Check for updates

OPEN ACCESS

EDITED BY Hongxun Tao, Jiangsu University, China

REVIEWED BY Amosy E M'Koma, Meharry Medical College, United States Guang Chen, Huazhong University of Science and Technology, China

*CORRESPONDENCE Kaihua Qin, qkh0135@163.com Qiaobo Ye, yeqiaobo@cdutcm.edu.cn

[†]These authors share first authorship

SPECIALTY SECTION This article was submitted to Ethnopharmacology, a section of the journal Frontiers in Pharmacology

RECEIVED 04 September 2022 ACCEPTED 11 October 2022 PUBLISHED 21 October 2022

CITATION

Li Y, Ye Z, He H, Hu Y, Wu M, Li L, Chen L, Qian H, Shi Q, Zhang C, Yu H, Zhao Q, Liu X, Qin K and Ye Q (2022), The application of Tong-fu therapeutic method on ulcerative colitis: A systematic review and meta-analysis for efficacy and safety of rhubarbbased therapy. *Front. Pharmacol.* 13:1036593. doi: 10.3389/rphar.2022.1036593

COPYRIGHT

© 2022 Li, Ye, He, Hu, Wu, Li, Chen, Qian, Shi, Zhang, Yu, Zhao, Liu, Qin and Ye. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The application of Tong-fu therapeutic method on ulcerative colitis: A systematic review and meta-analysis for efficacy and safety of rhubarb-based therapy

Yuzheng Li^{1†}, Zhen Ye^{1†}, Haiqing He¹, Yu Hu¹, Mingquan Wu², Linzhen Li¹, Liulin Chen¹, Huanzhu Qian¹, Qingyu Shi³, Chen Zhang⁴, Han Yu¹, Qian Zhao¹, Xinglong Liu¹, Kaihua Qin^{5*} and Qiaobo Ye^{1*}

¹School of Basic Medical Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, China, ²Department of Pharmacy, Sichuan Orthopedic Hospital, Chengdu, China, ³School of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, China, ⁴State Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu, China, ⁵Health Preservation and Rehabilitation College, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Background: Tong-fu therapeutic method (TFTM) is a traditional Chinese medicine treatment method for ulcerative colitis, which is a novel treatment strategies and have purgative effect. As the most representative medicinal of TFTM, Rhubarb has been reported to have a therapeutic impact on ulcerative colitis by regulating intestinal flora, anti-inflammation, and improving intestinal microcirculation. Although rhubarb has been widely used in Chinese medicine for the treatment of ulcerative colitis, the appropriate protocol is still demanded to its rational use in clinic, which promoted to evaluate the efficacy and safety for rhubarb-based therapy on ulcerative colitis.

Method: Clinical trials were searched through PubMed, Cochrane Library, Web of Science, Excerpta Medica Database, Chinese National Knowledge Infrastructure, WAN FANG Database, Chinese Scientific Journal Database, and Chinese Biomedical Literature Database. The subgroup analyses were performed with three groups: medication, course of treatment, and route of administration. The statistical analyses were performed on Review Manager software (version 5.4.1).

Results: A total of 2, 475 patients in 30 original studies were analyzed in this article. It was found that rhubarb-based therapy could increase clinical efficacy

Abbreviations: CBM, Chinese Scientific Journal Database; CNKI, Chinese National Knowledge Infrastructure; CRP, C-reaction protein; EMBASE, Excerpta Medica Database; FIB, fibrinogen; IBD, inflammatory bowel disease; IL-6, interleukin-6; PLT, platelet; PT, prothrombin time; RCTs, Randomized clinical trials; TCM, traditional Chinese medicine; TFTM, Tong-fu therapeutic method; TNF-a, tumor necrosis factor-a; UC, Ulcerative colitis; XXD, Xiexin decoction.

and reduce the recurrence rate. Subgroup analyses showed that rhubarb-based therapy was more effective than 5-aminosalicylic acid or sulfasalazine alone. In addition, the hypercoagulable state of ulcerative colitis could be ameliorated by decreasing platelet (PLT) and fibrinogen (FIB), and increasing prothrombin time (PT) significantly. Moreover, C-reaction protein (CRP), tumor necrosis factor- α (TNF- α), interleukin (IL)-6, IL-8, and IL-1 β expression were significantly reduced, while IL-10 production was increased, which mediated the alleviation of intestinal inflammation stress.

Conclusion: Rhubarb-based therapy could effectively improve ulcerative colitis. Of note, the rhubarb-based medicinal formulas combined with 5-ASA or SASP are more effective than the 5-ASA or SASP alone. In addition, although rhubarb has side effect, the results of our analysis showed that rhubarb-based therapy did not exhibit significant side effects. This means it has a high safety profile in clinical use. Moreover, the use of rhubarb-based therapy is recommend to use within 1–13 weeks or 3 months *via* administered orally or by enema, which is contributes to ensure the curative effect and avoid its toxic and side effects. As an important case of TFTM, rhubarb-based therapy provides evidence for the practical application of TFTM.

KEYWORDS

rhubarb, *dà huáng*, Tong-fu therapeutic method, traditional Chinese medicine, metaanalysis, ulcerative colitis

Introduction

Ulcerative colitis (UC) is a subtype of inflammatory bowel disease (IBD). The prevalence of IBD in the western world has reached as high as 0.5% of the total population (Kaplan, 2015). UC has evolved into a global burden given its high incidence in developed countries and the substantial increase in incidence in developing countries (Sood et al., 2003; Molodecky et al., 2012; Kobayashi et al., 2020). Even though the pathogenesis of UC has not been revealed ultimately, immunological abnormalities are considered to play an essential role, and drugs regulating the innate immune system have become the mainstream treatment. 5-aminosalicylic acid (5-ASA), corticosteroids, and thiopurines can effectively alleviate UC as first-line therapeutic agents (Kobayashi et al., 2020). However, several limitations of the treatments have attracted increasing attention. 5-ASA is beneficial to mild to moderate UC but undesirable for severe UC. Meanwhile, corticosteroids, as a supplement to 5-ASA, are considered to lack long-term efficacy and safety. The application of thiopurines is challenged with increasing evidence of potential serious adverse reactions such as bone marrow and liver toxicity, pancreatitis, increased risk of non-melanoma skin cancer and lymphoma (Ko et al., 2019; Kobayashi et al., 2020). Due to the lack of satisfactory treatment, UC patients relapse continually even after routine treatment (Kobayashi et al., 2020). In essence, more effective treatment options with less adverse reactions still expected.

Tong-fu therapeutic method (TFTM) as an important traditional Chinese medicine therapy, can produce purgative

effect and restore gastrointestinal motility. According to traditional Chinese medicine (TCM) theory, TFTM can descend qi, which discharges toxic and harmful products, breaks the vicious circle caused by toxin retention, improves intestinal microcirculation, and regulates the internal environment of the host, to treat and prevent the deterioration of the disease. Study has demonstrated that TFTM, whenever administered orally, rectally, or by nasal feeding, can improve gastrointestinal dysfunction and reduce case-fatality rate (Zhang et al., 2021). Rhubarb (Rheum palmatum L.) [dà huáng; Polygonaceae; Rheum palmatum root and rhizome], as one of the most representative medicinals of TFTM, was first recorded in Shen Nong's Classic of the Materia Medica (Shén Nóng Běn Căo Jīng), which can play a powerful role in TFTM and improve digestive diseases (Teng et al., 2019). It was referred that rhubarb combined with conventional medication (somatostatin or trypsin inhibitor) in the treatment of acute pancreatitis was superior to conventional medication alone (Zhou et al., 2016; Hu et al., 2018). Also, rhubarb could modulate gut microbiota, which indirectly changed purine Metabolism in the intestine and subsequently alleviated DSS-induced chronic colitis (Wu et al., 2020). Additionally, rhubarb acted as an anti-platelet (PLT) aggregator that could significantly alleviate the hypercoagulable state associated with UC (Gao et al., 2020). In general, the rhubarb-based therapy is effective and authentic in improving UC, and its underlying mechanism appears to be multifaceted and meaningful. Presently, a large number preclinical and clinical evidence has clarified the positive effect of rhubarb and the rhubarb-based medicinal formulas on UC, however, the evidence is scattered. Because the influence of TFTM represented by rhubarb on UC has not been systematically supported by evidence-based medicine analysis, its scientific validity and potential clinical value have not been fully revealed. In this paper, a Meta-analysis of rhubarb-based therapy is conducted to assess the efficacy and safety. Meanwhile, the mechanisms of rhubarb improving hypercoagulable state of UC was systematically reviewed. Through the analysis and systematic review, it was given thata reliable application protocol of the rhubarb-based therapy could ensure the curative effect and its mechanism.

Methods

This study was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The requirements considered relevant in recent best practice guidelines for manuscripts of natural products have been taken into account (Heinrich et al., 2020).

Search strategies

The search of the original studies was carried out until 7 October 2021 through Chinese National Knowledge Infrastructure (CNKI), the WANFANG Database, the Chinese Scientific Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), Excerpta Medica Database (EMBASE), Web of Science, PubMed, and Cochrane Library. The medical subject headings were "ulcerative colitis" and "Rheum."

The search formulation adopted a combination of free texts and medical subject headings (MeSH). According to the search habits of each database, the retrieval method that met the requirements was developed. The search formulas for each database are shown in Supplementary Data S1. At the same time, there is no restriction of search formulation on language or country.

Study selection

Type of participants

In this study, all participants met the UC diagnostic criteria. As there is no gold standard for UC diagnosis, patients were subjected to comprehensive analysis, including symptom evaluation, endoscopic examination, and histopathological manifestations (Ungaro et al., 2017). Specifically, patients with a definite diagnosis of UC were included in the study and those with Crohn's disease or unspecified IBD subtypes were excluded.

Type of interventions

Interventions in the treatment group were rhubarb-based therapeutic regimen, including rhubarb-based medicinal formulas alone or combined with UC routine treatment, including 5-ASA, sulfasalazine (SASP), olsalazine sodium, bifidobacterium triple viable capsules, glutamine, infliximab, prednisolone, hydrocortisone sodium succinate, and by oral or enema. Patients in the control group were treated with UC routine treatment. The trial was excluded if external TCM treatments such as acupuncture, massage, and moxibustion were present in the treatment group.

Type of outcome measures

Outcomes were divided into main outcome and secondary outcomes. The primary outcome was the clinical efficiency. The Mayo score, Geboes score, recurrence rate, PLT, adverse events, symptoms integral, and inflammatory cytokines and protein, including C-reaction protein (CRP), tumor necrosis factor- α (TNF- α), Interleukin (IL)-6, IL-8, IL-1 β , and IL-10 were the secondary outcomes.

Type of studies

Randomized clinical trials (RCTs) were selected for Metaanalysis. Animal experiments, non-randomized controlled trials, and repeated data studies were excluded.

Data extraction

Firstly, YL was responsible for formulating retrieval strategies and extracting retrieval records. Secondly, ZY and YH, and QZ independently screened the title and abstract of the articles, excluding the content that did not meet the standard. After combining the two results, YL, HH, and LC entered the full-text screening stage. When they encountered differences, the literatures were handed over to MW and CZ for judgment. In the end, from the included studies, information was extracted by two reviewers: HQ extracted the data, and YL was in charge of reviewing it.

Assessment of the risk of bias

Based on the Cochrane Handbook, YL and HH independently assessed the bias risk of each study. The standard included the following seven items: 1) sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessments (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); 7) other sources of bias. On the basis of methodological quality, the studies were classified as high risk, low risk, and unclear risk in each domain.



Data analysis

Meta-analysis was performed by Review Manager (V.5.4.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2021). Depending on the result category, the risk ratio (RR) and 95% confidence interval (CI) were used to calculate the categorical data, and the weighted mean difference (WMD) and 95% CI were used to calculate the continuous data. p < 0.05 was considered statistically significant. Heterogeneity was estimated by Cochran's Q test and assessed using I^2 . When $I_2 > 50\%$, it is considered to have significant heterogeneity and a random-effects model is used to estimate the pooled effect. In contrast, a fixed-effects model was used. Besides, if there were heterogeneity in the results, we would look for heterogeneity sources and perform a sensitivity analysis by converting the random effect model and fixed effect model to determine whether the results are stable. Publication bias was analyzed visually through funnel plots.

Association rules of Chinese medicinals were analyzed by SPSS Modeler 18.0. Cytoscape V3.9.0 established the topological network.

Results

Study identification

Based on the search strategy, 2,475 potential associated articles were obtained by searching the databases. After deleting 95 repetitive articles, 2,380 articles were obtained. In the process of title and abstract screening, a total of 2,074 articles were excluded due to not meeting the inclusion criteria, and 306 papers were searched for further evaluation. Finally, 30 studies were finally retained for this Meta-analysis (Nong, 2009; Li, 2012; Deng, 2015; You et al., 2015; Ding, 2016; Wang, 2016; Zhang, 2016; Fei, 2017; Sheng



et al., 2017; Shi and Sun, 2017; Tian, 2017; Wang et al., 2017; Wen and Sun, 2017; Yang et al., 2017; Wang, 2018; Guo and Ding, 2019; Li, 2019; Liu, 2019; Chen and Li, 2020; Deng and Chen, 2020; Sun and Zhang, 2020; Tan et al., 2020; Wang, 2020; Yuan, 2020; Zhang, 2020; Zhao, 2020; Li et al., 2021; Xue and Xu, 2021; Yang and Wang, 2021; Yin et al., 2021). Exclusive reasons are shown in Figure 1.

Study characteristics

Supplementary Table S1 shows the general characteristics of 30 studies. A total of 2,507 patients were included from 2009 to 2020, with 1,257 cases in the treatment group and 1,250 cases in the control group. 5-ASA was selected as the control group measure in 20 studies, SASP in seven studies. The rhubarb-based medicinal formulas were used alone in the treatment group for four studies. And the rest are in combination with the UC routine treatment. All 30 studies were conducted in China.

Risk of bias

Figure 2 shows the methodological quality of 30 studies. The risk of bias in the study was evaluated according to the criteria in the *Handbook for Systematic Evaluation of Cochrane Interventions* (Higgins et al., 2011).

All studies mentioned "randomness" and described the specific random assignment method for random sequence generation and were therefore judged as low risk. None of the studies described allocation concealment, blind of participants and personnel, or blind of outcomes, so the risks were unknown. Since the pre-registered protocols could not be acquired from the main authors, the selective report was rendered as unknown. Other risks of bias were also considered unclear.

Primary outcome Clinical efficiency

The clinical efficiency was recorded in 29 trials. There was no heterogeneity among studies, and a fixed-effects model was used for analysis. The Meta-analysis results showed that the clinical efficiency of rhubarb-based treatment group was significantly higher than that of control group (n = 2421, I² = 0%, RR = 1.24, 95% CI [1.20, 1.29], p < 0.00001) (Figure 3). Next, the subgroup analyses were performed.

To further analyze the effect of rhubarb-based medicinal formulas alone or combined with first-line drugs 5-ASA, SASP, or other different routine drugs in the experiment, the clinical efficiency was selected for subgroup analysis. There was no heterogeneity among the studies. A fixed-effect model was selected for Meta-analysis.

In the treatment group, 16 studies combined with 5-ASA (n = 1456, $I^2 = 0\%$, RR = 1.22, 95% CI [1.16, 1.27], p < 0.00001) (Figure 4), six studies combined with SASP (n = 430, $I^2 = 0\%$, RR = 1.27, 95% CI [1.17, 1.38], p < 0.00001) (Figure 4), three studies combined with other routine drugs (n = 208, $I^2 = 0\%$, RR = 1.24, 95% CI [1.10, 1.39], p = 0.0003) (Figure 4), and four studies were conducted by the rhubarb-based medicinal formulas administered alone (n = 327, $I^2 = 43\%$, RR = 1.32, 95% CI [1.18, 1.47], p < 0.00001) (Figure 4). Compared with the control group, the clinical efficiency of the treatment group was significantly higher. The rhubarb-based medicinal formulas alone or combined with common drugs showed good therapeutic effects.

Among the 29 studies, 21 were treated with rhubarb-based therapy oral administration and seven were treated with enema. Statistical analysis showed that no matter oral administration (n = 1318, $I^2 = 0\%$, RR = 1.25, 95% CI [1.19, 1.30], p < 0.00001) (Figure 5) or enema administration (n = 496, $I^2 = 0\%$, RR = 1.24, 95% CI [1.15, 1.34], p < 0.00001), the clinical efficiency was significantly improved (Figure 5).

The course of the treatments is one of the factors affecting the efficacy. In the studies where total effective rates were reported, treatment courses were divided into 2–5 weeks (n = 14);

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.1.1 Clinical effectiv	e rate (Tot	al Grou	o)				
Chen B.Q.2020	41	43	34	43	3.7%	1.21 [1.02, 1.43]	
Deng P.2015	33	36	28	36	3.1%	1.18 [0.96, 1.44]	
Deng S.H.2020	43	45	36	45	4.0%	1.19 [1.02, 1.40]	
Ding S.L.2016	44	45	36	45	4.0%	1.22 [1.05, 1.42]	
ei X.Y.2017	70	75	58	75	6.4%	1.21 [1.05, 1.38]	
Guo G.J.2019	24	25	17	25	1.9%	1.41 [1.07, 1.87]	
_i R.2019	42	46	37	46	4.1%	1.14 [0.96, 1.34]	
iu Y.H.2019	35	41	25	40	2.8%	1.37 [1.04, 1.79]	
i Z.M.2012	20	20	17	20	1.9%	1.17 [0.96, 1.43]	
Vong Z.B.2009	28	30	22	30	2.4%	1.27 [1.01, 1.61]	
Sheng R.D.2017	43	48	39	48	4.3%	1.10 [0.93, 1.30]	
Shi A.P.2017	47	50	37	50	4.1%	1.27 [1.06, 1.52]	
Sun J.X.2020	54	60	46	60	5.1%	1.17 [1.00, 1.38]	
Tan G.Z.2020	32	34	26	34	2.9%	1.23 [1.00, 1.51]	
Fian G.D.2017	33	38	25	35	2.9%	1.22 [0.95, 1.55]	
Wang F.T.2016	28	29	21	29	2.3%	1.33 [1.05, 1.69]	
Vang H.S.2017	30	32	25	32	2.8%	1.20 [0.98, 1.47]	+
Wang J.X.2018	44	48	36	47	4.0%	1.20 [1.00, 1.43]	
Wang P.L.2020	45	48	37	48	4.1%	1.22 [1.03, 1.44]	
Wen B.2017	45	49	37	49	4.1%	1.22 [1.02, 1.46]	
Kue H.C.2021	29	32	19	32	2.1%	1.53 [1.12, 2.08]	
Yang M.M.2017	34	37	26	36	2.9%	1.27 [1.02, 1.59]	
Yang X.Q.2021	43	45	37	45	4.1%	1.16 [1.00, 1.35]	
Yin P.2021	45	50	37	50	4.1%	1.22 [1.01, 1.47]	
You C.M.2016	39	42	28	42	3.1%	1.39 [1.11, 1.75]	
Yuan X.H.2020	30	32	22	31	2.5%	1.32 [1.04, 1.68]	
Zhang G.R.2020	46	49	39	49	4.3%	1.18 [1.01, 1.38]	
Zhang H.Y.2016	38	40	24	40	2.6%	1.58 [1.22, 2.06]	· · · · ·
Zhao J.H.2020	42	45	33	45	3.6%	1.27 [1.05, 1.54]	
Subtotal (95% CI)		1214		1207	100.0%	1.24 [1.20, 1.29]	•
Total events	1127		904				
Heterogeneity: Chi ² =	14.19, df =	28 (P =	0.99); l ² =	= 0%			
Test for overall effect:	Z = 11.64 (P < 0.00	001)				
Total (95% CI)		1214		1207	100.0%	1.24 [1.20, 1.29]	•
Total events	1127		904				
Heterogeneity: Chi ² =	14.19. df =	28 (P =	0.99): l ² =	= 0%			
Test for overall effect:	Z = 11.64 (P < 0.00	001)	570			0.5 0.7 1 1.5 2
Test for subaroup diffe	rences: No	t applica	ble				Favours [control] Favours [experimental]

6–9 weeks (n = 11) or 12–13 weeks (n = 4). None of these analyses showed heterogeneity, so the fixed effects model was chosen for the Meta-analysis. The results showed that the clinical efficiency significantly increased at 2–5 weeks (n = 1180, I² = 0%, RR = 1.21, 95% CI [1.15, 1.28], p < 0.00001) (Figure 6), 6–9 weeks (n = 924, I² = 0%, RR = 1.27, 95% CI [1.20, 1.35], p < 0.00001) (Figure 6), and 12–13 weeks (n = 317, I² = 0%, RR = 1.24, 95% CI [1.13, 1.37], p < 0.0001) (Figure 6).

Secondary outcomes

Mayo score

Three trials reported Mayo score. The random-effect Meta-analysis showed that the Mayo score in the treatment group was significantly lower than that in the control group $(n = 254, I^2 = 88\%; MD = -1.28; 95\%$ CI [-2.09, -0.46], p = 0.002) (Figure 7). The sensitivity analysis showed that the study reported by Yin P. was the source of heterogeneity. Excluding this study reduced the inter-study heterogeneity ($I^2 = 0\%$).

Geboes score

The Geboes score was assessed in three studies. The heterogeneity among studies was obvious, so the randomeffect model was used for Meta-analysis. A significant reduction in Geboes scores was seen in the treatment group compared to the control group. (n = 336, $I^2 = 89\%$; MD = -0.48; 95% CI [-0.59, -0.36], p < 0.00001) (Figure 7). According to sensitivity analysis, the source of heterogeneity was reported by Li Z.W. After excluding this study, heterogeneity was reduced to $I^2 = 0\%$.

Recurrence rate

Three studies evaluated the reduction in recurrence rate. There was no heterogeneity among studies. The fixed-effects model was used in the analysis. The results revealed that the rhubarb-based treatment could significantly reduce the recurrence rate of UC patients compared with the control group (n = 215, $I^2 = 0\%$. RR = 0.27; 95% CI [0.11, 0.63], p = 0.003) (Figure 8).

1.6.1 Clinical effective rate (C Deng S.H.2020 43 Fei X.Y.2017 70 Guo G.J.2019 24 Li R.2019 42 Liu Y.H.2019 35 Sheng R.D.2017 43 Sun J.X.2020 54 Wang H.S.2017 30 Wang P.L.2020 45 Wang P.L.2020 45 Wang P.L.2020 45 Wang P.L.2020 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 42 Subtotal (95% Cl) 70 Total events 672 Heterogeneity: Chi ² = 5.00, df = 72 Test for overall effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 20 Subtotal (95% Cl) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effectiv	$\begin{array}{c} \text{ompared v} \\ 45 \\ 75 \\ 25 \\ 46 \\ 41 \\ 48 \\ 60 \\ 32 \\ 48 \\ 49 \\ 37 \\ 50 \\ 32 \\ 49 \\ 45 \\ 730 \\ 15 \left(P = 0.9 \right) \\ 45 \\ 730 \\ 15 \left(P = 0.9 \right) \\ (P < 0.0000 \\ ompared v \\ 43 \\ 36 \\ 45 \\ 30 \\ 29 \\ 32 \\ 215 \\ 5 \left(P = 0.75 \right) \\ (P < 0.0000 \\ ompared v \\ 20 \\ ompared v \\ ompared v$	vith 5-AS 36 58 17 37 25 39 46 25 36 37 25 39 46 25 30 37 26 37 26 37 22 39 33 550 99); l ² = (0) vith SAS 36 22 21 19 160 5); l ² = 0 01) vith Othe 17 17 160 17 17 17 17 17 19 10 10 17 17 10 10 10 10 17 17 17 17 17 17 17 17 17 17	SA) 45 75 25 46 40 40 40 40 40 40 40 40 40 40	4.0% 6.4% 1.9% 4.1% 2.8% 4.3% 5.1% 2.8% 4.0% 4.1% 4.1% 2.9% 4.1% 2.9% 4.1% 2.9% 4.1% 2.9% 4.3% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.19 [1.02, 1.40] 1.21 [1.05, 1.38] 1.41 [1.07, 1.87] 1.14 [0.96, 1.34] 1.37 [1.04, 1.79] 1.10 [0.93, 1.30] 1.17 [1.00, 1.38] 1.20 [0.98, 1.47] 1.20 [1.00, 1.43] 1.22 [1.01, 1.47] 1.22 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
Deng S.H.2020 43 Fei X.Y.2017 70 Guo G.J.2019 24 Li R.2019 42 Li R.2019 42 Li R.2019 42 Li R.2019 42 Liu Y.H.2019 35 Sheng R.D.2017 43 Sun J.X.2020 54 Wang H.S.2017 30 Wang P.L.2020 45 Wen B.2017 45 Yang M.M.2017 34 Yin P.2021 45 Yaang M.M.2017 34 Yin P.2021 45 Zhao J.H.2020 40 Subtotal (95% CI) 672 Total events 672 Heterogeneity: Chi ² = 5.00, df = 7 Test for overall effect: Z = 8.26 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Xue H.C.2021 29 Subtotal (95% CI) 70 Total events 203 <	45 75 25 46 41 48 60 32 48 49 9 37 50 32 49 45 730 ($P < 0.0000$ ompared v 43 36 45 30 29 32 215 5 ($P = 0.7$ ($P < 0.0000$ ompared v 20 5 ($P = 0.7$	36 58 17 37 25 39 46 25 36 37 22 39 33 550 99); l ² = 0 01) vith SAS 34 28 36 22 21 19 160 5); l ² = 0 01) vith Othe 17	45 75 25 46 40 48 60 32 47 48 49 36 50 31 49 49 43 36 50 31 49 49 43 36 50 31 49 50 31 49 50 31 49 50 31 22 50 50 50 50 50 50 50 50 50 50 50 50 50	4.0% 6.4% 1.9% 4.1% 2.8% 4.0% 4.1% 2.8% 4.0% 4.1% 2.5% 4.3% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1%	$\begin{array}{c} 1.19 \left[1.02 , 1.40 \right] \\ 1.21 \left[1.05 , 1.38 \right] \\ 1.41 \left[1.07 , 1.87 \right] \\ 1.14 \left[0.96 , 1.34 \right] \\ 1.37 \left[1.04 , 1.79 \right] \\ 1.10 \left[0.93 , 1.30 \right] \\ 1.17 \left[1.00 , 1.38 \right] \\ 1.20 \left[0.98 , 1.47 \right] \\ 1.22 \left[1.03 , 1.44 \right] \\ 1.22 \left[1.02 , 1.46 \right] \\ 1.22 \left[1.02 , 1.46 \right] \\ 1.22 \left[1.02 , 1.46 \right] \\ 1.22 \left[1.01 , 1.47 \right] \\ 1.32 \left[1.04 , 1.68 \right] \\ 1.22 \left[1.05 , 1.54 \right] \\ 1.22 \left[1.16 , 1.27 \right] \\ 1.22 \left[1.16 , 1.27 \right] \\ 1.22 \left[1.16 , 1.27 \right] \\ 1.23 \left[1.21 , 1.46 \right] \\ 1.23 \left[1.22 , 1.46 \right] \\ 1.25 \left[1.5 , 1.54 \right] \\ 1.25 \left[1.5 , 1.62 \right] \\ 1.53 \left[1.12 , 2.08 \right] \\ 1.27 \left[1.17 , 1.38 \right] \\ \end{array}$			
Fei X,Y.2017 70 Guo G.J.2019 24 Li R.2019 42 Liu Y,H.2019 35 Sheng R.D.2017 43 Sun J.X.2020 54 Wang H.S.2017 30 Wang J.X.2018 44 Wang P.L.2020 45 Wang P.L.2020 45 Wang P.L.2020 45 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 42 Subtotal (95% CI) Total events Total events 672 Heterogeneity: Chi ² = 5.00, df = Test for overall effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effective rate (C Li Z.M.2012 20 Subtot	75 25 46 41 48 60 32 48 48 49 37 50 32 49 37 50 32 49 37 50 32 49 45 730 30 29 9 215 5 (P = 0.75) (P < 0.0000) 2000 215 5 (P = 0.75) (P < 0.0000) 215 5 (P = 0.75) (P < 0.0000) 225 5 (P = 0.75) (P < 0.0000) 255 (P < 0.0000) 255 (P < 0.0000) 255 (P < 0.0000) 255 (P < 0.0000) 255 (P < 0.0000) (P < 0.	58 17 37 25 39 46 25 36 37 22 39 33 550 99); l ² = (01) vith SAS 36 22 21 19 160 5); l ² = 0 01) vith Othe 17	75 25 46 40 48 60 32 47 48 49 36 50 31 49 45 50 31 49 45 726 0% 6P) 43 36 45 30 0% 6P) 43 36 45 30 29 32 215 80 80 9 45 50 80 9 80 9 80 9 80 9 80 9 80 9 80 9	6.4% 1.9% 4.1% 2.8% 4.3% 5.1% 2.8% 4.0% 4.1% 4.1% 4.1% 4.1% 4.1% 4.1% 4.3% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 [1.05, 1.38] 1.41 [1.07, 1.87] 1.14 [0.96, 1.34] 1.37 [1.04, 1.79] 1.10 [0.93, 1.30] 1.20 [0.98, 1.47] 1.20 [0.98, 1.47] 1.20 [1.00, 1.43] 1.22 [1.03, 1.44] 1.22 [1.02, 1.46] 1.27 [1.02, 1.46] 1.27 [1.02, 1.45] 1.22 [1.01, 1.61] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.54] 1.23 [1.05, 1.59] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
Guo G.J.2019 24 Li R.2019 42 Li R.2019 42 Li Y.H.2019 35 Sheng R.D.2017 43 Sun J.X.2020 54 Wang H.S.2017 30 Wang J.X.2018 44 Wang P.L.2020 45 Wang B.2017 44 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 30 Zhao J.H.2020 42 Subtotal (95% CI) 70 Total events 672 Heterogeneity: Chi ² = 5.00, df = 72 Heterogeneity: Chi ² = 5.00, df = 72 Total events 672 Heterogeneity: Chi ² = 5.00, df = 73 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 24 Subtotal (95% CI) 70 Total e	25 46 41 48 60 32 48 48 49 37 50 32 49 45 730 15 (P = 0.3 (P < 0.0000) compared v 43 36 45 30 29 32 215 5 (P = 0.75) (P < 0.0000) compared v 22 215 25 (P = 0.75) (P < 0.0000) 22 215 5 (P = 0.75) (P < 0.0000) 20 2	17 37 25 39 46 25 36 37 37 26 37 22 39 33 550 99); l ² = (01) with SAS 22 21 19 160 5); l ² = 0 01) with Othe 17	25 46 40 48 60 32 47 48 49 36 50 31 49 45 726 0% 6P) 43 36 45 30 0% 6P) 43 36 45 30 29 32 215 %	1.9% 4.1% 2.8% 4.3% 5.1% 2.8% 4.0% 4.1% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.41 [1.07, 1.87] 1.14 [0.96, 1.34] 1.37 [1.04, 1.79] 1.10 [0.93, 1.30] 1.17 [1.00, 1.38] 1.20 [0.98, 1.47] 1.20 [1.00, 1.43] 1.22 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.01, 1.47] 1.32 [1.01, 1.47] 1.32 [1.01, 1.47] 1.32 [1.01, 1.47] 1.22 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
Li R.2019 42 Liu Y.H.2019 35 Sheng R.D.2017 43 Sheng R.D.2017 43 Shun J.X.2020 54 Wang H.S.2017 30 Wang P.L.2020 45 Wang P.L.2020 40 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 42 Subtotal (95% CI) Total events Total events 672 Heterogeneity: Chi ² = 5.00, df = 1 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Subtotal (95% CI) Total events Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effective rate (CLi Z.M.2012 20 Shi A.P.2017 <	46 46 41 48 60 32 48 49 37 50 32 49 45 730 15 (P = 0.4) (P < 0.0000) ompared v 43 36 45 30 29 32 215 5 (P = 0.7) (P < 0.0000) 5 (P < 0.0000) 29 32 215 5 (P = 0.7) (P < 0.0000) 20 32 215 5 (P = 0.7) (P < 0.0000) 20	37 25 39 46 25 36 37 37 26 39 33 550 99); ² = (0)] () ³ = (0)]	200 40 40 40 40 40 40 40 40 40 40 40 40 4	4.1% 4.3% 5.1% 2.8% 4.0% 4.1% 2.9% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.14 [0.96, 1.34] 1.37 [1.04, 1.79] 1.10 [0.93, 1.30] 1.17 [1.00, 1.38] 1.20 [0.98, 1.47] 1.20 [1.00, 1.43] 1.22 [1.01, 1.47] 1.22 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.66] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		↓	
Liu Y.H.2019 35 Sheng R.D.2017 43 Sun J.X.2020 54 Wang H.S.2017 30 Wang H.S.2017 30 Wang P.L.2020 45 Wang P.L.2020 45 Wang P.L.2020 45 Wang P.L.2020 45 Yuan X.H.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 42 Subtotal (95% CI) 72 Total events 672 Heterogeneity: Chi ² = 5.00, df = Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Waug F.T.2016 28 Waug F.T.2016 20 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df =	$\begin{array}{c} 41\\ 41\\ 48\\ 60\\ 32\\ 48\\ 48\\ 48\\ 49\\ 37\\ 50\\ 32\\ 49\\ 45\\ 730\\ 15 \ (P = 0.0000\\ 000000\\ 0000000\\ 0000000\\ 000000\\ 29\\ 32\\ 215\\ 5 \ (P = 0.75\\ (P < 0.0000\\ 000000\\ 000000\\ 000000\\ 000000\\ 000000$	25 39 46 25 36 37 26 37 26 37 22 39 33 550 99); l ² = (0 01) vith SAS 22 21 19 160 5); l ² = 0 01) vith Othe 17	40 48 60 32 47 48 49 36 50 31 49 36 50 31 49 36 45 726 0% 29 32 215 %	2.8% 4.3% 5.1% 2.8% 4.0% 4.1% 2.9% 4.1% 2.9% 4.1% 2.9% 4.3% 3.6% 60.8% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.37 [1.04, 1.79] 1.10 [0.93, 1.30] 1.17 [1.00, 1.38] 1.20 [0.98, 1.47] 1.20 [1.00, 1.43] 1.22 [1.03, 1.44] 1.22 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.66] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
Sheng R.D.2017 43 Sun J.X.2020 54 Wang H.S.2017 30 Wang H.S.2017 30 Wang P.L.2020 45 Wang P.L.2020 45 Wang P.L.2020 45 Yang M.M.2017 34 Yin P.2021 45 Yang M.M.2017 34 Yin P.2021 45 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhao J.H.2020 46 Subtotal (95% CI) 672 Total events 672 Heterogeneity: Chi ² = 5.00, df = Test for overall effect: Z = 8.26 Mang F.T.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Xue H.C.2021 29 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (CLi Z.M.2012 Subtotal (95% CI) <t< td=""><td>$\begin{array}{c} 48\\ 48\\ 60\\ 32\\ 48\\ 49\\ 9\\ 37\\ 50\\ 32\\ 49\\ 45\\ 730\\ 15\ (P=0.9, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,$</td><td>29 39 46 25 36 37 26 37 22 39 33 550 99); ² = 0 01) with SAS 34 28 36 22 21 19 160 5); ² = 0 01) with Othe 17</td><td>48 60 32 47 48 49 36 50 31 49 45 726 0% 6P) 43 36 45 20% 29 32 215 %</td><td>3.7% 3.1% 2.8% 4.0% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%</td><td>1.10 [0.93, 1.30] 1.17 [1.00, 1.38] 1.20 [0.98, 1.47] 1.20 [0.98, 1.47] 1.22 [1.03, 1.44] 1.22 [1.03, 1.44] 1.22 [1.02, 1.46] 1.27 [1.02, 1.46] 1.28 [1.01, 1.68] 1.29 [1.01, 1.61] 1.20 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.28 [0.96, 1.44] 1.22 [1.05, 1.64] 1.23 [1.02, 1.43] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]</td><td></td><td></td><td></td></t<>	$\begin{array}{c} 48\\ 48\\ 60\\ 32\\ 48\\ 49\\ 9\\ 37\\ 50\\ 32\\ 49\\ 45\\ 730\\ 15\ (P=0.9, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,$	29 39 46 25 36 37 26 37 22 39 33 550 99); ² = 0 01) with SAS 34 28 36 22 21 19 160 5); ² = 0 01) with Othe 17	48 60 32 47 48 49 36 50 31 49 45 726 0% 6P) 43 36 45 20% 29 32 215 %	3.7% 3.1% 2.8% 4.0% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.10 [0.93, 1.30] 1.17 [1.00, 1.38] 1.20 [0.98, 1.47] 1.20 [0.98, 1.47] 1.22 [1.03, 1.44] 1.22 [1.03, 1.44] 1.22 [1.02, 1.46] 1.27 [1.02, 1.46] 1.28 [1.01, 1.68] 1.29 [1.01, 1.61] 1.20 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.28 [0.96, 1.44] 1.22 [1.05, 1.64] 1.23 [1.02, 1.43] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
Skin J.X.2020 54 Wang H.S.2017 30 Wang J.X.2018 44 Wang P.L.2020 45 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhao J.H.2020 42 Subtotal (95% CI) Total events Total events 672 Heterogeneity: Chi ² = 5.00, df = Test for overall effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effective rate (C Li Z.M.2012 Li Z.M.2012 20 Subtotal (95% CI) Total events Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63	40 32 48 49 37 50 32 49 45 730 15 (P = 0.4 (P < 0.0000 0000 at 20 215 5 (P = 0.75 (P < 0.0000 0000 at 20 215 5 (P = 0.75 (P < 0.0000 0000 at 20 215 5 (P = 0.75 (P < 0.0000 0000 at 20 20 20 20 20 20 20 20 20 20	46 25 36 37 37 22 39 33 550 99); ² = 0 01) vith SAS 36 22 21 19 160 5); ² = 0 01) vith Othe 17	40 32 47 48 49 36 50 31 49 45 726 0% 6P) 43 36 45 30 29 32 215 %	3.7% 3.1% 4.1% 4.1% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.17 [1.00, 1.38] 1.20 [0.98, 1.47] 1.20 [1.00, 1.43] 1.22 [1.03, 1.44] 1.22 [1.02, 1.46] 1.27 [1.02, 1.46] 1.27 [1.02, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.69] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
Wang H.S.2017 30 Wang J.X.2018 44 Wang P.L.2020 45 Wang P.L.2020 45 Wang B.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhang G.R.2020 46 Zhao J.H.2020 30 Subtotal (95% CI) 70 Total events 672 Heterogeneity: Chi ² = 5.00, df = 72 Total events 672 Heterogeneity: Chi ² = 5.00, df = 73 Total events 672 Heterogeneity: Chi ² = 5.00, df = 73 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Xue H.C.2021 29 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (CLi Z.M.2012 20 Subtotal (95% CI) 70 Total events 9	32 48 48 49 37 50 32 49 45 730 15 (P = 0.9) (P < 0.0000) ompared v 43 36 45 30 29 32 215 5 (P = 0.7) (P < 0.0000) (P < 0.0000) 5 (P = 0.7) (P < 0.0000) (P < 0.0000) 22 215 5 (P = 0.7) (P < 0.0000) (P < 0.0000) 22 215 5 (P = 0.7) (P < 0.0000) (P	25 36 37 37 26 37 22 39 33 550 99); l ² = (01) with SAS 34 28 36 22 21 19 160 5); l ² = 0 01) with Othe 17	32 47 48 49 36 50 31 49 45 726 0% 8P) 43 36 45 30 0% 8P) 43 36 45 30 29 32 32 215 %	3.7% 4.1% 4.1% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.20 [1.00, 1.43] 1.20 [1.00, 1.43] 1.22 [1.03, 1.44] 1.22 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		↓	
Wang J.X.2018 44 Wang J.X.2018 44 Wang P.L.2020 45 Wen B.2017 45 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 30 Subtotal (95% CI) Total events Total events 672 Heterogeneity: Chi² = 5.00, df = 16.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 203 Heterogeneity: Chi² = 2.66, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Subtotal (95% CI) 7 Total events 203 Heterogeneity: Chi² = 0.36, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.201	$\begin{array}{c} 48\\ 48\\ 49\\ 37\\ 50\\ 32\\ 49\\ 45\\ 730\\ 15 \ (P = 0.9, 000)\\ 000000\\ 00000000\\ 00000000\\ 0000000\\ 29\\ 32\\ 215\\ 5 \ (P = 0.7, 000)\\ 32\\ 215\\ 5 \ (P = 0.7, 000)\\ 000000\\ 000000\\ 000000\\ 000000\\ 000000$	26 36 37 37 26 37 22 39 33 550 99); ² = (01) vith SAS 36 22 21 19 160 5); ² = 0 01) vith Othe 17	22 47 48 49 36 50 31 49 45 726 0% 43 36 45 36 45 36 45 32 215 2215 %	2.5% 4.1% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 60.8% 3.6% 60.8% 4.0% 2.4% 2.3% 2.1% 17.6%	1.20 [0.00, 1.43] 1.20 [1.00, 1.43] 1.22 [1.00, 1.43] 1.22 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.66] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		· · · · · · · · · · · · · · · · · · ·	- - - - - - - - - - - - - - - - - - -
Wang P.L.2020 45 Wang P.L.2020 45 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 30 Subtotal (95% CI) 72 Total events 672 Heterogeneity: Chi ² = 5.00, df = 72 Fest for overall effect: Z = 8.26 44 Nong Z.B.2000 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 28 Wath C.2021 29 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = 72 Test for overall effective rate (CLi Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi ² = 0.36, df = T	$\begin{array}{c} 48\\ 48\\ 49\\ 37\\ 50\\ 32\\ 49\\ 9\\ 45\\ 730\\ \end{array}$	37 37 26 37 22 39 33 550 99); l ² = (01) vith SAS 28 36 22 21 19 160 5); l ² = 0 01) 160 5); l ² = 0 01)	48 49 36 50 31 49 45 726 0% 43 36 45 30 0% 29 32 215 %	4.1% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.22 [1.03, 1.44] 1.22 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.66] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		• •	- - - - - - - - - -
Wan B. 2017 45 Yang M.M.2017 34 Yin P.2021 45 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhao J.H.2020 46 Subtotal (95% CI) 672 Total events 672 Heterogeneity: Chi ² = 5.00, df = Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Xue H.C.2021 29 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Test for overall effect: Z = 5.52 1 1.6.3 Clinical effective rate (C 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t Tian G.D.2017	49 49 37 50 32 49 45 730 15 (P = 0.9 (P < 0.0000 pmpared v 43 36 45 30 29 32 215 5 (P = 0.7 (P < 0.0000 pmpared v 20 215 5 (P = 0.7 (P < 0.0000 pmpared v 20 215 5 (P = 0.7 (P < 0.0000 pmpared v 20 215 5 (P = 0.7 (P < 0.0000 pmpared v 22 215 5 (P < 0.0000 pmpared v 20 22 215 5 (P < 0.0000 pmpared v 20 22 215 5 (P < 0.0000 pmpared v 20 22 22 23 25 5 (P < 0.0000 pmpared v 20 20 20 20 20 20 20 20 20 20	37 26 37 22 39 33 550 99); l ² = (01) with SAS 34 28 36 22 21 19 160 5); l ² = 0 01) with Othe 17	49 36 50 31 49 45 726 0% 6P) 43 36 45 30 29 32 215 %	4.1% 4.1% 2.9% 4.1% 2.5% 4.3% 3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.22 [1.02, 1.46] 1.27 [1.02, 1.46] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.22 [1.05, 1.64] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	
Yang M.M.2017 34 Yang M.M.2017 34 Yin P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 30 Subtotal (95% CI) 10 Total events 672 Heterogeneity: Chi ² = 5.00, df = 72 Test for overall effect: Z = 8.26 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Yue H.C.2021 29 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (C Tian G.D.2017 33 You C.M.2016 39	43 50 32 49 45 730 15 (P = 0.4 (P < 0.0000 0000 at 2 30 29 32 215 5 (P = 0.75 (P < 0.0000 0000 at 2 215 5 (P = 0.75 (P < 0.0000 0000 225 225 225 225 225 225	26 37 22 39 33 550 99); ² = (01) with SAS 34 28 36 22 21 19 160 5); ² = 0 01) with Othe 17	436 50 31 49 45 726 0% 6P) 43 36 45 30 29 32 215 %	3.7% 3.6% 60.8% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.27 [1.02, 1.59] 1.27 [1.02, 1.59] 1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.69] 1.23 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		 	
Yian P.2021 45 Yuan X.H.2020 30 Zhang G.R.2020 46 Zhao J.H.2020 42 Subtotal (95% CI) Total events 672 Heterogeneity: Chi ² = 5.00, df = Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Subtotal (95% CI) Total events 203 Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 5.52 1.6.4 Clinical effective rate (C 12 Total events 99 Heterogeneity: Chi ² = 0.36, df = 15 Total events 99 Heterogeneity: Chi ² = 0.36, df = 16.4 Clinical effective rate (T Tian G.D.2017 33 3	50 32 49 45 730 15 (P = 0.9 (P < 0.0000 compared v 43 36 45 30 29 32 215 5 (P = 0.75 (P < 0.0000 compared v 20 compared v	237 22 39 33 550 99); $l^2 = (0)$ with SAS 34 28 36 22 21 19 160 5); $l^2 = 0$ 01) with Other 17	50 31 49 45 726 0% 45 0% 45 0% 45 30 29 32 215 %	3.7% 3.6% 60.8% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.22 [1.01, 1.47] 1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.22 [1.16, 1.27] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	
1111 + 12021 30 Zhang G.R.2020 46 Zhao J.H.2020 42 Subtotal (95% CI) 1 Total events 672 Heterogeneity: Chi ² = 5.00, df = 1 Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Xue H.C.2021 29 Subtotal (95% CI) 10 Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 10 Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t Tian G.D.2017 33 Yang X.Q.2021 43	32 49 45 730 15 (P = 0.1 (P < 0.0000 000000000 43 36 45 30 29 32 215 5 (P = 0.7 (P < 0.00000 29 32 215 5 (P = 0.1 7 (P < 0.0000000000000000000000000000000000	5, 39 33 550 99); ² = (01) vith SAS 34 28 36 22 21 19 160 5); ² = 0° 01) vith Othe 17	31 49 45 726 0% 43 36 45 30 29 32 215 %	3.7% 3.6% 60.8% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.32 [1.04, 1.68] 1.18 [1.01, 1.38] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.22 [1.16, 1.27] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	
Nam Chillogo 30 Zhang G, R. 2020 46 Zhao J, H. 2020 42 Subtotal (95% CI) 72 Total events 672 Heterogeneity: Chi ² = 5.00, df = 72 Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B, Q. 2020 41 Deng P.2015 33 Ding S, L.2016 44 Nong Z, B.2009 28 Wang F, T.2016 28 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = 72 Test for overall effective rate (C Li Z.M.2012 20 Shi A, P.2017 47 Tan G, Z.2020 32 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi ² = 0.36, df = 74 Tan G, Z.2020 32 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t Tian G, D.2017 33 </td <td>49 45 730 15 (P = 0.9) (P < 0.0000) ompared v 43 36 45 30 29 32 215 5 (P = 0.7) (P < 0.0000) 5 (P < 0.0000) 29 32 215 5 (P = 0.7) (P < 0.0000) 20</td> <td>32 39 550 $99); ^2 = (0)$ with SAS 34 28 36 22 21 19 160 $5); ^2 = 0$ 01) with Other 17</td> <td>49 45 726 0% 43 36 45 30 29 32 215 %</td> <td>3.7% 3.6% 60.8% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%</td> <td>1.31 [1.02, 1.43] 1.27 [1.05, 1.54] 1.22 [1.05, 1.54] 1.22 [1.16, 1.27] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]</td> <td></td> <td>• •</td> <td></td>	49 45 730 15 (P = 0.9) (P < 0.0000) ompared v 43 36 45 30 29 32 215 5 (P = 0.7) (P < 0.0000) 5 (P < 0.0000) 29 32 215 5 (P = 0.7) (P < 0.0000) 20	32 39 550 $99); ^2 = (0)$ with SAS 34 28 36 22 21 19 160 $5); ^2 = 0$ 01) with Other 17	49 45 726 0% 43 36 45 30 29 32 215 %	3.7% 3.6% 60.8% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.31 [1.02, 1.43] 1.27 [1.05, 1.54] 1.22 [1.05, 1.54] 1.22 [1.16, 1.27] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		• •	
Lang U.1.2020 40 Sublation (195% CI) 672 Total events 672 Heterogeneity: Chi ² = 5.00, df = 7 Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi ² = 0.36, df = 7 Tan G.Z.2020 32 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi ² = 0.36, df = 7 Test for overall effect: Z = 3.63 1 1.6.4 Clinical effective rate (t 1 Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	45 730 (P < 0.000) ompared v 43 36 45 30 29 32 215 5 (P = 0.75) (P < 0.000) ompared v 20 20	33 550 99); ² = (01) with SAS 34 28 36 22 21 19 160 5); ² = 0 01) with Othe 17	45 726 0% 43 36 45 30 29 32 215 %	3.6% 60.8% 3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.27 [1.05, 1.54] 1.27 [1.05, 1.54] 1.22 [1.16, 1.27] 1.18 [0.96, 1.44] 1.22 [1.05, 1.69] 1.23 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	
August 1 42 Subtotal (95% CI) 42 Total events 672 Heterogeneity: Chi² = 5.00, df = 7 Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Subtotal (95% CI) 7 Total events 203 Heterogeneity: Chi² = 2.66, df = 7 Test for overall effective rate (C 1.1.2.2.020 Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi² = 0	730 15 (P = 0.9 (P < 0.0000 compared v 43 36 45 30 29 32 215 5 (P = 0.75 (P < 0.0000 compared v 20 20 20 20 20 20 20 20 20 20	550 99); ² = (01) vith SAS 34 28 36 22 21 19 160 5); ² = 0 01) vith Othe 17	726 726 0% 43 36 45 30 29 32 215 % er Drug	3.7% 60.8% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 [1.02, 1.43] 1.22 [1.16, 1.27] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		 ▲ ▲ 	- -
Constant (50% 67) Total events 672 Heterogeneity: Chi² = 5.00, df = Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Subtotal (95% CI) 7 Total events 203 Heterogeneity: Chi² = 2.66, df = 7 Test for overall effective rate (C 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Tian G.D.2017 33 Yang X.Q.2021<	15 (P = 0.9 (P < 0.0000 ompared v 43 36 45 30 29 32 215 5 (P = 0.7 (P < 0.0000 (P < 0.0000 (P < 0.0000) (P < 0.0000) (P < 0.0000) (P < 0.0000) 29 32 215	550 99); ² = (01) vith SAS 34 28 36 22 21 19 160 5); ² = 0 01) vith Othe 17	20% 6P) 43 36 45 30 29 32 215 % er Drug	3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			- - -
None events 672 Heterogeneity: Chi² = 5.00, df = Test for overall effect: Z = 8.26 1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi² = 2.66, df = 7 Test for overall effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	15 (P = 0.9 (P < 0.0000) ompared v 43 36 45 30 29 32 215 5 (P = 0.7 (P < 0.0000) ompared v 20	99); ² = (01) vith SAS 34 28 36 22 21 19 160 5); ² = 0 01) vith Othe 17	0% 5P) 43 36 45 30 29 32 215 % er Drug	3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			-
Test for overall effect: Z = 8.26 1.6.2 Clinical effect: Z = 8.26 1.6.2 Clinical effect: Z = 8.26 1.6.2 Clinical effect: Z = 8.26 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 28 Subtotal (95% CI) 70 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Test for overall effect: Z = 5.52 1 1.6.3 Clinical effective rate (CLi Z.M.2012 20 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi ² = 0.36, df = 7 Test for overall effect: Z = 3.63 1 I.6.4 Clinical effective rate (t tl 1 Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	(P < 0.0000 compared v 43 36 45 30 29 32 215 5 (P = 0.75 (P < 0.0000 compared v 20	vith SAS 34 28 36 22 21 19 160 5); l ² = 0 ⁵ 01) vith Other 17	67% 43 36 45 30 29 32 215 % er Drug	3.7% 3.1% 4.0% 2.4% 2.3% 17.6%	1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			-
1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Xue H.C.2021 29 Subtotal (95% Cl) 7 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% Cl) 7 Total events 99 Heterogeneity: Chi ² = 0.36, df = 7 Total events 99 Heterogeneity: Chi ² = 0.36, df = 7 Total events 99 Heterogeneity: Chi ² = 0.36, df = 7 Test for overall effect: Z = 3.63 1 1.6.4 Clinical effective rate (t 1 Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	ompared v 43 36 45 30 29 32 215 5 (P = 0.75 (P < 0.0000 compared v 20	vith SAS 34 28 36 22 21 19 160 5); l ² = 0 ⁰ 01) vith Othe 17	6P) 43 36 45 30 29 32 215 %	3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			- -
1.6.2 Clinical effective rate (C Chen B.Q.2020 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 29 Subtotal (95% CI) 7 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Test for overall effective rate (C 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (ttl) Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	ompared v 43 36 45 30 29 32 215 5 (P = 0.74 (P < 0.0000 ompared v 20	vith SAS 34 28 36 22 21 19 160 5); l ² = 0 01) vith Other 17	6P) 43 36 45 30 29 32 215 %	3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
1.0.2 clinical effective rate (c Chen B, Q.2020 41 Deng P.2015 33 Ding S, L.2016 44 Nong Z, B.2009 28 Wang F, T. 2016 28 Xue H, C.2021 29 Subtotal (95% CI) 7 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Test for overall effective rate (C 20 Li Z.M.2012 20 Shi A.P.2017 47 Tan G, Z.2020 32 Subtotal (95% CI) 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t Tian G, D.2017 33 Yang X, Q.2021 43 You C.M.2016 39	43 36 45 30 29 32 215 5 (P = 0.73 (P < 0.0000) cmpared v 20 cm	34 28 36 22 21 19 160 5); l ² = 0 01) vith Other 17	43 36 45 30 29 32 215 %	3.7% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 [1.02, 1.43] 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]			
Arrow Data (2020) 41 Deng P.2015 33 Ding S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Subtotal (95% CI) 5 Total events 203 Heterogeneity: Chi² = 2.66, df = 1 Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C.i.i Z.M.2012 20 Shi A.P.2017 47 7 Tan G.Z.2020 32 Subtotal (95% CI) Total events 99 - Heterogeneity: Chi² = 0.36, df = 1 - Total events 99 - Heterogeneity: Chi² = 0.36, df = - - Total events 99 - - Heterogeneity: Chi² = 0.36, df = - - - Tian G.D.2017 33 - - - Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39 - -	43 36 45 30 29 32 215 5 (P = 0.79) (P < 0.0000) compared v 20 5	34 28 36 22 21 19 160 5); ² = 0 ⁶ 01) vith Other 17	43 36 45 30 29 32 215 %	3.1% 3.1% 4.0% 2.4% 2.3% 2.1% 17.6%	1.21 (1.02, 1.43) 1.18 [0.96, 1.44] 1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	:
Joing S.L.2016 44 Nong Z.B.2009 28 Wang F.T.2016 28 Wang F.T.2016 28 Wang F.T.2016 28 Subtotal (95% CI) 203 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C.i.i Z.M.2012 20 Shi A.P.2017 47 47 Tan G.Z.2020 32 Subtotal (95% CI) Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t Tian G.D.2017 33 Yang X.Q.2021 You C.M.2016 39	45 30 29 32 215 5 (P = 0.79 (P < 0.0000 pompared v 20	28 36 22 21 19 160 5); I ² = 09 01) vith Other 17	45 30 29 32 215 %	4.0% 2.4% 2.3% 2.1% 17.6%	1.22 [1.05, 1.42] 1.22 [1.05, 1.42] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	
Julig S.L.2010 44 Nong Z.B.2009 28 Wang F.T.2016 28 Kue H.C.2021 29 Subtotal (95% CI) 7 Total events 203 Heterogeneity: Chi ² = 2.66, df = 7 Fest for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C. Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (ttl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	43 30 29 32 215 5 (P = 0.75) (P < 0.0000) compared v 20 5	22 21 19 160 5); I ² = 09 01) with Other 17	45 30 29 32 215 %	4.0% 2.4% 2.3% 2.1% 17.6%	1.22 [1.05, 1.42] 1.27 [1.01, 1.61] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		-	<u> </u>
Vang F.T.2016 28 Wang F.T.2016 28 Kue H.C.2021 29 Subtotal (95% CI) 10 Total events 203 Heterogeneity: Chi² = 2.66, df = 10 Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C. Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 10 Total events 99 Heterogeneity: Chi² = 0.36, df = 1.6.4 Clinical effect: Z = 3.63 1.6.4 Clinical effective rate (ttl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	30 29 32 215 5 (P = 0.73) (P < 0.0000) compared v 20 5	22 21 19 160 5); I ² = 09 01) with Other 17	29 32 215 %	2.4% 2.3% 2.1% 17.6%	1.27 [1.07, 1.67] 1.33 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	
warig P. 1. 2016 20 Xue H.C.2021 29 Subtotal (95% CI) 10 Total events 203 Heterogeneity: Chi ² = 2.66, df = 16.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 10 Total events 99 Heterogeneity: Chi ² = 0.36, df = 76.3 Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t tlinical effective rate (t tlinia G.D.2017 Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	29 32 215 5 (P = 0.75) (P < 0.0000) compared v 20 5	160 5); I ² = 09 01) vith Othe 17	29 32 215 %	2.3% 2.1% 17.6%	1.53 [1.05, 1.69] 1.53 [1.12, 2.08] 1.27 [1.17, 1.38]		•	·
Alle H.C.2021 29 Subtotal (95% CI) 203 Total events 203 Heterogeneity: Chi ² = 2.66, df = 1 Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C. 1.6.3 Clinical effective rate (C. 1 Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 99 Total events 99 Heterogeneity: Chi ² = 0.36, df = 1 Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	32 215 5 (P = 0.79 (P < 0.0000) compared v 20	160 5); I ² = 09 01) vith Othe 17	215 %	2.1% 17.6%	1.33 [1.12, 2.08] 1.27 [1.17, 1.38]		•	
Total events 203 Total events 203 Heterogeneity: Chi ² = 2.66, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C. Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% Cl) Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (t ti Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	5 (P = 0.79 (P < 0.0000 ompared v 20	160 5); I ² = 09 01) vith Othe 17	215 % er Drug	17.0%	1.27 [1.17, 1.30]			
Total events 203 Heterogeneity: Chi² = 2.66, df = Test for overall effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% Cl) 32 Total events 99 Heterogeneity: Chi² = 0.36, df = Test for overall effective rate (tlinical effective rate) 1.6.4 Clinical effective rate (tlinical effective rate) Yang X.0.2021 43 You C.M.2016 39	5 (P = 0.75 (P < 0.0000 ompared v 20	(100) (5); $l^2 = 0$ (01) (01) (01) (01) (01) (01) (01) (01)	% er Drug	15)				
Test for overall effect: Z = 5.52 1.6.3 Clinical effect: Z = 5.52 1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 50 Total events 99 Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (ttl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	5 (P = 0.73 (P < 0.0000 ompared v 20	o); 1 ² = 09 01) vith Othe 17	% er Drug	(21				
1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Test for overall effect: Z = 3.63 1 1.6.4 Clinical effective rate (tt 1 Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	ompared v	vith Othe 17	er Drug	is)				
1.6.3 Clinical effective rate (C Li Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 7 Total events 99 Heterogeneity: Chi² = 0.36, df = 7 Total events 93 1.6.4 Clinical effect: Z = 3.63 33 Yang X.Q.2021 43 You C.M.2016 39	ompared v 20	vith Othe 17	er Drug	(at				
i Z.M.2012 20 Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% CI) 70 Total events 99 Heterogeneity: Chi² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (tl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	20	17						
Shi A.P.2017 47 Tan G.Z.2020 32 Subtotal (95% Cl) 99 Heterogeneity: Chi² = 0.36, df = 7 Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (the final of the	20		20	1.9%	1 17 [0 96 1 43]			-
Tan G.Z.2020 32 Subtotal (95% Cl) 99 Total events 99 Heterogeneity: Chi ² = 0.36, df = 1 Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (tlinical effec	50	37	50	4 1%	1 27 [1 06 1 52]			
Subtotal (95% CI) 99 Total events 99 Heterogeneity: Chi ² = 0.36, df = 7 Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (the state of the s	34	26	34	2.9%	1 23 [1 00 1 51]			_
Total events 99 Heterogeneity: Chi² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (th Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	104	20	104	8.9%	1.24 [1.10, 1.39]			
Heterogeneity: Chi ² = 0.36, df = Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (tl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39		80		01070				
Test for overall effect: Z = 3.63 1.6.4 Clinical effective rate (tl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	2(P = 0.8)	3)· 12 = 00	0/					
1.6.4 Clinical effective rate (tl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	P = 0.003	3), 1 = 0.	/0					
1.6.4 Clinical effective rate (tl Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	(1 - 0.0000	5)						
Tian G.D.2017 33 Yang X.Q.2021 43 You C.M.2016 39	ne Rhubar	b-based	Medici	inal Form	ulas only)			
Yang X.Q.2021 43 You C.M.2016 39	38	25	35	2.9%	1.22 [0.95, 1.55]			
You C.M.2016 39	45	37	45	4 1%	1 16 [1 00 1 35]			
	42	28	42	3 1%	1.39 [1.11 1.75]			
Zhang H Y 2016 38	40	20	40	2.6%	1.58 [1.22.2.06]			
Subtotal (95% CI)	165	24	162	12.7%	1.32 [1.18, 1.47]		-	•
Total events 152	100	114						
Heterogeneity: $Chi^2 = 5.23$ df =	3(P = 0.1)	6): $l^2 = 4^{\circ}$	3%					
Test for overall effect: $7 = 5.00$	(P < 0.000)	01)	. 10					
. 551. 61 070101 511601. Z = 0.00		.,						
Total (95% CI)	1214		1207	100.0%	1.24 [1.20, 1.29]		•	
Total events 1127		904						
Heterogeneity: $Chi^2 = 14.19$ df	= 28 (P = 0).99): l ² =	0%					++
Test for overall effect: $7 = 11.62$	(P < 0.000	001)	2,3			0.5 0.7	1	1.5 2
Test for subaroup differences: ($chi^2 = 2.22$	df = 3 (F	P = 0.53	3), $ ^2 = 0\%$		Favours [experime	ntal] Favours [col	ntrol]
			0.00					
4	<i>L.LL</i> .							

PLT

PLT increase was evaluated in three trials. There was no heterogeneity among the studies, and the fixed-effects model was used in the analysis. The results showed that the rhubarbbased treatment could reduce PLT levels compared with the control group (n = 226, $I^2 = 0\%$. RR = -32.95; 95% CI [-39.21, -26.69], p < 0.00001) (Figure 9). Furthermore, it could also influence the coagulation-related indexes of prothrombin time (PT) and fibrinogen (FIB) (Supplementary Figure S1).



Inflammatory cytokines and protein

The regulation of cytokines towards multiple inflammatory signaling pathways are the central component of chronic inflammation in UC. IL-6, one of the major cytokines, can bind to IL-6R to activate STAT3 signaling and further induce differentiation of Th17 cells, leading to excessive release of proinflammatory cytokines such as IL-17 and IL22 (Waldner and Neurath, 2014). IL-6 also stimulates the production of the regulatory inflammatory marker C-reactive protein (CRP) (Pepys and Hirschfield, 2003). Meanwhile, the synergy effect of IL-1β, IL-23, and IL-6 strengthens Th17 cell differentiation and maintains the expression of pro-inflammatory cytokines (Chung et al., 2009). Moreover, IL-6 and IL-8, as inducers of neutrophil recruitment, can amplify the inflammatory response by interacting with a large number of inflammatory cells exuding from inflamed areas (Kim and Kim, 2010; Waldner and Neurath, 2014). TNF-a stimulates death receptor signaling leads to excessive crypt cell death, which increases the intestinal

inflammatory response (Günther et al., 2011). The results showed that the rhubarb-based therapy significantly reduced the level of IL-6 (n = 794, $I^2 = 99\%$. MD = -18.60; 95% CI [-24.51, -12.68], p < 0.00001) (Figure 10A), IL-8 (n = 718, $I^2 = 99\%$. MD = -25.44; 95% CI [-34.36, -16.52], p < 0.00001) (Figure 10B), IL-1 β (n = 494, $I^2 = 97\%$. MD = -4.92; 95% CI [-6.69, -3.16], p < 0.00001) (Figure 10C), TNF- α (n = 1243, $I^2 = 99\%$. MD = -13.08; 95% CI [-17.18, -8.98], p < 0.00001) (Figure 10D), and CRP (n = 311, $I^2 = 98\%$. MD = -3.97; 95% CI [-6.22, -1.73], p = 0.0005) (Figure 11A) when compared with the control group. Overall, IL-6, IL-8, IL-1 β , and TNF- α are all considered to be essential mediators of chronic intestinal inflammation, and the rhubarb-based treatment showed a better effect on pro-inflammatory cytokines.

Besides, the relative deficiency of IL-10 in UC patients may contribute to persistent inflammatory changes (Wang et al., 2020). IL-10 down-regulates the production of Th1-derived cytokines to exert anti-inflammatory effects (Glocker et al.,

study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
1.5.1 Clinical effective	e rate (2-5	weeks)						
Deng P.2015	33	36	28	36	3.1%	1.18 [0.96, 1.44]		
Deng S.H.2020	43	45	36	45	4.0%	1.19 [1.02, 1.40]		
Li R.2019	42	46	37	46	4.1%	1.14 [0.96, 1.34]	+	
Liu Y.H.2019	35	41	25	40	2.8%	1.37 [1.04, 1.79]		_
Nong Z.B.2009	28	30	22	30	2.4%	1.27 [1.01, 1.61]		
Sheng R.D.2017	43	48	39	48	4.3%	1.10 [0.93, 1.30]		
Shi A.P.2017	47	50	37	50	4.1%	1.27 [1.06, 1.52]		
Sun J.X.2020	54	60	46	60	5.1%	1.17 [1.00, 1.38]		
Wang F.T.2016	28	29	21	29	2.3%	1.33 [1.05, 1.69]		-
Wang H.S.2017	30	32	25	32	2.8%	1.20 [0.98, 1.47]		
Wang P.L.2020	45	48	37	48	4.1%	1.22 [1.03, 1.44]		
Wen B.2017	45	49	37	49	4.1%	1.22 [1.02, 1.46]		
Yang X.Q.2021	43	45	37	45	4.1%	1.16 [1.00, 1.35]		
Yuan X.H.2020	30	32	22	31	2.5%	1.32 [1.04, 1.68]		-
Subtotal (95% CI)		591		589	49.6%	1.21 [1.15, 1.28]	•	
Total events	546		449					
Heterogeneity: Chi ² = 4	169 df = 1	3(P = 0)	98): l ² =	0%				
Test for overall effect:	7 = 7.45 (F	< 0.000	01)	070				
		0.000	01)					
1.5.2 Clinical effective	e rate (6-9	weeks)						
Ding S.L. 2016	44	45	36	45	4.0%	1.22 [1.05, 1.42]		
Fei X Y 2017	70	75	58	75	6.4%	1 21 [1 05 1 38]		
Guo G .1 2019	24	25	17	25	1.9%	1 41 [1 07 1 87]	· · · · · ·	
i 7 M 2012	20	20	17	20	1.9%	1 17 [0 96 1 43]		
Tian G D 2017	33	38	25	35	2.9%	1 22 [0 95 1 55]		
Nang 1 X 2018	44	48	36	47	4.0%	1 20 [1 00 1 43]		
Kup H C 2021	29	32	10	32	2 1%	1.53 [1.12, 2.08]		
Vin D 2021	29	50	37	50	2.170	1.00 [1.12, 2.00]		
You C M 2016	30	42	28	42	3 1%	1.22 [1.01, 1.47]		_
7bang G P 2020	46	42	20	42	1 3%	1 18 [1 01 1 38]		
Zhang H X 2016	38	40	24	49	2.6%	1.58 [1.22, 2.06]		
Subtotal (95% CI)	50	464	24	460	37.3%	1.27 [1.20, 1.35]	•	
Total overta	432	404	226	400	07.070	1.27 [1.20, 1.00]		
Heterogeneity: Chi ² = 8	432 36 df = 1	0 (P = 0	50) 12 -	0%				
Test for overall effect:	7 - 7 83 (E		01)	0 /0				
rest for overall effect.	2 – 7.03 (F	< 0.000	01)					
1 5 3 Clinical effective	a rate (12-	13 weeks	(2					
Chen B O 2020	/14	12	24	42	3 70/	1 21 [1 02 1 42]		
Tan G 7 2020	41	43	34	40	2 0%	1 23 [1 00 1 54]		
Vana M M 2017	32	34	20	34	2.9%	1.23 [1.00, 1.51]		
	10	37	20	30 4E	2.9%	1.27 [1.02, 1.39]		
Subtotal (95% CI)	42	40	33	40	3.0%	1 24 [1 13 1 37]	-	
Total overta	140	155	110	150	13.2 /0	1.24 [1.10, 1.07]		
Hotorogonolity Ohi2 - C	149	(D = 0.0)	7)-12 - 0	0/				
Telefogeneity: Chi* = (7 = 4.20	(P = 0.9	$(1); r^{*} = 0$	70				
est for overall effect:	2 = 4.38 (F	< 0.000	1)					
Fotal (95% CI)		1214		1207	100.0%	1.24 [1.20, 1.29]	•	
Total events	1127		904					
Heterogeneity: Chi ² = 1	4.19, df =	28 (P = 0).99); l ² =	= 0%		-		2
Test for overall effect:	Z = 11.64 (P < 0.00	001)				0.0 0.7 I 1.5 Eavours (experimental) Eavours (contr	2
Test for subaroup diffe	rences: Ch	i ² = 1.56	df = 2 (P = 0.4	6). I ² = 0%		ravous [experimental] Favous [contr	

2011). The pooled analysis suggested that the difference between the two groups was statistically significant (n = 258, $I^2 = 92\%$. MD = 11.26; 95% CI [6.50, 16.01], p < 0.00001) (Figure 11B).

Adverse events

Six studies reported adverse reactions. Nevertheless, the results were not statistically significant (n = 521, $I^2 = 33\%$, RR = 0.71, 95% CI [0.41, 1.23], p = 0.22) (Figure 12A). Due to the different courses of treatment, another subgroup analysis was set up. After 6–9 weeks of administration, rhubarb-based therapy had an obvious effect on reducing the incidence of

adverse events (n = 180, $I^2 = 0\%$, RR = 0.31, 95% CI [0.12, 0.81], p = 0.02) (Figure 12A). However, the course of 2–5 weeks (n = 160, $I^2 = 0\%$, RR = 1.00, 95% CI [0.21, 4.82], p = 1.00) (Figure 12A) did not show statistical significance.

Symptoms integral

The TCM symptoms integral mainly includes the total symptom score, individual symptom scores such as abdominal pain, diarrhea, urgency, pus and blood stool, and burning pain in the anus. The total symptom score mainly observes symptoms such as diarrhea, abdominal pain, and pus and blood stool, from

٨							
A	Experimental Control			Mean Difference	Mean Difference		
Study or Subgroup Mean	SD Tota	l Mean	SD	Total	Weight	IV. Random, 95% CI	IV, Random, 95% Cl
Li Z.W.2021 2.03	0.26 43	2.83	0.32	43	38.7%	-0.80 [-0.92, -0.68]	
Tan G.Z.2020 3.8	1.16 34	4.63	1.38	34	32.1%	-0.83 [-1.44, -0.22]	
Yin P.2021 2.26	1.63 50	4.66	2.21	50	29.2%	-2.40 [-3.16, -1.64]	
Total (95% CI)	127			127	100.0%	-1.28 [-2.09, -0.46]	•
Heterogeneity: Tau ² = 0.45; Ch	i ² = 16.54. c	f = 2 (P =	= 0.000)3); l ² =	88%	-	
Test for overall effect: Z = 3.06	(P = 0.002)	,					-4 -2 0 2 4
							Favours [experimental] Favours [control]
В							
Expe	rimental	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup Mean	SD Tota	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fei X.Y.2017 0.38	0.07 75	0.93	0.2	75	36.2%	-0.55 [-0.60, -0.50]	+
Li Z.W.2021 1.03	0.26 43	1.32	0.27	43	28.6%	-0.29 [-0.40, -0.18]	
Shi A.P.2017 0.38	0.07 50	0.93	0.2	50	35.2%	-0.55 [-0.61, -0.49]	+
Total (95% CI)	168			168	100.0%	-0.48 [-0.59, -0.36]	◆
Heterogeneity: Tau ² = 0.01: Chi	i² = 18.64. d	f=2(P<	: 0.000	(1): $ ^2 =$	89%	-	
Test for overall effect: Z = 7.87	(P < 0.0000	1)		.,, .			-0.5 -0.25 0 0.25 0.5 Favours [experimental] Favours [control]
FIGURE 7							
Forest plot showing the resu	ult of (A) Ma	vo score	- (B) (Geboes	sscore		

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
Guo G.J.2019	2	25	8	25	36.0%	0.25 [0.06, 1.06]	
Li R.2019	3	46	8	46	36.0%	0.38 [0.11, 1.33]	
Tian G.D.2017	1	38	6	35	28.1%	0.15 [0.02, 1.21]	
Total (95% CI)		109		106	100.0%	0.27 [0.11, 0.63]	◆
Total events	6		22				
Heterogeneity: Chi ² = 0 Test for overall effect: 2).56, df = 2 Z = 3.01 (F	2 (P = 0. P = 0.003	0.001 0.1 1 10 1000				
FIGURE 8							

Forest plot displaying the results of the Meta-analysis for recurrence rate.



10

Study or Subgroup	Mean	srimenta SD	Total	Mean	SD	Total	Weight	IV. Random. 95% CI	IV. Random. 95% Cl
Chen B.Q.2020	6.3	2.12	43	9.52	2.2	43	10.6%	-3.22 [-4.13, -2.31]	- 1
Liu Y.H.2019	68.52	6.11	41	123.49	16.78	40	9.8%	-54.97 [-60.50, -49.44]	
Mong E T 2016	21.6	1.70	34	10.9	1.94	34	10.7%	-5.43 [-0.31, -4.55]	
Wang P.L.2010	36.19	6.21	49	47.3	7 34	29	10.0%	-15.70 [-17.40, -14.00]	
Wang P.L.2020	100 15	24 12	40	41.13	20.13	40	8.6%	-4.95 [-7.07, -2.25]	-
Xue H C 2021	72 54	7 62	32	124 04	12 58	32	9.0%	-18.80 [-27.80, -10.00]	-
Yang X O 2021	33 79	14.09	45	45 33	9.88	45	9.9%	-11 54 [-16 57 -6 51]	+
Yuan X H 2020	42.36	4 05	32	51 43	4.38	31	10.5%	-9 07 [-11 15 -6 99]	•
Zhao J.H 2020	99.65	17.58	45	114.25	21.03	45	8.9%	-14 60 [-22 61 -6 59]	-
Subtotal (95% CI)			398			396	100.0%	-18.60 [-24.51, -12.68]	•
Heterogeneity: Tau ² = Test for overall effect:	85.38; Ch Z = 6.16 ($hi^2 = 779$ P < 0.00	.86, df	= 9 (P <	< 0.000	01); I² =	99%		
Total (95% CI)			398			396	100.0%	-18.60 [-24.51, -12.68]	•
Heterogeneity: Tau ² = Test for overall effect: Test for subaroup diffe	85.38; Ch Z = 6.16 (erences: N	ni² = 779 P < 0.00 lot applie	.86, df)001) cable	= 9 (P <	< 0.000	01); l² =	99%		-100 -50 0 50 100 Favours [experimental] Favours [control]
3	Exper	imental		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD T	otal	Mean	SD	Total	Neight	IV. Random. 95% CI	IV. Random. 95% CI
Li R.2019	14.23	3.72	46	23.61	5.63	46	14.2%	-9.38 [-11.33, -7.43]	-
Liu Y.H.2019	168.48	10.17	41	214.1	13.54	40	13.6%	-45.62 [-50.84, -40.40]	
Shi A.P.2017	420	100	50	760	180	50	2.1% -	340.00 [-397.08, -282.92]	•
Wang J.X.2018	13.39	3.15	48	21.33	3.49	47	14.2%	-7.94 [-9.28, -6.60]	
Wang P.L.2020	37.57	6.65	48	44.48	8.29	48	14.0%	-6.91 [-9.92, -3.90]	. 1
Xue H.C.2021	160.87	8.17	32 2	00.27	6.84	32	13.9%	-39.40 [-43.09, -35.71]	· · · ·
rang X.Q.2021	45.79	2.15	45	68.22	11.23	45	13.7%	-22.43 [-27.26, -17.60]	
Subtotal (95% CI)	9.83	2.15	00	10.92	2.23	359	14.3%	-1.09 [-1.95, -0.23]	
Heterogeneity: Tau ² = 1 Test for overall effect: 2	145.18; Ch Z = 5.59 (P	i ² = 856. < 0.000	83, df 01)	= 7 (P <	0.0000	1); l ² = !	99%	10111[01100, 10101]	
			260			250	100.0%	-25 44 1-24 26 -16 521	•
Heterogeneity: Tau ² = 1	145 18· Ch	i ² = 856	83 df	= 7 (P <	0 0000	1)- 12 = 1	00%	-20.44 [-04.00, -10.02]	······
riotorogeneity. ruu -	140.10, 01		WW . W I	- / 11 -	0.0000		00/0		
Test for overall effect: Z Test for suboroup differ	Z = 5.59 (P rences: No	< 0.000 t applica	01) ble	c	ontrol	,		Mean Difference	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference
Test for overall effect: 2 Test for suboroup differ C Study or Subgroup	Z = 5.59 (P rences: No Expe Mean	erimenta	01) ible al Total	C Mean	ontrol SD	Total	Weight	Mean Difference IV. Random. 95% CI	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: 2 Test for subaroup differ C Study or Subgroup Chen B.Q.2020	Z = 5.59 (F rences: No Expe Mean 2.63	erimenta	01) ible al <u>Total</u> 43	C <u>Mean</u> 4.57	ontrol SD 0.28	Total 43	Weight 28.2%	Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: 2 Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020	Z = 5.59 (P rences: No Expe <u>Mean</u> 2.63 40.17	erimenta 0.31 11.75	01) ible Total 43 60	C <u>Mean</u> 4.57 62.46	0.28 10.66	<u>Total</u> 43 60	Weight 28.2% 11.5%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for subaroud differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017	Z = 5.59 (P rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51	erimenta SD 0.31 11.75 12.72	01) ble Total 43 60 49	C <u>Mean</u> 4.57 62.46 21.62	0.28 0.28 10.66 14.33	Total 43 60 49	Weight 28.2% 11.5% 7.8%	Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: 2 Test for subarouo differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021	Z = 5.59 (F rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51 3.91	 < 0.000 tabolica erimenta SD 0.31 11.75 12.72 0.83 	01) bble Total 43 60 49 50	C Mean 4.57 62.46 21.62 4.93	0.28 0.28 10.66 14.33 1.25	Total 43 60 49 50	Weight 28.2% 11.5% 7.8% 27.8%	Mean Difference IV, Random, 95% Cl -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Vin P.2021 Zhao J.H.2020	Z = 5.59 (F rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51 3.91 28.36	erimenta SD 0.31 11.75 12.72 0.83 2.75	01) bble Total 43 60 49 50 45	4.57 62.46 21.62 4.93 32.95	0.28 0.28 10.66 14.33 1.25 3.25	Total 43 60 49 50 45	Weight 28.2% 11.5% 7.8% 27.8% 24.7%	Mean Difference IV, Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for suboroup differ C Study or Subgroup Chen B.Q. 2020 Sun J.X. 2020 Wen B.2017 Yin P.2021 Zhao J.H. 2020 Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch ; Z = 5.47	 < 0.000 application application<	01) bble Total 43 60 49 50 45 247 02, df 0001)	4.57 62.46 21.62 4.93 32.95 = 4 (P <	0.28 10.66 14.33 1.25 3.25	Total 43 60 49 50 45 247 01); l ² =	Weight 28.2% 11.5% 7.8% 27.8% 24.7% 100.0% 97%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-6.83, -3.35] -4.92 [-6.69, -3.16]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random, 95% Cl
Test for overall effect: Z Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Vin P.2021 Zhao J.H.2020 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: Total (95% Cl)	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47	 < 0.000 application application<	01) ble 1 Total 43 60 49 50 45 247 02, df 0001) 247	4.57 62.46 21.62 4.93 32.95 = 4 (P <	0.28 10.66 14.33 1.25 3.25	Total 43 60 49 50 45 247 01); l ² =	Weight 28.2% 11.5% 7.8% 27.8% 24.7% 100.0% 97%	Mean Difference IV, Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
Test for overall effect z Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² =	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47	 < 0.000 tabolica erimenta SD 0.31 11.75 12.72 0.83 2.75 i² = 136. (P < 0.0 i² = 136. (P < 0.0 	01) bble al Total 43 60 49 50 45 247 02, df 0001) 247 02, df	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P <	0.28 10.66 14.33 1.25 3.25	Total 43 60 49 50 45 247 01); l ² = 247 01); l ² =	Weight 28.2% 11.5% 7.8% 27.8% 24.7% 100.0% 97% 100.0% 97%	Mean Difference IV. Random, 95% Cl -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect Test for subaroup diffi	Z = 5.59 (P rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47	< 0.000 the application of the application of th	01) ble 43 60 49 50 45 247 02, df 0001) 247 02, df 0001) icable	4.57 62.46 21.62 4.93 32.95 = 4 (P <	0.28 10.66 14.33 1.25 3.25 0.000	Total 43 60 49 50 45 247 01); l ² = 247 01); l ² =	Weight 28.2% 11.5% 7.8% 27.8% 24.7% 100.0% 97%	Mean Difference IV, Random, 95% Cl -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.36] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control]
Test for overall effect: Z Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: Test for overall effect: Test for suboroup diffe	z = 5.59 (P rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47 Expe	< 0.000 t application t application t application 0.31 11.75 12.72 0.83 2.75 $i^2 = 136.$ (P < 0.0 t application $i^2 = 136.$ (P < 0.0 Not application ariment:	01) bble 1 Total 43 60 49 50 45 247 02, df 0001) 247 02, df 0001) icable	4.57 62.46 21.62 4.93 32.95 = 4 (P <	0.28 10.66 14.33 1.25 3.25 < 0.000 < 0.000	Total 43 60 49 50 45 247 01); ² = 247 01); ² =	Weight 28.2% 11.5% 7.8% 27.8% 24.7% 100.0% 97%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference
Test for overall effect : Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup. Heterogeneity: Tau ² Etest for subgroup diffect	Z = 5.59 (P rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47 erences: I <u>Expr</u> <u>Mean</u>	< 0.000 t application t applica	01) bble Total Total 43 60 49 50 52 247 02, df 0001) 247 02, df 0001) icable al Total	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P < C Mean	0.28 10.66 14.33 1.25 3.25 < 0.000 control	Total 43 60 49 50 45 247 701); I ² = 247 21); I ² =	Weight 28.2% 11.5% 27.8% 24.7% 100.0% 97% 100.0% 97% Weight	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
Test for overall effect: Z Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for overall effect: Test for subdroup diffect D Study or Subgroup Chen B.Q.2020	Z = 5.59 (F rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47 ierences: 1 <u>Expr</u> <u>Mean</u> 18	 < 0.000 t application t application 0.31 11.75 12.72 0.83 2.75 i² = 136. (P < 0.0 vot application vot application sp 2.27 	01) bble al Total 43 60 49 5 247 02, df 0001) icable al Total 43	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P < C Mean 27.13	0.28 10.66 14.33 1.25 3.25 < 0.0000	Total 43 60 49 50 045 247 701); I ² = 247 247 701); I ² =	Weight 28.2% 11.5% 7.8% 24.7% 100.0% 97% 100.0% 97% weight 7.4%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect z Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for subaroup diffe D Study or Subgroup Chen B.Q.2020 Liu Y.H.2019	Z = 5.59 (F rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47 Erences: I <u>Exp</u> <u>Mean</u> 18 45.33	 < 0.000 t anolica sp on 31 11.75 12.72 0.83 2.75 i² = 136. (P < 0.0 i² = 136. (P < 0.0 ion and ion and ion and sp 2.27 7.26 	01) bble Total 43 60 49 50 45 247 02, df 0001) 247 02, df 0001) icable al Total 43 43 43 44 43 45 247 02, df 0001 10 247 02, df 00 10 10 10 10 10 10 10 10 10	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P < C Mean 27.13 62.15	0.28 10.66 14.33 3.25 < 0.000 control SD 2.05 8.03	Total 43 60 49 50 01); I ² = 247 701); I ² = 247 701); I ² = 101; I ² =	Weight 28.2% 11.5% 7.8% 27.8% 24.7% 100.0% 97% 100.0% 97% Weight 7.4% 7.1%	Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for subgroup Chen B.Q.2020 Liu Y.H.2019	Z = 5.59 (F rences: No <u>Expe</u> Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47 erences: I <u>Exp</u> Mean 45.33 21.7	 < 0.000 t anolica sp on 31 11.75 12.72 0.83 2.75 i² = 136. (P < 0.0 Not anol priment: SD 2.27 7.26 3.39 	01) bble Total 43 60 49 50 45 247 02, df 0001) icable al Total 43 43 43 43 50	C Mean 4.57 62.46 4.93 32.95 = 4 (P < C Mean 27.13 62.15 27.55	SD 0.28 10.66 14.33 1.25 3.25 c 0.0000 Control SD 2.05 8.03 4.02	Total 43 60 49 52 247 701); ² = 247 247 247 247 247 247 247 247 247 247	Weight 28.2% 11.5% 7.8% 24.7% 100.0% 97% 100.0% 97% Weight 7.4% 7.1% 7.4% 7.1%	Mean Difference IV. Random, 95% Cl -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% Cl -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subaroup diffe C Study or Subgroup. Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Shi A.P.2017	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47; Ch :	 < 0.000 taoolica spinoretta SD 0.31 11.75 12.72 0.83 2.75 i² = 136. (P < 0.0 Not anoi spinoretta SD 2.277 7.26 3.39 6.99 	01) bble al Total 43 60 49 50 45 247 02, df 0001) icable al Total 43 43 41 50 60 49 50 49 50 49 50 49 50 49 50 49 50 60 49 50 49 50 60 49 50 50 50 50 50 50 50 50 50 50	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P < C Mean 27.13 62.15 27.55	Control SD 0.28 10.66 14.33 1.25 3.25 c 0.0000 c 0.0000 c 0.0000 SD 2.05 8.03 4.02 7.41	Total 43 60 49 50 247 217); ² = 247 217); ² = 247 217); ² = 701); ² = 43 40 50 60	Weight 28.2% 11.5% 7.8% 27.8% 24.7% 100.0% 97% 100.0% 97% Weight 7.4% 7.4% 7.4% 7.2%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.38 [-17.96, -12.80] -17.38 [-17.96, -12.80]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect z Test for subaroub differ Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for subaroub diffe Study or Subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020	Z = 5.59 (F rences: No <u>Expe</u> <u>Mean</u> 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47; Ch : Z =	< 0.000 t acolica erimenta SD 0.31 11.75 12.72 0.83 2.75 i² = 136.6 (P < 0.0 Not acol erimenta SD 2.277 7.26 3.39 6.99 5.99	01) bble al 43 60 49 50 02, df 0001) 247 02, df 00001) icable al Total 43 41 50 60 34	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P < C Mean 27.13 62.15 27.55 48.84 81.07	0.28 0.28 10.66 14.33 1.25 3.25 < 0.0000	Total 43 60 49 50 45 247 01); ² = 247 01); ² = 247 01); ² = 43 40 50 60 34	Weight 28.2% 11.5% 27.8% 27.8% 24.7% 97% 100.0% 97% 100.0% 97% Weight 7.4% 7.4% 7.4% 7.4% 7.4%	Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.27 [-18.44, -12.10]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for subaroup differ Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (85% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Wang F.T.2016	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 erences: 1 Expe Mean 18 45.33 2.17 33.46 65.8 23.5	 < 0.000 taoolica spinore spinore	01) bble al 43 60 49 50 02, df 0001) 247 02, df 0001) icable al Total 43 41 50 60 60 45 247 247 02, df 0001)	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P = 4 (P C Mean 62.15 62.15 62.15 48.84 81.07 47.2	0.28 0.28 10.66 14.33 1.25 3.25 < 0.0000 //>	Total 43 60 49 50 247 217 21); ² = 247 247 21); ² = 247 247 247 247 247 247 247 247 247 247	Weight 28.2% 11.5% 27.8% 27.8% 27.8% 27.8% 27.8% 27.8% 97% 100.0% 97% 100.0% 97% 100.0% 97%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -5.38 [-17.96, -12.80] -15.27 [-18.44, 12.10] -23.70 [-26.03, -21.37]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
Test for overall effect: Z Test for subaroub differ Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup Study or Subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Wang J.T.2016 Wang J.T.2018	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47; Ch : Z = 5.4	 < 0.000 taoolica arimenta SD 0.31 11.75 12.72 0.83 2.75 i² = 136.6 (P < 0.0 i² = 136.6 (P < 0.0 i² = 136.6 (P < 0.0 axio i² = 136.6 (P < 0.0 i³ = 136.6 i³ = 136.6	01) bble al Total 43 60 49 50 45 247 02, df 0001) icable al Total 43 41 50 60 34 42 43 43 43 50 60 45 52 47 52 47 52 47 52 47 52 47 52 47 52 47 52 47 52 52 47 52 52 52 52 52 52 52 52 52 52	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P • C Mean 27.13 62.15 27.55 48.84 81.07 47.2 31.21	Control SD 0.28 10.66 14.33 1.25 3.25 c 0.000 c c c c c c c c c c c c c c c c c c	Total 43 60 49 50 247 217; ² = 247 247 247 201); ² = 247 247 201); ² = 247 247 201); ² =	Weight 28.2% 11.5% 27.8% 27.8% 24.7% 97% 97% 100.0% 597% Weight 7.4% 7.1% 7.2% 7.1% 7.2%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.38 [-7.36, -12.30] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for suboroup differ Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Wang F.T.2016 Wang J.X.2018 Wang J.X.2018	Z = 5.59 (F rences: No Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.543 = 2.545 = 2.555 = 2.555 = 2.555 = 2.555 = 2.5555 = 2.5555 = 2.5555 = 2.5555 = 2.5555 = 2.55555 = 2.5555 = 2.55	 < 0.000 t applies primenta SD 0.31 11.75 12.72 0.83 2.75 I² = 136. (P < 0.0 0.04 applies applies 	01) bble al 70tal 43 60 49 5247 02, df 0001) 247 02, df 0001) icable al 70tal 43 41 50 60 34 29 84 848	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P • C Mean 27.13 62.15 27.55 48.84 81.07 47.2 31.21 30.72	Control SD 0.28 10.66 14.33 1.25 3.25 c 0.0000 c c c 0.0000 c c c c c c c c c c c c c c c c c c	Total 43 60 49 50 247 701); ² = 247 247 247 247 247 247 247 247 247 247	Weight 28.2% 11.5% 27.8% 27.8% 24.7% 97% 97% 100.0% 97% 100.0% 97% * * * * * * * * * * * * * * * * * * *	Mean Difference IV, Random, 95% Cl -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV, Random, 95% Cl -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.27 [-18.44, -12.10] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect Z Test for subaroub differ Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (85% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Wang F.T.2016 Wang J.X.2018 Wang P.L.2020	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 erences: I Expr Mean 18 45.33 21.7 33.46 65.8 20.2 25.43 79.22	 < 0.000 t applies spinore spinore	01) bble 43 60 49 50 45 247 702, df 0001) icable 43 41 50 0001 43 41 50 60 43 41 50 60 43 43 44 43 43 43 43 43 43 43	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P < C Mean 27.13 62.15 27.55 48.84 81.07 47.2 31.21 30.72 97.35	control SD 0.28 10.66 14.33 1.25 3.25 c 0.0000 c 0.0000 c 0.0000 c c 0.00000 c c 0.00000000 c c 0.00000 c c 0.00000 c c 0.0000000000	Total 43 60 49 50 01; ² = 247 247 01); ² = 247 01); ² = 247 01]; 2 = 247 01]; 2 = 247 01]; 2 = 247 01]; 2 = 247 01]; 2 = 247 0];	Weight 28.2% 11.5% 27.8% 27.8% 27.8% 27.8% 27.8% 27.8% 27.8% 27.8% 100.0% 97% 100.0% 97% 100.0% 97% 400.0% 7.4% 7.4% 7.4% 7.2% 7.2% 7.2% 7.3%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, 4.39] -15.38 [-17.96, -12.80] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for subaroub differ Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup Study or Subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Wang J.X.2018 Wang P.L.2020 Wen B.2017 Yang X.Q.2021	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47; Ch : Z = 5.47	 < 0.000 t applied t applied<!--</td--><td>01) bble 43 60 45 50 45 50 45 50 45 50 49 50 247 70 22 47 02, df 60 00 01 1 247 50 247 50 247 50 247 50 247 50 247 50 247 50 247 50 247 50 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 50 50 50 50 50 50 50 50 50 50 50</td><td>C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P - C Mean 27.13 62.15 27.55 27.55 27.55 27.55 27.55 27.55 27.53 27.55 27.55 27.55 27.55 27.55 27.55 27.</td><td>Control SD 0.28 10.66 14.33 3.25 < 0.0000 Control SD 2.05 8.03 4.02 7.41 7.27 5.89 6.85 5.39 6.85 7.88</td><td>Total 43 60 49 50 45 247 701); ² = 247 701); ² = 247 701); ² = 247 701); ² = 43 40 50 60 34 29 9 47 48 49 9 45</td><td>Weight 28.2% 11.5% 27.8% 27.8% 24.7% 97% 97% 97% 100.0% 7.9% 7.1% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2%</td><td>Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.38 [-17.96, -12.80] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.86, -19.74]</td><td>-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl</td>	01) bble 43 60 45 50 45 50 45 50 45 50 49 50 247 70 22 47 02, df 60 00 01 1 247 50 247 50 247 50 247 50 247 50 247 50 247 50 247 50 247 50 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 49 50 50 50 50 50 50 50 50 50 50 50 50 50	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P - C Mean 27.13 62.15 27.55 27.55 27.55 27.55 27.55 27.55 27.53 27.55 27.55 27.55 27.55 27.55 27.55 27.	Control SD 0.28 10.66 14.33 3.25 < 0.0000 Control SD 2.05 8.03 4.02 7.41 7.27 5.89 6.85 5.39 6.85 7.88	Total 43 60 49 50 45 247 701); ² = 247 701); ² = 247 701); ² = 247 701); ² = 43 40 50 60 34 29 9 47 48 49 9 45	Weight 28.2% 11.5% 27.8% 27.8% 24.7% 97% 97% 97% 100.0% 7.9% 7.1% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2%	Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.38 [-17.96, -12.80] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.86, -19.74]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect 2 Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for overall effect Test for subgroup Chen B.Q.2020 Liu Y.H.2019 Study or Subgroup Chen B.Q.2020 Liu Y.H.2017 Sun J.X.2020 Tan G.Z.2020 Tan G.Z.2020 Wang F.T.2016 Wang J.X.2018 Wang J.X.2018 Wang D.Z.2021	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 erences: 1 Expr Mean 18 45.33 21.7 33.46 65.8 23.5 20.2 25.43 79.22 20.33 12.36	 < 0.000 t applies spinenta spinenta<	01) bble al Total 43 60 45 50 45 247 002, df 0001) icable al Total 43 41 50 60 34 43 43 41 50 60 948 848 48 48 45 50	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P < C Mean 27.13 62.15 27.55 48.84 81.07 47.2 31.21 47.2 31.21 43.07 97.35 43.17	Control SD 0.28 10.66 14.33 1.25 3.25 c 0.0000 Control SD c 0.0000 Control SD CONTRO SD CONTRO SC CONTRO SD SD CONTRO SD CONTRO SD CONTRO SD CONTRO SD CONTRO SD CONTRO SD	Total 43 60 49 5247 217 217); ² = 247 247 217); ² = 247 247 217); ² = 247 247 247 247 247 247 247 247 247 247	Weight 28.2% 11.5% 7.8% 27.8% 27.8% 97% 100.0% 97% 100.0% 97% 100.0% 97% 100.0% 97%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -8.13 [-25.28, -10.43] -22.84 [-25.96, -19.72] -4.17 [-5.23, -3.11]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = test for overall effect: Test for subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Yang X.Q.2021 Yin P.2021 Yian X.Q.2021 Yin P.2021 Yian X.Q.2021	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 erences: 1 Exp Mean 18 45.33 21.7 33.46 65.8 20.2 25.43 79.22 20.33 12.36	 < 0.000 t apolica rimenta SD 0.31 11.75 0.83 2.75 12.72 0.83 2.75 i² = 136. (P < 0.0 i² = 136. (P < 0.0 Not apol i² = 136. Not apol i² = 136. i³ = 136. i³ = 136. i³ = 136. i⁴ = 136.<td>01) bble 1 Total Total 43 60 49 50 49 50 49 50 49 50 49 50 49 50 49 50 49 50 49 50 247 02, df 0001) icable al Total 43 60 60 49 50 247 02, df 00001) icable 43 43 50 60 60 60 60 60 60 60 60 60 6</td><td>C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P - C Mean 27.13 62.15 27.55 48.84 81.07 47.2 31.21 30.72 31.21 30.72 43.17 16.53 36.541</td><td>Control SD 0.28 10.66 14.33 1.25 3.25 c 0.0000 Control SD 2.05 8.03 4.02 7.41 7.27 5.8 5.39 6.85 5.39 7.88 2.81 8.29 7.88 2.81 8.39 7.88 2.81 8.39 7.88 2.81 8.39 7.88 2.81 8.39 7.88 2.81 7.88 7.89 7.888 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.897 7.888 7.888 7.888 7.897 7.888 7.888 7.888 7.888 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.897 7.897 7.888 7.897 7.8887 7.897 7.897 7.897 7.888 7.8</td><td>Total 43 60 49 50 45 247 711); ² = 247 701); ² = 247 701); ² = 247 701); ² = 43 40 60 50 60 60 34 49 47 48 49 45 50 60 31</td><td>Weight 28.2% 11.5% 27.8% 27.8% 27.8% 27.8% 27.7.8% 27.7.8% 27.7.8% 7.9% 7.9% 7.1% 7.2% 7.1% 7.2% 7.1% 7.2% 7.1%</td><td>Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.38 [-17.96, -12.80] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.96, -19.72] -4.17 [-5.28, -13.11] -15.25 [-18.28, -12.23]</td><td>-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl </td>	01) bble 1 Total Total 43 60 49 50 49 50 49 50 49 50 49 50 49 50 49 50 49 50 49 50 247 02, df 0001) icable al Total 43 60 60 49 50 247 02, df 00001) icable 43 43 50 60 60 60 60 60 60 60 60 60 6	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P - C Mean 27.13 62.15 27.55 48.84 81.07 47.2 31.21 30.72 31.21 30.72 43.17 16.53 36.541	Control SD 0.28 10.66 14.33 1.25 3.25 c 0.0000 Control SD 2.05 8.03 4.02 7.41 7.27 5.8 5.39 6.85 5.39 7.88 2.81 8.29 7.88 2.81 8.39 7.88 2.81 8.39 7.88 2.81 8.39 7.88 2.81 8.39 7.88 2.81 7.88 7.89 7.888 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.888 7.897 7.888 7.897 7.888 7.888 7.888 7.897 7.888 7.888 7.888 7.888 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.888 7.897 7.897 7.897 7.888 7.897 7.8887 7.897 7.897 7.897 7.888 7.8	Total 43 60 49 50 45 247 711); ² = 247 701); ² = 247 701); ² = 247 701); ² = 43 40 60 50 60 60 34 49 47 48 49 45 50 60 31	Weight 28.2% 11.5% 27.8% 27.8% 27.8% 27.8% 27.7.8% 27.7.8% 27.7.8% 7.9% 7.9% 7.1% 7.2% 7.1% 7.2% 7.1% 7.2% 7.1%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.38 [-17.96, -12.80] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.96, -19.72] -4.17 [-5.28, -13.11] -15.25 [-18.28, -12.23]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for subaroup diffe D Study or Subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Wang J.T.2016 Wang J.Z.2018 Wang P.L.2020 Wen B.2017 Yang X.Q.2021 Yin P.2021 Yuan X.H.2020 Zhang G.R.2020	Z = 5.59 (F rences: No Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47; Ch	 < 0.000 t applied applied applied	01) bble 1 Total 7 7 7 7 7 7 7 7	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P • C Mean 27.13 62.15 27.55 48.84 81.07 47.2 31.21 30.72 97.35 81.07 47.2 31.21 16.53 85.41 1.33	0.28 0.28 10.66 3.25 3.25 4.0000 2.05 2.05 2.05 2.05 2.05 2.05 2.05	Total 43 60 49 50 247 217 217); ² = 247 247 247 247 247 247 247 247 247 247	Weight 28.2% 11.5% 27.8% 27.8% 24.7% 97% 100.0% 97% Weight 7.4% 7.4% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.3%	Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] 4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.27 [-18.44, -12.10] -15.27 [-18.44, -12.10] -15.27 [-18.44, -12.10] -15.27 [-78.44, -12.10] -15.27 [-78.44, -12.10] -15.27 [-78.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-72.7, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.96, -19.72] -4.17 [-5.23, -3.11] -15.25 [-18.28, -12.22] -0.38 [-0.47, -0.29]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for suboroup diffe C Study or Subgroup. Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Tan G.Z.2020 Wang F.T.2016 Wang J.X.2018 Wang P.L.2020 Wen B.2017 Yang X.Q.2021 Yin P.2021 Yuan X.H.2020 Zhao J.H.2020	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 erences: 1 Expe Mean 18 45.33 21.7 33.46 65.8 23.5 20.2 25.43 79.22 20.33 12.36 70.16 0.95 75.5	 < 0.000 t anolica sD 0.31 11.75 0.83 2.75 i² = 136. (P < 0.0 i² = 136. (P < 0.0 via anol e² = 136. (P < 0.0 via anol via anol e² = 136. (P < 0.0 via anol e² = 136. e²	01) bble 1 Total 7 7 7 7 7 7 7 7	C Mean 4.57 62.46 4.93 32.95 = 4 (P < C Mean 27.13 62.15 48.84 81.07 7.73 31.21 30.72 97.35 48.84 48.10,72 97.35 43.17 1.6.53 85.41 1.33 97.58	Control 0.28 10.66 14.33 1.25 3.25 c 0.0000 Control SD 2.05 8.03 4.02 4.02 Control SD 2.05 8.03 4.02 4.02 Control SD 2.05 8.03 4.02 Control SD 2.05 8.03 4.02 Control SD 2.05 8.03 4.03 4.03 Control SD SD Control SD SD Control SD SD SD SD SD SD SD SD SD SD	Total 43 60 49 50 45 247 247 201); ² = 247 247 247 247 247 247 247 247 247 247	Weight 28.2% 11.5% 7.8% 27.8% 27.8% 27.8% 27.8% 27.8% 97% 100.0% 97% 100.0% 97% 100.0% 97% 7.4% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, 0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.38 [-17.96, -12.80] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.53, -10.73] -4.17 [-5.23, -3.11] -5.25 [-18.28, -12.22] -0.38 [-0.47, -0.29] -22.86 [-6.31, -18.86]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup. Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Yang X.Q.2021 Yin P.2021 Yuan X.H.2020 Zhang G.R.2020 Zhang G.R.2020 Zhang G.R.2020 Zhang G.R.2020 Zhao J.H.2020	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.17 =	 < 0.000 t aoolica rimenta SD 0.31 11.75 2.75 2.75 2.75 2.76 2.76 2.77 7.26 3.39 2.77 7.26 3.39 2.77 7.26 3.39 2.77 2.27 7.26 3.39 2.77 2.27 2.27 7.26 3.39 2.27 2.48 5.21 0.24 6.28 	01) bble al Total 43 60 49 50 50 247 02, df 00001) icable al 43 41 50 60 0001) icable al 43 41 50 60 34 43 41 50 60 34 9 45 50 62 32 49	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P - C Mean 27.13 62.15 27.55 48.84 81.07 47.2 97.35 43.17 16.53 85.41 1.33 97.58	Sontrol 0.28 10.66 10.32 10.66 11.433 1.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.25 3.20 2.050 8.03 4.02 2.055 8.03 4.02 2.055 8.03 4.02 2.055 8.03 4.02 2.055 8.03 4.02 2.055 8.03 9.000 10.100 10.100 10.100 10.100 10.100 10.100 10.100 10.100	Total 43 60 49 50 247 701); ² = 247 701); ² = 247 701); ² = 247 247 247 247 247 247 247 34 40 50 60 34 45 550 31 49 45 55 50 31 49 50 620	Weight 28.2% 11.5% 27.8% 27.8% 27.8% 27.8% 27.8% 27.7.8% 7.8% 7.9% 7.9% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.38 [-7.79, 6, -12.80] -15.29 [-7.27, -2.86] -15.29 [-7.72, -2.86] -18.13 [-25.38, -10.43] -22.84 [-25.96, -19.72] -4.17 [-5.23, -3.11] -15.25 [-18.28, -12.22] -0.38 [-0.47, -0.29] -22.08 [-25.31, -18.85] -13.08 [-0.47, -0.29] -22.08 [-25.31, -18.85] -13.08 [-0.47, -0.29]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for subaroup diffe C Study or Subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Wang J.T.2016 Wang J.T.2018 Wang P.L.2020 Wang P.L.2020 Wang P.L.2020 Zhang G.R.2020 Zhang G.R.2020 Zhang G.R.2020 Subtotal (95% CI)	Z = 5.59 (F rences: No Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.47; Ch	 < 0.000 t applied spinore spinore	01) bble al Total 43 60 49 50 45 247 02, df 0001) 247 02, df 0001) 247 02, df 0001) 1 247 02, df 0001) 247 02, df 0001) 247 50 02, df 0001) 247 50 02, df 0001) 247 50 02, df 0001) 247 50 02, df 0001) 247 50 02, df 0001) 247 50 02, df 0001) 247 50 02, df 0001) 247 50 02, df 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 0001) 247 50 60 60 0001 247 50 60 60 60 34 248 50 60 60 60 60 60 60 60 60 60 6	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P • C Mean 27.13 62.55 48.84 81.07 47.2 31.21 30.72 97.35 81.07 47.2 31.21 16.53 85.41 1.33 97.58 df = 13	Control SD 0.28 10.66 3.25 3.25 4.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.0000 2.05 5.00000 5.0000 5.0000 5.0000 5.0000 5.00000 5.00000 5.00000 5.00000 5.00000 5.0000000 5.00000000	Total 43 60 49 50 247 701); ² = 247 701); ² = 247 247 247 247 247 247 34 43 40 50 60 34 429 45 50 31 49 45 50 31 49 9 50 620 00001)	Weight 28.2% 11.5% 27.8% 27.8% 24.7% 100.0% 97% 100.0% 7.4% 7.4% 7.4% 7.2% 7.4% 7.2% 7.4% 7.2% 7.4% 7.	Mean Difference IV. Random, 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] 4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.27 [-18.44, -12.10] -15.27 [-18.44, -12.10] -15.27 [-18.44, -12.10] -15.27 [-78.44, -12.10] -15.27 [-78.44, -12.10] -15.27 [-78.44, -12.10] -23.70 [-26.03, -12.37] -11.01 [-27.0, -332] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.96, -19.72] -0.38 [-0.47, -0.29] -22.08 [-25.31, -18.85] -13.08 [-17.18, -8.98]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for subaroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Wang J.T.2016 Wang J.T.2018 Wang P.L.2020 Wang J.Z.2018 Wang P.L.2020 Zhang G.R.2020 Zhang G.R.2020 Zhang G.R.2020 Subtotal (95% CI) Heterogeneity: Tau ² =	Z = 5.59 (F rences: No Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 = 2.87; Ch : Z = 5.87; Ch :	 < 0.000 t applies erimenta SD 0.31 11.75 12.72 0.83 2.75 I² = 136. (P < 0.0 Vot appl F 136. (P < 0.0 vot appl r 7.26 3.39 2.97 2.48 5.21 2.0.43 7.19 2.57 6.21 2.0.44 6.98 th² = 17 (P < 0.0 (P < 0.0 	01) bble al Total 43 60 49 50 45 247 002, df 0001) 247 02, df 0001) 247 02, df 0001) 247 43 43 41 50 60 60 49 95 48 49 49 43 43 43 43 43 45 50 45 52 47 50 60 45 52 47 50 50 45 52 47 50 50 50 50 50 50 50 50 50 50	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P • C Mean 27.13 77.55 48.84 81.07 47.2 31.21 30.72 97.35 85.41 1.33 97.58 df = 13	0.28 10.66 31.25 3.25 < 0.0000 € 0.00000 € 0.00000 € 0.00000 € 0.0000 € 0.00000 € 0.0000000 € 0.00000 € 0.00000 € 0.00000 € 0.0000000000	Total 43 60 49 50 247 701); ² = 247 701); ² = 247 247 247 247 247 247 247 247 247 34 43 40 50 60 34 45 50 31 49 45 50 620 000001)	Weight 28.2% 11.5% 27.8% 27.8% 24.7% 100.0% 97% Weight 7.4% 7.4% 7.4% 7.4% 7.2% 7.3% 7.4% 7.2% 7.4% 7.2% 7.4% 7.4% 7.4% 7.4% 7.4% 7.2% 7.4% 7.2% 7.4% 7.4% 7.4% 7.4% 7.2% 7.4% 7.4% 7.4% 7.2% 7.4% 7.2% 7.4% 7.2% 7.4% 7.2% 7.4% 7.2% 7.4% 7.2% 7.4% 7.2% 7.4% 7.2% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.2% 7.4% 7.4% 7.4% 7.4% 7.2% 7.1% 7.4% 7.4% 7.4% 7.4% 7.2% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.2% 7.4% 7.4% 7.4% 7.4% 7.2% 7.4% 7.	Mean Difference IV. Random, 95% Cl -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] 4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random, 95% Cl -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.27 [-18.44, -12.10] -15.27 [-18.44, -12.10] -15.27 [-18.44, -12.10] -15.27 [-78.44, -12.10] -15.27 [-78.44, -12.10] -15.27 [-78.44, -12.10] -23.70 [-26.03, -12.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.96, -19.72] -0.38 [-0.47, -0.29] -22.08 [-25.31, -18.85] -13.08 [-17.18, -8.98]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Test for overall effect: Z Test for suboroup differ C Study or Subgroup Chen B.Q. 2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect Test for suboroup diffe D Study or Subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Sun J.X.2020 Tan G.Z.2020 Wang F.I.2016 Wang Y.L.2018 Wang P.L.2020 Wen B.2017 Yang X.Q.2021 Yuan X.H.2020 Zhao J.H.2020 Zhao J.H.2020 Zhao J.H.2020 Zhao J.H.2020 Zhao J.H.2020 Subtotal (95% CI)	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 erences: 1 Expe Mean 18 45.33 21.7 33.46 65.8 23.5 20.2 26.43 79.22 20.33 12.36 70.16 0.95 75.5 = 58.97; CC : Z = 6.25	 < 0.000 t anolica SD 0.31 11.75 0.83 2.75 i² = 136. (P < 0.0 i² = 136. (P < 0.0 vol anol vol an	01) bble al Total 43 60 49 50 45 247 02, df 0001) icable al Total 43 43 49 45 50 0001) icable 43 44 43 40 247 702, df 00001) 60 80 45 50 247 702, df 60 80 80 80 80 80 80 80 80 80 8	C Mean 4.57 62.46 4.93 32.95 = 4 (P < 221.62 = 4 (P < C Mean 27.13 62.15 48.84 81.07 47.2 31.21 30.72 97.35 43.17 1.6.53 85.41 1.30.72 97.55 43.17 1.6.53 85.41 1.30.72 97.55 43.17 4.57 43.17 4.57 4.57 4.57 4.57 4.57 4.57 4.57 4.5	Control 0.28 10.66 14.33 1.25 3.25 c 0.0000 Control SD 2.05 8.03 7.41 7.27 7.8 5.39 6.85 18.39 7.88 2.81 6.05 0.19 8.58 (P < 0.	Total 43 60 49 50 45 247 701); l ² = 247 701); l ² = 247 70000000000000000000000000000000000	Weight 28.2% 11.5% 7.8% 27.8% 27.8% 97% 100.0% 97% 100.0% 97% 100.0% 7.4% 7.2% 7.3% 7.2% 7.3% 7.2% 7.3% 7.2% 7.1% 7.4% 7.1% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4% 7.4	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.96, -17.22] -0.38 [-0.47, -0.29] -22.08 [-25.31, -18.88] -13.08 [-17.18, -8.98]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
Test for overall effect: Z Test for suboroup differ C Study or Subgroup Chen B.Q.2020 Sun J.X.2020 Wen B.2017 Yin P.2021 Zhao J.H.2020 Subtatal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup Chen B.Q.2020 Liu Y.H.2019 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Shi A.P.2017 Yang X.Q.202 Tan G.Z.2020 Wang F.I.2016 Wang J.X.2018 Wang P.L.2020 Zhao J.H.2020 Zhao J.(5% CI) Heterogeneity: Tau ² =	Z = 5.59 (F rences: No Expe Mean 2.63 40.17 16.51 3.91 28.36 = 2.87; Ch : Z = 5.47 erences: I Exp Mean 18 45.33 21.7 33.46 65.8 23.5 20.2 25.43 79.22 20.33 12.36 65.8 23.5 20.2 25.43 79.55 = 58.97; C : Z = 6.25	 < 0.000 t aoolica t aoolica t aoolica t aoolica t aoolica 0.31 11.75 2.75 12.72 0.83 2.75 i² = 136.6 (P < 0.0 i² = 136.6 (P < 0.0 i² = 136.6 (P < 0.0 i³ = 136.6 (P < 0.0 i⁴ = 17.0 (P < 0.24 6.98 hi² = 17.0 (P < 0.24 hi² = 17.1 	01) ble al Total 43 60 49 50 45 247 02, df 0001) icable al Total 43 43 45 00, df 0001) icable 43 43 43 43 43 43 43 43 43 43	C Mean 4.57 62.46 21.62 4.93 32.95 = 4 (P - C Mean 27.13 62.15 7.55 48.84 81.07 47.2 31.21 30.72 31.21 30.75 48.541 1.33 97.58 df = 13 df = 13	Control SD 0.28 10.66 14.33 1.25 3.25 < 0.0000 Control SD 2.05 8.03 4.02 2.05 8.03 4.02 7.41 7.27 7.88 5.39 6.85 8.39 7.88 2.81 8.59 8.019 8.58 (P < 0.	Total 43 60 49 50 247 701); ² = 247 701); ² = 247 700]; ² = 2 700]; ² = 2 7	Weight 28.2% 11.5% 27.8% 27.8% 27.8% 27.8% 97% 97% 100.0% 7.4% 7.1% 7.4% 7.1% 7.2% 7.1% 7.2% 7.1% 7.2% 7.1% 7.2% 7.2% 7.2% 7.3% 7.2% 7.3% 7.2% 7.3% 7.2% 7.3% 7.2% 7.3% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.4% 7.2% 7.2% 7.4%	Mean Difference IV. Random. 95% CI -1.94 [-2.06, -1.82] -22.29 [-26.30, -18.28] -5.11 [-10.48, 0.26] -1.02 [-1.44, -0.60] -4.59 [-5.83, -3.35] -4.92 [-6.69, -3.16] -4.92 [-6.69, -3.16] Mean Difference IV. Random. 95% CI -9.13 [-10.04, -8.22] -16.82 [-20.16, -13.48] -5.85 [-7.31, -4.39] -15.38 [-17.96, -12.80] -15.27 [-18.44, -12.10] -23.70 [-26.03, -21.37] -11.01 [-12.70, -9.32] -5.29 [-7.72, -2.86] -18.13 [-25.83, -10.43] -22.84 [-25.96, -19.72] -4.17 [-5.23, -3.11] -15.25 [-18.28, -12.22] -0.38 [-0.47, -0.29] -22.08 [-25.31, -18.85] -13.08 [-17.18, -8.98]	-200 -100 0 100 200 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -50 -25 0 25 50 Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl

FIGURE 10

Forest plot displaying the results of the Meta-analysis for inflammation-related cytokines and protein. The results of (A) IL-6; (B) IL-8; (C) IL-1 β ; (D) TNF- α ; (E) CRP; (F) IL-10.



mild to severe, and scores 0, 1, 2, and 3, respectively. The higher the score, the more serious the symptoms. Three studies evaluated the total symptom score. The random-effect Meta-analysis suggested that the difference between the two groups was statistically significant (n = 257, I² = 55%; MD = -3.40; 95% CI [-4.02, -2.78], p < 0.00001) (Figure 12B). The sensitivity analysis showed that the study reported by Zhang G.R was the source of heterogeneity because excluding this study resulted in an I² = 0%.

Furthermore, the investigation also evaluated the individual symptom scores of abdominal pain, diarrhea, urgency, pus and blood stool, and burning anal pain. Although the heterogeneity was high, it indicated that rhubarb-based therapy could improve UC symptoms to some extent (Supplementary Figures S2, S3).

Publication bias

Publication bias was assessed by funnel plots for the included 29 studies which reported the primary outcome. The funnel plots were asymmetrical, suggesting a possible publication bias (Supplementary Figure S4).

Discussion

UC is one of the modern intractable diseases regarded by the World Health Organization (Pedersen et al., 2014). Longstanding UC bears a high risk of developing colitis-associated colon cancer (Ekbom et al., 1990). Recently, 5-ASA is the most widely used first-line drug which is obviously beneficial to mild to moderate UC but limited for severe UC (Ko et al., 2019). As the supplementary drugs, corticosteroids and immunosuppressive drugs often required by the severe patients. However, the longterm application of corticosteroids and immunosuppressive drugs always brings about significant side effects (Ko et al., 2019; Kobayashi et al., 2020). What's more, surgery, as an optional therapy for sever UC, is mentioned to delay the progression of the disease, but the prognosis of surgery still carries the risk of colon cancer (Windsor et al., 2013). Basically, TCM has attracted increasing attention for the potential effective and safe treatment.

TFTM is a typical therapeutic method in TCM. According to TCM theory, TFTM mainly refers to those medicinals with purgative method. There are many representative medicinals of TFTM, such as *Citrus* × *aurantium* L. [Rutaceae; *Citrus* × *aurantium* young fruit], *Magnolia officinalis* Rehder & E.H.Wilson [Magnoliaceae; *Magnolia officinalis* bark], *Aloe vera* (L.) Burm.f. [Asphodelaceae; Aloe vera sap], *Cannabis sativa* L. [Cannabaceae; *Cannabis sativa* ripe fruit], which have been shown to treat experimental UC mainly by antiinflammation and modulating intestinal flora (He et al., 2018; Naini et al., 2021; Eom et al., 2022; Xie et al., 2022). But compared with those medicinals, rhubarb is the most representative, and it is also the most widely used in the treatment of gastrointestinal diseases (Zhang et al., 2021). Rhubarb has been validated to treat UC through immunosuppression, anti-inflammation, intestinal

Study or Subara	Expe	te	Total	Event	Tetel	Main	ht 14	L Eivad 0E% C					
Study or Subgroup	(Tetel)	ts	lotal	Events	Total	vveig	nt IVI-	H, FIXED, 95% C		MI-H, FD	(ed, 95% CI		
9.1.1 Advers events	(Total)		10	-	10	10.0	0/						
Chen B.Q.2020		4	43	5	43	10.6	%	0.80 [0.23, 2.78]					
Sheng R.D.2017		1	48	2	48	4.3	%	0.50 [0.05, 5.33]				_	
Wang H.S.2017		2	32	1	32	2.1	% 2	2.00 [0.19, 20.97]		-			
Wang J.X.2018		8	48	4	47	8.6	%	1.96 [0.63, 6.07]		·	-		
Yin P.2021		2	50	3	50	6.4	%	0.67 [0.12, 3.82]					
Zhang H.Y.2016		3	40	13	260	27.6	% 9/	0.23[0.07, 0.75]					
Subtotal (95% CI)		0	201	20	200	59.0	70	0.71 [0.41, 1.23]			1		
Hotorogonoitu: Chi2 =	7 47 df	- 5 (D = 0.1	20	220/								
Test for overall offect:	7 - 12	- 5 (i 2 /D -	- 0.22	9), 1	5570								
rescior overall effect.	2 - 1.2	3 (F -	- 0.22)										
9.1.2 Advers events	(2-5 we	eks)											
Sheng R.D.2017		1	48	2	48	4.3	%	0.50 [0.05, 5.33]			+		
Wang H.S.2017		2	32	1	32	2.1	% 2	.00 [0.19, 20.97]			+ • • • •	_	
Subtotal (95% CI)		_	80		80	6.4	%	1.00 [0.21, 4.82]					
Total events		3		3									
Heterogeneity: Chi ² =	0.66, df	= 1 (P = 0.4	2); $I^2 = ($	0%								
Test for overall effect:	Z = 0.0	0 (P =	= 1.00)	<i>,</i> .									
			,										
9.1.3 Advers events	(6-9 we	eks)											
Yin P.2021		2	50	3	50	6.4	%	0.67 [0.12, 3.82]			<u> </u>		
Zhang H.Y.2016		3	40	13	40	27.6	%	0.23 [0.07, 0.75]			8		
Subtotal (95% CI)			90		90	34.0	1%	0.31 [0.12, 0.81]		•	·		
Total events		5		16									
Heterogeneity: Chi ² =	0.98, df	= 1 (P = 0.3	2); I ² = (0%								
Test for overall effect:	Z = 2.4	0 (P =	= 0.02)										
T-4-1 (05% OI)			404		400	400.0	0/						
Total (95% CI)			431		430	100.0	%	0.59 [0.38, 0.93]		•			
Total events	2	28	(5 0	47	0004				-	1	1		
Heterogeneity: Chi ² =	11.58, 0	f = 9	(P = 0.	24); I ² =	22%				0.002	0.1	1 10		500
lest for overall effect:	Z = 2.2	9 (P =	= 0.02)	11 0		00) 12	00 50/		F	avours [experimental]	Favours [co	ntrol]	
lest for subdroub diffe	erences		= 2.58	$a_1 = 20$	P = 0.2	281. 1- =	22.5%						
5	Expe	rimer	ntal	C	ontrol			Mean Difference	е	Mea	n Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total \	Neight	IV. Random, 95	% CI	IV. Ra	ndom. 95% C		
Li Z.W.2021	7.01	1.03	43	10.14	1.23	43	45.4%	-3.13 [-3.61, -2	.65]	-			
Tian G.D.2017	5.19	1.4	38	8.38	1.46	35	36.7%	-3.19 [-3.85, -2	.53]				
Zhang G.R.2020	8.01	2.43	49	12.55	3.69	49	17.9%	-4.54 [-5.78, -3	.30]				
Total (95% CI)			120			127	100 00/	3 40 [4 02 3	791	•			
Heterogeneity: Tau ² -	0 16. Ch	i ² = A	13 df -	- 2 (P -	0 111-12	2 = 550/	100.070	-3.40 [-4.02, -2	., 01 -	· · · ·		í	
Test for overall effect.	7 = 10.7	6 (P <	0.0000)1)	0. TTJ, F	- 55%				-4 -2	0 2	4	
reactor overall effect.	_ = 10.7		0.0000	,						Favours [experiment	al] Favours [control]	

flora regulation, and endotoxin inhibition (Miao et al., 2018; Xiang et al., 2020). The potential clinical value is necessary to be assessed with evidence-based methods.

In this study, 30 RCTs involving 2,421 patients were included in the Meta-analysis. The results reveal that the clinical efficiency of the rhubarb-based treatment group was significantly higher than that of the control group. Furthermore, a comparable number of RCTs evaluated the use of rhubarb-based medicinal formulas alone, supporting its effectiveness explicitly. 5-ASA and SASP belong to the 5-ASA class of medications, both of whom are the mainstay of treatment of mild to moderate UC (Ko et al., 2019). Long-term use of 5-ASA reduces the risk of relapse and cancer in UC patients, making it an indispensable drug for UC treatment (Kim, 2018; Wang et al., 2018). Nevertheless, for patients with severe UC, the therapeutic effect of 5-ASA is limited. Of note, the rhubarb-based medicinal formulas combined with 5-ASA or SASP were more effective than the use of 5-ASA or SASP alone, indicating that the synergistic effect of rhubarb is remarkable. The result suggests that rhubarb-based therapy might benefit patients who did not respond or could not tolerate 5-ASA treatment, thus avoiding the apparent side effects associated with the use of corticosteroid and thiopurine.

Further, patients with proctitis are always treated with 5-ASA suppositories, which target the site of inflammation directly and seem to be more effective than oral 5-ASA. In left-sided colitis, 5-ASA should be administered as an enema instead of a suppository in order to reach the splenic flexure (Gionchetti et al., 1998; Choi et al., 2015; Reinisch et al., 2015). As with 5-ASA, different administration routes of medicinals can directly

impact the efficiency rate. This study found that the rhubarbbased therapy was clinically more effective when administered either orally or by enema. What's more, it was meaningful to add it to any course of treatment.

The symptoms of UC mainly include abdominal pain, vomiting, diarrhea, and rectal bleeding, which seriously affect life quality of patients. Studies have shown that rhubarb could exert various pharmacological effects in the gastrointestinal tract (Xiang et al., 2020). The combination of anthraquinones in rhubarb played a role in inducing diarrhea, while tannic acid could inhibit the purgative effect of anthraquinones and thereby induced antidiarrheal effects (Qin et al., 2011; Cao et al., 2017). Through the review of TCM symptoms integral, it was found that rhubarb-based therapy could significantly improve the symptoms of abdominal pain, diarrhea, urgency, pus and blood stool, and burning anal pain in UC patients, and ultimately had a positive impact on the symptomology and quality of life of patients. Also, Mayo and Geboes scores revealed that the rhubarb-based therapy effectively improved the disease activity and the histological status of UC. And the result of the recurrence rate indicated that the disease process was effectively controlled and recurrence was delayed.

The hypercoagulable state is an essential part of the pathological mechanism of UC (Danese et al., 2007). Meanwhile, cytokines regulated by multiple inflammatory signaling pathways are a central component of chronic inflammation (Ungaro et al., 2017; Kobayashi et al., 2020). The imbalance of cytokines have been reported in patients with active IBD, including TNF-a, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17, IL-23, and TGF- β (Neurath, 2014). The simultaneous activation of coagulation and inflammation in colon injury foci are identified as the preservation mechanisms for repairing damaged areas (Lipinski et al., 2011). At the same time, the crosstalk between coagulation and inflammation has raised concerns. Inflammatory stimuli can trigger the coagulation cascade while coagulation also regulates inflammatory signaling pathways (de Maat et al., 2014). PLT, a principal coagulation marker, constitutes a crucial link between inflammation and coagulation, creating a vicious circle in which participating parameters conserve and propagate each other (Yoshida and Granger, 2009). PLT is activated at inflammatory sites and excrete large amounts of proinflammatory substances located in its intracellular granules (Smyth et al., 2009). The results of this Meta-analysis showed that rhubarb-based therapy significantly reduced PLT, TNF-a, IL-1β, IL-6, IL-1β, and CRP, and increased IL-10, as well as had some effects on PT and FIB. Thus, rhubarb-based therapy can improve the hypercoagulable state of UC and suppress intestinal inflammation. An important point to note was the highly heterogeneous results in the analysis of all six inflammatory cytokines, likely caused by the use of different measurement devices and measurement units in the original study. The results of this Meta-analysis should be interpreted with caution.

Moreover, rhubarb has a powerful blood-activating effect. It is a common medicinal for blood stasis syndrome (Liu et al., 2013; Gao et al., 2020). Studies have reported that rhubarb had significant anti-PLT effects and PLTs were the main effector cells of rhubarb in the promoting blood circulation to remove blood stasis method (Seo et al., 2012; Gao et al., 2020). It could significantly improve whole blood viscosity and plasma viscosity in high molecular dextran-induced hyperviscosity syndrome model in rats, and reduce the levels of PLT activation markers Plasma P-selectin and thromboxane (Gao et al., 2020). Additionally, rhubarb significantly affected local microcirculation, reducing local pancreatic blood flow in the pancreas and improving pancreatic microcirculation (Zhao et al., 2004). It protected the intestinal mucosal capillary endothelial cells and increased the number of functional capillaries, promoted blood flow through intestinal mucosal capillaries, reduced thrombogenesis, and improved the blood and oxygen supply of the intestinal mucosa (Cui et al., 2014; Cui et al., 2016). Derivatives of rhubarb also had anti-PLT aggregation effects, among which, chrysophanol-8-O-glucoside, an anthraquinone derivative isolated from rhubarb, was found to have the most potent inhibitory effect on collagen- and thrombin-induced PLT aggregation and was mightier than the positive drug aspirin. Specifically, it was found to inhibit PLT aggregation in vitro and ex vivo and prolong bleeding time and activate partial thromboplastin time (Seo et al., 2012). In addition, the mixture of five monomeric compounds of rhubarb could antagonize the matrix Metalloproteinase-9-induced human umbilical vein endothelial cell (HUVEC) monolayer permeability by promoting HUVEC proliferation and endothelial-cadherin reducing extracellular vascular concentrations (Cui et al., 2016). In addition, although the bioavailability of rhubarb and its monomers may be low, it seems that we can consider combining them with nanosystems (Zhang et al., 2022a; Zhang et al., 2022b). In conclusion, based on the characteristics of coagulation abnormalities associated with UC and the exact clinical efficacy and experimental evidence of rhubarb in UC, the rhubarb's coagulation-regulation effect is worthy of further investigation.

The incidence of adverse events is an important indicator to evaluate the safety of a treatment strategy. Several studies have reported that 5-ASA and SASP may cause adverse events such as fever, nausea, dizziness, and diarrhea (Sehgal et al., 2018). In five of the six studies that reported adverse events, the control drug was 5-ASA class. Although a number of studies have reported that medicinals could reduce the incidence of adverse time when used in combination with 5-ASA (Chen et al., 2020), the results showed that rhubarb-based therapy did not significantly improve these side effects. For the subgroup analysis, the incidence of side effects was not statistically different at 2–5 weeks of treatment while showed a significant difference at 6–9 weeks. In addition, although rhubarb has the side effect of purgative, the results of our analysis showed that



rhubarb-based therapy did not exhibit significant side effects. This means it has a high safety profile in clinical use. This article concludes that the rhubarb-based therapy can improve clinical efficacy, improve clinical symptoms, and reduce recurrence rate in UC. It can also meliorate the hypercoagulable and inflammatory status. In addition, subgroup analysis suggests that early intervention of rhubarb-based therapy will obtain better effects. There is a synergistic effect of the rhubarb-based medicinal formulas with 5-ASA or SASP. Nevertheless, the mechanism of the synergistic effect has not been revealed completely that require more investigations.

To determine the characteristics and patterns of specific medicinals used in the rhubarb-based medicinal formulas, this investigation analyzed the medicinals used in each original study (Supplementary Figure S5). The high-frequency medicinals (frequency \geq 14) were rhubarb, *Glycyrrhiza glabra* L. [gān cǎo; Fabaceae; *Glycyrrhiza glabra* root and rhizome], *Coptis chinensis* Franch. [huáng lián; Ranunculaceae; *Coptis chinensis* rhizome], *Scutellaria baicalensis* Georgi [huáng qín; Lamiaceae; *Scutellaria baicalensis* root], *Angelica sinensis*(Oliv.)Diels [dāng guī; Apiaceae; *Angelica sinensis* root], *Paeonia lactiflora* Pall. [bái sháo; Paeoniaceae; *Paeonia lactiflora* root], and *Dolomiaea costus*

(Falc.) Kasana & A.K.Pandey [mù xiāng; Asteraceae; Dolomiaea costus root], Areca catechu L. [bing láng; Arecaceae; Areca catechu seed], and Neolitsea cassia (L.) Kosterm. [ròu guì; Lauraceae; Neolitsea cassia bark], with frequencies of 30, 23, 22, 20, 18, 17, 17, 15, 14, respectively. In order to determine the characteristics and patterns of specific medicinals used in the included studies, an association analysis was performed (Figure 13). According to the frequency, correlation, and confidence, dà huáng, huáng lián, and huáng qín formed the major group of medicinals that make up the classic formula Xiexin decoction (XXD). XXD has been recorded since the Han Dynasty (early third century), in Essentials from the Golden Cabinet (Jin Guì Yào Lüè), which has been commonly used to treat patients with chronic gastritis, peptic ulcer, acute dysentery, UC, or other dysfunctions of the gastrointestinal tract in the clinic. According to the TCM, dà huáng, huáng lián, and huáng qín are all heat-clearing and damp-drying medicinals (Teng et al., 2019). And the dampness syndrome and large intestine dampheat syndrome are the most common syndrome of UC patients (Zhang et al., 2019). XXD can clear heat and dry dampness, which is often applied to treat UC patients effectively (Jia et al., 2021). Research has shown that XXD could promote the recovery of colitis and inhibit the colonic inflammation damage in UC rats by reducing the level of MPO and the expression of TNF- α and NF-ĸB, and increasing the production of IL-10 in colon tissues (Han et al., 2013). The pattern analysis provides a more precise decoction strategy for the clinical application of rhubarb-based medicinal formulas, which raises an optional protocol for UC patients.

Limitation

As the available studies only provided short-term assessments of 2-13 weeks, this investigation is not able to assess the long-term efficacy and safety of the rhubarb-based therapy for UC. Second, the lack of a large number of highquality, multicenter standard RCTs and the lack of description of random assignment procedures and blinding in some studies may also affect he quality of this Meta-analysis. Furthermore, even though this paper used sensitivity analysis to reduce the effect of different measurement units and methods on the results, the outcomes of inflammatory cytokines, and TCM symptoms integral to this Meta-analysis still showed a high level of heterogeneity. Hence, the results of the analysis should be identified carefully. It would be beneficial if more research would be conducted to promote the rational application of rhubarb-based therapy for UC. In addition, the other representative medicinals of TFTM are widely used in clinical practice, but there are few studies related to UC, and their recognition is not as high as rhubarb in the TCM industry. This makes them not the object of our Meta-analysis. But their value also deserves more exploration in the future.

Conclusion

In this article, rhubarb-based therapy is effective in improving UC, especially in terms of relieving clinical symptoms, reducing recurrences, and improving hypercoagulable states and inflammation. Furthermore, the rhubarb-based medicinal formulas combined with 5-ASA or SASP are more effective than 5-ASA or SASP alone. And rhubarb-based therapy is recommend use within 1-13 weeks or 3 months via administered orally or by enema, which is contributes to ensure the curative effect and avoid its side effects. As an important case of TFTM, rhubarb-based therapy provides evidence for the practical application of TFTM, and also provides ideas for further development and exploration.

Data availability statement

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

Author contributions

YL and ZY contributed to the conception and design of the study. ZY, YH, and HH searched the database separately. MW, YL, QZ, and CZ performed the studies selection separately. LC, YL, LL, QS, and HH carried out the statistical analysis. YL, ZY, and HQ wrote the first draft of the manuscript. QY, KQ, YH, and XL were responsible for technical guidance and quality control of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version. All divergences were resolved through discussion among all authors.

Funding

This research was funded by the National Natural Science Foundation of China (81973742) and National Traditional Chinese Medicine Characteristic Technology Inheritance Talent Training Project ((2019) No. 43).

Acknowledgments

The authors would like to express their sincere thanks to all the people who participated in the research and partner units.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

References

Cao, Y. J., Pu, Z. J., Tang, Y. P., Shen, J., Chen, Y. Y., Kang, A., et al. (2017). Advances in bio-active constituents, pharmacology and clinical applications of rhubarb. *Chin. Med.* 12, 36. doi:10.1186/s13020-017-0158-5

Chen, B. Q., and Li, Y. (2020). Effect of dachaihu decoction combined with sulfasalazine enteric-coated tablets in the treatment of ulcerative colitis. *Med. Innovation China* 17 (15). doi:10.3969/j.issn.1674-4985.2020.15.017

Chen, M., Ding, Y., and Tong, Z. (2020). Efficacy and safety of Sophora flavescens (kushen) based traditional Chinese medicine in the treatment of ulcerative colitis: Clinical evidence and potential mechanisms. *Front. Pharmacol.* 11, 603476. doi:10. 3389/fphar.2020.603476

Choi, C. H., Rutter, M. D., Askari, A., Lee, G. H., Warusavitarne, J., Moorghen, M., et al. (2015). Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: An updated overview. *Am. J. Gastroenterol.* 110 (7), 1022–1034. doi:10.1038/ajg.2015.65

Chung, Y., Chang, S. H., Martinez, G. J., Yang, X. O., Nurieva, R., Kang, H. S., et al. (2009). Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity* 30 (4), 576–587. doi:10.1016/j.immuni.2009.02.007

Cui, Y. L., Wang, L., Tian, Z. T., Lin, Z. F., and Chen, D. C. (2014). Effect of rhubarb pre-treatment on intestinal microcirculation in septic rats. *Am. J. Chin. Med.* 42 (5), 1215–1227. doi:10.1142/s0192415x14500761

Cui, Y. L., Zhang, S., Tian, Z. T., Lin, Z. F., and Chen, D. C. (2016). Rhubarb antagonizes matrix metalloproteinase-9-induced vascular endothelial permeability. *Chin. Med. J.* 129 (14), 1737–1743. doi:10.4103/0366-6999.185859

Danese, S., Papa, A., Saibeni, S., Repici, A., Malesci, A., and Vecchi, M. (2007). Inflammation and coagulation in inflammatory bowel disease: The clot thickens. *Am. J. Gastroenterol.* 102 (1), 174–186. doi:10.1111/j.1572-0241.2006.00943.x

de Maat, S., Tersteeg, C., Herczenik, E., and Maas, C. (2014). Tracking down contact activation - from coagulation in vitro to inflammation in vivo. *Int. J. Lab. Hematol.* 36 (3), 374–381. doi:10.1111/ijlh.12222

Deng, P. (2015). 36 cases of ulcerative colitis treated with compound Qinbo granules orally combined with retention enema. *Hunan J. TCM* 31 (4), 54–55. doi:10.16808/j.cnki.issn1003-7705.2015.04.026

Deng, S. H., and Chen, S. (2020). Efficacy observation of Zhikang capsule combined with mesalazine in the treatment of mild to moderate ulcerative colitis. *Electron. J. Clin. Med. Literature* 7 (34), 51–52. doi:10.16281/j.cnki.jocml. 2020.34.037

Ding, S. L. (2016). Clinical observation on the treatment of ulcerative colitis with large intestine damp-heat syndrome with qingrechangyufang enema. J. New Chin. Med. 48 (4). doi:10.13457/j.cnki.jncm.2016.04.086

Ekbom, A., Helmick, C., Zack, M., and Adami, H. O. (1990). Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 336 (8711), 357–359. doi:10.1016/0140-6736(90)91889-i

Eom, J. Y., Choi, S. H., Kim, H. J., Kim, D. H., Bae, J. H., Kwon, G. S., et al. (2022). Hemp-derived nanovesicles protect leaky gut and liver injury in dextran sodium sulfate-induced colitis. *Int. J. Mol. Sci.* 23 (17), 9955. doi:10.3390/ijms23179955

Fei, X. Y. (2017). Efficacy of Lishi Hexue Decoction assisted by mesalazine in the treatment of ulcerative colitis and its effect on quality of life and levels of inflammatory immune cytokines. *J. Emerg. Traditional Chin. Med.* 26 (6), 1097–1098. doi:10.3969/j.issn.1004-745X.2017.06.053

Gao, D., Wu, S. N., Zhang, C. E., Li, R. S., Liu, Z. J., Xiao, X. H., et al. (2020). Exploration in the mechanism of rhubarb for the treatment of hyperviscosity organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar. 2022.1036593/full#supplementary-material

syndrome based on network pharmacology. J. Ethnopharmacol. 261, 113078. doi:10. 1016/j.jep.2020.113078

Gionchetti, P., Rizzello, F., Venturi, A., Ferretti, M., Brignola, C., Miglioli, M., et al. (1998). Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. *Dis. Colon Rectum* 41 (1), 93–97. doi:10.1007/bf02236902

Glocker, E. O., Kotlarz, D., Klein, C., Shah, N., and Grimbacher, B. (2011). IL-10 and IL-10 receptor defects in humans. *Ann. N. Y. Acad. Sci.* 1246, 102–107. doi:10. 1111/j.1749-6632.2011.06339.x

Günther, C., Martini, E., Wittkopf, N., Amann, K., Weigmann, B., Neumann, H., et al. (2011). Caspase-8 regulates TNF- α -induced epithelial necroptosis and terminal ileitis. *Nature* 477 (7364), 335–339. doi:10.1038/nature10400

Guo, G. J., and Ding, Q. X. (2019). Clinical observation of Tiaochangjiening decoction combined with Western medicine in the treatment of intestinal dampheat ulcerative colitis. *China's Naturop.* 27 (10), 66–67. doi:10.19621/j.cnki.11-3555/r.2019.1035

Han, X. H., Zhong, J., Guo, J. Y., Shi, R., Wang, X. H., Wang, C. H., et al. (2013). Relationships between pharmacokinetics and efficacy of Xie-xin decoction in rats with experimental ulcerative colitis. *J. Ethnopharmacol.* 148 (1), 182–189. doi:10. 1016/j.jep.2013.04.008

He, W., Li, Y., Liu, M., Yu, H., Chen, Q., Chen, Y., et al. (2018). Citrus aurantium L. and its flavonoids regulate TNBS-induced inflammatory bowel disease through anti-inflammation and suppressing isolated jejunum contraction. *Int. J. Mol. Sci.* 19 (10), E3057. doi:10.3390/ijms19103057

Heinrich, M., Appendino, G., Efferth, T., Fürst, R., Izzo, A. A., Kayser, O., et al. (2020). Best practice in research - overcoming common challenges in phytopharmacological research. *J. Ethnopharmacol.* 246, 112230. doi:10.1016/j. jep.2019.112230

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 343, d5928. doi:10.1136/bmj.d5928

Hu, J., Li, P., and Zhang, T. (2018). Rhubarb combined with trypsin inhibitor for severe acute pancreatitis: A systematic review and meta-analysis. *Phytother. Res.* 32 (8), 1450–1458. doi:10.1002/ptr.6096

Jia, Y., Wang, Z. Z., Li, X. M., and Miao, M. S. (2021). Data mining of drug use rules based on traditional Chinese medicine treatment of ulcerative colitis. *Zhongguo Zhong Yao Za Zhi* 46 (10), 2594–2600. doi:10.19540/j.cnki.cjcmm. 20200911.501

Kaplan, G. G. (2015). The global burden of IBD: from 2015 to 2025. Nat. Rev. Gastroenterol. Hepatol. 12 (12), 720-727. doi:10.1038/nrgastro.2015.150

Kim, D. H. (2018). Gut microbiota-mediated pharmacokinetics of ginseng saponins. J. Ginseng Res. 42 (3), 255-263. doi:10.1016/j.jgr.2017.04.011

Kim, E. S., and Kim, W. H. (2010). Inflammatory bowel disease in korea: epidemiological, genomic, clinical, and therapeutic characteristics. *Gut Liver* 4 (1), 1–14. doi:10.5009/gnl.2010.4.1.1

Ko, C. W., Singh, S., Feuerstein, J. D., Falck-Ytter, C., Falck-Ytter, Y., Cross, R. K., et al. (2019). AGA clinical practice guidelines on the management of mild-tomoderate ulcerative colitis. *Gastroenterology* 156 (3), 748–764. doi:10.1053/j.gastro. 2018.12.009

Kobayashi, T., Siegmund, B., Le Berre, C., Wei, S. C., Ferrante, M., Shen, B., et al. (2020). Ulcerative colitis. *Nat. Rev. Dis. Prim.* 6 (1), 74. doi:10.1038/s41572-020-0205-x

Li, R. (2019). Analysis of curative effect and prognosis of modified Shaoyao decoction retention enema in the treatment of chronic ulcerative colitis. *Sichuan J. TCM* 37 (9), 95–98.

Li, Z. M. (2012). Shaoyao decoction with olsalazine sodium in the treatment of damp and activity of ulcerative colitis control study. *J. Pract. Traditional Chin. Intern. Med.* 26 (5), 74–75. doi:10.3969/j.issn.1671-7813.2012.05.38

Li, Z. W., Niu, D. L., and Zhao, S. W. (2021). Clinical observation of 43 cases of ulcerative colitis treated with combined Chinese and Western medicine. *Chin. J. Ethnomedicine Ethnopharmacy* 30 (15), 84–86.

Lipinski, S., Bremer, L., Lammers, T., Thieme, F., Schreiber, S., and Rosenstiel, P. (2011). Coagulation and inflammation. Molecular insights and diagnostic implications. *Hamostaseologie* 31 (2), 94104–95102. doi:10. 5482/ha-1134

Liu, Y. H. (2019). Effect of Jiawei Shaoyao Decoction retention enema on dampheat ulcerative colitis and its effect on inflammatory factors. *Guangxi J. TCM* 42 (2). doi:10.3969/j.issn.1003-0719.2019.02.010

Liu, Y., Yin, H., and Chen, K. (2013). Platelet proteomics and its advanced application for research of blood stasis syndrome and activated blood circulation herbs of Chinese medicine. *Sci. China. Life Sci.* 56 (11), 1000–1006. doi:10.1007/ s11427-013-4551-8

Miao, B., Li, F. W., Zhang, S. W., Wang, H., Qi, W. J., and Wang, C. (2018). Efficacy and safety of tongfu powder in acute pancreatitis patients with gastrointestinal dysfunction: a clinical trial. *Drug Des. devel. Ther.* 12, 3665–3673. doi:10.2147/dddt.S163645

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj* 339, b2535. doi:10.1136/bmj.b2535

Molodecky, N. A., Soon, I. S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., et al. (2012). Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 142 (1), 46–54. doi:10.1053/j.gastro.2011.10.001

Naini, M. A., Zargari-Samadnejad, A., Mehrvarz, S., Tanideh, R., Ghorbani, M., Dehghanian, A., et al. (2021). Anti-inflammatory, antioxidant, and healing-promoting effects of Aloe vera extract in the experimental colitis in rats. *Evid. Based. Complement. Altern. Med.* 2021, 9945244. doi:10.1155/2021/9945244

Neurath, M. F. (2014). Cytokines in inflammatory bowel disease. Nat. Rev. Immunol. 14 (5), 329-342. doi:10.1038/nri3661

Nong, Z. B. (2009). Clinical observation of 30 cases of ulcerative colitis treated with oral sulfasalazine plus traditional Chinese medicine retention enema. *Intern. Med.* 4 (6), 879–880. doi:10.16121/j.cnki.cn45-1347/r.2009.06.085

Pedersen, J., LaCasse, E. C., Seidelin, J. B., Coskun, M., and Nielsen, O. H. (2014). Inhibitors of apoptosis (IAPs) regulate intestinal immunity and inflammatory bowel disease (IBD) inflammation. *Trends Mol. Med.* 20 (11), 652–665. doi:10. 1016/j.molmed.2014.09.006

Pepys, M. B., and Hirschfield, G. M. (2003). C-reactive protein: a critical update. J. Clin. Invest. 111 (12), 1805–1812. doi:10.1172/jci18921

Qin, Y., Wang, J. B., Kong, W. J., Zhao, Y. L., Yang, H. Y., Dai, C. M., et al. (2011). The diarrhoeogenic and antidiarrhoeal bidirectional effects of rhubarb and its potential mechanism. *J. Ethnopharmacol.* 133 (3), 1096–1102. doi:10.1016/j.jep. 2010.11.041

Reinisch, W., Reinink, A. R., and Higgins, P. D. (2015). Factors associated with poor outcomes in adults with newly diagnosed ulcerative colitis. *Clin. Gastroenterol. Hepatol.* 13 (4), 635–642. doi:10.1016/j.cgh.2014.03.037

Sehgal, P., Colombel, J. F., Aboubakr, A., and Narula, N. (2018). Systematic review: safety of mesalazine in ulcerative colitis. *Aliment. Pharmacol. Ther.* 47 (12), 1597–1609. doi:10.1111/apt.14688

Seo, E. J., Ngoc, T. M., Lee, S. M., Kim, Y. S., and Jung, Y. S. (2012). Chrysophanol-8-O-glucoside, an anthraquinone derivative in rhubarb, has antiplatelet and anticoagulant activities. *J. Pharmacol. Sci.* 118 (2), 245–254. doi:10.1254/jphs. 11123fp

Sheng, R. D., Shi, L. P., Zhang, J. L., Zheng, F., Yang, D. Q., Ran, M. F., et al. (2017). Modified peony decoction combined with mesalazine on ulcerative colitis (internal dampness-heat syndrome type). *J. Emerg. Traditional Chin. Med.* 26 (9), 1619–1622. doi:10.3969/j.issn.1004-745X.2017.09.035

Shi, A. P., and Sun, A. X. (2017). Observation on the curative effect of Kangfuxin liquid combined with self-made Shaoyao decoction assisted by olsalazine in the treatment of ulcerative colitis (damp-heat syndrome). *J. Emerg. Traditional Chin. Med.* 26 (12), 2235–2236. doi:10.3969/j.issn.1004-745X.2017.12.052

Smyth, S. S., McEver, R. P., Weyrich, A. S., Morrell, C. N., Hoffman, M. R., Arepally, G. M., et al. (2009). Platelet functions beyond hemostasis. J. Thromb. Haemost. 7 (11), 1759–1766. doi:10.1111/j.1538-7836.2009.03586.x Sood, A., Midha, V., Sood, N., Bhatia, A. S., and Avasthi, G. (2003). Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut* 52 (11), 1587–1590. doi:10.1136/gut.52.11.1587

Sun, J. X., and Zhang, X. A. (2020). Discussion on the clinical study on yangwarming and qi-benefiting and Detoxifi-cating prescription for ulcerative colitis based on the theory of "toxic cold. J. New Chin. Med. 52 (2), 72–73. doi:10.13457/j. cnki.jncm.2020.02.020

Tan, G. Z., Sun, J., Qun, Y. Z., Zhou, F., Pei, C., and Feng, T. (2020). Clinical observation of Shaoyao decoction and infliximab on moderate or severe ulcerative colitis. *Shanxi J. TCM* 36 (7), 23–26. doi:10.3969/j.issn.1000-7156.2020.07.009

Teng, J. L., Zhang, Y. X., Wu, Q. G., Chen, Z., and Huang, X. W. (2019). *Chinese Materia medica*. China: People's Medical Publishing House, 106–107.

Tian, G. D. (2017). Clinical effect of modified Shaoyao decoction in the treatment of ulcerative colitis. *Neimenggu J. TCM* 36 (17), 3–4. doi:10.3969/j.issn.1006-0979.2017. 17.003

Ungaro, R., Mehandru, S., Allen, P. B., Peyrin-Biroulet, L., and Colombel, J. F. (2017). Ulcerative colitis. *Lancet* 389 (10080), 1756–1770. doi:10.1016/s0140-6736(16)32126-2

Waldner, M. J., and Neurath, M. F. (2014). Master regulator of intestinal disease: IL-6 in chronic inflammation and cancer development. *Semin. Immunol.* 26 (1), 75–79. doi:10.1016/j.smim.2013.12.003

Wang, C. S., Li, W. B., Wang, H. Y., Ma, Y. M., Zhao, X. H., Yang, H., et al. (2018). VSL#3 can prevent ulcerative colitis-associated carcinogenesis in mice. *World J. Gastroenterol.* 24 (37), 4254–4262. doi:10.3748/wjg.v24.i37.4254

Wang, F. T. (2016). Influence of ZhiKang capsules on serum TNF-α, IL-6 and CRP of the patients with ulcerative colitis. *West. J. Traditional Chin. Med.* 29 (2), 100–102. doi:10.3969/j.issn.1004-6852.2016.02.031

Wang, H. S., Shi, L. P., Zhao, F. L., Wu, H. X., Yang, D. Q., and Ran, M. F. (2017). Clinical effect of jiawei shaoyao decoction in treatment of ulcerative colitis with internal retention of damp-heat: an analysis of 32 cases. *Hunan J. TCM* 33 (11), 11–14. doi:10.16808/j.cnki.issn1003-7705.2017.11.004

Wang, J. X. (2018). Observation of curative effect of modified Lishihexue decoction combined with Bupi Yichang Pill in the treatment of 48 cases of ulcerative colitis. *Asia-Paeitic Tradit. Med.* 14 (3). doi:10.11954/ytctyy.201803068

Wang, P. L. (2020). Treatment of ulcerative colitis with Shaoyao Decoction and Gegen Qinlian Decoction (Intestinal damp-heat syndrome) clinical curative effect observation. *Sichuan J. TCM* 38 (1), 101–103.

Wang, S., Wang, J., Ma, R., Yang, S., Fan, T., Cao, J., et al. (2020). IL-10 enhances T cell survival and is associated with faster relapse in patients with inactive ulcerative colitis. *Mol. Immunol.* 121, 92–98. doi:10.1016/j.molimm. 2020.03.001

Wen, B., and Sun, J. P. (2017). Efficacy observation of Zhikang capsule combined with mesalazine in the treatment of mild to moderate ulcerative colitis. *Hainan Med. J.* 28 (23), 3820–3822. doi:10.3969/j.issn.1003-6350.2017.23.012

Windsor, A., Michetti, P., Bemelman, W., and Ghosh, S. (2013). The positioning of colectomy in the treatment of ulcerative colitis in the era of biologic therapy. *Inflamm. Bowel Dis.* 19 (12), 2695–2703. doi:10.1097/MIB. 0b013e318292fae6

Wu, J., Wei, Z., Cheng, P., Qian, C., Xu, F., Yang, Y., et al. (2020). Rhein modulates host purine metabolism in intestine through gut microbiota and ameliorates experimental colitis. *Theranostics* 10 (23), 10665–10679. doi:10. 7150/thno.43528

Xiang, H., Zuo, J., Guo, F., and Dong, D. (2020). What we already know about rhubarb: a comprehensive review. *Chin. Med.* 15, 88. doi:10.1186/s13020-020-00370-6

Xie, Q., Li, H., Ma, R., Ren, M., Li, Y., Li, J., et al. (2022). Effect of Coptis chinensis franch and Magnolia officinalis on intestinal flora and intestinal barrier in a TNBSinduced ulcerative colitis rats model. *Phytomedicine*. 97, 153927. doi:10.1016/j. phymed.2022.153927

Xue, H. C., and Xu, Y. (2021). Clinical effect of jiawei shaoyao decoction on ulcerative colitis. *Inn. Mong. J. TCM* 40 (1), 35–36. doi:10.16040/j.cnki.cn15-1101. 2021.01.021

Yang, M. M., Luo, W. P., Li, K. Y., and Wang, Q. Z. (2017). Clinical effect of retention enema with qinbai granules in treatment of ulcerative colitis with dampheat accumulation: an analysis of 37 cases. *Hunan J. TCM* 33 (12), 10–12. doi:10. 16808/j.cnki.issn1003-7705.2017.12.004

Yang, X. Q., and Wang, Y. (2021). Clinical observation and mechanism study of pingkuiyichang recipe in treating ulcerative colitis. *Hubei J. TCM* 43 (2), 3–5.

Yin, P., Li, W., Yang, H. M., Dong, M., and Song, J. Y. (2021). Clinical study on retention enema with Jiawei Shaoyao Decoction and Kangfuxin Liquid combined with oral administration of mesalazine enteric-coated tablets in the treatment of ulcerative colitis of large intestine damp-heat type. *Hebei J. TCM* 43 (2), 278–279. doi:10.3969/j.issn.1002-2619.2021.02.02

Yoshida, H., and Granger, D. N. (2009). Inflammatory bowel disease: a paradigm for the link between coagulation and inflammation. *Inflamm. Bowel Dis.* 15 (8), 1245–1255. doi:10.1002/ibd.20896

You, C. M., Shen, Y. H., and Shen, T. C. (2015). Clinical observation on 42 cases of ulcerative colitis treated with modified Gancao Xiexin decoction. *Neimenggu J. TCM* 35 (01), 18–19. doi:10.16040/j.cnki.cn15-1101.2016.01.018

Yuan, X. H. (2020). Effects of Zhikang Capsules combined with mesalazine on inflammatory indexes in patients with mild to moderate ulcerative colitis. *Med. Forum* 24 (29), 4240–4241. doi:10.19435/j.1672-1721.2020.29.060

Zhang, C., Li, J., Xiao, M., Wang, D., Qu, Y., Zou, L., et al. (2022a). Oral colontargeted mucoadhesive micelles with enzyme-responsive controlled release of curcumin for ulcerative colitis therapy. *Chin. Chem. Lett.* 33 (11), 4924–4929. doi:10.1016/j.cclet.2022.03.110

Zhang, C., Wang, X., Xiao, M., Ma, J., Qu, Y., Zou, L., et al. (2022b). Nano-inmicro alginate/chitosan hydrogel via electrospray technology for orally curcumin delivery to effectively alleviate ulcerative colitis. *Mater. Des.* 221, 110894. doi:10. 1016/j.matdes.2022.110894

Zhang, G. R. (2020). Effect and mechanism of shaoyao decoction in the treatment of patients with ulcerative colitis. *China J. Pharmaceut. Econ.* 15 (11), 100–103. doi:10.12010/j.issn.1673-5846.2020.11.025

Zhang, H. Y. (2016). Observation on the therapeutic effect of banxiaxiexin decoction in the treatment of 40 cases of ulcerative colitis. *Asia-Paeitic Tradit. Med.* 12 (2), 109–110. doi:10.11954/ytctyy.201602052

Zhang, L., Wu, Q., Chen, P., Xu, Y., Zheng, Y., Ma, S., et al. (2021). Effect of tongfu traditional Chinese medicine preparation on patients with septic gastrointestinal dysfunction: a systematic review and meta-analysis. *Ann. Palliat. Med.* 10 (12), 12072–12085. doi:10.21037/apm-21-2461

Zhang, Y. L., Cai, L. T., Qi, J. Y., Lin, Y. Z., Dai, Y. C., Jiao, N., et al. (2019). Gut microbiota contributes to the distinction between two traditional Chinese medicine syndromes of ulcerative colitis. *World J. Gastroenterol.* 25 (25), 3242–3255. doi:10. 3748/wjg.v25.i25.3242

Zhao, J. H. (2020). Effect of Changwei'an pill combined with mesalazine on serum inflammatory index levels in patients with ulcerative colitis. *J. Chende Med. Coll.* 37 (6), 487–490. doi:10.15921/j.cnki.cyxb.2020.06.011

Zhao, Y. Q., Liu, X. H., Ito, T., and Qian, J. M. (2004). Protective effects of rhubarb on experimental severe acute pancreatitis. *World J. Gastroenterol.* 10 (7), 1005–1009. doi:10.3748/wjg.v10.i7.1005

Zhou, Y., Wang, L., Huang, X., Li, H., and Xiong, Y. (2016). Add-on effect of crude rhubarb to somatostatin for acute pancreatitis: A meta-analysis of randomized controlled trials. *J. Ethnopharmacol.* 194, 495–505. doi:10.1016/j.jep.2016.09.053