Research article

Efficacy and safety of Chinese patent medicine combined with 5-aminosalicylic acid for patients with ulcerative colitis: A network meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Given the widespread use of Chinese patent medicines (CPMs) in combination with 5-aminosalicylic acid (5-ASA) for Ulcerative colitis (UC) patients, this study aimed to evaluate the efficacy and safety of nine CPMs combined with 5-ASA in the treatment of UC.

Methods: A systematic literature search was conducted in eight databases from inception to May 2023 to identify eligible RCTs evaluating the effects of CPM combined with 5-ASA for the treatment of UC. The methodological quality of the included RCTs was assessed using the Cochrane risk of bias tool in Review Manager 5.4. The primary outcome of the meta-analysis was the overall response rate. The secondary outcomes included excellent rate, disease activity index (DAI), IL-6, IL-8, and TNF-α levels, mean platelet volume (MPV), fibrinogen (FIB) levels, recurrence rate, and adverse event rate. Network meta-analysis was performed using Review Manager 5.4 and Stata 15.0.

Results: In total, 70 RCTs including 5973 patients and 10 treatment regimens were included. The combination of Kangfuxin Liquid (KFL) and 5-ASA showed the greatest efficacy in improving FIB levels and the overall response rate. Bupi Yichang Pill (BYP) combined with 5-ASA was associated with the fewest adverse events and the lowest recurrence rate. Hudi Enteric-coated Capsule (HEC) combined with 5-ASA ranked first in improving DAI. ZhiKang Capsule (ZKC), ChangYanNing

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Capsule (CYN), and Danshen Injection (DSI) combined with 5-ASA ranked first in improving IL-6, IL-10, and TNF-α levels, respectively. Shenling Baizhu Powder (SBP) combined with 5-ASA was associated with the highest excellent rate.

Conclusions: CPM combined with 5-ASA may be more effective than 5-ASA alone for treating UC. Besides, CPM combined with 5-ASA could better reduce the recurrence rate and adverse event rate in UC patients. The current meta-analysis provides statistical evidence for clinical application.

Systematic Review Registration: International Prospective Register of Systematic Reviews (PROSPERO), No. CRD42023433672.

1. Introduction

Ulcerative colitis (UC) is a chronic, non-specific inflammatory bowel disease that primarily involves the mucosa and submucosa of the rectum and colon. UC is characterized by pathological features such as chronic inflammation and superficial mucosal ulceration, which lead to clinical manifestations including abdominal pain, diarrhea, tenesmus, mucus pus and bloody stool. These symptoms are subsequently accompanied by extraintestinal symptoms, including fever, emaciation, and arthritis [1]. The difficulties in curing UC, along with its high recurrence rate, repeatability, continuity, aggregation, and regionality, have raised clinical concerns [2]. For over 70 years, 5-aminosalicylic acid (5-ASA) has been extensively used in patients with mild to moderate UC. Research has demonstrated
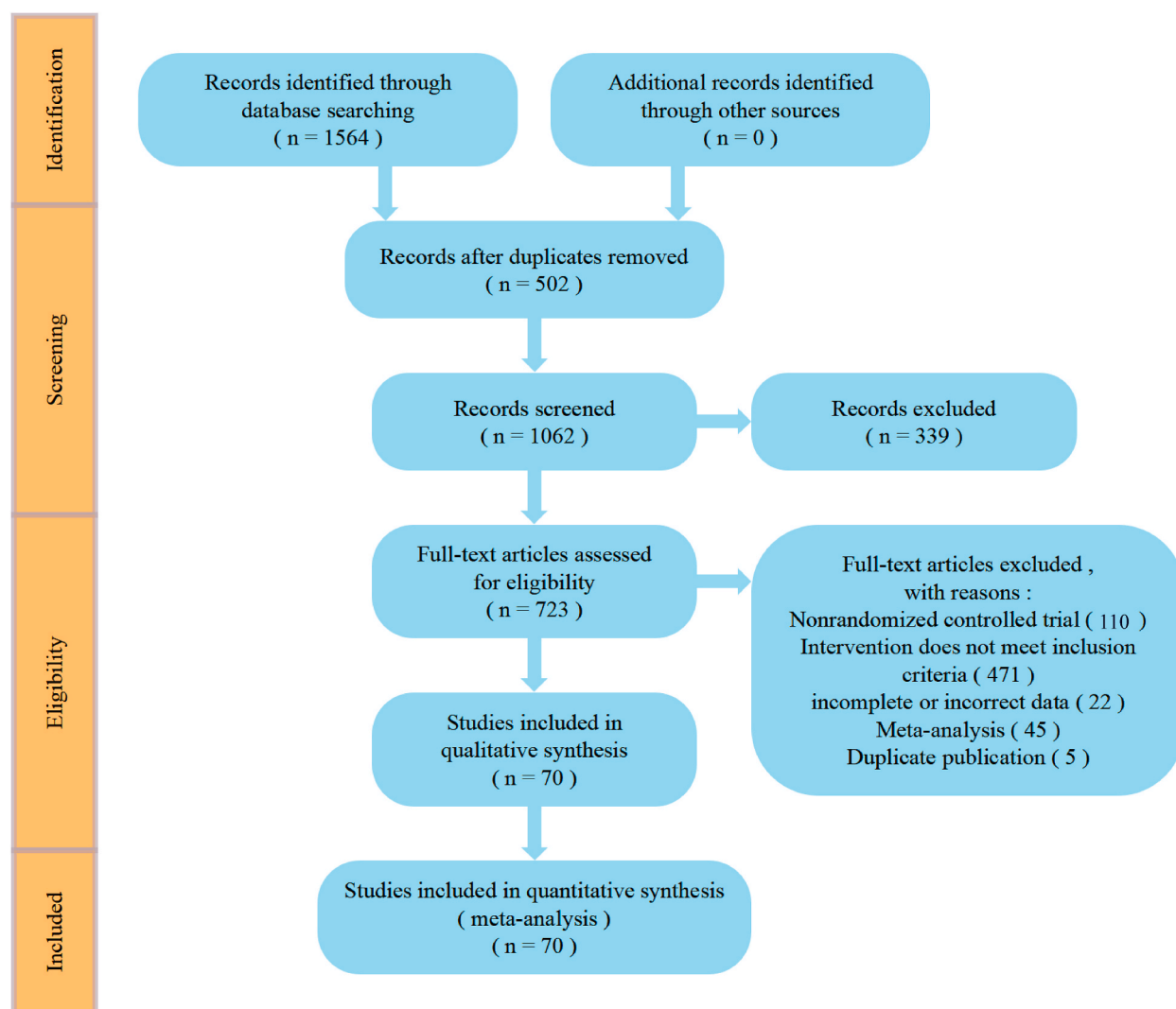

Fig. 1. Flow chart of the search for eligible RCTs.

Table 1
Characteristics of included literature.

Included studies	Sample size (C/T)	Male/female		Age (y)		Course of disease (m)		Intervention of group		Course of treatment		Usage and Dosage		Outcomes
		C	T	C	T	C	T	C	T	C	T	C	T	
Cao XX 2017 [11]	36/37	20/16	21/16	44.34	45.7	0.53	0.42	1	5	30 d	30 d	3g p.o/d	1.8 g/d	ADE
Chen QR 2019 [12]	50/50	30/20	31/19	49.3 ± 5.10	49.2 ± 5.10	3.2 ± 2.10	3.2 ± 2.10	1	5	8 w	8 w	3g p.o/d	1.2 g/d	AC
Dai L 2017 [13]	30/30	17/13	18/12	45.8 ± 6.40	50.4 ± 11.30	0.57 ± 0.12	0.59 ± 0.18	1	5	8 w	8 w	3g p.o/d	1.2 g/d	AD
Lu W 2021 [14]	35/35	25/10	25/10	48.21 ± 2.12	48.89 ± 2.67	4.26 ± 1.10	4.31 ± 1.14	1	5	8 w	8 w	3g p.o/d	2.7 g/d	AC
Shao DZ 2019 [15]	46/46	24/22	25/21	43.93 ± 7.46	44.25 ± 7.25	4.28 ± 1.34	4.46 ± 1.27	1	5	1 m	1 m	4g p.o/d	1.2 g/d	ACE
Shen SP 2020 [16]	42/42	22/20	24/18	40.25 ± 3.79	40.38 ± 3.26	–	–	1	5	30 d	30 d	3g p.o/d	1.2 g/d	ACD
Wang P 2020 [17]	36/37	20/16	21/16	44.3 ± 4.80	45.7 ± 4.30	0.53 ± 0.15	0.54 ± 0.38	1	5	30 d	30 d	3g p.o/d	1.8 g/d	AD
Yao ZY 2018 [18]	36/36	15/21	16/20	41.7 ± 12.80	42.3 ± 13.60	6.7 ± 2.30	6.9 ± 2.40	1	5	4 w	4 w	3g p.o/d	1.2 g/d	ACDE
Zhao QH 2017 [19]	30/30	15/15	14/16	46.14 ± 6.28	43.22 ± 5.92	6.4 ± 1.90	6.7 ± 1.50	1	5	8 w	8 w	4.5g p.o/d	4.5 g/d	AE
Zheng HY 2017 [20]	42/42	25/17	26/16	49.7 ± 3.10	49.5 ± 3.20	3.1 ± 0.60	3.4 ± 0.70	1	5	2 m	2 m	1g p.o/d	0.84 g/d	AC
Chen XX 2018 [21]	39/39	19/20	23/16	46.48 ± 6.34	47.13 ± 6.61	5.41 ± 3.67	5.67 ± 3.24	1	6	2 w	2 w	1.2g p.o/d	20 ml i.v./d	ABC
Deng WJ 2016 [22]	55/55	23/32	25/30	57.6 ± 7.50	58.3 ± 8.20	4.5 ± 1.30	4.8 ± 1.40	1	6	4 w	4 w	3g p.o/d	20 ml i.v./d	ACDEF
Du XT 2019 [23]	36/36	19/17	20/16	44.6 ± 2.50	44.2 ± 2.70	3.2 ± 1.20	3.3 ± 1.40	1	6	1 m	1 m	2g p.o/d	8 ml i.v./d	ACDE
Liang T 2017 [24]	60/60	25/35	34/26	55.1 ± 11.70	53.2 ± 10.80	6.3 ± 1.20	6.1 ± 1.50	1	6	30 d	30 d	4g p.o/d	20 ml i.v./d	ACDEF
Wang XM 2020 [25]	46/46	32/14	33/13	37.6 ± 5.80	38.34 ± 5.93	4.23 ± 0.87	4.21 ± 0.96	1	6	1 m	1 m	3g p.o/d	20 ml i.v./d	ACD
Xu DY 2020 [26]	44/44	24/20	25/19	39 ± 3.50	39.5 ± 3.50	5 ± 1.50	5.5 ± 1.50	1	6	1 m	1 m	4g p.o/d	8 ml i.v./d	ACE
Zhu HY 2018 [27]	27/27	16/11	15/12	39.84 ± 9.68	38.53 ± 10.37	2.75 ± 1.28	2.51 ± 1.74	1	6	4 w	4 w	4g p.o/d	10 ml i.v./d	ABE
Zhu YS 2019 [28]	49/49	29/20	28/21	37.6 ± 5.80	37.4 ± 5.70	4.2 ± 0.80	4.2 ± 0.90	1	6	4 w	4 w	3g p.o/d	20 ml i.v./d	CDE
Deng TY 2016 [29]	60/60	36/24	32/28	56.8 ± 8.60	56.2 ± 9.20	5.5 ± 1.30	5.1 ± 1.20	1	7	8 w	8 w	3g p.o/d	200 ml pr./d	ACE
Li D 2022 [30]	50/52	28/22	31/21	–		5.13 ± 1.88	5.24 ± 1.47	1	7	12 w	12 w	4g p.o/d	100 ml pr./d	BC
Ma TW 2019 [31]	32/32	15/17	14/18	41.62 ± 10.58	40.23 ± 11.06	4.31 ± 1.76	4.98 ± 1.24	1	7	12 w	12 w	4g p.o/d	100 ml pr./d	ACF
Zhang Y 2022 [32]	60/60	33/27	34/26	30.06 ± 5.20	29.56 ± 5.14	1.82 ± 0.29	1.73 ± 0.32	1	7	4 w	4 w	3g p.o/d	100 ml pr./d	ABC
Zhang Y 2019 [31]	45/45	24/21	23/22	45.39 ± 4.61	46.14 ± 4.73	6.09 ± 0.62	6.13 ± 0.63	1	7	3 m	3 m	4g p.o/d	100 ml pr./d	AB

Table 1 (*continued*)

Included studies	Sample size (C/T)	Male/female		Age (y)		Course of disease (m)		Intervention of group		Course of treatment		Usage and Dosage		Outcomes
		C	T	C	T	C	T	C	T	C	T	C	T	
Gong JQ 2015 [33]	40/40	24/16	18/22	58.1 ± 8.20	58.4 ± 9.00	3.3 ± 1.40	3.6 ± 1.60	1	8	4 w	4 w	3g p.o/d	50 ml pr./d	ADE
Guo S 2020 [34]	53/53	30/23	28/25	35.12 ± 21.03	35.01 ± 20.78	–		1	8	30 d	30 d	3g p.o/d	50 ml pr./d	ABEF
Han ZH 2016 [35]	39/39	19/20	18/21	64.2 ± 8.10	63.2 ± 7.60	–		1	8	30 d	30 d	3g p.o/d	30 ml pr./d	ACDEF
He PL 2018 [36]	40/40	25/15	26/14	36.26 ± 2.74	36.13 ± 2.77	3.73 ± 0.26	3.78 ± 0.21	1	8	28 d	28 d	3g p.o/d	50 ml pr./d	ACE
Huang DX 2013 [37]	40/40	20/20	17/23	68.5 ± 8.60	67.1 ± 10.40	–		1	8	30 d	30 d	3g p.o/d	30 ml pr./d	ACDEF
Li Y 2017 [38]	36/36	23/13	21/15	37.3	34.8	–		1	8	30 d	30 d	1g p.o/d	50 ml pr./d	ACE
Liu XY 2022 [39]	41/41	23/18	24/17	42.79 ± 5.36	42.38 ± 5.44	4.72 ± 0.96	4.92 ± 0.76	1	8	1 m	1 m	3g p.o/d	30 ml pr./d	ACDE
Tang QF 2016 [40]	30/30	12/18	11/19	68.21 ± 3.19	68.39 ± 3.24	4.22 ± 1.34	4.13 ± 1.26	1	8	4 w	4 w	3g p.o/d	30 ml pr./d	ACDEF
Hou CJ 2022 [41]	39/39	23/16	21/18	43.48 ± 5.02	42.67 ± 5.64	29.31 ± 4.54	29.1 ± 4.79	2	8	4 w	4 w	4g p.o/d	50 ml pr./d	AE
Luo F 2017 [42]	30/30	16/14	18/12	48.94 ± 3.56	49.63 ± 4.21	–		1	8	4 w	4 w	4g p.o/d	50 ml pr./d	AF
Cai Y 2022 [43]	38/38	19/19	17/21	30.17 ± 2.06	30.24 ± 2.17	3.03 ± 1.06	3.02 ± 1.17	1	9	8 w	–	3g p.o/d	1g pr./d	ACE
Liu R 2016 [44]	25/25	10/15	11/14	35.7 ± 7.10	36.9 ± 8.40	–		1	9	4 w	4 w	1.5g p.o/d	1g pr./d	AE
Liu WJ 2015 [45]	26/30	11/15	14/16	37.4 ± 2.50	38.9 ± 3.40	–		1	9	8 w	–	4g p.o/d	2g pr./d	AE
Ni GT 2011 [46]	30/30	22/8	24/6	50.8	53.6	–		1	9	4 w	4 w	1.25–1.75g p.o/d	1g pr./d	AB
Zhang GY 2013 [47]	35/35	21/14	22/13	35.8 ± 7.20	35.3 ± 6.80	–		1	9	15 d	15 d	4g p.o/d	1g pr./d	AB
Cai JF 2003 [48]	25/23	17/8	16/7	50.2	50.38	–		2	9	30 d	30 d	3g p.o/d	1g pr./d	A
Dong BL 2010 [49]	50/50	51/49		–		1.3 ± 3.40		1	9	45 d	45 d	2g p.o/d	10g pr./d	AB
Yang HZ 2020 [50]	40/40	29/11	27/13	37.7 ± 3.5	36.9 ± 3.80	2.8 ± 1.40	2.6 ± 1.70	2	9	30 d	30 d	0.5g pr./d	2g pr./d	AB
Ye W 2010 [51]	30/30	18/12	19/11	45.2	46.1	4.7	5.2	1	9	4 w	4 w	4–6g p.o/d	1.5g pr./d	AB
Yang XB 2018 [52]	60/60	36/24	32/28	47.25 ± 7.73	45.92 ± 8.86	19.75 ± 6.23	21.12 ± 7.32	1	10	12 w	12 w	4g p.o/d	18g p.o/d	ABE
Tian LQ 2013 [53]	28/28	17/11	16/12	35 ± 9	34 ± 9	–		3	10	6 m	–	6.7g p.o/d 5	18g p.o/d	A
Jiang CF 2011 [54]	109/109	62/47	59/50	42	41	–		2	10	8 w	–	4g p.o/d	18g p.o/d	A
Zhang C 2012 [55]	39/40	39/35	36/4	–		–		1	10	30 d	30 d	1.5g p.o/d	18g p.o/d	AEF
Hu JC 2021 [56]	40/40	25/15	24/16	50.5	49.5	–		1	10	1 m	1 m	1.5–3g p.o/d	18g p.o/d	A
Wang WL 2003 [57]	30/30	22/8	22/8	36 ± 10		–		2	10	2 w	3 w	4g p.o/d	6g p.o/d	AE

Table 1 (*continued*)

Included studies	Sample size (C/T)	Male/female		Age (y)		Course of disease (m)		Intervention of group		Course of treatment		Usage and Dosage		Outcomes
		C	T	C	T	C	T	C	T	C	T	C	T	
Xie M 2010 [58]	48/68	33/15	45/35	37.7	37.2	6.7 ± 5.3	6.3 ± 4.9	2	10	8 w	8 w	4g p.o/d	18g p.o/d	A
Zhang X 2018 [59]	14/16	8/8	6/8	51.31 ± 14.71	50 ± 15.14	–		1	11	12 w	12 w	1.2g p.o/d	18g p.o/d	AF
Yang Y 2018 [60]	43/43	22/18	26/17	37.85 ± 7.06	38.25 ± 7.36	8.64 ± 1.74	8.26 ± 1.225	1	11	12 w	12 w	4g p.o/d	18g p.o/d	ACE
Xu BQ 2015 [61]	55/55	29/26	30/25	44.7 ± 5.2	45.3 ± 5.3	8.3 ± 3.3	8.2 ± 3.5	1	11	12 w	12 w	4g p.o/d	18g p.o/d	AC
Li K 2015 [62]	37/36	23/14	21/15	40.8 ± 7.6	39.5 ± 8.2	9.6 ± 3.1	9.1 ± 2.7	1	11	8 w	8 w	4g p.o/d	18g p.o/d	AC
Huang XC 2016 [63]	50/50	35/15	33/17	41.5 ± 8.4	42.5 ± 8.5	–		1	11	12 w	12 w	4g p.o/d	18g p.o/d	AB
Xu JW 2015 [64]	40/40	51/29		34.25 ± 4.56		2.66 ± 1.47		1	11	2 m	2 m	4g p.o/d	18g p.o/d	AC
Zhang AQ 2019 [65]	42/40	26/16	18/22	39.1 ± 6.4	38.9 ± 6.2	4.4 ± 2.3	4.6 ± 2.5	1	11	1 m	1 m	1.5g p.o/d	18g p.o/d	AC
Liang X 2020 [66]	61/61	42/19	44/17	44.32 ± 10.63	43.02 ± 11.36	3.42 ± 1.03	3.52 ± 1.23	1	11	8 w	8 w	4g p.o/d	18g p.o/d	ABC
Zou H 2015 [67]	48/49	30/18	31/18	42.1 ± 1.8	41.8 ± 2.1	9,1 ± 3.3	9.7 ± 2.9	1	11	8 w	8 w	4g p.o/d	18g p.o/d	B
Xin Q 2015 [68]	38/37	22/15	17/21	39.5 ± 8.2	40.8 ± 7.6	9.1 ± 2.7	9.6 ± 3.1	1	11	8 w	8 w	4g p.o/d	18g p.o/d	ABC
Pan Z 2021 [69]	51/51	32/19	31/20	46.18 ± 8.98	45.38 ± 7.67	6.79 ± 1.76	6.85 ± 1.97	4	12	8 w	8 w	0.75g p.o/d	4.8g p.o/d	ABC
Shen H 2019 [70]	104/113	–		45.87 ± 12.07	44.9 ± 11.92	–		1	12	6 w	6 w	3g p.o/d	4.8g p.o/d	AB
Yang XQ 2022 [71]	51/51	24/27	26/25	43.25 ± 3.87	43.07 ± 3.05	5.57 ± 1.17	5.49 ± 1.04	1	12	12 w	12 w	4g p.o/d	4.8g p.o/d	ABE
Lin Y 2019 [72]	62/62	35/27	33/29	42.21 ± 1.13	42.49 ± 1.38	9.36 ± 1.02	9.72 ± 1.34	1	12	2 m	2 m	4g p.o/d	4.8g p.o/d	ABCE
Sun RQ 2020 [73]	35/35	20/15	21/14	53.6 ± 7.1	54.2 ± 7.5	3.8 ± 1.6	3.9 ± 1.7	1	12	30 d	30 d	4g p.o/d	4.8g p.o/d	AB
Li W 2017 [74]	49/49	23/26	21/28	36.3 ± 5.6	35.6 ± 5.2	–		2	13	14 d	14 d	0.25g p.o/d	2.7g p.o/d	ACD
Wang FT 2016 [75]	29/29	12/17	11/18	36.2 ± 5.4	35.7 ± 5.1	–		2	13	14 d	14 d	0.25g p.o/d	2.7g p.o/d	ACD
Cai LW 2001 [76]	21/34	13/8	22/12	46.3	43.2	–		2	13	60 d	60 d	2g p.o/d	1.8g pr./d	A
Yuan XH 2020 [77]	31/32	15/16	16/16	43.28 ± 3.64	43.35 ± 3.47	–		1	13	15 d	15 d	0.75g p.o/d	2.7g p.o/d	AC
Wen B 2017 [78]	49/49	25/24	29/20	36.7 ± 3.1	37.7 ± 3.8	5.47 ± 2.63	4.84 ± 2.93	1	13	4 w	4 w	4g p.o/d	2.7g p.o/d	AC
Liu J 2011 [79]	23/27	–		30.2 ± 3.6	29 ± 4.2	–		1	13	2 w	2 w	2g pr./d	2.4g pr./d	ABF

1,mesalazine; 2, sulfasalazine; 3, balsalazide; 4, Olsalazine; 5, 5-aminosalicylic acid + ChangYanNing Capsule; 6, 5-aminosalicylic acid + Danshen Injection; 7, 5-aminosalicylic acid + Compound Cortex Phellodendri Solution; 8, 5-aminosalicylic acid + Kangfuxin Liquid; 9, 5-aminosalicylic acid + Xilei Powder; 10, 5-aminosalicylic acid + Bupi Yichang Pill; 11, 5-aminosalicylic acid + Shenling Baizhu Powder; 12, 5-aminosalicylic acid + Hudi Enteric-coated Capsule; 13, 5-aminosalicylic acid + ZhiKang Capsule; C, Control group; T, Treatment group. Outcomes: A, overall response rate; B, disease activity index; C, inflammatory factors; D, coagulation factor; E, adverse event rate; F, recurrence rate.
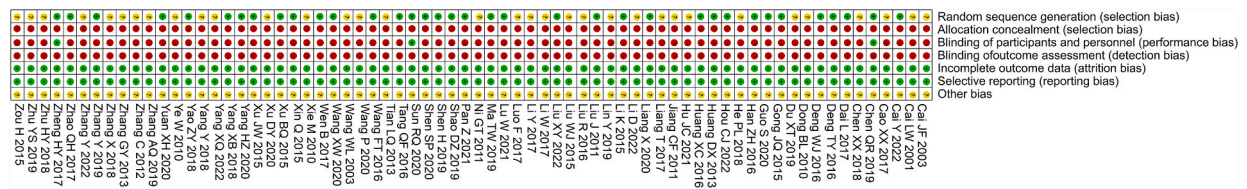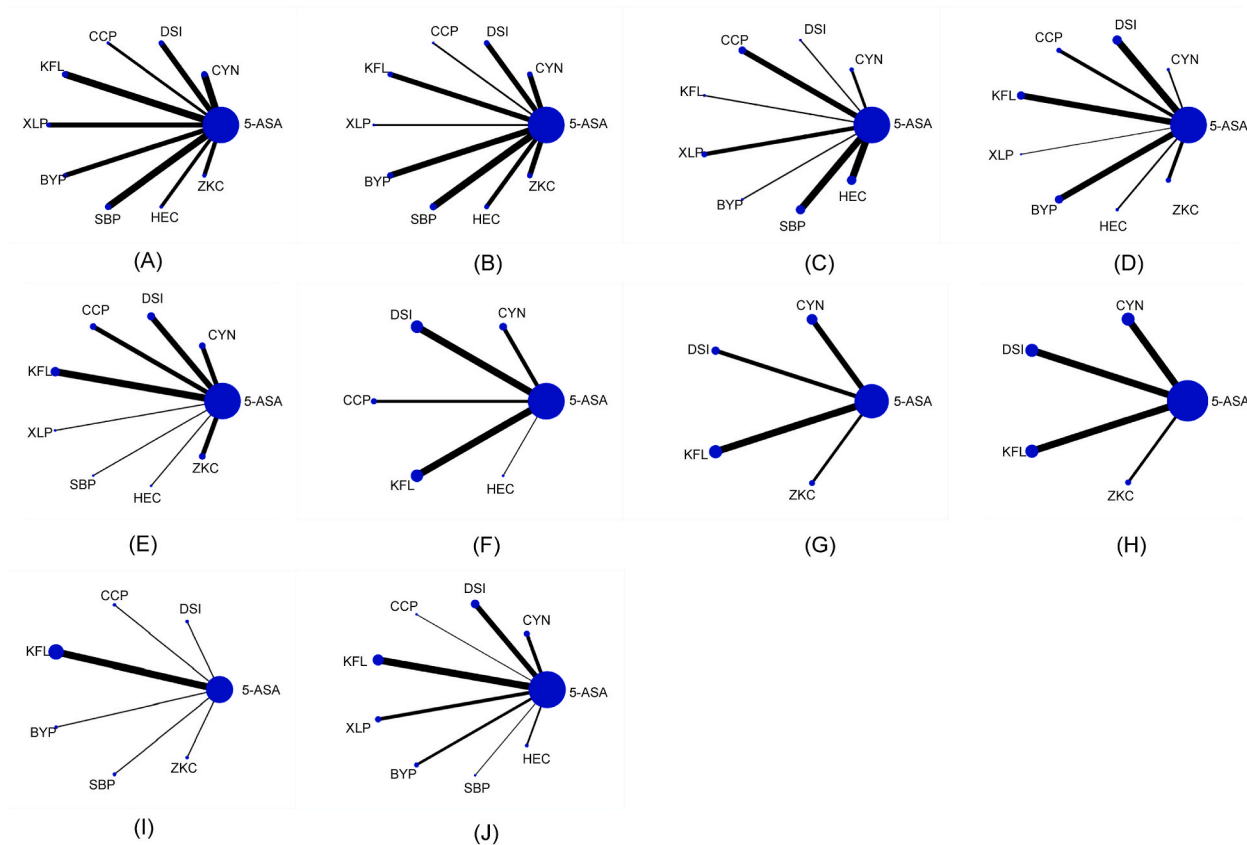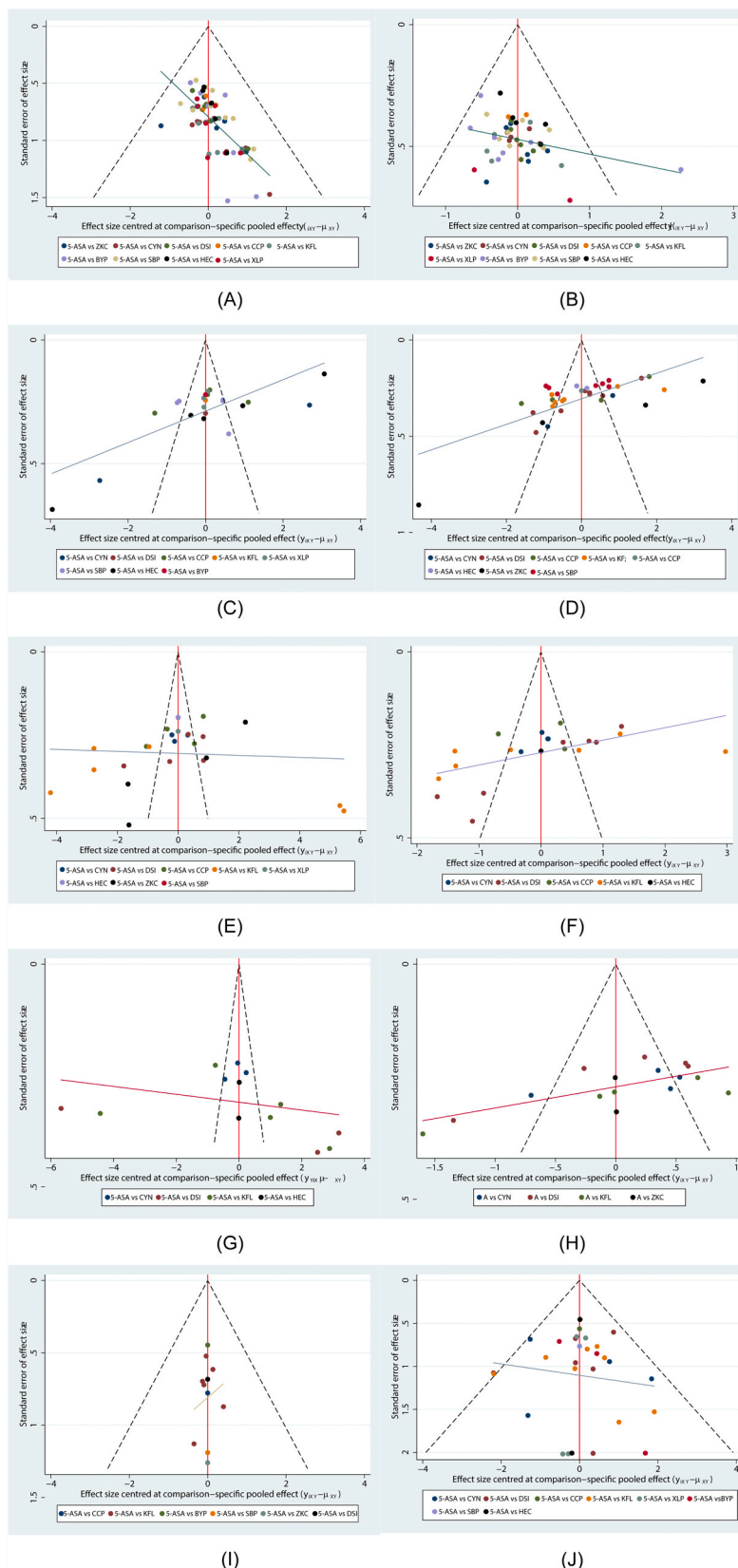
Fig. 2. Risk of bias.

Fig. 3. Network diagrams of outcome indicators. (A) Overall response rate. (B) Excellent rate. (C) disease activity index. (D) TNF-α. (E) IL-6. (F) IL-8. (G) mean platelet volume. (H) fibrinogen. (I) Recurrence rate. (J) Adverse event rate. 5-ASA, 5-aminosalicylic acid; CYN, ChangYanNing Capsule+5-ASA; DSI, Danshen Injection+5-ASA; CCP, Compound Cortex Phellodendri Solution+5-ASA; KFL, Kangfuxin Liquid+5-ASA; XLP, Xilei Powder+5-ASA; BYP, Bupi Yichang Pill+5-ASA; SBP, Shenling Baizhu Powder+5-ASA; HEC, Hudi Enteric-coated Capsule+5-ASA; ZKC, ZhiKang Capsule+5-ASA.

that 5-ASA exerts therapeutic effects through mechanisms such as anti-inflammatory, antioxidant, and anti-apoptotic effects [3]. Although 5-ASA medications have proven clinical efficacy, some of them can cause serious side effects. For instance, sulfasalazine has been associated with drug eruptions, drug-induced hypersensitivity syndrome, and acute pancreatitis [4–6]. Salicylic acid preparation and immunosuppressive therapy won't cause any effective effects on some patients [7]. Therefore, there is an urgent need to develop effective and safe adjuvant therapies for patients who do not respond to treatment with salicylic acid preparations and immunosuppression agents, as well as stubborn cases of glucocorticoid-resistant or -dependent patients.

Chinese patent medicines (CPMs) are commercial traditional Chinese medicine (TCM) preparations made with the approval of China's drug regulatory department under the guidance of TCM theory. Several clinical Randomized controlled trials (RCTs) have demonstrated that the combination of CPMs with 5-ASA could maintain long-term remission and reduce the recurrence rate [8,9]. However, the wide range of CPMs available for UC treatment poses a challenge for clinicians in selecting the most suitable option, particularly for patients with varying disease presentations. Network meta-analyze (NMA) offers an advantage over traditional meta-analysis by enabling the identification of the most effective intervention among multiple options. Therefore, we compared the effects of combinations of 5-ASA with various CPMs in the treatment of UC and evaluated their intervention effectiveness and clinical safety by NMA. We hope that the results of this study can provide better choices for clinical doctors in providing personalized

(A)

(B)

(C)

(D)

(E)

(F)

(G)

(H)

(I)

(J)

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Fig. 4. Funnel plots of outcome indicators. (A) Overall response rate. (B) Excellent rate. (C) disease activity index. (D) TNF-α. (E) IL-6. (F) IL-8. (G) mean platelet volume. (H) fibrinogen. (I) Recurrence rate. (J) Adverse event rate. 5-ASA, 5-aminosalicylic acid; CYN, ChangYanNing Capsule+5-ASA; DSI, Danshen Injection+5-ASA; CCP, Compound Cortex Phellodendri Solution+5-ASA; KFL, Kangfuxin Liquid+5-ASA; XLP, Xilei Powder+5-ASA; BYP, Bupi Yichang Pill+5-ASA; SBP, Shenling Baizhu Powder+5-ASA; HEC, Hudi Enteric-coated Capsule+5-ASA; ZKC, ZhiKang Capsule+5-ASA.

CPMs+5-ASA treatment plans for UC patients, and provide more inspiration for basic researchers in pharmacy and biology. According to the literature search results, nine kinds of TCM included in this study are ChangYanNing Capsule (CYN), Danshen Injection (DSI), Compound Cortex Phellodendri Solution (CCP), Kangfuxin Liquid (KFL), Xilei Powder (XLP), Bupi Yichang Pill (BYP), Shenling Baizhu Powder (SBP), Hudi Enteric-coated Capsule (HEC), ZhiKang Capsule (ZKC). This study aims to inform clinical decision-making by providing a comprehensive evaluation of CPMs+5-ASA combination therapies for UC, thus enabling personalized treatment strategies. Additionally, the findings may inspire basic research in pharmacy and biology, fostering a deeper understanding of UC pathogenesis and treatment.

2. Materials and methods

2.1. Inclusion criteria

(1) Study type. RCTs reporting the use of CPM combined with 5-ASA for UC treatment were included. The search was restricted to studies published in Chinese or English.
(2) Study subjects. Patient diagnosis of UC was based on the series of Guidelines for Consensus Opinions on the Diagnosis and Treatment of Inflammatory Bowel Disease published by the Chinese Medical Association [10].
(3) Intervention measures. Patients in the experimental group were treated with 5-ASA combined with CPM, and patients in the control group were treated with 5-ASA alone.
(4) Outcomes: The primary outcome of this study is overall response rate. The secondary outcomes are excellent rate, disease activity index (DAI), inflammatory factors, mean platelet volume (MPV), fibrinogen (FIB) levels, recurrence rate, and adverse event rate. Eligible trials must include data on at least one of these outcomes.

2.2. Exclusion criteria

(1) Patients in the control group or experimental group took other medicines besides 5-ASA or CPM combined with 5-ASA.
(2) Duplicate studies.
(3) Incomplete data.
(4) The components, dosage, and administration method described in the CPMs used were unclear or inconsistent with those reported in Table S2.

2.3. Outcome measures

Based on a review of clinical trials published in academic journals evaluating UC, outcome indicators were determined. These indicators included overall response rate, excellent rate, DAI, inflammatory factors, MPV, FIB, recurrence rate, and adverse event rate.

(1) Effective cases: The clinical symptoms were significantly relieved, and colonoscopy showed that mucosal inflammation turned mild.
(2) Excellent effective cases: Clinical symptoms resolved, and colonoscopy revealed either a near-normal mucosal appearance or the absence of active inflammation.
(3) Overall response rate = [(number of excellently effective cases + number of effective cases)/total number of cases] × 100 %.
(4) Excellent rate = (number of excellently effective cases)/(total number of cases) × 100 %.
(5) Disease activity index: Modified Mayo score.
(6) Inflammatory factors: IL-6, IL-10, TNF-α.

2.4. Search strategies

We searched the following databases: Cochrane Library, Elton B. Stephens. Company Research Databases, Embase, PubMed, Web of Science, CNKI, VIP, and WanFang. The publication time of the literature is from the establishment of the database to May 31, 2023. The search strategy is provided in Table S1.

2.5. Study selection and data extraction

Two reviewers (Qian Gao and Miaomiao Zhou) conducted a literature search based on the predefined search strategy and imported the retrieved literature into footnote X9. After removing duplicate literature, the full text of potentially eligible articles was

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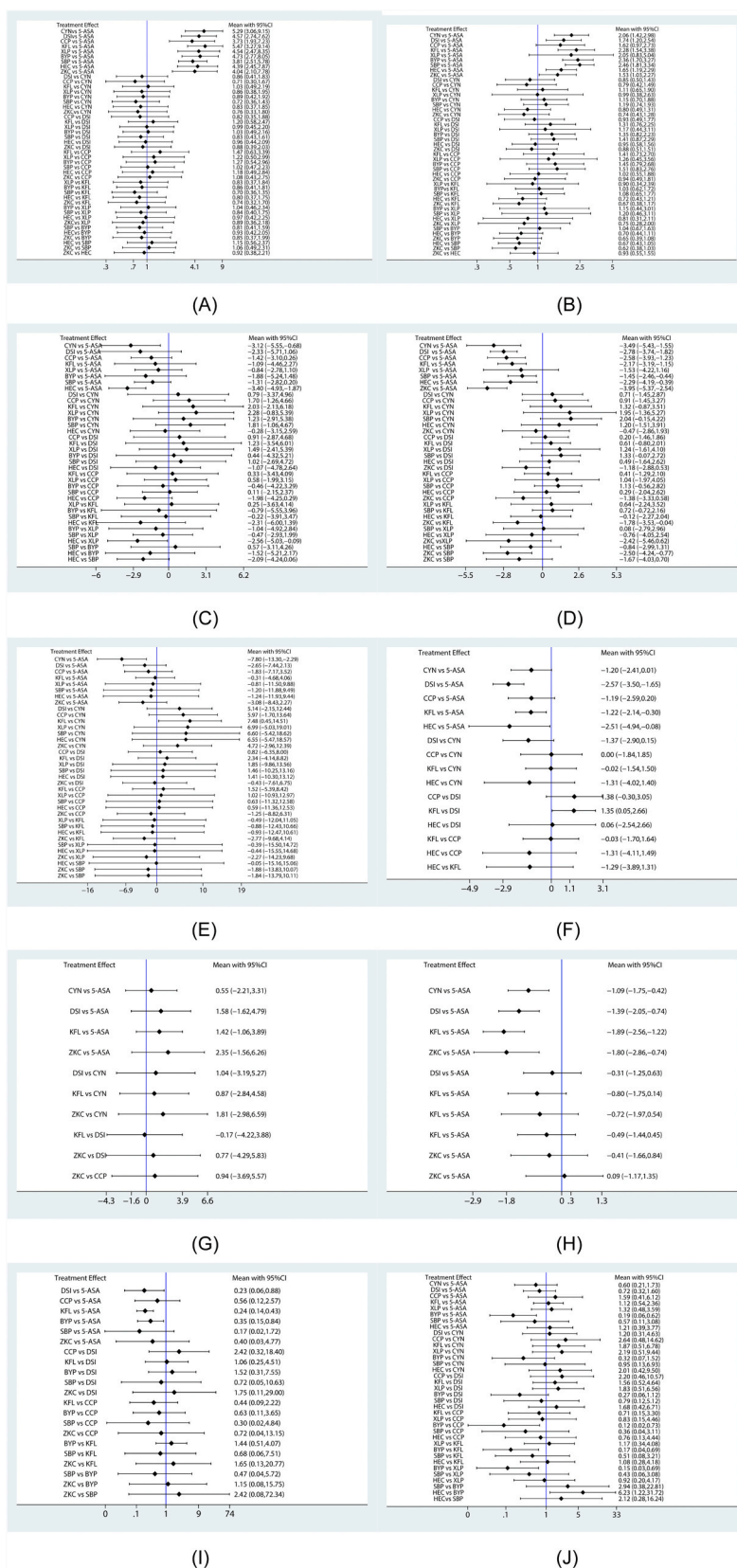
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Fig. 5. Pairwise comparison forest graph of outcome indicators. (A) Overall response rate. (B) Excellent rate. (C) disease activity index. (D) TNF-α. (E) IL-6. (F) IL-8. (G) mean platelet volume. (H) fibrinogen. (I) Recurrence rate. (J) Adverse event rate. 5-ASA, 5-aminosalicylic acid; CYN, ChangYanNing Capsule+5-ASA; DSI, Danshen Injection+5-ASA; CCP, Compound Cortex Phellodendri Solution+5-ASA; KFL, Kangfuxin Liquid+5-ASA; XLP, Xilei Powder+5-ASA; BYP, Bupi Yichang Pill+5-ASA; SBP, Shenling Baizhu Powder+5-ASA; HEC, Hudi Enteric-coated Capsule+5-ASA; ZKC, ZhiKang Capsule+5-ASA.

downloaded. Articles that deviated from the inclusion criteria based on their titles and abstracts were excluded. Any disagreements were resolved through discussion with the third reviewer (Xiwen Geng). Data were extracted using predefined data extraction tables (Zhibin Chen and Zifa Li). The following data items were extracted: first author, year of publication, sample size per group, sex ratio, age distribution, control intervention, experimental intervention, course of treatment, outcome measures, disease duration, measurement results, and adverse effects.

2.6. Bias risk assessment

The Cochrane Handbook for Systematic Reviews of Interventions' risk of bias assessment tool for randomized controlled trials (RCTs) was used to independently assess the risk of bias in the included studies. This tool evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, completeness of outcome data, selective reporting, and other potential sources of bias. The quality of the studies was assessed using Review Manager (Rev Man) 5.4 software. The literature quality assessment process was conducted independently by two authors (Ying Xing and Xiaoyu Liu). Any disagreements between the two authors were resolved through discussion with the other authors of the study. Each potential bias source is classified as 'high', "low" or "unclear", and is annotated in the "Risk of Bias" table by 'red', 'green' and 'yellow' colors respectively.

2.7. Statistical investigation

In this study, Review Manager 5.4 was used to evaluate the quality of the included literature. The data extracted from the literature were entered into Stata 15.0 software, and statistical analysis was performed using computer commands. Data processing, network evidence plots, funnel plots, forest plots, and Surface Under the Cumulative Ranking (SUCRA) analysis were performed successively. The odds ratio (OR) and 95 % confidence interval (CI) were used as effect size indicators for the binary outcomes (total response rate, recurrence rate, and incidence of adverse reactions). Continuous outcomes (inflammatory factors, FIB, MPV, DAI) were measured using mean difference (MD) and 95 % CI. A fixed-effects model was used for the analysis. The defining characteristic of the fixed-effects model is that it assumes a common effect size across all studies included in the analysis. All the studies included in this study compared interventions to 5-ASA, so the studies were considered to be clinically homogeneous and no heterogeneity test was required. For each intervention, SUCRA was calculated, with a SUCRA score of 1 indicating perfect efficacy and a SUCRA score of 0 indicating no efficacy. Additionally, a heatmap was generated using GraphPad Prism 9.0 to illustrate the improvement in outcomes when CPMs were combined with 5-ASA compared to 5-ASA alone.

3. Results

3.1. Literature review

A total of 1564 studies were retrieved by searching various databases. Removed 502 duplicate documents. Excluded 339 studies unrelated to this topic after reviewing the full text. Of the remaining 723 studies, 110 were excluded because they were not RCTs, 471 because they did not match the intervention measures, 22 because they had incomplete data, 45 because they were meta-analyses, and 5 because they involved repeated publication. A total of 70 studies met the inclusion criteria (Fig. 1).

3.2. Basic characteristics of included studies

In total, 70 studies were included, including 5973 patients. Basic information is provided in Table 1.

3.3. Bias risk assessment of included studies

The 70 included studies all used a randomized method, 29 using random number tables generated from random sequences [13–15, 22,29,31,33–35,37,40,41,43,62,63,66,69,70,79], 2 RCTs used the drawing of lots [39,64], 1 study used the two-color ball method [16], and 4 RCT used block randomization [12,20,73,77]. All of them were classified as "low risk" in random sequence generation. The remaining 34 studies did not report blinded set-up and were therefore rated as "unclear risk". Three trials used the double-blind method for participants and personnel [12,20,73], and others provided no detailed information. These were therefore rated as "high risk". None of the included studies reported implementing allocation concealment and were therefore rated as "high risk" of bias. The data integrity evaluation results and selective reporting result were "low risk" and other biases were "unclear risk". The bias assessment was shown in Fig. 2.

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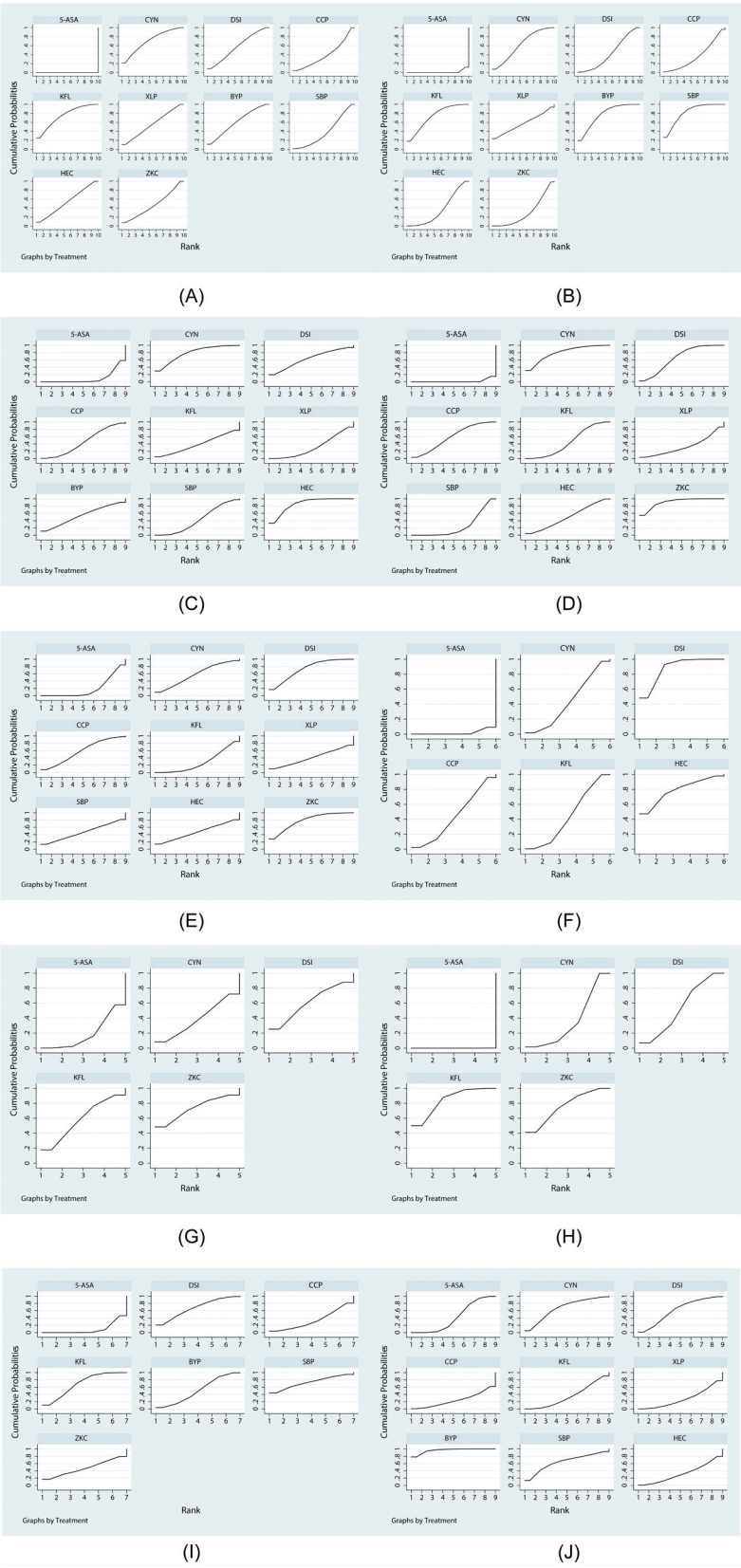
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Fig. 6. Curve diagram of SUCRA of outcome indicators. (A) Overall response rate. (B) Excellent rate. (C) disease activity index. (D) TNF-α. (E) IL-6. (F) IL-8. (G) mean platelet volume. (H) fibrinogen. (I) Recurrence rate. (J) Adverse event rate. 5-ASA, 5-aminosalicylic acid; CYN, ChangYanNing Capsule+5-ASA; DSI, Danshen Injection+5-ASA; CCP, Compound Cortex Phellodendri Solution+5-ASA; KFL, Kangfuxin Liquid+5-ASA; XLP, Xilei Powder+5-ASA; BYP, Bupi Yichang Pill+5-ASA; SBP, Shenling Baizhu Powder+5-ASA; HEC, Hudi Enteric-coated Capsule+5-ASA; ZKC, ZhiKang Capsule+5-ASA.

3.4. Outcome indicators

3.4.1. Overall response rate

(1) Evidence network. The overall response rate was reported in 67 studies, involving nine CPM treatment regimens (Fig. 3A).
(2) Publication bias. Fig. 4A presents the funnel plot of overall response rates for nine CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed a symmetrical distribution of studies around the X = 0 line, with no studies falling outside the funnel. This suggests a low likelihood of small-sample effects influencing the research network.
(3) NMA. This study included 67 studies that reported overall response rates for nine different CPM treatment regimens. A network meta-analysis was performed on these nine CPMs, resulting in a total of 45 pairwise comparisons (Figs. 5A and 7A). Of these, nine comparisons yielded statistically significant differences. Compared with 5-ASA alone, the OR and 95 % CI of 5-ASA combined with KFL, CYN, BYP, DSI, XLP, HEC, ZKC, CCP, and SBP were 5.47 and [3.27, 9.14], 5.29 and [3.06, 9.15], 4.73 and [2.77, 8.05], 4.57 and [2.74, 7.62], 4.54 and [2.47, 8.35], 4.39 and [2.45, 7.87], 4.04 and [2.10, 7.78], 3.73 and [1.93, 7.23], and 3.81 and [2.51, 5.78].
(4) SUCRA probability ranking. According to the SUCRA scores, the overall response rates of nine CPMs and 5-ASA alone were arranged in order: KFL (74.6 %) > CYN (70.9 %) > BYP (60.9 %) > DSI (57.5 %) > XLP (55.9 %) > HEC (53.7 %) > ZKC (47.3 %) > CCP (39.9 %) > SBP (39.4 %) > 5-ASA (0.0 %) (Fig. 6A).

3.4.2. Excellent rate

(1) Evidence network. Excellent rates were reported in 48 studies involving nine CPM treatment regimens (Fig. 3B).
(2) Publication bias. Fig. 4B presents the funnel plot for excellent response rates of nine CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed a symmetrical distribution of studies around the X = 0 line, with only one study falling outside the funnel. This suggests a low likelihood of small-sample effects influencing the research network.
(3) NMA. This study included 48 studies that reported excellent response rates for nine different CPM treatment regimens. A network meta-analysis was performed on these nine CPMs, resulting in a total of 45 pairwise comparisons (Figs. 5B and 7B). Of these, seven comparisons yielded statistically significant differences. Compared with 5-ASA alone, the OR and 95 % CI of 5-ASA combined with SBP, BYP, KFL, CYN, DSI, CCP, HEC, and ZKC were 2.46 and [1.81, 3.34], 2.36 and [1.70, 3.27], 2.28 and [1.54, 3.38], 2.06 and [1.42, 2.98], 1.74 and [1.20, 2.54], 1.62 and [0.97, 2.73], 1.85 and [1.19, 2.29], and 1.53 and [1.03, 2.27].
(4) SUCRA probability ranking. According to the SUCRA scores, the excellent rates of nine CPMs and 5-ASA alone were were arranged in order: SBP (81.6 %) > BYP (77.5 %) > KFL (73.6 %) > CYN (61.6 %) > XLP (58.8 %) > DSI (42.7 %) > CCP (36.9 %) > HEC (36.6 %) > ZKP (29.6 %) > 5-ASA (1.3 %) (Fig. 6B).

3.4.3. Disease activity index

(1) Evidence network. The DAI was reported in 22 studies, including eight CPM treatment regimens (Fig. 3C).
(2) Publication bias. Fig. 4C presents the funnel plot for the DAI of eight CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed an asymmetrical distribution of studies around the X = 0 line, with nine studies falling outside the funnel. This finding suggests that the small-sample effect may affect the reliability of the results.
(3) NMA. This study included 22 studies that reported the DAI for eight different CPM treatment regimens. A network meta-analysis was performed on these eight CPMs, resulting in a total of 36 pairwise comparisons (Figs. 5C and 7C). Of these, three comparisons yielded statistically significant differences. Compared with 5-ASA alone, MD and 95 % CI of 5-ASA combined with HEC and CYN were −3.40 and [4.93, −1.87] and −3.12 and [−5.55, −0.68].
(4) SUCRA probability ranking. According to the SUCRA scores, the reduced DAI rates of eight CPMs and 5-ASA alone were arranged in order: HEC (85.7 %) > CYN (78.5 %) > DSI (63.0 %) > BYP (54.2 %) > CCP (45.7 %) > SBP (42.8 %) > KFL (38.6 %) > XLP (31.6 %) > 5-ASA (9.9 %) (Fig. 6C).

3.4.4. TNF-α

(1) Evidence network. TNF-α levels were reported in 35 studies, involving eight CPM treatment regimens (Fig. 3D).
(2) Publication bias. Fig. 4D presents the funnel plot for TNF-α levels of eight CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed an asymmetrical distribution of studies around the X = 0 line, with twenty-three studies falling outside the funnel. No approval of the small-sample effect was shown in the research network.

(A)

KLF									
1.03 (0.49,2.19)	CYN								
1.16 (0.55,2.43)	1.12 (0.52,2.40)	BYP							
1.20 (0.58,2.47)	1.16 (0.55,2.45)	1.03 (0.49,2.16)	DSI						
1.20 (0.54,2.67)	1.16 (0.51,2.64)	1.04 (0.46,2.34)	1.01 (0.45,2.23)	XLP					
1.25 (0.57,2.71)	1.20 (0.54,2.69)	1.08 (0.49,2.38)	1.04 (0.48,2.26)	1.04 (0.44,2.41)	HEC				
1.35 (0.59,3.11)	1.31 (0.56,3.07)	1.17 (0.50,2.72)	1.13 (0.49,2.60)	1.12 (0.46,2.75)	1.07 (0.45,2.61)	ZKC			
1.47 (0.63,3.39)	1.42 (0.60,3.35)	1.27 (0.54,2.96)	1.22 (0.53,2.83)	1.22 (0.50,2.99)	1.18 (0.49,2.84)	1.08 (0.43,2.75)	CCP		
1.44 (0.74,2.79)	1.39 (0.70,2.77)	1.24 (0.63,2.44)	1.20 (0.62,2.32)	1.19 (0.57,2.50)	1.15 (0.56,2.37)	1.06 (0.49,2.31)	0.98 (0.45,2.14)	SBP	
5.47 (3.27,9.14)	**5.29 (3.06,9.15)**	**4.73 (2.77,8.05)**	**4.57 (2.74,7.62)**	**4.54 (2.47,8.35)**	**4.39 (2.45,7.87)**	**4.04 (2.10,7.78)**	**3.73 (1.93,7.23)**	**3.81 (2.51,5.78)**	5-ASA

(B)

SBP									
1.04 (0.67,1.63)	BYP								
1.08 (0.65,1.77)	1.03 (0.62,1.72)	KFL							
1.19 (0.74,1.93)	1.15 (0.70,1.88)	1.11 (0.65,1.90)	CYN						
1.20 (0.46,3.11)	1.15 (0.44,3.01)	1.12 (0.42,2.98)	1.01 (0.38,2.66)	XLP					
1.41 (0.87,2.29)	1.35 (0.82,2.23)	1.31 (0.76,2.25)	1.18 (0.70,2.00)	1.17 (0.44,3.11)	DSI				
1.51 (0.83,2.76)	1.45 (0.79,2.68)	1.41 (0.73,2.70)	1.27 (0.67,2.40)	1.26 (0.45,3.56)	1.07 (0.57,2.04)	CCP			
1.49 (0.95,2.33)	1.43 (0.90,2.27)	1.38 (0.83,2.31)	1.25 (0.76,2.04)	1.24 (0.47,3.23)	1.06 (0.64,1.74)	0.98 (0.53,1.82)	HEC		
1.61 (0.97,2.65)	1.54 (0.92,2.58)	1.49 (0.86,2.61)	1.35 (0.78,2.31)	1.34 (0.50,3.58)	1.14 (0.66,1.97)	1.06 (0.55,2.04)	1.08 (0.65,1.81)	ZKC	
2.46 (1.81,3.34)	**2.36 (1.70,3.27)**	**2.28 (1.54,3.38)**	**2.06 (1.42,2.98)**	2.05 (0.83,5.04)	**1.74 (1.20,2.54)**	1.62 (0.97,2.73)	**1.65 (1.19,2.29)**	**1.53 (1.03,2.27)**	5-ASA

(C)

HEC								
-0.28(-3.15,2.59)	CYN							
-1.07(-4.78,2.64)	0.79(-3.37,4.96)	DSI						
-1.52(-5.21,2.17)	1.23(-2.91,5.38)	0.44(-4.32,5.21)	BYP					
-1.98(-4.25,0.29)	1.70(-1.26,4.66)	0.91(-2.87,4.68)	-0.46(-4.22,3.29)	CCP				
-2.09(-4.24,0.06)	1.81(-1.06,4.67)	1.02(-2.69,4.72)	0.57(-3.11,4.26)	0.11(-2.15,2.37)	SBP			
-2.31(-6.00,1.39)	2.03(-2.13,6.18)	1.23(-3.54,6.01)	-0.79(-5.55,3.96)	0.33(-3.43,4.09)	-0.22(-3.91,3.47)	KFL		
-2.56(-5.03,-0.09)	2.28(-0.83,5.39)	1.49(-2.41,5.39)	-1.04(-4.92,2.84)	0.58(-1.99,3.15)	-0.47(-2.93,1.99)	0.25(-3.63,4.14)	XLP	
-3.40(-4.93,-1.87)	**-3.12(-5.55,-0.68)**	-2.33(-5.71,1.06)	-1.88(-5.24,1.48)	-1.42(-3.10,0.26)	-1.31(-2.82,0.20)	-1.09(-4.46,2.27)	-0.84(-2.78,1.10)	5-ASA

(D)

ZKC								
-0.47(-2.86,1.93)	CYN							
-1.18(-2.88,0.53)	0.71(-1.45,2.87)	DSI						
-1.38(-3.33,0.58)	0.91(-1.45,3.27)	0.20(-1.46,1.86)	CCP					
-1.67(-4.03,0.70)	1.20(-1.51,3.91)	0.49(-1.64,2.62)	0.29(-2.04,2.62)	HEC				
-1.78(-3.53,-0.04)	1.32(-0.87,3.51)	0.61(-0.80,2.01)	0.41(-1.29,2.10)	-0.12(-2.27,2.04)	KFL			
-2.42(-5.46,0.62)	1.95(-1.36,5.27)	1.24(-1.61,4.10)	1.04(-1.97,4.05)	-0.76(-4.05,2.54)	0.64(-2.24,3.52)	XLP		
-2.50(-4.24,-0.77)	2.04(-0.15,4.22)	1.33(-0.07,2.72)	1.13(-0.56,2.82)	-0.84(-2.99,1.31)	0.72(-0.72,2.16)	0.08(-2.79,2.96)	SBP	
-3.95(-5.37,-2.54)	**-3.49(-5.43,-1.55)**	**-2.78(-3.74,-1.82)**	**-2.58(-3.93,-1.23)**	**-2.29(-4.19,-0.39)**	**-2.17(-3.19,-1.15)**	-1.53(-4.22,1.16)	**-1.45(-2.46,-0.44)**	5-ASA

(E)

ZKC								
-0.47(-2.86,1.93)	CYN							
-1.18(-2.88,0.53)	0.71(-1.45,2.87)	DSI						
-1.38(-3.33,0.58)	0.91(-1.45,3.27)	0.20(-1.46,1.86)	CCP					
-1.67(-4.03,0.70)	1.20(-1.51,3.91)	0.49(-1.64,2.62)	0.29(-2.04,2.62)	HEC				
-1.78(-3.53,-0.04)	1.32(-0.87,3.51)	0.61(-0.80,2.01)	0.41(-1.29,2.10)	-0.12(-2.27,2.04)	KFL			
-2.42(-5.46,0.62)	1.95(-1.36,5.27)	1.24(-1.61,4.10)	1.04(-1.97,4.05)	-0.76(-4.05,2.54)	0.64(-2.24,3.52)	XLP		
-2.50(-4.24,-0.77)	2.04(-0.15,4.22)	1.33(-0.07,2.72)	1.13(-0.56,2.82)	-0.84(-2.99,1.31)	0.72(-0.72,2.16)	0.08(-2.79,2.96)	SBP	
-3.95(-5.37,-2.54)	**-3.49(-5.43,-1.55)**	**-2.78(-3.74,-1.82)**	**-2.58(-3.93,-1.23)**	**-2.29(-4.19,-0.39)**	**-2.17(-3.19,-1.15)**	-1.53(-4.22,1.16)	**-1.45(-2.46,-0.44)**	5-ASA

(F)

DSI					
0.06(-2.54,2.66)	HEC				
1.35(0.05,2.66)	-1.29(-3.89,1.31)	KFL			
1.38(-0.30,3.05)	-1.31(-4.11,1.49)	-0.03(-1.70,1.64)	CCP		
-1.37(-2.90,0.15)	-1.31(-4.02,1.40)	-0.02(-1.54,1.50)	0.00(-1.84,1.85)	CYN	
-2.57(-3.50,-1.65)	**-2.51(-4.94,-0.08)**	**-1.22(-2.14,-0.30)**	-1.19(-2.59,0.20)	-1.20(-2.41,0.01)	5-ASA

(G)

ZKC				
0.77(-4.29,5.83)	DSI			
0.94(-3.69,5.57)	-0.17(-4.22,3.88)	KFL		
1.81(-2.98,6.59)	1.04(-3.19,5.27)	0.87(-2.84,4.58)	CYN	
2.35(-1.56,6.26)	1.58(-1.62,4.79)	1.42(-1.06,3.89)	0.55(-2.21,3.31)	5-ASA

(H)

KFL				
0.09(-1.17,1.35)	ZKC			
-0.49(-1.44,0.45)	-0.41(-1.66,0.84)	DSI		
-0.80(-1.75,0.14)	-0.72(-1.97,0.54)	-0.31(-1.25,0.63)	CYN	
-1.89(-2.56,-1.22)	**-1.80(-2.86,-0.74)**	**-1.39(-2.05,-0.74)**	**-1.09(-1.75,-0.42)**	5-ASA

(I)

SBP						
0.68 (0.06,7.51)	KFL					
0.72 (0.05,10.63)	1.06 (0.25,4.51)	DSI				
0.47 (0.04,5.72)	0.69 (0.25,1.96)	0.66 (0.13,3.25)	BYP			
0.41 (0.01,12.32)	0.60 (0.05,7.59)	0.57 (0.03,9.47)	0.87 (0.06,11.96)	ZKC		
0.30 (0.02,4.84)	0.44 (0.09,2.22)	0.41 (0.05,3.14)	0.63 (0.11,3.65)	0.72 (0.04,13.15)	CCP	
0.17 (0.02,1.72)	**0.24 (0.14,0.43)**	**0.23 (0.06,0.88)**	**0.35 (0.15,0.84)**	0.40 (0.03,4.77)	0.56 (0.12,2.57)	5-ASA

(J)

BYP								
0.32 (0.07,1.52)	CYN							
0.34 (0.04,2.65)	1.06 (0.14,7.73)	SBP						
0.27 (0.06,1.12)	0.84 (0.22,3.23)	0.79 (0.12,5.12)	DSI					
0.19 (0.06,0.62)	0.60 (0.21,1.73)	0.57 (0.11,3.08)	0.72 (0.32,1.60)	5-ASA				
0.17 (0.04,0.69)	0.54 (0.15,1.94)	0.51 (0.08,3.21)	0.64 (0.22,1.91)	0.89 (0.42,1.87)	KFL			
0.16 (0.03,0.82)	0.50 (0.11,2.35)	0.47 (0.06,3.61)	0.60 (0.15,2.38)	0.83 (0.27,2.57)	0.93 (0.24,3.61)	HEC		
0.15 (0.03,0.69)	0.46 (0.11,1.97)	0.43 (0.06,3.08)	0.55 (0.15,1.96)	0.76 (0.28,2.07)	0.85 (0.25,2.96)	0.92 (0.20,4.17)	XLP	
0.12 (0.02,0.73)	0.38 (0.07,2.10)	0.36 (0.04,3.11)	0.45 (0.09,2.18)	0.63 (0.16,2.43)	0.71 (0.15,3.30)	0.76 (0.13,4.44)	0.83 (0.15,4.46)	CCP

(caption on next page)

Fig. 7. Results from the NMA showing the effect of each of the interventions. (A) Overall response rate. (B) Excellent rate. (C) disease activity index. (D) TNF-α. (E) IL-6. (F) IL-8. (G) mean platelet volume. (H) fibrinogen. (I) Recurrence rate. (J) Adverse event rate. 5-ASA, 5-aminosalicylic acid; CYN, ChangYanNing Capsule+5-ASA; DSI, Danshen Injection+5-ASA; CCP, Compound Cortex Phellodendri Solution+5-ASA; KFL, Kangfuxin Liquid+5-ASA; XLP, Xilei Powder+5-ASA; BYP, Bupi Yichang Pill+5-ASA; SBP, Shenling Baizhu Powder+5-ASA; HEC, Hudi Enteric-coated Capsule+5-ASA; ZKC, ZhiKang Capsule+5-ASA.

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(3) NMA. This study included 35 studies that reported TNF-α levels for eight different CPM treatment regimens. A network meta-analysis was performed on these eight CPMs, resulting in a total of 36 pairwise comparisons (Figs. 5D and 7D). Of these, nine comparisons yielded statistically significant differences. Compared with 5-ASA alone, MD and 95 % CI of 5-ASA combined with ZKC, CYN, DSI, CCP, HEC, KFL, and SBP were −3.95 and [−5.37, −2.54], −3.49 and [−5.43, −1.55], −2.78 and [−3.74, −1.82], −2.58 and [−3.93, −1.23], −2.29 and [−4.19, −0.39], −2.17 and [−3.19, −1.15], and −1.45 and [−2.46, −0.44], respectively. Moreover, there was a benefit of ZKC+5-ASA over SBP+5-ASA, the results were statistically significant, WMD and 95 % CIs were −2.50 and [-4.24, −0.77].

(4) SUCRA probability ranking. According to the SUCRA scores, the reduced TNF-α rates of eight CPMs and 5-ASA alone were arranged in order: ZKC (91.0 %) > CYN (79.9 %) > DSI (65.1 %) > CCP (58.7 %) > HEC (50.0 %) > KFL (45.0 %) > XLP (33.1 %) > SBP (25.3 %) > 5-ASA (1.9 %) (Fig. 6D).

3.4.5. IL-6

(1) Evidence network. IL-6 levels were reported in 26 studies, involving eight CPM treatment regimens (Fig. 3E).

(2) Publication bias. Fig. 4E presents the funnel plot for IL-6 levels of eight CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed a symmetrical distribution of studies around the X = 0 line, with fifteen studies falling outside the funnel. No approval of the small-sample effect was shown in the research network.

(3) NMA. This study included 26 studies that reported IL-6 levels for eight different CPM treatment regimens. A network meta-analysis was performed on these eight CPMs, resulting in a total of 36 pairwise comparisons (Figs. 5E and 7E). Of these, two comparisons yielded statistically significant differences. Compared with 5-ASA alone, MD and 95 % CI of 5-ASA combined with CYN were −7.80 and [−13.30, −2.29].

(4) SUCRA probability ranking. According to the SUCRA scores, the reduced IL-6 rates of eight CPMs and 5-ASA alone were arranged in order: CYN (91.3 %) > ZKC (60.3 %) > DSI (56.8 %) > CCP (49.5 %) > SBP (45.6 %) > HEC (44.1 %) > XLP (41.1 %) > KFL (33.4 %) > 5-ASA (27.9 %) (Fig. 6E).

3.4.6. IL-8

(1) Evidence network. IL-8 levels were reported in 22 studies, involving five CPM treatment regimens (Fig. 3F).

(2) Publication bias. Fig. 4F presents the funnel plot for IL-8 levels of five CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed a symmetrical distribution of studies around the X = 0 line, with thirteen studies falling outside the funnel. No approval of the small-sample effect was shown in the research network

(3) NMA. This study included 22 studies that reported IL-8 levels for five different CPM treatment regimens. A network meta-analysis was performed on these five CPMs, resulting in a total of 15 pairwise comparisons (Figs. 5F and 7F). Of these, four comparisons yielded statistically significant differences. Compared with 5-ASA alone, MD and 95 % CI of 5-ASA combined with DSI, HEC, and KFL were −2.57 and [−3.50, −1.65], −2.51, and [−4.94, −0.08], and −1.22 and [−2.14, −0.30], respectively. Moreover, there was a benefit of DSI+5-ASA over KFX+5-ASA, the results were statistically significant, WMD and 95 % CIs were 1.35 (0.05, 2.66).

(4) SUCRA probability ranking. According to the SUCRA scores, the reduced IL-8 rates of five CPMs and 5-ASA alone were arranged in order: DSI (88.0 %) > HEC (78.7 %) > KFL (44.2 %) > CCP (43.8 %) > CYN (43.4 %) > 5-ASA (1.9 %) (Fig. 6F).

3.4.7. MPV

(1) Evidence network. The MPV was reported in 14 studies, involving four CPM treatment regimens (Fig. 3G).

(2) Publication bias. Fig. 4G presents the funnel plot for MPV levels of four CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed a symmetrical distribution of studies around the X = 0 line, with seven studies falling outside the funnel. No approval of the small-sample effect was shown in the research network

(3) NMA. This study included 14 studies that reported MPV levels for four different CPM treatment regimens. A network meta-analysis was performed on these four CPMs, resulting in a total of 10 pairwise comparisons (Figs. 5H and 7H). The results showed no significant difference in MPV levels between the five interventions.

(4) SUCRA probability ranking. According to the SUCRA scores, the MPV rate of four CPMs and 5-ASA alone were arranged in order: KFL (73.9 %) > DSI (60.9 %) > CCP (58.7 %) > CYN (37.2 %) > 5-ASA (19.4 %) (Fig. 6G).

3.4.8. FIB

(1) Evidence network. FIB levels were reported in 17 studies, involving four CPM treatment regimens (Fig. 3H).
(2) Publication bias. Fig. 4H presents the funnel plot for FIB levels of four CPMs combined with 5-ASA in UC treatment. The funnel plot revealed an asymmetrical distribution of studies around the X = 0 line, with eight studies falling outside the funnel. This suggests the presence of a small-sample effect in the research network. The funnel plot also suggests that the sample size of the included studies is generally medium, with a lack of studies with large sample sizes.
(3) NMA. This study included 17 studies that reported FIB levels for four different CPM treatment regimens. A network meta-analysis was performed on these four CPMs, resulting in a total of 10 pairwise comparisons (Figs. 5H and 7H). Of these, four comparisons yielded statistically significant differences. Compared with 5-ASA alone, MD and 95 % CI of 5-ASA combined with KFL, ZKC, DSI, and CYN were −1.89 and [−2.56, −1.22], −1.80 and [−2.86, −0.74], −1.39 and [−2.05, −0.74], and −1.09 and [−1.75, −0.42].
(4) SUCRA probability ranking. According to the SUCRA scores, the FIB rate of four CPMs and 5-ASA alone were arranged in order: KFL (83.9 %) > ZKC (76.7 %) > DSI (53.6 %) > CYN (35.8 %) > 5-ASA (0.0 %) (Fig. 6H).

3.4.9. Recurrence rate

(1) Evidence network. Recurrence rates are reported in 11 studies, involving six CPM treatment regimens (Fig. 3I).
(2) Publication bias. Fig. 4I presents the funnel plot for recurrence rates of six CPMs combined with 5-ASA in UC treatment. The comparison-corrected funnel plot revealed a symmetrical distribution of studies around the X = 0 line, with no studies falling outside the funnel. No approval of the small-sample effect was shown in the research network.
(3) NMA. This study included 11 studies that reported recurrence rates for six different CPM treatment regimens. A network meta-analysis was performed on these six CPMs, resulting in a total of 21 pairwise comparisons (Figs. 5I and 7I). Of these, three comparisons yielded statistically significant differences. Compared with 5-ASA alone, OR and 95 % CI of 5-ASA combined with KFL, DSI, and BYP were 0.24 and [0.14, 0.43], 0.23 and [0.06, 0.88], and 0.35 and [0.15, 0.84], respectively.
(4) SUCRA probability ranking. According to the SUCRA scores, the reduced recurrence rates of four CPMs and 5-ASA alone were arranged in order: SBP (73.2 %) > KFL (68.5 %) > DSI (67.6 %) > BYP (50.6 %) > ZKC (47.2 %) > CCP (33.7 %) > 5-ASA (9.2 %) (Fig. 6I).

3.4.10. Adverse event rate

(1) Evidence network. The adverse event rate was reported in 29 studies, involving eight CPM treatment regimens (Fig. 3J).
(2) Publication bias. Fig. 4J presents the funnel plot for adverse event rates of eight CPMs combined with 5-ASA in UC treatment. The funnel plot revealed a symmetrical distribution of studies around the X = 0 line, with only one study falling outside the funnel. No approval of the small-sample effect was shown in the research network.
(3) NMA. This study included 29 studies that reported adverse event rates for eight different CPM treatment regimens. A network meta-analysis was performed on these eight CPMs, resulting in a total of 36 pairwise comparisons (Figs. 5J and 7H). Of these, five comparisons yielded statistically significant differences. Compared with 5-ASA alone, OR and 95 % CI of 5-ASA combined with BYP were 0.19 and [0.06, 0.62].
(4) SUCRA probability ranking. According to the SUCRA scores, the reduced adverse event rates of eight CPMs and 5-ASA alone were arranged in order: BYP (96.2 %) > CYN (66.8 %) > SBP (64.3 %) > DSI (60.9 %) > 5-ASA (41.8 %) > KFL (35.1 %) > HEC (32.5 %) > XLP (28.1 %) > CCP (24.1 %) (Fig. 6J).

4. Discussion

Based on 70 related studies and 10 main outcomes, we systematically evaluated the efficacy of 10 commonly used CPMs combined with 5-ASA in the treatment of UC. The results showed that different CPMs + 5-ASA combinations had varying advantages in the adjuvant treatment of UC. 5-ASA alone had a lower efficacy, while the combination of CPM and 5-ASA was superior to 5-ASA alone. In this study, analysis of the effective rates showed that the top four CPMs combined with 5-ASA were KFL, CYN, BYP, and DSI. Regarding the excellent rate, the top four CPMs combined with 5-ASA were SBP, BYP, KFL, and CYN. Compared with 5-ASA alone, the combination of BYP and 5-ASA can reduce the recurrence rate. The combination of BYP, DSI, or KFL and 5-ASA can reduce the adverse event rate. With respect to the DAI, the top four CPMs combined with 5-ASA were HE, CYN, DSI, and BYP. As regards TNF-α, the top four CPMs combined with 5-ASA were ZKC, CYN, DSI, and CCP. In addition, the combination of CYN and 5-ASA can effectively reduce the level of IL-6. The combination of DSI, HEC, or KFL and 5-ASA can effectively reduce the level of IL-8. The combination of KFL, HEC, DSI, or CYN with 5-ASA can be used for reducing FIB levels. But 5-ASA combined with CPM did not improve the level of MPV compared to 5-ASA alone. MPV is one of the indicators that reflect coagulation function. Clinical studies have also shown that MPV levels exhibit different trends in different types of UC patients, with a more significant decrease in MPV levels observed in patients in remission [80]. Therefore, MPV is one of the best indicators to evaluate disease activity in UC patients and is closely related to the patient's course of disease. The studies included in this meta-analysis did not differentiate between different UC disease stages; this may be one of the reasons why CPM combined with 5-ASA did not improve MPV. However, we cannot exclude the possibility that CPMs combined with 5-ASA affect coagulation function in patients with UC, as 5-ASA combined with KFL, ZKC, DSI or CYN can effectively increase FIB

levels. Previous NMA study had shown that the clinical efficacy of CPMs+5-ASA is superior to that of 5-ASA alone, our results support this conclusion. The earlier study suggested that XLP+5-ASA had a statistically lower incidence of adverse events than 5-ASA alone, and that KFL+5-ASA was effective in reducing the recurrence rate. This study supports the potential of KFL+5-ASA in reducing recurrence rates. However, our findings indicate that compared to 5-ASA alone, XLP+5-ASA showed no significant difference in adverse event incidence, while BYP+5-ASA significantly reduced adverse events. This discrepancy may be due to variations in the literature included in analysis [81]. Given the individualized treatment goals for UC patients in clinical practice, the study results were visualized as heat maps to assist clinicians in selecting the optimal combination therapy of CPMs and 5-ASA, as illustrated in Fig. 8.

The diverse composition of CPMs (detailed in Table S2) allows for a range of therapeutic effects through various mechanisms in the human body. Based on the findings of various outcome indicators in this study, KFL, CYN, and BYP combined with 5-ASA demonstrate promising clinical potential. Their pharmacological mechanisms are summarized below. KFL, a Chinese herbal medicine derived from *Periplaneta americana*, demonstrated the greatest efficacy in enhancing clinical response rates. It has been extensively employed in the treatment of various ulcerative conditions [82]. Modern pharmacological research shows that the effective ingredients of KFL are polyols and peptides, which have the functions of removing putrefaction, promoting granulation tissue growth, promoting angiogenesis, improving mucosal wound microcirculation, accelerating the repair and regeneration of diseased tissue, inhibiting bacteria and inflammation, eliminating edema, and enhancing body immunity [83–85]. Chen et al. found that the combined treatment of KFL and mesalazine could reduce IL-23, IL-17, IL-1β, LPO, and NO levels and increase SOD levels, thereby reducing intestinal damage due to free oxygen radicals and inflammatory reactions [86]. In addition, animal experiments confirmed that KFL can reduce the expression of TNF-α and MPO in the colon tissue of an induced UC rat model and increase the expression of EGF; EGF and MPO can promote cell proliferation and differentiation in UC rats and play an important role in intestinal mucosal injury and repair, suggesting that KFL can alleviate the symptoms of UC by participating in immune regulation [87]. Additionally, in all clinical studies included in this meta-analysis, KFL was administered via enema. This method may be advantageous in enhancing the localized therapeutic effects of KFL and mitigating the reduction in efficacy associated with oral administration.

The combination of CYN and 5-ASA significantly improves the overall response rate, clinical remission rate, DAI score, and levels of IL-6, TNF-α, and FIB, indicating its promising clinical efficacy. The medicinal ingredients of CYN are Dijincao (*Euphorbia humifusa* Willd.), Jinmaoercao (*Hedyotis Chrysotricha* (Palib.) Merr.), Zhangshugen (*Cinnamomum camphora* (L.) Presl), Fengxiangshuye (*Liquidambar formosana* Hance), and Xiangru(*Mosla chinensis* Maxim.) [88]. Liquid chromatography coupled with tandem mass spectrometry analysis revealed that the primary constituents of CYN are gallic acid, methyl gallate, catechol, asperulosidic acid, kaempferol, and quercetin [89]. Animal studies showed that CYN reduces the levels of pro-inflammatory cytokines in the serum of a murine colitis model, downregulating IL-17 and HIF-1α and upregulating PPARγ and CCL2 in the colon, facilitating the alternative activation of peritoneal macrophages [90]. Additionally, CYN treatment has been shown to enhance the diversity and richness of the intestinal microbiota in UC mice, while restoring the metabolic profile during colitis [91]. This is consistent with the observation that CYN improves IL-6 and TNF-α levels. Thus, CYN exerts its anti-colitis effects by modulating both inflammatory responses and the gut microbiota.

Additionally, the combination of BYP and 5-ASA demonstrated favorable clinical efficacy, particularly in reducing the risk of disease recurrence and the incidence of adverse reactions. The medicinal ingredients of BYP are Huangqi(astragali radix), Danggui (*Angelica sinensis* (Oliv.) Diels), Rougui(*Cinnamomum cassia* Presl), Baishao(*Paeonia lactiflora* Pall.), Baizhu(*Atractylodes macrocephala* Koidz.).etc. [92]. Animal experiments revealed that BYP treatment significantly reduced the proportions of Tfh1, Tfh17, and Tem-Tfh cells, while increasing the proportion of Tfr cells in colitis mice [93]. In addition, the enteric-soluble components of BYP also play a key role in regulating the differentiation of T lymphocytes. For example, *Codonopsis pilosula* polysaccharide (one of the effective components of *C. pilosula*) can maintain the CD4$^+$/CD8$^+$ T cells, Th1/Th2 cells, Treg/Th17 cells, IL-10/TNF-α, and IL-10/IL-1β of mice after hydrocortisone treatment and IL-10/IL12 that BYP treatment decreased the percentages of Tfh1, Tfh17, and Tem-Tfh cells and upregulate-1β Immune homeostasis [94]. Astragalus polysaccharide (one of the effective components of Astragali radix) can upregulate Tregs and the levels of its associated nuclear transcription factor Foxp3 and IL-10 in colitis mice, reshaping the balance of Tfh/Treg cells [95]. All the above studies suggested that BYP can improve the immune function of UC rats by enhancing the cellular immune function and inhibiting the humoral immune function, to help repair the ulcerated surface of colon tissue in rats. BYP did not show superiority in improving IF-6, IF-8, and TNF levels in this study. BYP's mechanism of action may primarily involve modulating the Tfh/Treg balance to mitigate the inflammatory response; however, further experimental studies are warranted to validate this hypothesis.

After comprehensive analysis, it was found that this study has four limitations: (1) The methodological quality of the 70 RCTs was generally poor. Although all trials showed that the principle of randomized treatment grouping was followed, only a few described methods used to generate random sequences, such as two-color ball method. Only three studies mentioned blinding of patients and medical staff during treatment. Additionally, considering the small sample sizes in some trials, the validity of the results is questionable. (2) Most of the included studies were not registered in a clinical trial registry. To enhance transparency and reduce reporting bias, future clinical trials should be registered in a clinical trial registry prior to enrolling subjects. (3) The studies included in this meta-analysis employed an "5-ASA + CPM vs. 5-ASA" design without a rigorous control group for placebo effects. Only Mesalamine and Sulfasalazine were used as comparators in the included studies. No clinical studies have evaluated CPM combined with other 5-ASA medications, such as olsalazine or balsalazide disodium. (4) The network diagram actually only forms a radial distribution, precluding the conduct of an inconsistency test. This limitation affects the reliability of the study results. The NMA was solely based on indirect comparisons, as there were no direct comparisons between CPMs. Some scholars argue that indirect comparisons may not always align with the findings of direct comparisons, warranting a cautious interpretation of the conclusions drawn from this study [96]. Given the aforementioned limitations, we emphasize the need for more high-quality RCTs with large sample sizes, multicenter designs, and
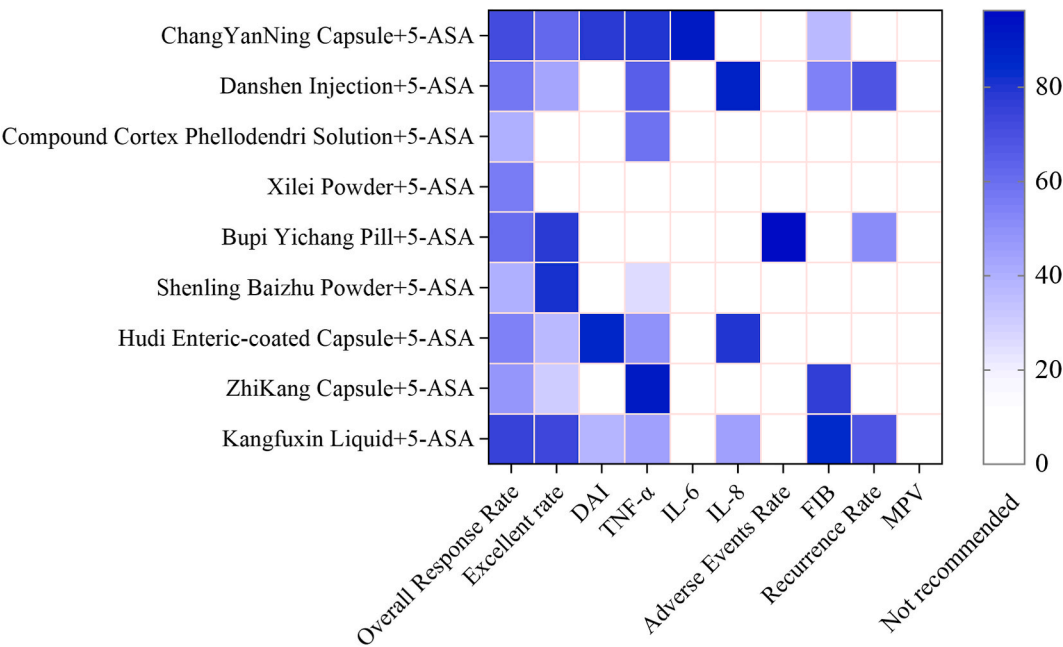
Fig. 8. Recommended regimens for treating UC with 5-ASA combined with TCM. Highly recommended regimens are indicated in dark blue; white blocks indicate regimens that are not recommended. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

rigorous methodologies to provide more robust and reliable evidence to guide clinical drug use.

5. Conclusion

The current evidence suggests that CPMs in combination with 5-ASA may provide greater benefits for UC patients compared to 5-ASA monotherapy. The NMA results demonstrated that CPMs combined with 5-ASA were more effective than 5-ASA alone in treating UC, evidenced by significantly improved overall response rates, excellent response rates, and reduced levels of TNF-α, IL-6, IL-8, and FIB. CPMs combined with 5-ASA were also found to be more effective in reducing recurrence rates and adverse event rates in UC patients. KFL, CYN, BYP, and DSI emerged as the most effective CPMs when combined with 5-ASA. The findings of this NMA should be interpreted cautiously due to the limited number and quality of included studies. Further high-quality, large-scale, double-blind RCTs are necessary to validate these results.

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because [This work is a review of the literature and does not address the ethical considerations of animal, cell, and human experimentation.]

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [SW], upon reasonable request.

CRediT authorship contribution statement

Mingkuan Zhang: Writing – original draft, Conceptualization. **Yuan Su:** Writing – review & editing, Writing – original draft, Conceptualization. **Qian Gao:** Resources, Data curation. **Miaomiao Zhou:** Resources, Data curation. **Ying Xing:** Validation, Software.

Zhibin Chen: Validation, Software, Methodology. **Xiaoyu Liu:** Validation, Software. **Zifa Li:** Validation, Software, Methodology. **Xiwen Geng:** Project administration, Data curation. **Guimao Cao:** Writing – review & editing, Funding acquisition. **Hao Zhang:** Visualization, Validation. **Sheng Wei:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31182.

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