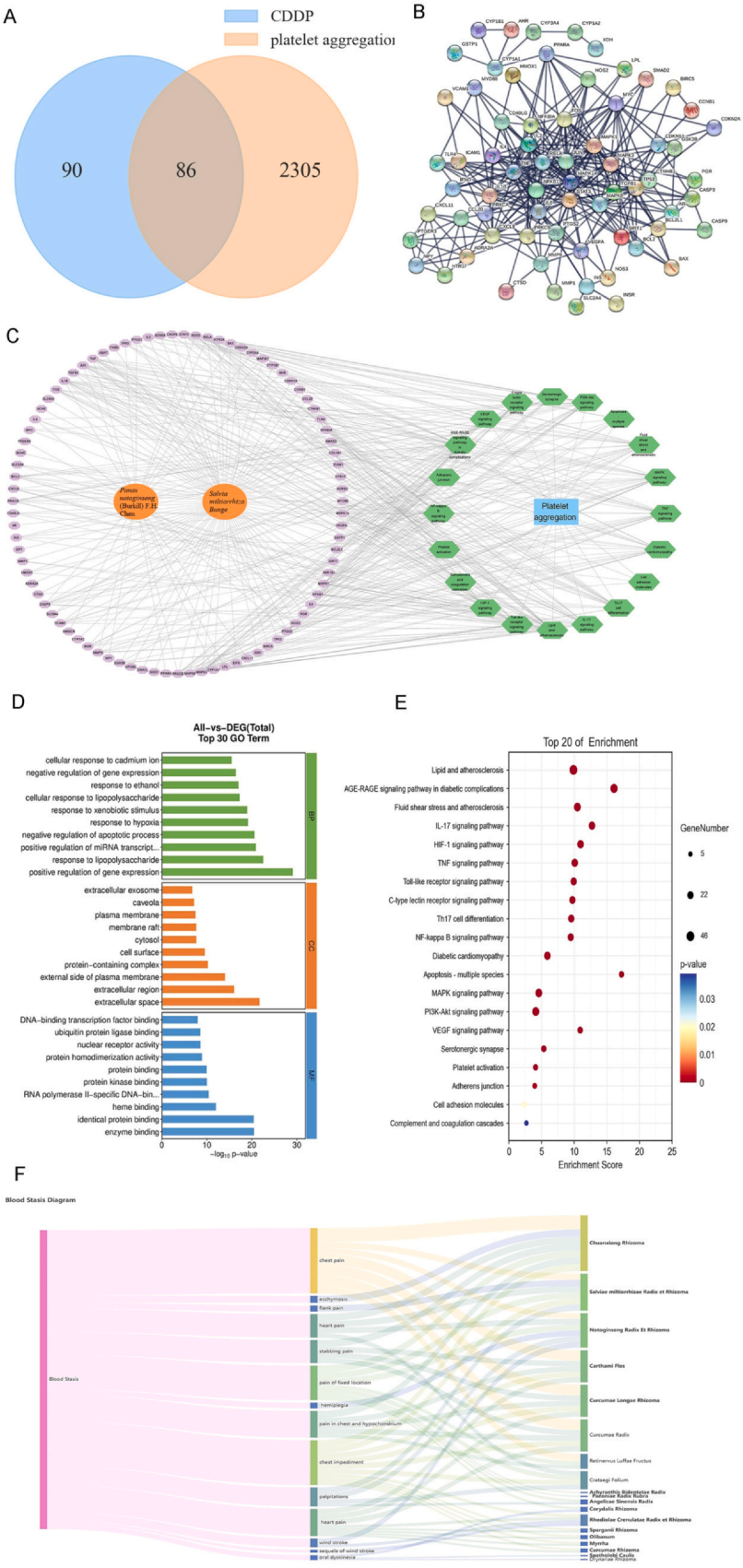


Fig. 2. Network pharmacology analysis on CDDP against platelet aggregation. (A) The number of overlapping target genes between CDDP and platelet aggregation; (B) The PPI of overlapping target genes between CDDP and platelet aggregation; (C) The network of CDDP-genes-pathways-platelet aggregation; (D) The results of GO enrichment analysis; (E) The results of KEGG enrichment analysis; (F) TCM for promoting blood circulation and removing blood stasis.

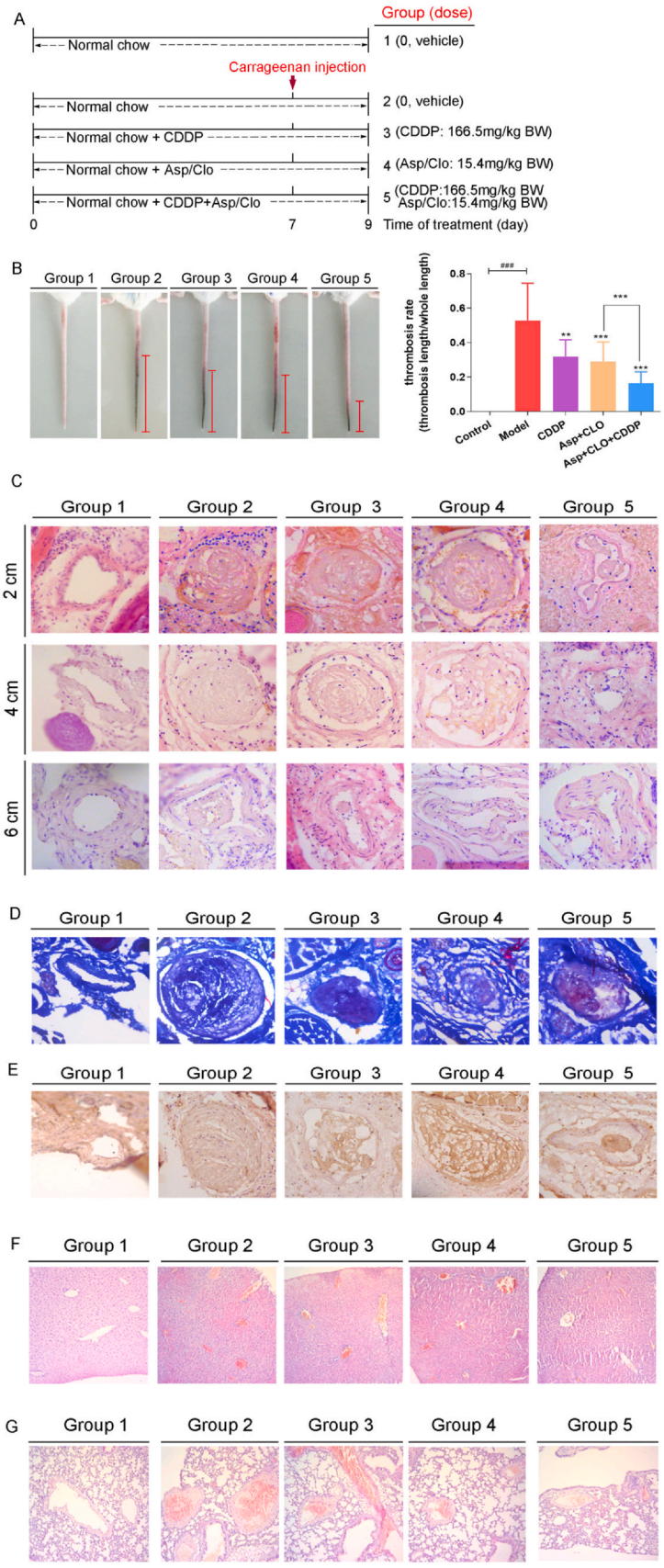


Fig. 3. CDDP inhibits carrageenan-induced thrombosis in mouse tail vein, liver and lung tissues. (A) Mouse grouping and establishment of thrombus model (experimental design); (B) Mouse tails were photographed and showed the representative photographs; the thrombosis rate (the ratio of tail length with thrombus to whole tail length) was calculated in this experiment; (C) The cross sections of tail at the different locations were prepared for the HE staining assays; (D) Masson trichrome staining of tail cross sections at the 2-cm position; (E) Immunohistochemical staining with anti-MMP-2 antibody; (F, G): liver (F) and lung (G) paraffin sections were prepared for HE staining. $^{###}P < 0.001$ *vs.* Control; $^{**}P < 0.01$, $^{***}P < 0.001$ *vs.* Model ($n = 10$).

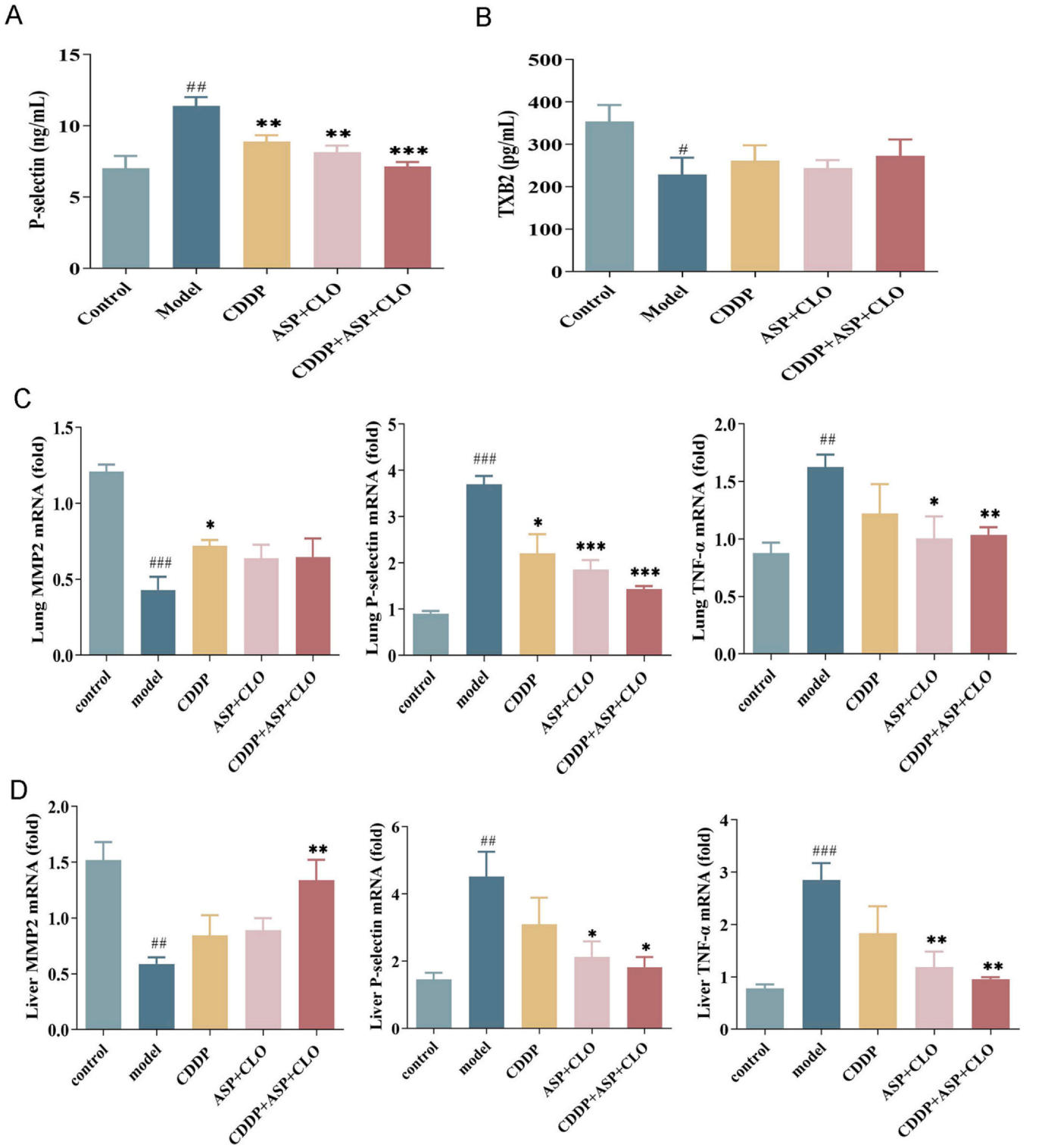


Fig. 4. CDDP inhibits the levels of collagen content in mouse serum, lungs and livers tissue. (A, B) The serum P-selectin (A) and TXB2 (B) levels were determined by ELISA kit; (C, D) The expression of MMP-2, P-selectin and TNF-α mRNA in lung (C) and liver (D) tissue were determined by qRT-PCR. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ *vs.* Control; $^{**}P < 0.01$, $^{***}P < 0.001$ *vs.* Model ($n = 6$).

the release of bioactive substances such as P-selectin, TXA_2, TXB_2, MMP2, and TNF-α from platelets can further damage vascular endothelium, increase platelet aggregation and promote thrombosis, and then exacerbate the occurrence and development of many pathological conditions.[28,29]

The meta-analysis revealed that CDDP plus anti-platelet drugs could more significantly reduce platelet aggregation rate and improve blood lipid levels (TC, TG, HDL and LDL) than anti-platelet drugs alone. Blood stasis syndrome and 'promoting blood circulation and removing blood stasis' are the hot spots in the Chinese and Western Integrative Medicine. The underlying mechanisms of the formation and progression of blood stasis syndrome may be associated with activation, aggregation, and release phases of platelets.[30,31] CDDP is a commercial Chinese polyherbal preparation for promoting blood circulation and removing

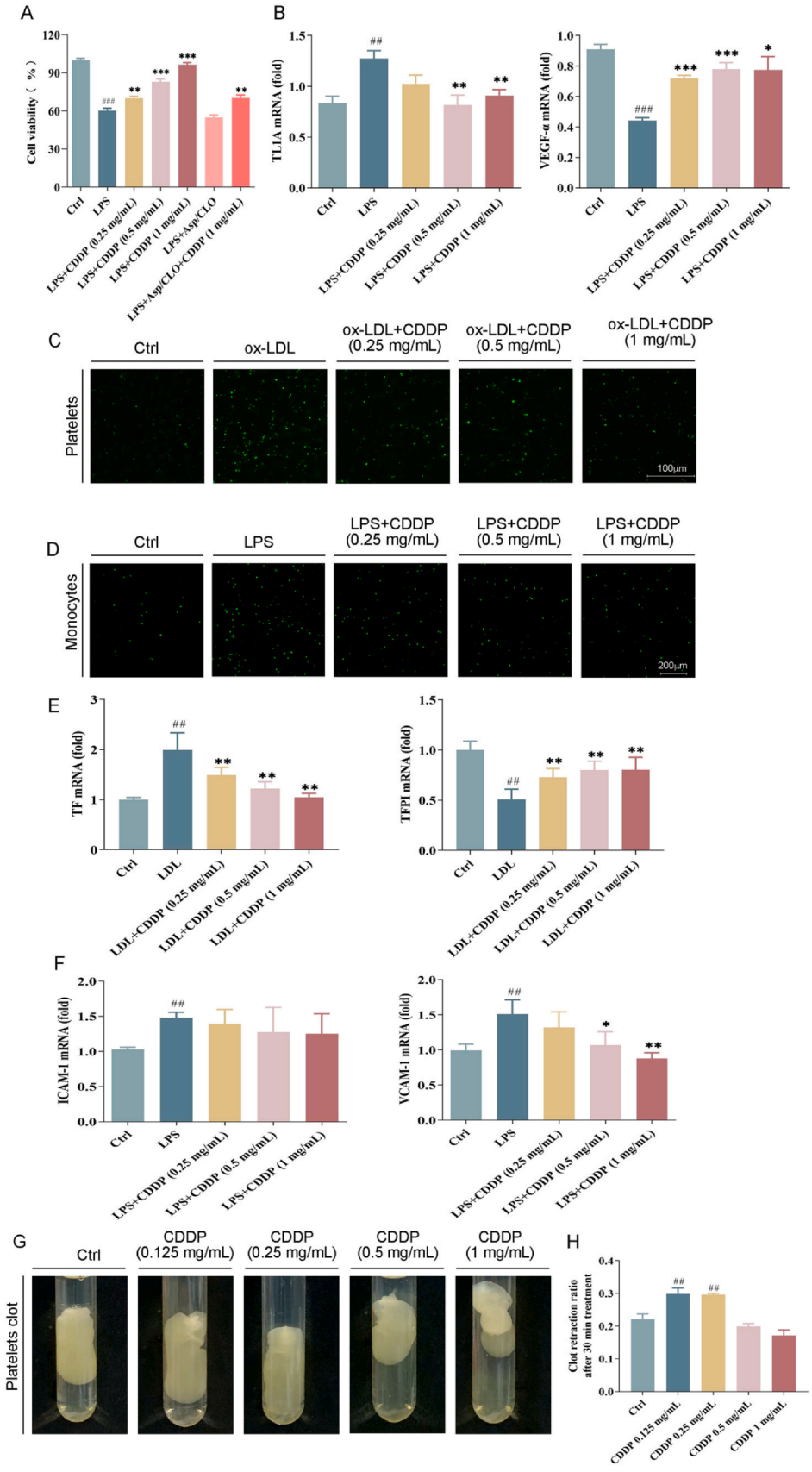


Fig. 5. CDDP protects HUVECs against LPS induced cell death and inhibits adhesion of HUVECs with platelets or monocytes. (A) CDDP improved the cell viability of HUVECs induced by LPS; (B) The expression of TL1A and VEGF-α mRNA in HUVECs was determined by qRT-PCR; (C, D) HUVECs in 24-well plates were treated with ox-LDL (100 μg/mL) and ox-LDL plus CDDP (C) or LPS (1 mg/mL) and LPS plus CDDP (D), the platelets (C) or THP-1 monocytes (D) were added to HUVECs for incubation at 37°C, then photographed by a fluorescent microscope; (E) The expression of TF and TFPI mRNA in platelet adhesion to HUVECs induced by ox-LDL; (F) The expression of ICAM-1 and VCAM-1 mRNA in monocytes adhesion to HUVECs induced by LPS; (G) Thrombin and CDDP were added to the platelet suspension and fully mixed, and then the clot was photographed. (H) The clot retraction ratio after 30 min treatment with CDDP. $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ *vs.* Control; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs.* LPS or LDL.

blood stasis. Based on the results of network pharmacology analysis, we speculated that CDDP might regulate platelet aggregation *via* the 'TNF', 'PI3K-Akt' or 'VEGF' signal pathway. These pathways on platelet aggregation have also been confirmed in previous studies.[32–34] Therefore, we further used *in vitro* and *in vivo* experiments to verify the hypothesized potential mechanism. In the basic experiments, CDDP combined with aspirin and clopidogrel had a better effect in inhibiting thrombus compared with CDDP alone or 'aspirin plus clopidogrel', which was also proved intuitively by the lowered tail thrombosis rate. Notably, after CDDP combined with aspirin and clopidogrel treatments, there was a significant reduction in thrombosis within the liver and lung tissues, and the P-selectin and TNF-α associated with thrombogenesis were also decreased. The cell viability assay showed that CDDP had a protective effect on cells and could slightly mitigate the cytotoxicity caused by the combination of aspirin and clopidogrel. Additionally, the results of reducing the adhesion of monocytes and platelets to endothelial cells, decreasing the expression of tissue factors (TL1A, ICAM-1, VCAM-1) and increasing the expression of tissue factor pathway inhibitors (VEGF, TFPI) demonstrated that CDDP might effectively inhibit platelet coagulation and relieve thrombosis.

Thrombosis is an important factor affecting the prognosis of diseases. However, the relevant preventive and therapeutic measures are limited. The novelty and scientific value of this study lies in proving the role of CDDP in anti-platelet aggregation through the integration of research methods. Nevertheless, this study still has some limitations. Firstly, the sample sizes in the included RCTs are relatively small. Secondly, the results from network pharmacology analysis should be interpreted cautiously because of any unknown potential bias. Thirdly, the CDDP-containing serum was not utilized in the study of HUVECs cells. Finally, it cannot directly confirm the independent anti-platelet effect of CDDP.

Conclusion

The integrated study of meta-analysis, network pharmacology and *in vitro* and *in vivo* experiments suggests that CDDP have a potential anti-platelet aggregation effect. It may provide a new option for anti-platelet aggregation in clinical practice.

List of abbreviations

CDDP	Compound Danshen Dripping Pill
CIs	confidence intervals
HUVECs	human umbilical vein endothelial cells
ICAM-1	intercellular adhesion molecule-1
MD	mean difference
MMP2	matrix metalloproteinase 2
Ox-LDL	oxidized low-density lipoprotein
RCTs	randomized controlled trials
RR	relative risk
SMD	standardized mean difference
TCM	traditional Chinese medicine
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TL1A	tumor necrosis factor–like cytokine 1A
TNF-α	tumor necrosis factor α
TXB2	thromboxane B2
VCAM-1	vascular cell adhesion molecule-1
VEGF-α	vascular endothelial growth factor α

Declarations

Not applicable.

Authors' contributions

Bo Pang, Haofan Xu: Writing-original draft, Statistical analysis. **Zhouyi Xie:** Methodology. **Yi Chen, Mengying Zhang:** Data collection and collation. **Yu Wei, Qian Zhao:** Conceptualization, Formal analysis. **Wenjia Wang:** Supervision. **Jingbo Zhai, Yunhui Hu:** Writing – review & editing, Funding acquisition, Project administration.

Ethics approval and consent to participate

The animal studies were granted by the Ethics Committee of Nankai University (Tianjin, China; Approval number: 2023-SYDWLL-000638) and the studies were performed in compliance with the Guide for the Care and Use of Laboratory Animals (Publications No. 8023, revised 1978) published by the National Institutes of Health (NIH).

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This research was funded by Tianjin Natural Science Foundation, grand number: 22JCYBJC00180.

Declarations of Competing Interests

Bo Pang, Yu Wei, Mengying Zhang, Qian Zhao, Wenjia Wang and Yunhui Hu are employed by Tianjin Tasly Digital Intelligence Chinese Medicine Technology Co., Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Acknowledgements

Not applicable.

Authors' other information

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prmedi.2025.100062.

References

1. Mailer RK, Kuta P, Renné T. An Update on Safe Anticoagulation [J]. *Hamostaseologie.* 2022;42(1):65–72.
2. Koupenova M, Kehrel BE, Corkrey HA, et al. Thrombosis and platelets: an update [J]. *Eur Heart J.* 2017;38(11):785–791.
3. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity [J]. *Nat Rev Immunol.* 2013;13(1):34–45.
4. Patrono C, Andreotti F, Arnesen H, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis [J]. *Eur Heart J.* 2011;32(23):2922–2932.
5. Luo JC, Peng YL, Chen TS, et al. Clopidogrel inhibits angiogenesis of gastric ulcer healing via downregulation of vascular endothelial growth factor receptor 2 [J]. *J Formos Med Assoc.* 2016;115(9):764–772.
6. Zheng AS, Churilov L, Colley RE, et al. Association of aspirin resistance with increased stroke severity and infarct size [J]. *JAMA Neurol.* 2013;70(2):208–213.
7. Hankey GJ, Eikelboom JW. Aspirin resistance [J]. *Lancet.* 2006;367(9510):606–617.
8. Nicola H, Ho KM. Aspirin Resistance Incidence and Associations Between Aspirin Effect and Outcomes in Cardiac Surgery [J]. *Ann Thorac Surg.* 2019;108(6):1815–1821.

9. Yi X, Zhou Q, Lin J, et al. Aspirin resistance in Chinese stroke patients increased the rate of recurrent stroke and other vascular events [J]. *Int J Stroke.* 2013;8(7):535–539.
10. Zhao Y, Yang S, Wu M. Mechanism of Improving Aspirin Resistance: Blood-Activating Herbs Combined With Aspirin in Treating Atherosclerotic Cardiovascular Diseases [J]. *Front Pharm.* 2021;12:794417.
11. Chen H, Shen Z, Chen J, et al. Chinese Herbal Medicine for Aspirin Resistance: A Systematic Review and Meta-Analysis [J]. *PLoS One.* 2016;11(5):e0154897.
12. Liao W, Ma X, Li J, et al. A review of the mechanism of action of Dantonic(®) for the treatment of chronic stable angina [J]. *Biomed Pharm.* 2019;109:690–700.
13. Cao BY, Chen JL, Shi XX, et al. Mechanism of Compound Danshen Dripping Pills against myocardial ischemiabased on LOX-NF-κB pathway [J]. *Chin Herb Med.* 2023;54(01):151–159.
14. Chen C, Wang F, Xiao W, et al. Effect on platelet aggregation activity: extracts from 31 Traditional Chinese Medicines with the property of activating blood and resolvingstasis [J]. *J Tradit Chin Med.* 2017;37(1):64–75.
15. Xu ZY, Xu Y, Xie XF, et al. Anti-platelet aggregation of Panax notoginseng triol saponins by regulating GP1BA for ischemic stroke therapy [J]. *Chin Med.* 2021;16(1):12.
16. Liu Y, Liu T, Ding K, et al. Phospholipase Cγ2 Signaling Cascade Contribute to the Antiplatelet Effect of Notoginsenoside Fc [J]. *Front Pharm.* 2018;9:1293.
17. Gao YH, Wu JX. Advances in research on anti-platelet mechanism of Chinese herbs for promoting blood circulation and removing blood stasis [J]. *Contemp Med.* 2019;25(35):190–192.
18. Chen Y, Zhang N, Ma J, et al. A Platelet/CMC coupled with offline UPLC-QTOF-MS/MS for screening antiplatelet activity components from aqueous extract of Danshen [J]. *J Pharm Biomed Anal.* 2016;117:178–183.
19. Zou J, Chen Y, Hoi MPM, et al. Discovery of a Novel ERp57 Inhibitor as Antiplatelet Agent from Danshen (Salvia miltiorrhiza) [J]. *Evid Based Complement Altern Med.* 2018;2018:9387568.
20. Xu S, Zhong A, Bu X, et al. Salvianolic acid B inhibits platelets-mediated inflammatory response in vascular endothelial cells [J]. *Thromb Res.* 2015;135(1):137–145.
21. Liu SQ, Guo JY, Du J, et al. Anticoagulant effect of Huisheng Oral Solution in a rat model of thrombosis [J]. *Indian J Pharm.* 2013;45(4):359–364.
22. Zhang YL, Xi MZ, Choi YB, et al. Antithrombotic Effect of Fermented Ophiopogon japonicus in Thrombosis-Induced Rat Models [J]. *J Med Food.* 2017;20(7):637–645.
23. Cambien B, Wagner DD. A new role in hemostasis for the adhesion receptor P-selectin [J]. *Trends Mol Med.* 2004;10(4):179–186.
24. Qiu MK, Wang SC, Tang Y, et al. Tim-3 inhibits low-density lipoprotein-induced atherogenic responses in human umbilical vein endothelial cells [J]. *Oncotarget.* 2017;8(37):61001–61010.
25. Chen R, Chen X, Salomon RG, et al. Platelet activation by low concentrations of intact oxidized LDL particles involves the PAF receptor [J]. *Arterioscler Thromb Vasc Biol.* 2009;29(3):363–371.
26. Holinstat M. Normal platelet function [J]. *Cancer Metastas Rev.* 2017;36(2):195–198.
27. Wang F, Chen Q, Xia Z, et al. The Application of Platelets in the Research of Traditional Chinese Medicine for Promoting Blood Circulation and Resolving Stasis [J]. *China J Chin Mater Med.* 2014;39(16):2993–3003.
28. Yan LG, Ruan JS, Zhang L, et al. Effect of aqueous extracts of several kinds of herbs on human platelet aggregation and expression of P-selectin in vitro [J]. *Chin J Integr Med.* 2015;21(4):286–290.
29. Xiao S, Ding S, Sun Z, et al. Platelet function tests and Chinese medicine with antiplatelet function:a review [J]. *China J Chin Mater Med.* 2021;46(19):4907–4921.
30. Li Y, Sun MQ, Li L, et al. Application and Prospect of Platelet Multi-Omics Technology in Study of Blood Stasis Syndrome [J]. *Chin J Integr Med.* 2022;28(2):99–105.
31. Wang ZY, Li L, Liu JX, et al. Research progress of change of platelet in blood stasis syndrome and effect of traditional Chinese medicine [J]. *Chin J Chin Mater Med.* 2021;46(20):5201–5209.
32. Oggero S, De Gaetano M, Marcone S, et al. Extracellular vesicles from monocyte/platelet aggregates modulate human atherosclerotic plaque reactivity [J]. *J Extra Vesicles.* 2021;10(6):12084.
33. Dong J, Lin J, Wang B, et al. Inflammatory cytokine TSLP stimulates platelet secretion and potentiates platelet aggregation via a TSLPR-dependent PI3K/Akt signaling pathway [J]. *Cell Physiol Biochem.* 2015;35(1):160–174.
34. Arisato T, Hashiguchi T, Sarker KP, et al. Highly accumulated platelet vascular endothelial growth factor in coagulant thrombotic region [J]. *J Thromb Haemost.* 2003;1(12):2589–2593.