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Efficacy and safety of caffeic acid tablets in the treatment of thrombocytopenia
A systematic review and meta-analysis

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Abstract

Background: Caffeic acid tablets (CFA) are a proprietary Chinese medicine in treating thrombocytopenia. The efficacy and safety of CFA compared with other platelet-raising drugs for the treatment of thrombocytopenia have been widely reported in the literature, but there is no systematic evaluation. Therefore, we designed this meta-analysis to further establish the efficacy and safety of CFA in treating thrombocytopenia.

Methods: A computerized search was conducted in the Chinese biomedical database (CBM), Chinese National Knowledge Infrastructure (CNKI), Wanfang database, Chinese Scientific Journal Database (VIP), PubMed, and Web of Science databases using the keywords "caffeic acid tablets" and "thrombocytopenia." All randomized controlled trials were selected for the timeframe of build to 02/2023 and then screened and analyzed using RevMan 5.4 and stata17.0 software.

Results: A total of 35 publications with an overall 2533 patients were included in the study. The results of the meta-analysis showed that CFA were effective in the treatment of thrombocytopenia with a statistically significant difference [relative risk ratio (RR) = 1.24, 95% CI (1.17, 1.31), $P < .00001$] and in increasing platelet counts [standardized mean difference (SMD) = 1.50, 95% CI (1.09, 1.91), $P < .00001$], white blood cell count [SMD = 1.08, 95% CI (0.77, 1.39), $P < .00001$], and neutrophil count [SMD = 0.73, 95% CI (0.19, 1.28), $P = .009$], and CFA reduced myelosuppression [RR = 0.19, 95% CI (0.1, 0.37), $P < .00001$] and adverse effects [RR = 0.75, 95% CI (0.58, 0.96), $P = .02$].

Conclusion: CFA can effectively improve the clinical outcome of patients with thrombocytopenia with a good safety profile and are worth promoting. However, due to the low quality and small sample size of the included literature, a larger sample size and more standardized, high-quality studies are needed to validate these results.

Abbreviations: CFA = caffeic acid tablets, ITP = immune thrombocytopenic purpura, PLT = platelet count, RR = relative risk ratio, SMD = standardized mean difference.

Keywords: caffeic acid tablets, efficacy, meta-analysis, safety, thrombocytopenia

1. Introduction

Platelets are derived from megakaryocytes, and their production and maturation in the bone marrow is regulated by thrombopoietin.[1] Platelets play an important role not only in thrombosis and wound repair, but also in inflammation, immunity and cancer biology.[2] Thrombocytopenia refers to a platelet count (PLT) $<100 \times 10^9$/L. The main pathogenesis of thrombocytopenia is a decrease in platelet production, increased destruction and accumulation in the spleen, usually due to bacterial or viral infections, liver diseases, hematologic diseases, malignant tumors, pregnancy, autoimmune diseases, thrombotic microangiopathy, etc.[3] Thrombocytopenia is a common problem that affects 40% to 50% of medical and surgical intensive care units.[4] For thrombocytopenia caused by immune thrombocytopenic purpura (ITP), the main first-line treatment is glucocorticosteroids, immunoglobulins, etc.[5–7] Second-line treatment strategies include thrombopoietin receptor agonists; however, these agents often fail to achieve durable remission and require additional treatment options.[8] For chemoradiotherapy-induced thrombocytopenia, treatment includes platelet transfusions and administration of platelet growth factors, but the side effects are numerous and expensive.[9]

The main ingredient of caffeic acid tablets (CFA) is caffeic acid (CA). CA is a hydroxycinnamic acid that belongs to the phenolic acid family of polyphenols. And also known as
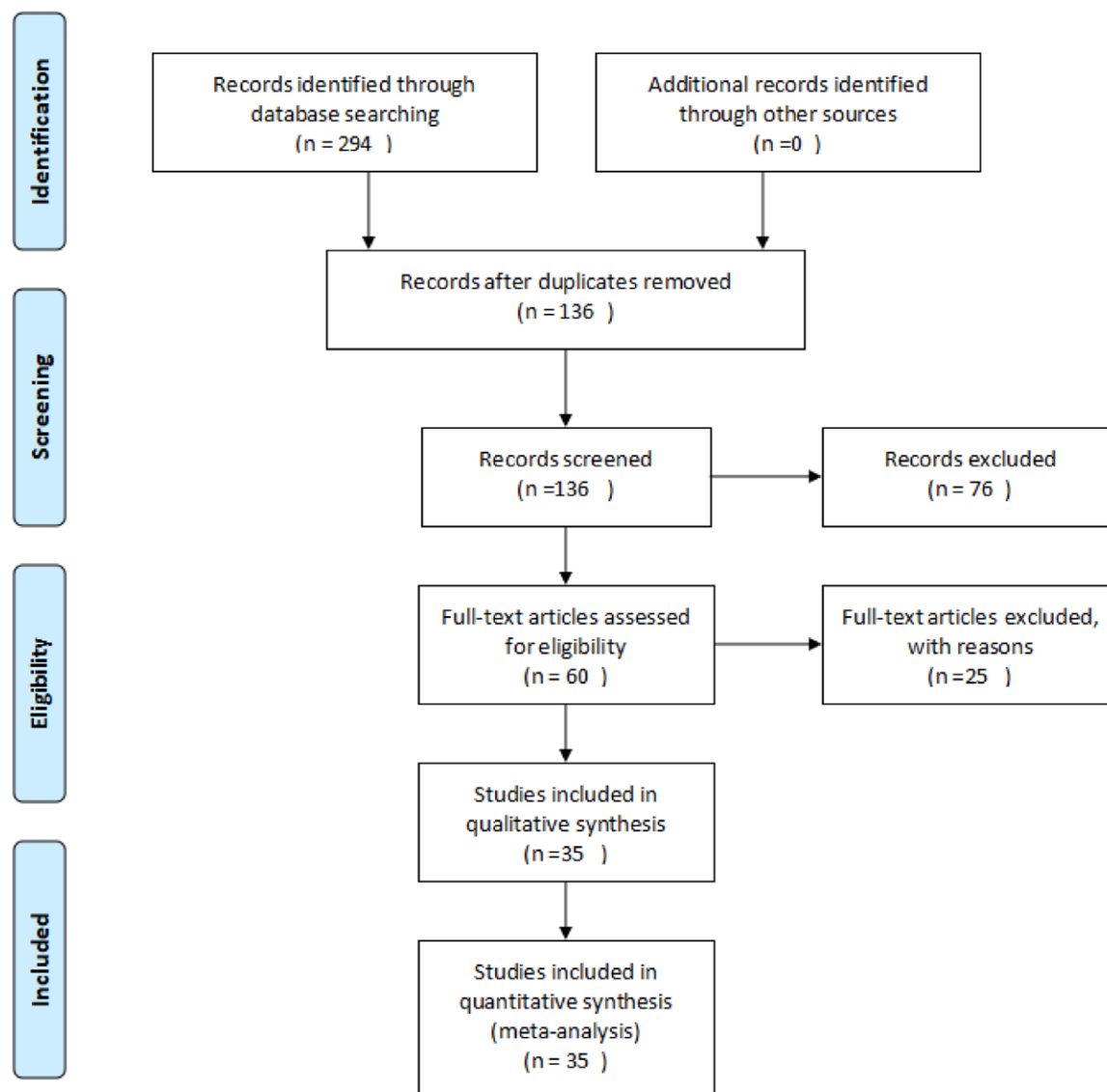
Figure 1. Flowchart of literature screening.

"3,4-hydroxycinnamic acid" or "3,4-dihydroxy phenyl acrylic acid."[10] Its molecular formula: $C_9H_8O_4$, relative molecular weight: 180.16 Da.[11] It is the main hydroxycinnamic acid present in the human diet, with the highest content being found in blueberries, kiwis, plums, cherries, and apples, although also present in cereals, carrots, salad, eggplants, cabbage, artichoke, and coffee.[12–14] In vitro and in vivo experiments have been performed, proving innumerable physiological effects of CA and its derivatives, such as antibacterial activity,[15,16] antiviral activity,[17–20] antioxidant activity,[16–20] anti-inflammatory activity,[16–20] anti-atherosclerotic activity,[15,16] immunostimulatory activity,[15,21] antidiabetic activity,[17,20] cardioprotective activity,[17,22] antiproliferative activity,[15,22,23] hepatoprotective activity,[24,25] anticancer activity,[16–20] and anti-hepatocellular carcinoma activity.[26–28] Besides these important activities, CA and its derivatives have shown a very high potential for treating and preventing cardiovascular and cancer diseases in preclinical studies.[10,29] In addition, CA also has the effects of hemostasis, raising white blood cells and platelets, and is clinically used in the treatment of leukopenia and thrombocytopenia caused by various reasons.[30]

The efficacy and safety of CFA compared with other platelet-raising drugs in the treatment of thrombocytopenia have been widely reported in the literature, but there is no systematic evaluation, so this study used meta-analysis to compare the efficacy and safety of CFA with other platelet-raising drugs in the treatment of thrombocytopenia, with the aim of providing a reliable basis for clinical use and evidence-based guidelines.

2. Methods

2.1. Ethical approval and consent to participate

The PRISMA guidelines[31] were used for designing and reporting this study, and this study was in accordance with the ethical guidelines of the Declaration of Helsinki (as revised in 2013).[32]This study is a systematic evaluation type article and does not require ethical approval.

2.2. Literature search strategy

Four Chinese databases (CNKI, Sinomed, VIP, and Wanfang) and 4 English databases (Web of Science, PubMed, Embase, and Cochrane Library) were searched for the terms: "Caffeic acid", "Caffeic acid tablet", "Thrombocytopenia", "Thrombocytopenias", "Thrombopenia", "Thrombopenias",

Table 1

Basic information of included studies.

Author/yr	Disease type	Age (yr) T	Age (yr) C	Platelet count ($\bar{x} \pm s$, x10⁹/L) T	Platelet count ($\bar{x} \pm s$, x10⁹/L) C	Number of cases T	Number of cases C	Intervention T	Intervention C	Treatment (wk)	Outcome indicators
Beiyuexian, 2015[35]	ITP	35.7±12.4	33.42±10.2	156.9±52.4	141.5±61.7	55	55	CFA	Hormone therapy	4	(a)(b)(c)
Chenming, 2012[36]	ITP	35.2	33.3	81.5±16.48	69.5±5.42	41	23	CFA	Hormone therapy	5	(a)
Donghanzhi, 2020[37]	Squamous lung cancer	54	54	189.22±55.86	156.38±59.88	25	25	CFA	Conventional chemotherapy	2	(a)(d)
Duzunming A, 2018[38]	Lymphoma	56	55	173.94±51.7	123.85±46.67	41	41	CFA	G-CSF	3	(a)(c)(e)(f)
Duzunming B, 2018[39]	Lung cancer	62	60	217.26±19.74	111.59±20.41	60	60	CFA	G-CSF	4	(a)(b)(c)(e)(f)
Hedi, 2020[40]	ITP	46.28±5.19	48.79±6.14	121.56±21.95	78.22±16.44	52	52	CFA	Hormone therapy	4	(a)(b)(c)
Huangzhenhua, 2013[41]	Uremia	50.8	49.6	193.61±11.03	99.68±12.09	12	12	CFA	Conventional Hemostatic Drugs	4	(a)
Jiaxiaohui, 2013[42]	Systemic lupus erythematosus	35.2±18.4	36.8±16.7	97±38.5	72±36.7	30	30	CFA	Leucogen Tablets	4	(a)(d)(e)
Kangjide, 2013[43]	ITP	30.9±10.8	31.5±7.5	144.6±45.3	132.5±50.8	45	45	CFA	Hormone therapy	4	(a)(b)(c)
Linwei, 2022[44]	Leukemia	16.82±3.32	17.73±3.07	57.86±4.72	38.25±3.94	40	40	CFA	rhIL-11	2	(a)(c)(d)(e)
Linwenyuan, 2019[45]	ITP	36	36	147.3±69.8	138.3±58.2	34	41	CFA	Hormone therapy	8	(a)(b)
Liudan, 2015[46]	ITP	30.8±5.1	31.4±5.2	NR	NR	26	26	CFA	Hormone therapy	6	(b)(c)
Liufeng, 2011[47]	Aplastic anemia	33	33	76±15	50±14	49	43	CFA	Hormone therapy	12	(a)(b)(e)
Liuke, 2012[48]	ITP	30	30	145±60.1	140±50.1	49	49	CFA	Hormone therapy	8	(a)
Liuxueru, 2016[49]	Esophageal cancer	58	56	NR	NR	24	24	CFA	Leucogen Tablet, Vitamin B tablet	4	(b)(c)(e)
Lixiansong, 2013[50]	ITP	35	35	NR	NR	14	14	CFA	Anti-HP conventional treatment drugs	4	(b)
Lixiaohong, 2013[51]	ITP	65	65	86.00±44.74	64.26±29.22	31	31	CFA	Herbs for clearing heat and cooling the blood	12	(a)(b)
Luoyihui, 2017[52]	Cirrhosis of the liver	56	56	NR	NR	50	50	CFA	Leucogen Tablet	4	(b)
Majun, 2017[53]	ITP	32.9	32.9	79.90±43.95	57.87±24.25	60	60	CFA	Coffee acid tablet mockups	4	(a)(c)(e)
Mengdeqian, 2018[54]	Systemic lupus erythematosus	39.4±17.6	37.3±14.1	128.70±52.55	102.50±35.70	31	32	CFA	Hormone therapy	4	(a)(c)(e)
Mengdeqian, 2021[55]	Dryness syndrome	44.6±11.7	42.4±10.5	156.03±87.92	123.72±64.38	36	36	CFA	Hormone therapy	4	(a)(c)(e)
Miudong, 2013[56]	ITP	41.32±7.38	41.32±7.38	NR	NR	15	15	CFA	Conventional chemotherapy	NR	(b)
Panbo, 2013[57]	Chemotherapy prevention	44.6±11.7	42.4±10.5	178.8±40.3	89.4±30.5	41	41	CFA	Conventional chemotherapy	3	(a)
Pangying, 2012[58]	lymphadenoma	55.6	53	223±121	143.5±94.5	30	30	CFA	Batilol tablet	2	(a)(c)(e)
Pengaihua, 2015[59]	Breast Cancer	48±8.47	49±9.37	327±67.55	274±48.02	30	30	CFA	G-CSF	3	(a)(c)(d)(e)(f)
Tangtianbi, 2017[60]	Tuberculosis	43.4±12.3	41.4±11.2	118.77±39.72	93.23±19.29	29	28	CFA	Leucogen Tablet	3	(a)(b)(c)
Wanghaicun, 2016[61]	Breast Cancer	44.23±6.26	45.49±6.51	319.00±72.32	286.00±62.52	40	40	CFA	G-CSF	2	(a)(b)(d)(e)
Wangjun, 2013[62]	ITP	NR	NR	113±26.61	79.7±27.36	20	20	CFA	Hormone therapy	4	(a)
Xinxiaohai, 2015[63]	Chemotherapy prevention	53.2±2.1	53.2±2.1	178.9±40.2	89.2±30.4	40	40	CFA	Conventional chemotherapy	3	(a)
Xudan, 2019[64]	ITP	42.7±3.1	44.8±4.4	NR	NR	40	40	CFA	Leucogen Tablet	12	(b)
Yangxi, 2019[65]	Children ITP	7.1±0.6	7.2±0.8	91.52±21.31	80.88±20.65	49	49	CFA	Hormone therapy	4	(a)(b)
Zhangxiaomeng, 2022[66]	Hematologic Tumors in children	7.5±2.31	7.5±2.61	201.25±45.52	152.25±41.52	49	49	CFA	G-CSF	2	(a)(c)(d)(e)(f)
Zhangxuejuan, 2013[67]	ITP	37.3±10.92	36.7±9.17	86±12	36±11	33	27	CFA	Hormone therapy	4	(a)(b)
Zhaobianfeng, 2017[68]	Lung cancer	55.1	54.3	227.9±100.5	193.5±84.2	32	32	CFA	Batilol tablet	2	(a)(c)(e)
Zhoucaixia, 2022[69]	Aplastic anemia	37.58±6.89	36.48±6.43	81.39±0.54	67.84±2.58	25	25	CFA	Hormone therapy	12	(a)(b)

T is the test group and C is the control group. Outcome indicators: (a) platelet count; (b) clinical efficacy; (c) incidence of adverse effects; (d) neutrophil count; (e) leucocyte count; and (f) myelosuppression.

CFA = control group on the basis of caffeic acid tablets, G-CSF = recombinant human granulocyte colony-stimulating factor, NR = not reported, rhIL-11 = platelet-producing drugs.
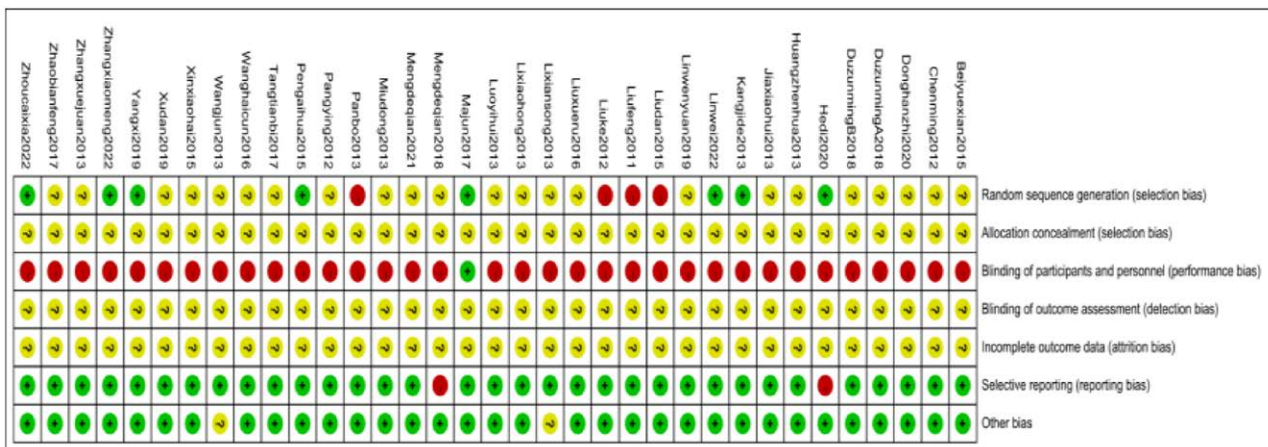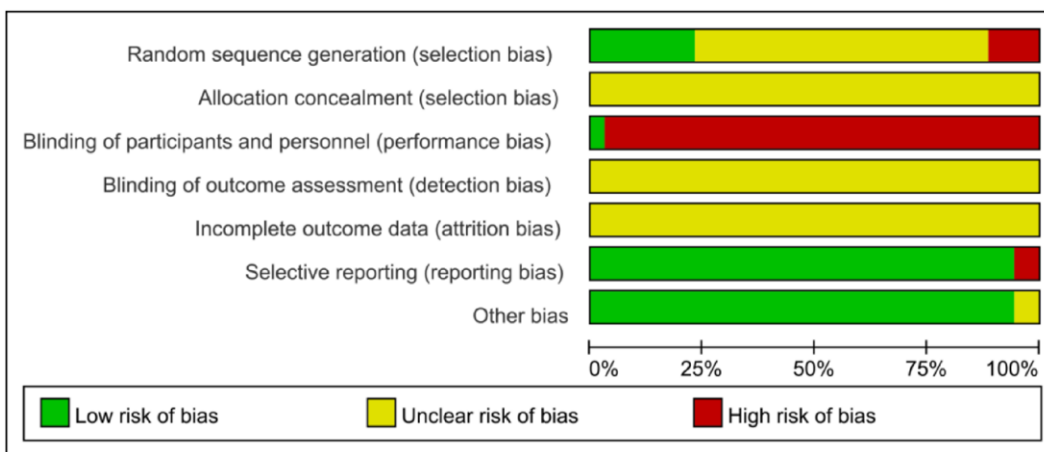
Figure 2. Risk of bias map.
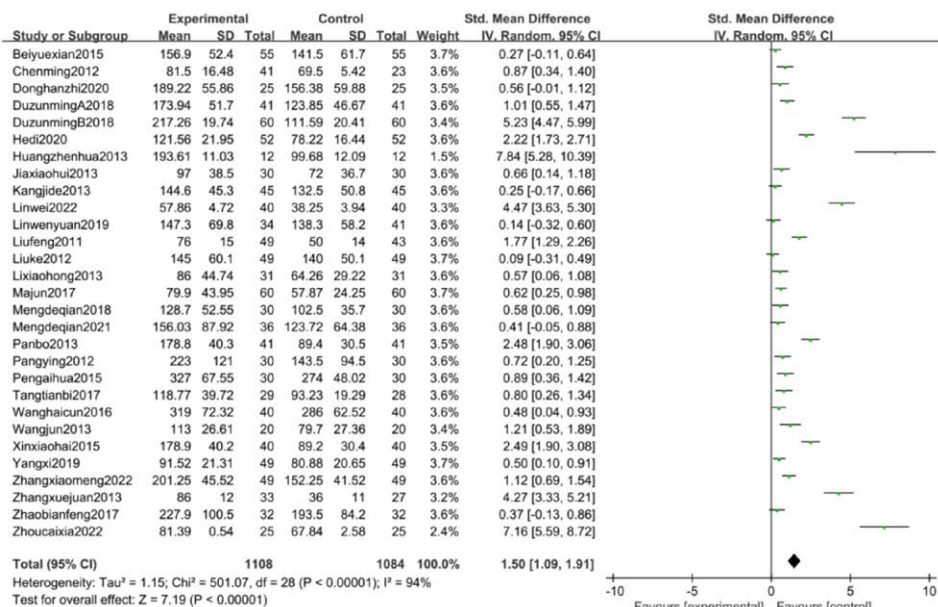

Figure 3. Risk of bias bar chart.

Figure 4. Meta-analysis of platelet count.

Table 2

Platelet count subgroup analysis.

Indicators	Number of included studies	SMD (95% CI)	Heterogeneity test		Effect model	P	Heterogeneity test	
			P	I²(%)			P	I²(%)
Oncological diseases	11[37–39,44,57–59,61,63,66,68]	1.77 (0.99, 2.55)	P < .00001	96	Random effects model	P < .00001	P = .04	68.8
ITP	11[35,36,40,43,45,48,51,53,62,65,67]	0.93 (0.44, 1.41)	P < .00001	92	Random effects model	P = .0002		
Other diseases	7[41,42,47,54,55,60,69]	2.17 (1.15, 3.18)	P < .00001	94	Random effects model	P < .0001		
Hormone therapy group	13[35,36,40,43,45,47,48,54,55,62,67,69]	1.33 (0.75, 1.90)	P < .00001	94	Random effects model	P < .00001	P = .43	0
Non-hormonal therapy group	16[37–39,41,42,44,51,53,57–61,63,66,68]	1.65 (1.07, 2.24)	P < .00001	95	Random effects model	P < .00001		
≤2 wk	6[37,44,58,61,66,68]	1.24 (0.38, 2.09)	P < .00001	94	Random effects model	P = .005	P = .48	0
>2 wk	23[35,36,38–43,45,47,48,51,53–55,57,59,60,62,63,65,67,69]	1.59 (1.11, 2.06)	P < .00001	95	Random effects model	P < .00001		

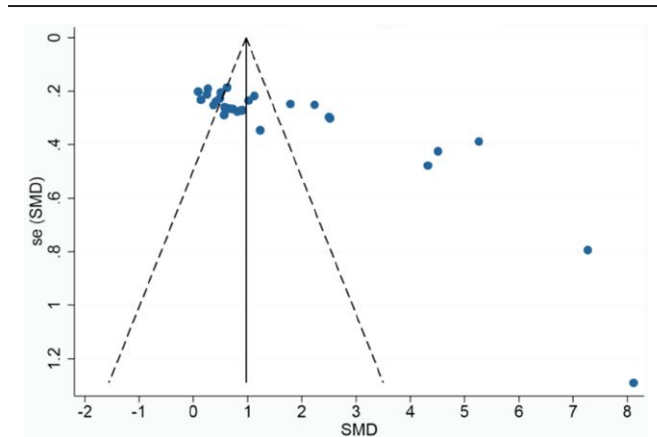ITP = immune thrombocytopenic purpura, SMD = standardized mean difference.

Figure 5. Funnel plot of platelet count.

and "randomized controlled trial," in both Chinese and English. The search time frame was established for each database until September 2022.

2.3. Inclusion criteria

Research type: Only randomized controlled trials were included and the languages were limited to Chinese and English. Research object: The included study cases were all patients with a diagnosis of thrombocytopenia. Refer to Consensus on the clinical diagnosis, treatment, and prevention of chemotherapy-induced thrombocytopenia in China (2019 version),[9] Thrombocytopenia is classified as degree I–IV, degree I: $(50–100) \times 10^9/L$; degree II: $(30–50) \times 10^9/L$; degree III: $(20–30) \times 10^9/L$; degree IV: less than $10 \times 10^9/L$. Patients with a white blood cell count below $100 \times 10^9/L$ can be diagnosed with thrombocytopenia, and the patient age and gender are not limited. Intervention measures: Patients in the test group were treated with CFA (200–300 mg/time, 3 times/d. Dezhou Deyao Pharmaceutical Co., Ltd., approved by Chinese medicine H37020537, production batch number: 2102140503.) or CFA combined with conventional platelet-raising drugs, while the control group was treated with conventional drugs (hormonal drugs, recombinant human granulocyte-stimulating factor and other platelet-raising drugs), and the dose and duration of administration were not limited. Outcome indicators: The primary indicators were PLT changes and clinical efficacy (complete remission: PLT ≥ $100 \times 10^9/L$; partial remission: $50 \times 10^9/L$ < PLT < $100 \times 10^9/L$; ineffective: PLT ≤ $50 \times 10^9/L$, clinical efficacy = complete remission + partial remission). Secondary indicators were incidence of adverse reactions, bone marrow suppression, change in white blood cell count, change in neutrophil count, and change in hemoglobin.

2.4. Exclusion criteria

Have any serious medical condition such as heart, brain, and kidney injury; no studies of any of the outcome indicators included in this study or literature not available in full; no control group or self-control; cohort studies, animal studies, clinical experience, etc.; and conference articles.

2.5. Literature screening and data extraction

The literature was screened and cross-checked by 2 investigators independently and in case of disagreement, both parties negotiated and requested a ruling from a third investigator. Information extracted from the literature included the first author, year of publication, type of disease, number of patients, mean age, interventions, outcome indicators, and duration of treatment.

2.6. Literature quality assessment

The quality of the included literature was evaluated using the risk of bias assessment tool recommended in the Cochrane Systematic Evaluator Handbook 5.1.0. This specifically included random sequence generation, allocation concealment, blinding, completeness of outcome data, and other sources of bias. Each item was categorized into content rated as high risk, unclear and low risk.[33]

2.7. Statistical methods

Meta-analysis was performed using RevMan 5.3 and Stata 17.0 software. Count data were analyzed by relative risk ratio (RR), and continuous data were analyzed by mean difference (MD) or standardized mean difference (SMD). Also, their combined effect sizes and their 95% confidence intervals (CI) were calculated. Heterogeneity was analyzed using the Q test and I2 test.[34] If there was no statistical heterogeneity between studies (I2 < 50%, P > .10), a fixed-effects model was used for analysis, otherwise, a random-effects model was used. The same outcome indicators were analyzed in subgroups according to disease type, treatment regimen, and the duration of treatment. Sensitivity analysis was performed using Stata 17.0 software. The publication bias analysis was performed using inverted funnel plots. P < .05 was considered statistically significant.

3. Results

3.1. Literature screening results

A total of 294 pieces of relevant literature were obtained from the initial review and after reading the title, abstract and full text of 35 studies with a total of 2533 patients including 1278 in the trial group and 1255 in the control group according to the
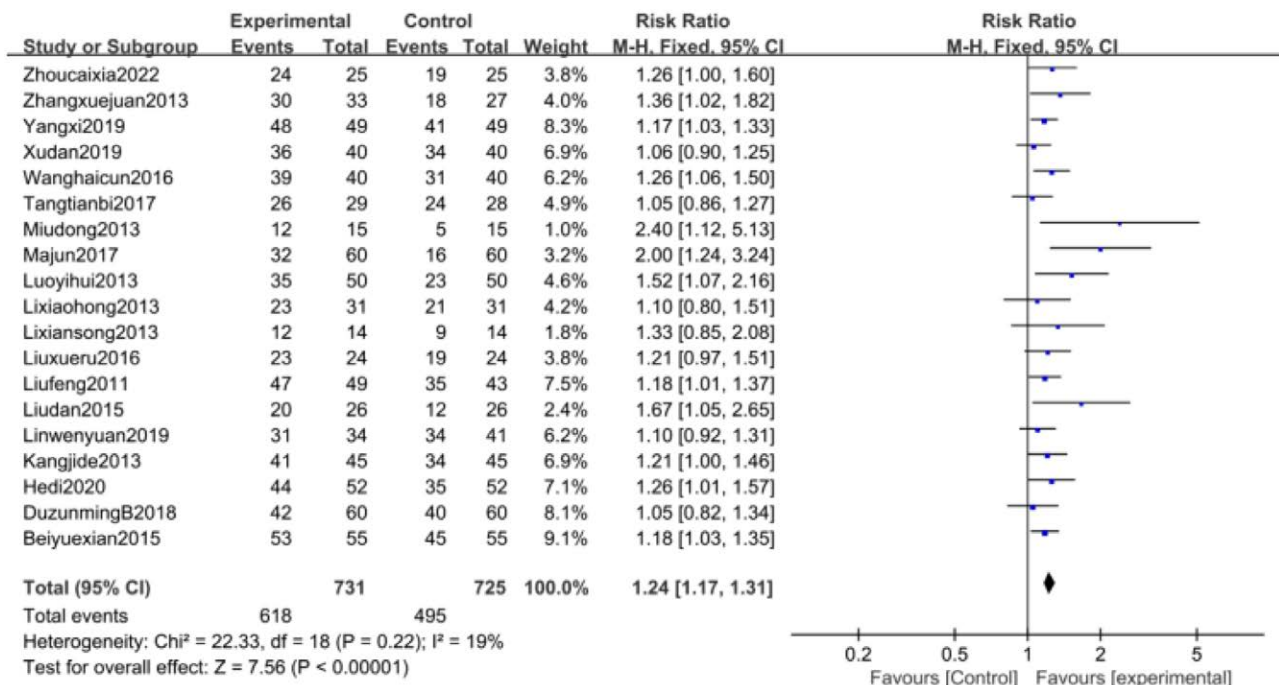
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhoucaixia2022	24	25	19	25	3.8%	1.26 [1.00, 1.60]
Zhangxuejuan2013	30	33	18	27	4.0%	1.36 [1.02, 1.82]
Yangxi2019	48	49	41	49	8.3%	1.17 [1.03, 1.33]
Xudan2019	36	40	34	40	6.9%	1.06 [0.90, 1.25]
Wanghaicun2016	39	40	31	40	6.2%	1.26 [1.06, 1.50]
Tangtianbi2017	26	29	24	28	4.9%	1.05 [0.86, 1.27]
Miudong2013	12	15	5	15	1.0%	2.40 [1.12, 5.13]
Majun2017	32	60	16	60	3.2%	2.00 [1.24, 3.24]
Luoyihui2013	35	50	23	50	4.6%	1.52 [1.07, 2.16]
Lixiaohong2013	23	31	21	31	4.2%	1.10 [0.80, 1.51]
Lixiansong2013	12	14	9	14	1.8%	1.33 [0.85, 2.08]
Liuxueru2016	23	24	19	24	3.8%	1.21 [0.97, 1.51]
Liufeng2011	47	49	35	43	7.5%	1.18 [1.01, 1.37]
Liudan2015	20	26	12	26	2.4%	1.67 [1.05, 2.65]
Linwenyuan2019	31	34	34	41	6.2%	1.10 [0.92, 1.31]
Kangjide2013	41	45	34	45	6.9%	1.21 [1.00, 1.46]
Hedi2020	44	52	35	52	7.1%	1.26 [1.01, 1.57]
DuzunmingB2018	42	60	40	60	8.1%	1.05 [0.82, 1.34]
Beiyuexian2015	53	55	45	55	9.1%	1.18 [1.03, 1.35]
Total (95% CI)		731		725	100.0%	1.24 [1.17, 1.31]
Total events	618		495			

Heterogeneity: Chi² = 22.33, df = 18 (P = 0.22); I² = 19%
Test for overall effect: Z = 7.56 (P < 0.00001)

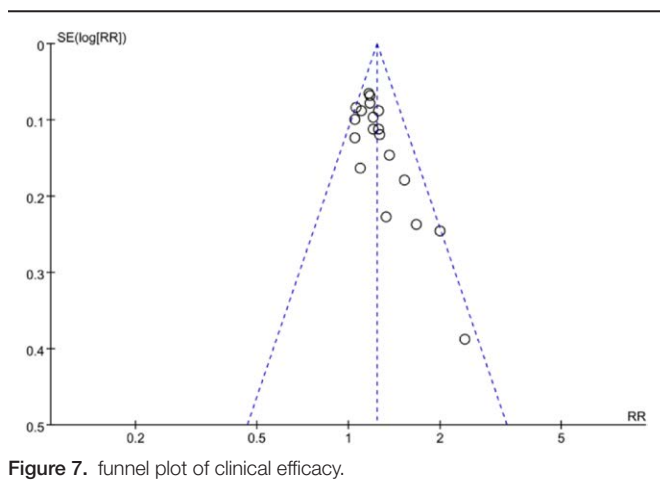**Figure 6.** Meta-analysis of clinical efficacy.

Figure 7. funnel plot of clinical efficacy.

inclusion and exclusion criteria. The literature screening process has been done as shown in Figure 1.

3.2. Basic characteristics of the included literature

The basic information of the literature included were shown in Table 1.[20] Most of the patients were cancer patients with the youngest participant being 7 years old and the oldest being 62 years old. The shortest duration of treatment in the study was 2 weeks and the longest was 12 weeks.

3.3. Risk of bias assessment for inclusion in the literature

All included trials were found to have a high risk of bias due to inadequate or insufficient reporting of information on study design and methods. All studies were randomized controlled trials, However, only 12 studies[40,43,44,46–48,53,57,59,65,66,69] elucidated the method of random sequence generation, Five of them[40,43,44,59,65] used the random number table method, one[66] used the computerized randomization method, one[69] used the touch

ball method, and one[53] followed the stratified block group to generate the random assignment and were therefore assessed as having a low risk of bias. Four items[46–48,57] described the use of visit order to generate random assignment and were therefore assessed as having a high risk of bias. Since CFA were only used in the trial group, it seems unlikely that any of the trials blinded participants and staff, except for Majun 2017[53] which used double blinding. Information on allocation concealment and blinding of outcome assessment was not reported in any of the trials and was therefore judged as unclear. Withdrawal information was not reported in any of the trials and was therefore assessed as unclear. As none of the trials provided information on trial registration, we assessed reporting bias by judging the consistency between results in the methods section of the publication, and 2 of the trials[40,54] were assessed to be at high risk of selective reporting bias because it had apparent problems with primary outcome reporting. The remaining trials were assessed as having a low risk of selective reporting bias due to studies reporting all outcomes mentioned in the methods section. Other bias was assessed by comparability of baseline data between the 2 groups, with 2[51,62] trials reporting baseline data, including age and sex, with no statistical description of comparability, and therefore they were assessed as having an unclear risk of bias. See Figures 2 and 3 for details.

3.4. Results of meta-analysis

3.4.1. Analysis of platelet count change and publication bias analysis. Platelet counts were counted in 29[35–45,47,48,51,53–55,57–63,65–69] papers and were analyzed using a random-effects model because of the high heterogeneity between groups (P < .00001, I² = 94%). Meta-analysis showed a statistically significant improvement in platelet counts in the CFA group compared with the control group [SMD = 1.50, 95% CI (1.09, 1.91, P < .00001)]. SMD = 1.50, 95% CI (1.09, 1.91), P < .00001] as detailed in Figure 4. Given the large heterogeneity, subgroup analysis was performed according to disease type, treatment regimen, and duration of treatment. The results of the subgroup analysis are detailed in Table 2. based on these results, it can be demonstrated that the source of
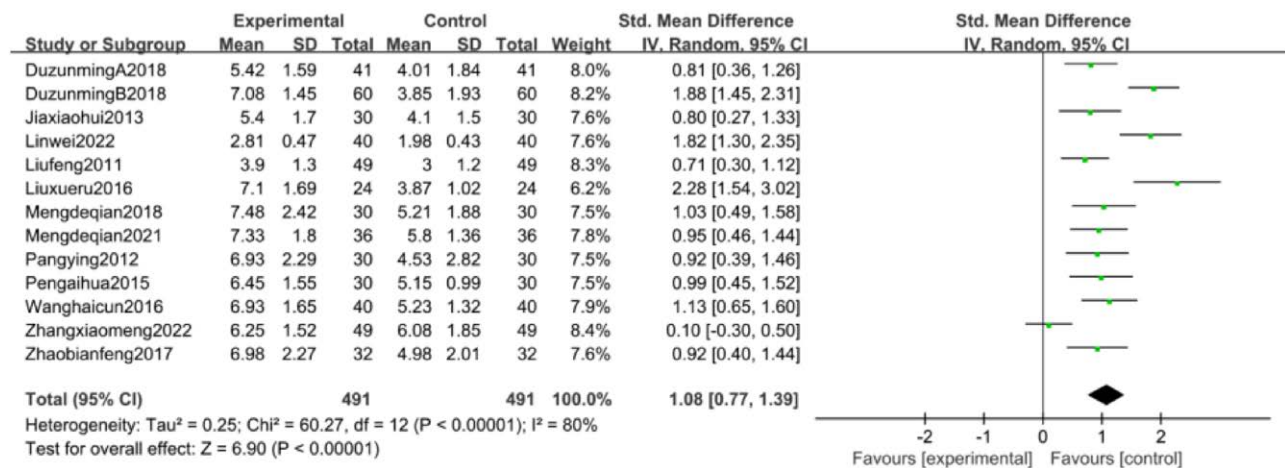
Figure 8. Meta-analysis of WBC.

Table 3

Leukocyte count subgroup analysis.

Indicators	Number of included studies	SMD (95% CI)	Heterogeneity test		Effect model	P	Heterogeneity test	
			P	I²(%)			P	I²(%)
Oncological diseases	9[44,48,49,58,61,66,68]	1.18 (0.74, 1.62)	P < .00001	86	Random effects model	P < .00001	P = .20	38.4
Other diseases	4[42,47,54,55]	0.86 (0.61, 1.10)	P = .79	0	Random effects model	P < .00001		
Hormone therapy group	5[38,39,59,61,66]	0.98 (0.37, 1.59)	P < .00001	89	Random effects model	P = .002	P = .64	0
Non-hormonal therapy group	8[42,44,47,49,54,55,58,68]	1.15 (0.81, 1.48)	P = .002	69	Random effects model	P < .00001		
≤2 wk	5[44,58,61,66,68]	0.97 (0.39, 1.54)	P < .0001	86	Random effects model	P = .001	P = .59	0
>2 wk	8[38,39,42,47,49,54,55,59]	1.15 (0.79, 1.51)	P = .0002	76	Random effects model	P < .00001		

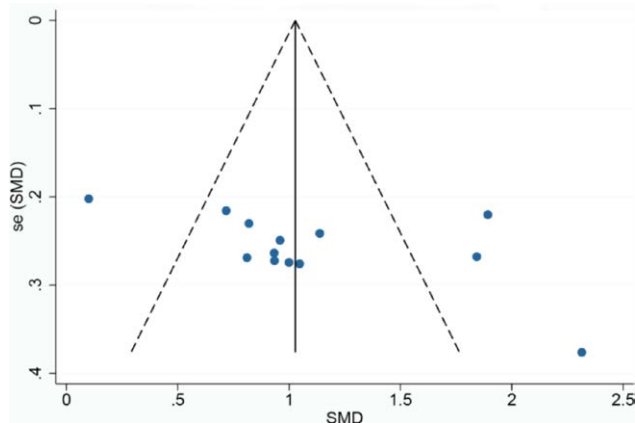SMD = standardized mean difference.

Figure 9. funnel plot of WBC.

heterogeneity may be related to the type of disease, but may not be related to the treatment regimen or the duration of treatment of the disease. Based on the changes in platelet counts, funnel plots were drawn using stata17.0 software with the standard error SE (SMD) of the effect size as the vertical coordinate and the SMD of the effect size for each study as the horizontal coordinate in Figure 5, which showed that the funnel plots were less symmetrical on both sides and there was a significant publication bias.

3.4.2. Clinical efficacy analysis and publication bias analysis. Clinical efficacy was counted in 19[35,39,40,43,45–47,49–53,56,60,61,64,65,67,69] papers and was analyzed using

a fixed-effects model because of high heterogeneity between groups (P = .22, I² = 19%). Meta-analysis showed that the clinical efficacy of the trial group for thrombocytopenia was better than that of the control group, and the difference was statistically significant [RR = 1.24, 95% CI (1.17, 1.31), P < .00001] Figure 6. its funnel plot is shown in Figure 7, the 2 sides of the funnel plot are not quite symmetrical, suggesting a possible publication bias.

3.4.3. White blood cell count analysis. Thirteen studies[38,39,42,44,47,49,54,55,58,59,61,66,68]reported changes in leukocyte counts before and after treatment. Meta-analysis results showed high heterogeneity (P < .00001, I² = 80%) between study groups, so random-effects model analysis was used. Meta-analysis showed that compared with the control group CFA group significantly improved PLT with a statistically significant difference [SMD = 1.08, 95% CI (0.77, 1.39), P < .00001] as detailed in Figure 8. considering the high heterogeneity, subgroup analysis was performed according to disease type, treatment regimen and duration of treatment. The results of the subgroup analysis are detailed in Table 3. Based on these results, it can be demonstrated that the source of heterogeneity may be related to the type of disease, but may not be related to the treatment regimen or the duration of treatment of the disease. Based on the changes in leukocyte counts, funnel plots were drawn using stata17.0 software with the standard error SE (SMD) of effect sizes as the vertical coordinate and the SMD of effect sizes for each study as the horizontal coordinate in Figure 9, which showed that the funnel plots were less symmetrical on both sides and that there was publication bias.

3.4.4. Analysis of neutrophil count. Six studies[37,42,44,59,61,66]reported changes in neutrophil counts before

and after treatment. Meta-analysis results showed a statistically significant improvement in neutrophil counts in the CFA group compared to the control group [SMD = 0.73, 95% CI (0.19, 1.28), $P = .009$], with heterogeneity ($P < .00001$, $I^2 = 86\%$), so a random-effects model analysis was used as detailed in Figure 10.

3.4.5. Myelosuppression rate at degrees III and IV.
Four studies[38,39,59,66] reported III and IV degrees of myelosuppression, and the meta-analysis showed that the CFA group may reduce the occurrence of myelosuppression compared to the

control group [RR = 0.19, 95% CI (0.1, 0.37), $P < .00001$], heterogeneity ($P = .68$, $I^2 = 0\%$), so a fixed-effect model analysis, as in Figure 11.

3.4.6. The incidence of adverse reactions.
Adverse reactions were reported in 12 studies[38–40,43,44,49,54,55,59,60,66,68] and the details of the included adverse reactions are shown in Table 4, while the others did not report the specifics of the adverse reactions. These results suggest that CFA have no or mostly mild adverse reactions in patients.
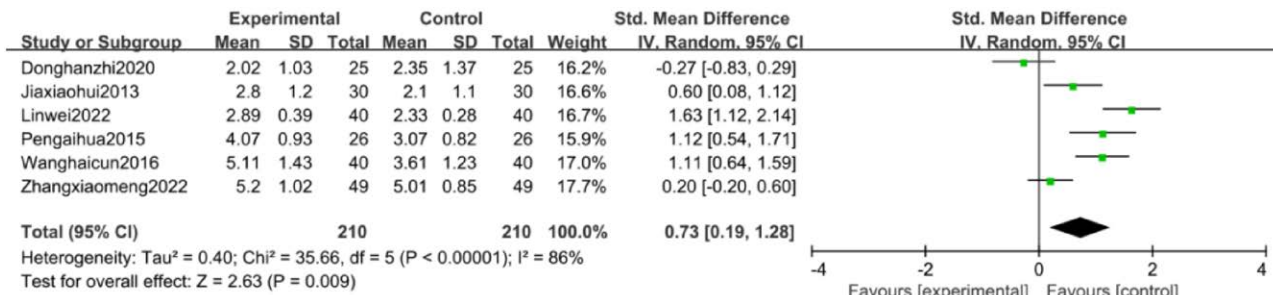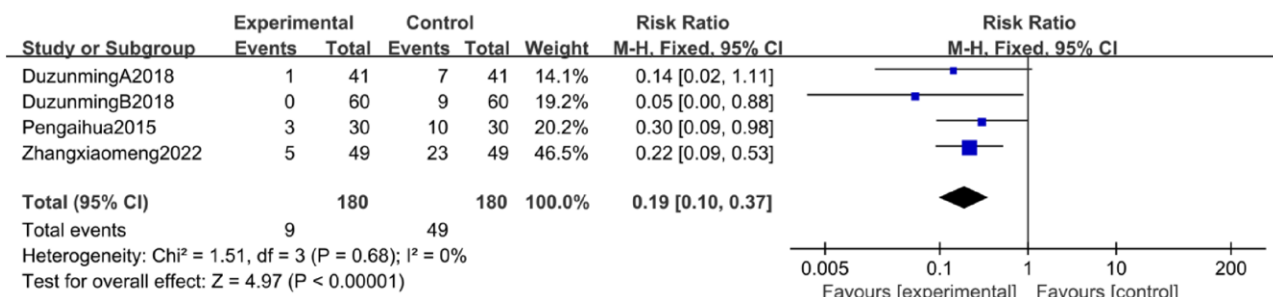

Figure 10. Meta analysis of neutrophil counts.

Figure 11. Meta-analysis of grade III and IV myelosuppression.

Table 4

The occurrence of adverse reactions.

	Adverse reaction	
Author/yr	T	C
Duzunming A., 2018[38]	4 cases of nausea and epigastric discomfort, 1 case of diarrhea, 2 cases of mildly elevated alanine aminotransferase, 6 cases of bleeding, and 10 cases of infection	15 cases of bleeding, 23 cases of infection
Duzunming B., 2018[39]	2 cases of nausea and epigastric discomfort, 1 case of mild diarrhea, and 1 case of mildly elevated alanine aminotransferase	0
Hedi, 2020[40]	6 cases of nausea, 1 case of renal dysfunction, 2 cases of peptic ulcer	5 cases of nausea, 2 cases of renal dysfunction, 1 case of peptic ulcer
Kangjide, 2013[43]	5	4
Linwei, 2022[44]	1 case of dizziness, 2 cases of headache, 1 case of fever, 1 case of malaise	1 case of dizziness, 1 case of fever, 1 case of malaise
Liuxueru, 2016[49]	1 case of mildly elevated alanine aminotransferase and 1 case of nausea	4
Mengdeqian, 2018[54]	1 case of epigastric discomfort, nausea	0
Mengdeqian, 2021[55]	3 cases of nausea, nausea	2 cases of loss of appetite
Pengaihua, 2015[59]	1 case of abnormal liver function, 2 cases of abnormal electrocardiogram	2 cases of abnormal liver function, 1 case of abnormal renal function, 3 cases of abnormal electrocardiogram, 1 case of infection
Tangtianbi, 2017[60]	3 cases of abnormal liver function	3 cases of abnormal liver function
Zhangxiaomeng, 2022[66]	1 case of local reaction, 2 cases of dizziness	1 musculoskeletal, 2 local reactions, 2 fever, 2 dizziness, 1 other
Zhaobianfeng, 2017[68]	2 cases of skin bleeding, 2 cases of urinary tract infection, 3 cases of respiratory tract infection	2 cases of rhinorrhea, 3 cases of skin bleeding, 2 cases of urinary tract infection, 7 cases of respiratory tract infection

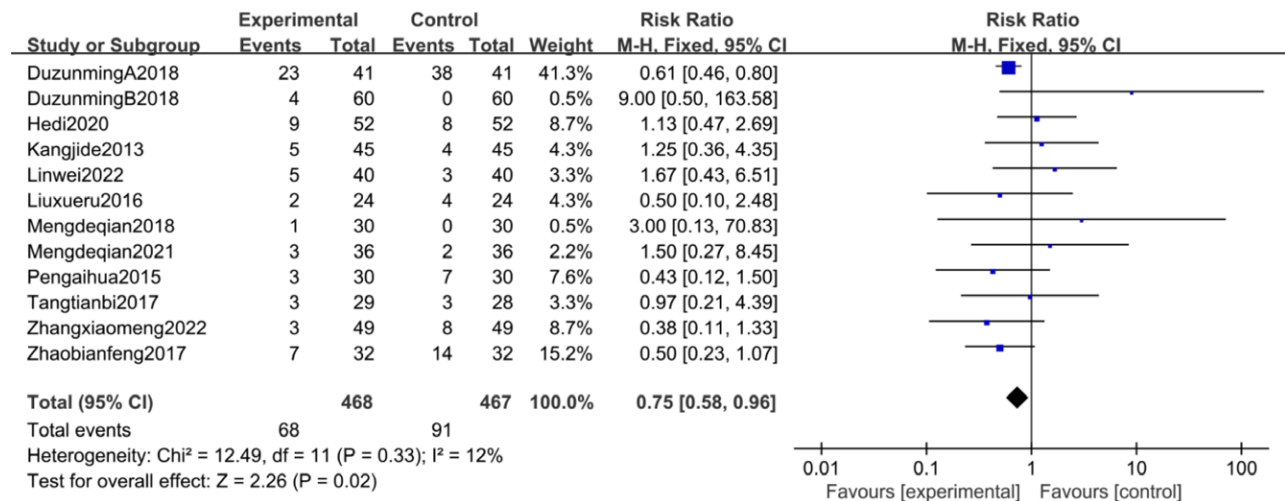| Study or Subgroup	Experimental		Control		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
DuzunmingA2018	23	41	38	41	41.3%	0.61 [0.46, 0.80]	
DuzunmingB2018	4	60	0	60	0.5%	9.00 [0.50, 163.58]	
Hedi2020	9	52	8	52	8.7%	1.13 [0.47, 2.69]	
Kangjide2013	5	45	4	45	4.3%	1.25 [0.36, 4.35]	
Linwei2022	5	40	3	40	3.3%	1.67 [0.43, 6.51]	
Liuxueru2016	2	24	4	24	4.3%	0.50 [0.10, 2.48]	
Mengdeqian2018	1	30	0	30	0.5%	3.00 [0.13, 70.83]	
Mengdeqian2021	3	36	2	36	2.2%	1.50 [0.27, 8.45]	
Pengaihua2015	3	30	7	30	7.6%	0.43 [0.12, 1.50]	
Tangtianbi2017	3	29	3	28	3.3%	0.97 [0.21, 4.39]	
Zhangxiaomeng2022	3	49	8	49	8.7%	0.38 [0.11, 1.33]	
Zhaobianfeng2017	7	32	14	32	15.2%	0.50 [0.23, 1.07]	
Total (95% CI)		468		467	100.0%	0.75 [0.58, 0.96]	
Total events	68		91				
Heterogeneity: Chi² = 12.49, df = 11 (P = 0.33); I² = 12%							
Test for overall effect: Z = 2.26 (P = 0.02)							

Figure 12. Meta-analysis of adverse reactions rate.

12 studies[38–40,43,44,49,54,55,59,60,66,68] reported the incidence of adverse reactions in patients after treatment. the meta-analysis showed heterogeneity ($P = .33$, $I^2 = 12\%$), so a fixed effects model was used to analyze the results. The results showed that the CFA group had a better safety profile compared to the treatment in the control group [RR = 0.75, 95% CI (0.58, 0.96), $P = .02$] and the difference was statistically significant, as shown in Figure 12.

3.4.7. Sensitivity analysis.
Sensitivity analysis of the included studies has shown no significant differences between the random-effects model and fixed-effects model. The exclusion of any of the studies had little effect on the results indicating low sensitivity and strong confidence in the results.

4. Discussion

Thrombocytopenia, usually defined as a PLT of $< 100 \times 10^9$/L in peripheral blood, is a common complication in oncology patients.[70] However, ITP can also present with symptoms of thrombocytopenia. ITP is a hemorrhagic disease characterized by an increase in platelet destruction due to the production of anti-auto-platelet antibodies in the patient body, resulting in a persistent reduction of platelets in the peripheral blood and a normal or increased number of bone marrow megakaryocytes with maturation disorders, and it is the most common type of thrombocytopenic disease in the clinic.[71] Thrombocytopenia may increase a patient risk of bleeding, thereby endangering the patient life and health, as well as affecting treatment outcomes and increasing medical costs.[72] Thrombocytopenia is mostly treated with glucocorticoids, splenectomy and immunomodulators vincristine, cyclophosphamide and rituximab in western medicine, which have greater adverse effects. Adverse effects of glucocorticoids include osteoporosis and even aseptic femoral head necrosis, water and sodium retention, centripetal obesity, acne and elevated blood pressure and blood glucose, which have a high incidence and seriously affect the quality of life of patients.[63]

CFA are rapidly absorbed after oral administration and have a high distribution in the blood and kidneys. The mechanism of action of CFA is complex and varied[73,74], Ferulic acid and isoferulic acid are the 2 main bioactive metabolites of caffeic acid. The $t_{1/2}$ of caffeic acid was 1.25 ± 0.26 hours. The reason for the difference in $t_{1/2}$ of caffeic acid in different pathways may be the rapid transfer from blood to tissue. Its absolute bioavailability was 3.4%, suggesting that caffeic acid may have a rapid biotransformation in vivo, with poor permeability through the intestinal epithelial membrane.[75] Caffeic acid also stimulates the differentiation of hematopoietic stem cells, the proliferation of endothelial cells and the expression of surface adhesion molecules, thus improving the hematopoietic function of the body. It also increases the synthesis of deoxyribonucleic acid in leukocytes, stimulates the synthesis of megakaryocyte proteins and antioxidants, which contribute to anti-apoptosis, regulates the function of T cells and reduces the destruction of peripheral blood cells, thus increasing the level of platelets and leukocytes.[65] Caffeic acid also improves microvascular and platelet function and coagulation factors by reducing the time to coagulation and hemostasis.[76] In patients with thrombocytopenia and leukopenia, caffeic acid has been found to have a rapid onset of action and precise efficacy.[77,78]

In this study, 35 papers were included through a search of relevant domestic and international literature, and the results of a clinical randomized controlled study comparing the CFA group with the non-CFA group by meta-analysis showed that the difference between the CFA group and the control group was statistically significant. From a clinical perspective, CFA did increase platelet counts and improve patient health. In addition, there were few serious adverse events and treatment-related safety issues, and our subgroup analysis of 2 outcome indicators, PLT and white blood cell count, showed that the classification of the disease may be of heterogeneous origin. The results of this study showed that the application of CFA for the treatment of thrombocytopenia does have good clinical efficacy, and that CFA are safe and effective, have mild adverse effects, are inexpensive and easy to use, and are clinically worth promoting. From the results of the funnel plot, it can be seen that there may be publication bias in the meta-analysis, and from the sensitivity analysis showed that the sensitivity analysis of each index was consistent with the original results, with good stability and high confidence of the conclusion.

Our study still has some limitations. Firstly, the included articles were all Chinese studies with geographical limitations. Secondly, the sample size of each study was mostly from 1 hospital, which is a small sample size that may affect the reliability and accuracy of the findings. Furthermore, only 12 of the 35 papers reported a specific randomization method, and 4 of them were high-risk biased. Since some of the original studies were published too early, many did not report the use of allocation concealment and blinding and therefore their quality was not high. However, the aim of this study was to investigate the effect of CFA on thrombocytopenia. We chose objective results from clinical

trials, such as PLT, white blood cell count, and neutrophil count, which were minimally affected by allocation concealment and blinding. Second, the heterogeneity between studies cannot be ignored because of the different interventions, drug doses, and treatment durations used in patients with different platelet levels in each trial. In our study, we performed a subgroup analysis to reduce heterogeneity to some extent. Finally, for adverse events, there were no clear conclusions about adverse effects of CFA due to the limited follow-up time of the included studies and the non-standardized reporting of some studies.

5. Conclusion

The results of this study showed that CFA are effective, safe and economical in the treatment of thrombocytopenia and are worthy of clinical application. However, due to the limitations of the quality of the included literature, sample size and study design, the above findings need to be validated by further large sample and high-quality clinical studies in the future.

Author contributions

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Writing – review & editing: Ruixiang Chen.

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