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Curative effect of anti-fibrosis Chinese patent medicines combined with ursodeoxycholic acid for primary biliary cholangitis: A systematic review and meta-analysis

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Objective: To delineate the curative effect and safety of anti-fibrosis Chinese patent medicines (CPMs) combined with ursodeoxycholic acid (UDCA) for primary biliary cholangitis (PBC).

Methods: A literature search was conducted using PubMed, Web of Science, Embase, Cochrane Library, Wanfang database, VIP database, China Biology Medicine Database, and Chinese National Knowledge Infrastructure from their inception until August 2022. Randomized controlled trials (RCTs) of the treatment of PBC with anti-fibrotic CPMs were collected. The eligibility of the publications was assessed using the Cochrane risk-of-bias tool. The evaluation indicators were the clinical efficacy rate, liver fibrosis, liver function, immune function, and symptom score. Meta-analysis and subgroup analysis were conducted to evaluate the effectiveness of anti-fibrosis CPMs. Risk ratio (RR) was used to assess dichotomous variables, and continuous variables with a 95% confidence interval were calculated using mean difference.

Results: Twenty-two RCTs including 1,725 patients were selected. The findings demonstrated that anti-fibrotic CPMs combined with UDCA improved the efficacy rate, liver function, liver fibrosis, immunological indicators, and clinical symptoms compared with UDCA alone (all p < 0.05).

Conclusion: This study demonstrates that the combination of anti-fibrotic CPMs and UDCA can improve both clinical symptoms and outcomes. Nevertheless, more high-quality RCTs are needed to assess the effectiveness of anti-fibrosis CPMs for PBC.

Abbreviations: ALHX, anluo huaxian pills; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APASL, asian pacific association for the study of the liver; Cl, confidence interval; CPM, Chinese patent medicine; FDA, United States Food and Drug Administration; FFBJRG, Fufang Biejia Ruangan tablets; FZHY, Fuzheng Huayu capsules; GGT, gamma-glutamyl transpeptidase; HA, hyaluronidase; IgG, immunoglobulin G; IgM, immunoglobulin M; IV-C, type IV collagen; LN, laminin; MD, mean difference; PBC, primary biliary cholangitis; PC-III, type III procollagen; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials; RR, risk ratio; SMD, standardized mean difference; TCM, traditional Chinese medicine; UDCA, ursodeoxycholic acid.

KEYWORDS

primary biliary cholangitis, Chinese patent medicine, anti-fibrosis, ursodeoxycholic acid, meta-analysis

1 Introduction

Primary biliary cholangitis (PBC), also called primary biliary cirrhosis, is a chronic autoimmune cholestatic liver disease whose pathogenesis has not been fully elucidated (European Association for the Study of the Liver, 2017). PBC frequently occurs in middle-aged women, and its clinical serological characteristics include positive anti-mitochondrial antibodies and elevated levels of alkaline phosphatase (ALP) or gamma-glutamyl transpeptidase (GGT) (You et al., 2022). The main pathological features of the liver include progressive, non-suppurative, and destructive intrahepatic cholangitis, leading to fibrosis and eventually cirrhosis (Zhang et al., 2021; You et al., 2022; European Association for the Study of the Liver, 2017). PBC is mainly caused by genetic and environmental factors, with unknown pathogenesis and hidden clinical manifestations (You et al., 2022). Some patients with PBC have cirrhosis at the time of diagnosis (Zhang et al., 2021), making anti-fibrotic therapy particularly important.

Ursodeoxycholic acid (UDCA) is an effective treatment for PBC (You et al., 2022), and its mechanism of action includes cholelithiasis, cytoprotection, anti-inflammatory effects, and immune regulation (Zhang et al., 2021). UDCA has greatly improved longevity in patients with PBC. However, 40% of patients with PBC still respond poorly to it (Cheung et al., 2016), and non-responders have a lower survival rate than the general population. Owing to rapid disease progression and poor long-term prognosis, patients who respond poorly to UDCA may require alternative treatment methods urgently; however, currently, no unified therapies exist.

Traditional Chinese medicine (TCM) has advantages in treating liver fibrosis, owing to its combination of ingredients and multiple pathways and targets. Previous studies have shown that Fuzheng Huayu capsules (FZHY) (Liu et al., 2019), Fufang Biejia Ruangan tablets (FFBJRG) (Ji et al., 2022), and Anluo Huaxian pills (ALHX) (Lu et al., 2017) are commonly used clinically as Chinese patent medicines (CPMs) for the anti-fibrosis treatment of liver these have been approved by the State Food and Drug Administration of China, with national medicine permission numbers of Z20020074 (FZHY), Z19991011 (FFBJRG), and Z20010098 (ALHX). The fibrosis stage is important in the progression of PBC. If anti-fibrosis treatment is administered in time at this stage, the occurrence of liver cancer or even liver failure will be reversed (Prince et al., 2002). Additionally, a recent study demonstrated that the treatment of PBC with TCM exerts anti-fibrotic effects and helps improve patients' pruritus, fatigue, and the response rate to UDCA (Chen et al., 2018). Meanwhile, several studies have revealed that FZHY, FFBJRG, and ALHX have unique advantages in improving biochemical indices, anti-fibrosis, and quality of life in patients with PBC (Chen et al., 2019; Jiang et al., 2019; Wang et al., 2020). Furthermore, a previous real-world cohort study (Chen et al., 2018) conducted by our research group found that TCM combined with UDCA increased the 1-year biochemical response rate of patients with PBC by 15.1% compared with that of UDCA alone (43.0% vs. 27.9%, p < 0.05).

Therefore, it is of great significance to explore the clinical curative effects of CPMs combined with UDCA on PBC. Therefore, a meta-analysis of randomized controlled trials (RCTs) was conducted to measure the efficacy of CPMs plus UDCA for treating PBC.

2 Materials and methods

2.1 Standards for inclusion and exclusion of literature

The inclusion criteria were: 1) the studies reported RCTs; 2) the participants were diagnosed with PBC based on the consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL); 3) the treatment involved anti-fibrotic CPMs plus UDCA; and 4) at least one of the following outcome indices was used: clinical efficacy rate, ALP, GGT, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hyaluronic acid (HA), laminin (LN), collagen type IV (IV-C), type III procollagen (PC-III), immunoglobulin M (IgM), immunoglobulin G (IgG), and clinical symptoms. The primary outcome was the clinical efficacy rate, whereas the secondary outcomes were liver function, hepatic fibrosis, immunological indicators, and clinical symptoms.

The exclusion criteria were: 1) the experimental group used none of the three aforementioned anti-fibrotic CPMs or other TCMs; 2) duplicate studies; 3) studies with incomplete research data; and 4) animal experiments, conferencing articles, reviews, non-RCTs, and other unrelated studies.

2.2 Search strategy

The meta-analysis followed the newest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table S1) (Page et al., 2021). A literature search was conducted using PubMed, Web of Science, Embase, Cochrane Library, Wanfang database, VIP database, China Biology Medicine Database, and Chinese National Knowledge Infrastructure from their inception until August 2022, with no language restriction. The search terms included: "Primary Biliary Cirrhosis," "Primary Biliary Cholangitis," "PBC," "Chinese patent medicine," "CPMs," "traditional Chinese medicine," "TCM," "Ursodeoxycholic Acid," "UDCA," "Fuzheng Huayu capsules," "FZHY," "Fufang Biejia Ruangan tablets," "FFBJRG," "Anluo huaxian Pills," "ALHX," "ursodeoxycholic acid," "UDCA," "randomized controlled trials," and "RCT." The search strategy is presented in Table 1.

2.3 Data acquisition and quality evaluation

The literature was independently screened by two researchers (BI and SHI) in terms of the inclusion and exclusion standards. Data

TABLE 1 The search strategy.

Order	Search items
#1	((Primary Biliary Cholangitis [Title/Abstract]) OR (Primary Biliary Cirrhosis [Title/Abstract])) OR (PBC [Title/Abstract])
#2	(ursodeoxycholic acid [Title/Abstract]) OR (UDCA [Title/Abstract])
#3	((((((((((((((((((((((((((((((((((((((
#4	((randomized controlled trial [Title/Abstract]) OR (RCTs [Title/Abstract])) OR (randomized [Title/Abstract])
#5	#1 AND #2 AND #3AND#4



acquisition consisted of 1) general information: title, first author, and publication year; 2) sex, age, sample size, intervention measures, and treatment course; and 3) observed outcome indicators.

Literature eligibility was estimated using the Cochrane collaboration tool, including incomplete outcome data, selective reporting, allocation concealment, random-sequence generation, blinding of outcome assessment, blinding of participants and personnel, and other biases. Based on these standards, the literature eligibility was categorized as three levels of risk of bias: high, unclear, and low.

2.4 Statistical methods

The statistical analysis was performed using RevMan 5.4 software. According to the type of outcome, continuous data

Included	Sample size		nder female	Ag	ge	Interventio	on	Treatment Duration	Outcome Index
Trial	N1/N2	N1	N2	N1	N2	N1	N2		
Liu 2020a	44/44	16/28	18/26	55.28 ± 6.28	55.19 ± 6.32	FZHY + UDCA	UDCA	48 W	2)7)
Jiang et al., 2019	41/41	4/37	5/36	Ν	Ν	FZHY + UDCA	UDCA	12 M	1)2)8)
Yang 2017	60/60	15/45	13/47	52.5 ± 7.4	51.6 ± 6.8	FZHY + UDCA	UDCA	12 W	1)2)
Gao et al. (2015)	31/30	2/29	2/28	43.60 ± 10.4	45.20 ± 9.6	FZHY + UDCA	UDCA	24 W	1)2)3)8)
Zhang et al. (2014)	30/30	3/27	3/27	56.52 ± 10.42	58.04 ± 9.80	FZHY + UDCA	UDCA	24 W	2)5)7)
Wu et al. (2012)	40/40	5/35	4/36	43.7 ± 12.0	45.0 ± 11.6	FZHY + UDCA	UDCA	48 W	1)2)3)5)6)7)8)
Ying 2012	65/65	19	111	Ν	Ν	FZHY + UDCA	UDCA	24 W	1)2)8)
Xie et al. (2012)	15/14	3	26	Ν	Ν	FZHY + UDCA	UDCA	6 M	1)3)5)
Zhang 2021	48/47	11/37	8/39	48.46 ± 5.66	47.91 ± 4.86	FFBJRG + UDCA	UDCA	6 M	3)4)8)
Ai 2021	43/43	5/38	4/39	42.69 ± 3.12	42.57 ± 3.09	FFBJRG + UDCA	UDCA	6 M	3)7)
Liu 2020b	38/38	6/32	5/33	35.65 ± 3.52	36.58 ± 4.21	FFBJRG + UDCA	UDCA	6 M	2)
Wang 2020	36/36	16/20	17/19	41.21 ± 2.37	41.56 ± 2.25	FFBJRG + UDCA	UDCA	6 M	2)
Zhang et al. (2020)	21/21	N	Ν	Ν	Ν	FFBJRG + UDCA	UDCA	6 M	1)2)3)5)8)
Zhang 2019	85/85	17/68	21/64	43.9 ± 13.6	42.7 ± 14.1	FFBJRG + UDCA	UDCA	6 M	1)5)7)
Chen et al. (2019)	41/37	N	Ν	Ν	Ν	FFBJRG + UDCA	UDCA	24 W	1)3)5)
Pang 2017	25/25	9/16	10/15	52.1 ± 6.7	52.3 ± 7.1	FFBJRG + UDCA	UDCA	24 M	1)2)
Zhang et al. (2015)	32/32	4	60	Ν	Ν	FFBJRG + UDCA	UDCA	12 M	1)2)3)
Wang 2015	39/39	8/31	6/33	53.7 ± 6.9	52.1 ± 7.4	FFBJRG + UDCA	UDCA	12 M	2)4)
Huang et al. (2015)	28/28	3/25	4/24	57.97 ± 9.07	57.59 ± 8.46	FFBJRG + UDCA	UDCA	12 M	1)4)5)
Qiu and Rao 2015	42/42	15/27	12/30	31.6 ± 1.9	31.2 ± 1.5	ALHX + UDCA	UDCA	24 W	1)2)3)5)6)7)8)

TABLE 2 Basic characteristics of the included studies.

Abbreviations: N1, experimental group; N2, control group; W, weeks; M, months; FZHY, fuzheng huayu capsules; FFBJRG, fufang biejia ruangan tablets; ALHX, anluo huaxian pills; Outcome Index: 1) clinical efficacy rate; 2) liver function; 3) hepatic fibrosis; 4) acoustic radiation force impulse imaging; 5) symptoms; 6) portal dynamics; 7) immune function; 8) adverse effects.

48.2

 $42.2~\pm~9.2$

ALHX + UDCA

ALHX + UDCA

UDCA

UDCA

3 M

24 W

1)2)3)

1)2)3)



Wang et al. (2015)

Li and Wu 2013

32/32

30/30

5/27

2/28

6/26

3/27

47.5

 $45.6\,\pm\,10.3$



are depicted as mean difference (MD) or standardized mean difference (SMD), while categorical data are presented as risk ratios (RRs); all are expressed with a 95% confidence interval (CI). Furthermore, the χ^2 and I^2 tests were used for heterogeneity analysis.

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The fixed-effects model was used for analysis if $p \ge 0.1$ and $I^2 \le 50\%$ in the subgroup or overall. Conversely, the random-effects model was employed if p < 0.1 and $I^2 > 50\%$. Additionally, we searched for sources of heterogeneity in the results and employed a sensitivity analysis to affirm whether the results were stable. Moreover, subgroup analyses were performed based on the use of three different CPMs. A *p*-value less than 0.05 was considered statistically significant. Publication bias was analyzed using funnel plots.

3 Results

3.1 Study selection

In total, 621 relevant studies were selected in the initial search. After duplicates were removed, 332 studies remained. After screening the titles, abstracts, and introductions of each article, 84 articles were deleted. Finally, after reading the full-text articles for further screening and evaluation, 22 publications (Wu et al., 2012; Xie et al., 2012; Ying, 2012; Li and Wu, 2013; Zhang et al., 2014; Gao et al., 2015; Huang et al., 2015; Qiu and Rao, 2015; Wang, 2015; Wang et al., 2015; Pang, 2017; Chen et al., 2019; Jiang et al., 2019; Zhang, 2019; Liu, 2020b; Wang, 2020; Zhang et al., 2020; Ai, 2021; Zhang, 2021) were included. The selection procedure for publications is shown in Figure 1.

3.2 Study characteristics

All 22 included studies were RCTs conducted in China and involved 1,725 patients with PBC. All studies were classified into an experimental group and a control group to compare the efficacies of CMPs combined with UDCA and UDCA monotherapy. The basic traits of each study are summarized in Table 2.

3.3 Quality assessment

We used the Cochrane risk-of-bias tool to estimate article quality. Of these, eight publications (Wu et al., 2012; Ying, 2012; Zhang et al., 2015; Yang, 2017; Jiang et al., 2019; Zhang et al., 2020; Ai, 2021; Zhang, 2021) used a random number table, 12 (Xie et al., 2012; Li and Wu, 2013; Zhang et al., 2014; Huang et al., 2015; Qiu and Rao, 2015; Wang, 2015; Wang et al., 2015; Cheung et al., 2016; Pang, 2017; Zhang, 2019; Liu, 2020a; Liu, 2020b) did not describe the randomization method, and two (Wang 2020; Chen et al., 2019 did not mention the word "random." Only one publication (Zhang et al., 2015) used a double-blind design and reported the number of missing cases in the experimental and control groups. In terms of hidden allocation, one publication (Huang et al., 2015) adopted a non-transparent envelope. The details of the risk of bias assessment are shown in Figures 2, 3.

3.4 CPMs drug composition

These studies used three anti-fibrosis CPMs, including FZHY, FFBJRG, and ALHX, and listed the TCMs used. Dongchongxiacao (*Cordyceps sinensis* (Berk.) Sacc) is an ingredient in FZHY and

TABLE 3 The herbal formula of FZHY, FFBJRRG and ALHX.

Herbal formula	Chinese name	Latin name	Picture
FZHY	Danshen	Salvia miltiorrhiza Bge	
	Dongchongxiacao	Cordyceps sinensis (Berk.) Sacc	
	Taoren	Prunus persica (L.) Batsch	
	Jiaogulan	Gynostemma aggregatum C.Y.Wu and S.K.Chen	
	Songhuafen	Pollen Pini	
	Wuweizi	Schisandra chinensis (Turcz.) Baill	
FFBJRG	Biejia	Shell of Trinyx sinensis Widgmann	
	Danggui	Angelica sinensis (Oliv.) Diels	
	Dangshen	Codonopsis pilosula (Franch.) Nannf	
	Chishao	Paeonia Lactiflora Pall	1000 g
	Ezhu	Rhizoma curcumae	Ś
	Sanqi	Panax notoginseng (Burk.) F. H. Chen	

(Continued on following page)

TABLE 3 (Continued) The herbal formula of FZHY, FFBJRRG and ALHX.

Herbal formula	Chinese name	Latin name	Picture
	Ziheche	Placenta hominis	(A)
	Dongchongxiacao	Cordyceps sinensis (Berk.) Sacc	
	Huangqi	Astragali Radix	138th
	Banlangen	Isatis indigotica Fortune ex Lindl	
	Lianqiao	Forsythia suspensa (Thunb.) Vahl	
ALHX	Sanqi	Panax notoginseng (Burk.) F. H. Chen	
	Shuizhi	Whitmania pigra Whitman	
	Shengdihuang	Rehmannia glutinosa Libosch	No.
	Jiangcan	Bombyx mori Linnaeus	- ANY
	Baizhu	Atractylodes macrocephala Koidz	
	Dilong	Pheretima aspergillum (E. Perrier)	T
	Yujin	Curcuma wenyujin Y.H.Chen and C.Ling	

(Continued on following page)

TABLE 3 (Continued)	The herbal	formula	of FZHY,	FFBJRRG and A	ALHX.
			•••••		

Herbal formula	Chinese name	Latin name	Picture
	Niuhuang	Bezoar	
	Walengzi	Arca subcrenata Lischke	
	Mudanpi	Paeonia suffruticosa Andr	
	Dahuang	Rheum officinale Baill	
	Shengmaiya	Hordeum vulgare L	
	Shuiniujiao	horn of Bubalus bubalis Linnaeus	
	Jineijin	Endothelium Corneum Gigeriae Galli	

FFBJRG, while Sanqi (*Panax notoginseng* (Burkill) F. H. Chen) is an ingredient in ALHX and FFBJRG. The compositions of the anti-hepatic fibrosis herbal formulations are listed in Table 3.

3.5 Outcome index

3.5.1 Clinical efficacy rate

A total of 13 clinical trials described the clinical efficacy rate as the main outcome, which was classified as markedly effective, effective, and ineffective grades. A random-effects model was implemented for analysis regarding heterogeneity testing (p = 0.0009, $I^2 = 64\%$), and anti-fibrosis CPMs plus UDCA improved the clinical efficacy rate compared with UDCA alone (RR = 0.11, 95% CI: 0.06, 0.16; p < 0.00001) (Figure 4A). Subgroup analysis showed that the clinical efficacy rate of FFBJRG was better than that of the other two CPMs and had no heterogeneity (p = 0.96, $I^2 = 0\%$) (Figure 4B).

3.6 Liver function

3.6.1 Alkaline phosphatase

We found 10 trials that reported the effects of anti-fibrotic CPMs plus UDCA on ALP levels. A random-effects model was implemented based on the *p*-value and I^2 value. The subgroup analyses showed that anti-fibrotic CPMs plus UDCA were superior to UDCA alone in terms of serum ALP levels (RR = -28.83, 95% CI: -36.57, -21.10; *p* < 0.00001) (Figure 5A).

3.6.2 Gamma-glutamyl transpeptidase

A total of 16 articles reported GGT levels as the outcome. In the subgroup analyses, random-effects models were used due to heterogeneity (p < 0.00001, $I^2 = 77\%$). Consequently, the anti-fibrotic CPMs plus UDCA were more effective at decreasing GGT levels than UDCA alone (MD = -14.69, 95% CI: -18.88, -10.50; p < 0.00001) (Figure 5B).

Study or Subarous	Experime		Contro		Woicht	Risk Ratio	Risk Ratio
Study or Subgroup Gao 2015	Events 30		Events 29	<u>1 otal</u> 30	10.9%	M-H, Random, 95% CI	M-H, Random, 95% Cl
	30	31				1.00 [0.91, 1.10]	
Jiang 2019	38	41	31	41	6.1%	1.23 [1.01, 1.49]	
Li 2013	30	30	29	30	11.0%	1.03 [0.94, 1.13]	
Pang 2017	25	25	21	25	6.5%	1.19 [0.99, 1.43]	
Qiu 2015	35	42	31	42	5.1%	1.13 [0.90, 1.41]	
Wang 2015b	29	32	22	32	4.3%	1.32 [1.02, 1.71]	
Wu 2012	39	40	37	40	10.4%	1.05 [0.95, 1.17]	
Yang 2017	57	60	45	60	7.6%	1.27 [1.08, 1.48]	
Ying 2012	65	65	62	65	12.5%	1.05 [0.99, 1.11]	-
Zhang 2015	30	32	24	32	5.3%	1.25 [1.00, 1.56]	
Zhang 2019	80	85	67	85	9.3%	1.19 [1.06, 1.35]	
Zhang 2020	20	21	15	21	3.7%	1.33 [1.00, 1.78]	
Zhang 2021	45	48	37	47	7.3%	1.19 [1.01, 1.41]	
Total (95% CI)		552		550	100.0%	1.13 [1.06, 1.21]	•
Total events	523		450			The sports of the Statement of Statement	
Heterogeneity: Tau ² =		= 33.27.		P = 0.0	$(009): ^2 = 6$	4%	
Test for overall effect:					// -		0.5 0.7 1 1.5 2
							Favours [experimental] Favours [control]
3							
	Experime	ental	Contro	ol		Risk Difference	Risk Difference
Study or Subgroup					Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 FZHY	Lvents	Total	Evenus	rotal	Aveight	m-n, Nanuom, 35% CI	
	1000	- 214			1000		
Gao 2015	30	31	29	30	10.3%	0.00 [-0.09, 0.09]	
Jiang 2019	38	41	31	41	6.3%	0.17 [0.02, 0.32]	
Wu 2012	39	40	37	40	9.9%	0.05 [-0.04, 0.14]	
Yang 2017	57	60	45	60	8.0%	0.20 [0.08, 0.32]	
Ying 2012	65	65	62	65	12.7%	0.05 [-0.01, 0.10]	-
Subtotal (95% CI)		237		236	47.0%	0.08 [0.00, 0.16]	
							\bullet
Total events	229	201	204		411070	0.00 [0.00, 0.10]	•
Total events	229		204			0.00 [0.00, 0.10]	
Heterogeneity: Tau ² =	0.01; Chi ² =	= 12.76,	df = 4 (P			0.00 [0.00, 0.10]	
	0.01; Chi ² =	= 12.76,	df = 4 (P			0.00 [0.00, 0.10]	
Heterogeneity: Tau ² = Test for overall effect:	0.01; Chi ² =	= 12.76,	df = 4 (P			0.00 [0.00, 0.10]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG	0.01; Chi² = Z = 2.06 (P	= 12.76, = 0.04)	df = 4 (P	= 0.01); l² = 69%		
Heterogeneity: Tau ² = Test for overall effect:	0.01; Chi ² =	= 12.76,	df = 4 (P			0.16 [0.01, 0.31]	•
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG	0.01; Chi² = Z = 2.06 (P	= 12.76, = 0.04)	df = 4 (P	= 0.01); l² = 69%		
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017	0.01; Chi² = Z = 2.06 (P 25	= 12.76, = 0.04) 25	df = 4 (P 21	= 0.01 25); l² = 69% 6.2%	0.16 [0.01, 0.31]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019	0.01; Chi ² = Z = 2.06 (P 25 30	= 12.76, = 0.04) 25 32	df = 4 (P 21 24	= 0.01 25 32); l² = 69% 6.2% 5.5% 9.5%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020	0.01; Chi ² = Z = 2.06 (P 25 30 80 20	= 12.76, = 0.04) 25 32 85 21	df = 4 (P 21 24 67 15	= 0.01 25 32 85 21); I ² = 69% 6.2% 5.5% 9.5% 4.0%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2021	0.01; Chi ² = Z = 2.06 (P 25 30 80	= 12.76, = 0.04) 25 32 85 21 48	df = 4 (P 21 24 67	= 0.01 25 32 85 21 47); I ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI)	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45	= 12.76, = 0.04) 25 32 85 21	df = 4 (P 21 24 67 15 37	= 0.01 25 32 85 21); I ² = 69% 6.2% 5.5% 9.5% 4.0%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45 200	= 12.76, = 0.04) 25 32 85 21 48 211	df = 4 (P 21 24 67 15 37 164	= 0.01 25 32 85 21 47 210); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29]	▼
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45 200 0.00; Chi ² =	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c	df = 4 (P 21 24 67 15 37 164 df = 4 (P =	= 0.01 25 32 85 21 47 210); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29]	 ▼ ▼ ▼
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45 200 0.00; Chi ² =	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c	df = 4 (P 21 24 67 15 37 164 df = 4 (P =	= 0.01 25 32 85 21 47 210); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29]	►
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45 200 0.00; Chi ² =	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c	df = 4 (P 21 24 67 15 37 164 df = 4 (P =	= 0.01 25 32 85 21 47 210); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29]	 ▼ ▼ ▼
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45 200 0.00; Chi ² = Z = 5.15 (P	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001)	= 0.01 25 32 85 21 47 210 : 0.96);); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23]	•
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45 200 0.00; Chi ² = Z = 5.15 (P 30	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29	= 0.01 25 32 85 21 47 210 : 0.96); 30); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42	df = 4 (P 21 24 67 15 37 164 1f = 4 (P = 001) 29 31	= 0.01 25 32 85 21 47 210 : 0.96); 30 42); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2019 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013	0.01; Chi ² = Z = 2.06 (P 25 30 80 20 45 200 0.00; Chi ² = Z = 5.15 (P 30	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29	= 0.01 25 32 85 21 47 210 : 0.96); 30); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Zhang 2020 Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42	df = 4 (P 21 24 67 15 37 164 1f = 4 (P = 001) 29 31	= 0.01 25 32 85 21 47 210 : 0.96); 30 42); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Zhang 2021 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32	df = 4 (P 21 24 67 15 37 164 1f = 4 (P = 001) 29 31	= 0.01 25 32 85 21 47 210 : 0.96); 30 42 32); $ ^2 = 69\%$ 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% $ ^2 = 0\%$ 10.4% 5.4% 4.8%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41]	
Heterogeneity: Tau ² = Test for overall effect: Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 32 104	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 82	25 32 85 21 47 210 6 0.96); 30 42 32 104); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4% 4.8% 20.6%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Zhang 2020 Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events Heterogeneity: Tau ² =	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94 0.01; $Chi^2 = 2$	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 82 sff = 2 (P =	25 32 85 21 47 210 6 0.96); 30 42 32 104); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4% 4.8% 20.6%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41]	
Heterogeneity: Tau ² = Test for overall effect: Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94 0.01; $Chi^2 = 2$	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 82 sff = 2 (P =	25 32 85 21 47 210 6 0.96); 30 42 32 104); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4% 4.8% 20.6%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Zhang 2020 Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events Heterogeneity: Tau ² =	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94 0.01; $Chi^2 = 2$	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 82 sff = 2 (P =	25 32 85 21 47 210 6 0.96); 30 42 32 104 6 0.10);); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4% 4.8% 20.6%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Jobard (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% CI)	0.01; $Chi^2 = Z = 2.06$ (P 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15$ (P 30 35 29 94 0.01; $Chi^2 = Z = 1.51$ (P	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c = 0.13)	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 82 eff = 2 (P =	25 32 85 21 47 210 6 0.96); 30 42 32 104 6 0.10);); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4% 4.8% 20.6% ² = 56%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41] 0.10 [-0.03, 0.23]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Total events	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94 0.01; $Chi^2 = Z = 1.51 (P)$ 523	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c = 0.13) 552	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 82 eff = 2 (P = 450	25 32 85 21 47 210 6 0.96); 30 42 32 104 6 0.10); 550); $ ^2 = 69\%$ 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% $ ^2 = 0\%$ 10.4% 5.4% 4.8% 20.6% $ ^2 = 56\%$ 100.0%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41] 0.10 [-0.03, 0.23] 0.11 [0.06, 0.16]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² =	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 45 200 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94 0.01; $Chi^2 = Z = 1.51 (P)$ 523 0.00; $Chi^2 = Z = 1.51 (P)$	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c = 0.13) 552 = 27.50,	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 82 aff = 2 (P = 450 df = 12 (F	25 32 85 21 47 210 6 0.96); 30 42 32 104 6 0.10); 550); $ ^2 = 69\%$ 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% $ ^2 = 0\%$ 10.4% 5.4% 4.8% 20.6% $ ^2 = 56\%$ 100.0%	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41] 0.10 [-0.03, 0.23] 0.11 [0.06, 0.16]	
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94 0.01; $Chi^2 = Z = 1.51 (P)$ 523 0.00; $Chi^2 = Z = 4.37 (P)$	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c = 0.13) 552 = 27.50, < 0.000	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 df = 2 (P = 450 df = 12 (F 01)	25 32 85 21 7 210 (0.96); 30 42 32 104 (0.10); 550 2 = 0.0); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4% 4.8% 20.6% ² = 56% 100.0% 07); ² = 56'	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41] 0.10 [-0.03, 0.23] 0.11 [0.06, 0.16]	-1 -0.5 0 0.5 1 Favours [experimental] Favours [control]
Heterogeneity: Tau ² = Test for overall effect: 1.1.2 FFBJRG Pang 2017 Zhang 2015 Zhang 2020 Zhang 2020 Zhang 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.1.3 ALHX Li 2013 Qiu 2015 Wang 2015b Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² =	0.01; $Chi^2 = Z = 2.06 (P)$ 25 30 80 20 0.00; $Chi^2 = Z = 5.15 (P)$ 30 35 29 94 0.01; $Chi^2 = Z = 1.51 (P)$ 523 0.00; $Chi^2 = Z = 4.37 (P)$	= 12.76, = 0.04) 25 32 85 21 48 211 = 0.62, c < 0.000 30 42 32 104 = 4.56, c = 0.13) 552 = 27.50, < 0.000	df = 4 (P 21 24 67 15 37 164 df = 4 (P = 001) 29 31 22 df = 2 (P = 450 df = 12 (F 01)	25 32 85 21 7 210 (0.96); 30 42 32 104 (0.10); 550 2 = 0.0); ² = 69% 6.2% 5.5% 9.5% 4.0% 7.2% 32.4% ² = 0% 10.4% 5.4% 4.8% 20.6% ² = 56% 100.0% 07); ² = 56'	0.16 [0.01, 0.31] 0.19 [0.02, 0.36] 0.15 [0.05, 0.25] 0.24 [0.02, 0.45] 0.15 [0.01, 0.29] 0.17 [0.10, 0.23] 0.03 [-0.05, 0.12] 0.10 [-0.08, 0.27] 0.22 [0.03, 0.41] 0.10 [-0.03, 0.23] 0.11 [0.06, 0.16]	

3.6.3 Alanine aminotransferase

Sixteen studies described ALT levels as the main outcome. A random-effects model was implemented for the analysis based on the heterogeneity test (p < 0.00001, $I^2 = 91\%$). Overall, ALT levels significantly decreased after the combination of anti-fibrotic CPMs and UDCA (MD = -10.01, 95% CI: -13.63, -6.39; p < 0.00001) (Figure 5C).

3.6.4 Aspartate aminotransferase

Sixteen studies reported serum AST levels as the main outcome. The AST data were processed using a random-effects model because AST was heterogeneous (p < 0.00001, $I^2 = 95\%$). The use of antifibrotic CMPs plus UDCA showed a greater decrease in serum AST levels than that with UDCA alone (MD = -10.83, 95% CI: -15.20, -6.46; p < 0.00001) (Figure 5D).

	Experimental	Control	Mean Differen				Experimental	Control		Mean Difference	Mean Diffe	
udy or Subgroup	Mean SD Total Me	an SD Total	Weight IV. Random.	% CI IV. Random. 95	5% CI	Study or Subgroup	Mean SD To	tal Mean SD	Total Weight	IV. Random. 95% CI	IV. Random	. 95% CI
	A					2.2.1 FZHY						
ng 2019 2020a	106.45 22.68 41 140 110.02 12.08 44 138		7.7% -34.24 [-42.62, - 8.2% -28.94 [-34.03, -			Gao 2015 Liu 2020a		31 69.2 35.2 44 82.56 9.98		-24.00 [-42.53, -5.47] -22.44 [-25.82, -19.06]	-	
											-	
2012	98.2 10.1 40 11 142 41 15		8.2% -17.90 [-22.90, -			Wu 2012 Xie 2012				-10.40 [-14.53, -6.27]		
2012 g 2017			3.5% -8.00 [-39.40, 1 5.4% -49.00 [-69.03, -1					15 161 32 60 135.67 68.24		-22.00 [-43.31, -0.69] -35.43 [-56.46, -14.40]		
										-26.00 [-39.37, -12.63]		
ing 2014 btotal (95% CI)	90.0 05.4 30 9		2.2% 1.30 [-43.15, -35.3% -27.16 [-36.27, -1	051		Ying 2012 Zhang 2014	43.2 37.1			-26.00 [-39.37, -12.63] -2.60 [-16.15, 10.95]	_	
	73.26; Chi ² = 22.66, df = 5 (F					Subtotal (95% CI)		30 59.4 20.1 85	283 40.0%	-18.72 [-26.33, -11.11]	•	
t for overall effect:	Z = 5.85 (P < 0.00001)	= 0.0004), 1" = 76%	2			Heterogeneity: Tau ² = 62 Test for overall effect: Z	2.29; Chi ² = 29.13,	df = 6 (P < 0.0001);		-10.72 [-20.35, -11.11]	•	
.2 FFBJRG												
021	169.24 26.25 43 231					2.2.2 FFBJRG						
en 2019	117.5 28.1 41 15					Chen 2019				-12.70 [-19.81, -5.59]		
ang 2015			3.7% -35.64 [-65.87,					28 69.96 28.75	28 5.0%			
2020b	148.35 12.36 38 148 102.32 50.12 25 140	36 12.35 38	8.1% -0.01 [-5.57 4.0% -37.89 [-66.22,					38 106.34 15.21 25 68.99 28.76	38 8.6% 25 4.9%			
ng 2017												
ng 2015a ng 2020	104.9 51.7 39 13 107.82 12.38 36 132		4.5% -34.70 [-59.65, 8.1% -24.87 [-30.43, -			Wang 2015a Wang 2020		39 70.2 26.4 36 67.24 4.96				
ng 2020 ing 2015			8.1% -24.87 [-30.43, - 6.6% -21.75 [-36.18,			Zhang 2015		36 67.24 4.96 32 74.31 24.86				
ang 2015 ang 2019	117.5 28.1 85 15					Subtotal (95% CI)	29.53 20.5			-10.27 [-14.33, -6.20]	•	
btotal (95% CI)	367		57.1% -31.13 [-44.67, -1			Heterogeneity: Tau ² = 11						
erogeneity: Tau ² = :	359.50; Chi ² = 121.21, df = 8 Z = 4.50 (P < 0.00001)					Test for overall effect: Z						
3 ALHX						2.2.3 ALHX						
	-					Li 2013	45.9 35.1			-12.30 [-30.34, 5.74]		
ng 2015b			7.5% -26.00 [-35.63, -			Wang 2015b		32 78 22		-22.00 [-31.63, -12.37]	T	
ototal (95% CI)	32	32	7.5% -26.00 [-35.63, -1	arj 🔻		Subtotal (95% CI)		62		-19.85 [-28.35, -11.35]	▼	
erogeneity: Not app						Heterogeneity: Tau ² = 0.	.00; Chi ² = 0.86, df = 4.58 (P < 0.0000		70			
	Z = 5.29 (P < 0.00001)					resciol overall effect. 2						
st for overall effect:	Z = 5.29 (P < 0.00001) 629	624	100.0% -28.83 [-36.57, -2	.10]		Total (95% CI)	5	86	580 100.0%	-14.69 [-18.88, -10.50]	•	
at for overall effect: 2 tal (95% CI) terogeneity: Tau ² =				-200 -100 0	100 200	Total (95% CI) Heterogeneity: Tau ² = 41	1.01; Chi ² = 65.34,	df = 15 (P < 0.00001		-14.69 [-18.88, -10.50]	-100 -50 0	50 100
tal (95% CI) terogeneity: Tau ² = st for overall effect: 2	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) erences: Chi ² = 0.37. df = 2 (F	5 (P < 0.00001); l² =	= 90%	-200 -100 0 Favours [experimental] Favo	burs [control]	Total (95% CI)	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000	df = 15 (P < 0.00001 1)); l² = 77%	-14.69 [-18.88, -10.50]	Favours [experimental]	avours [control]
st for overall effect: 2 tal (95% CI) terogeneity: Tau ² = st for overall effect: 2 st for subarouo diffe	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) rences: Chi ² = 0.37. df = 2 (F Experimental	5 (P < 0.00001); I ² = = 0.83). I ² = 0% Control	90% Mean Differen	-200 -100 0 Favours [experimental] Favo	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: Z : Test for suboroup differe	1.01; Ch ² = 65.34, = 6.88 (P < 0.0000 ences: Chi ² = 6.37. Experimental	df = 15 (P < 0.00001 1) df = 2 (P = 0.04). I ² = Control); l² = 77% : 68.6%	Mean Difference	Favours [experimental] F	Favours [control]
at for overall effect: 2 tal (95% CI) terogeneity: Tau ² = st for overall effect: 2 st for suborouo diffe	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) rences: Chi ² = 0.37. df = 2 (F Experimental	5 (P < 0.00001); I ² = = 0.83). I ² = 0% Control	90% Mean Differen	-200 -100 0 Favours [experimental] Favo	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: Z Test for suborouo differe Study or Suboroup	1.01; Ch ² = 65.34, = 6.88 (P < 0.0000 ences: Chi ² = 6.37. Experimental	df = 15 (P < 0.00001 1) df = 2 (P = 0.04). I ² = Control); l² = 77%		Favours [experimental]	Favours [control]
st for overall effect: 2 tal (95% CI) terogeneity: Tau ² = st for overall effect: 2 st for subaroup diffe udv or Subaroup 3.1 FZHY	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) erences: Chi ² = 0.37. df = 2 (F Experimental Mean SD Total Me	5 (P < 0.00001); I ² = = 0.83). I ² = 0% Control In SD Total V	90% Mean Differen Veloht IV. Random. 3	-200 -100 0 Favours [experimental] Favo Mean Differen % CI IV. Random. 9:	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: Z Test for suboroup differe <u>Study or Suboroup</u> 2.4.1 FZHY	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000 nnces: Chi ² = 6.37. Experimental Mean SD Tol	df = 15 (P < 0.00001 1) df = 2 (P = 0.04). I ^a = Control ial Mean SD 1); ² = 77% : 68.6% :otal Weight	Mean Difference IV. Random. 95% Cl	Favours [experimental] F	Favours [control]
at for overall effect: a late (95% CI) terogeneity: Tau ² = st for overall effect: a st for suboroup diffe udv or Subbroup 3.1 FZHY to 2015	629 183.34; Chi ^a = 145.79, df = 1 Z = 7.30 (P < 0.00001) erences: Chi ^a = 0.37. df = 2 (F Experimental Mean SD Total Me 42.4 10.2 31 62	5 (P < 0.00001); I ² = = 0.83). I ² = 0% Control In <u>SD Total V</u> .8 14.1 31	90% Mean Differen Veight IV. Random. 1 6.3% -20.40 [-26.53, -	-200 -100 0 Favours (experimental) Favo % CI IV. Random. 9: .27]	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: Z Test for subaroue differe <u>Study or Subgroup</u> 2.4.1 FZHY Jiang 2019	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000 nnces: Chi ² = 6.37. Experimental <u>Mean SD Tol</u> 44.2 11.25	df = 15 (P < 0.00001 1) df = 2 (P = 0.04). I ^a = Control <u>al Mean SD 1</u> 41 68.17 14.11); I ² = 77% 68.6% <u>fotal Weight</u> 41 6.8%	Mean Difference IV. Random. 95% Cl -23.97 [-29.49, -18.45]	Favours [experimental] F	Favours [control]
st for overall effect: 2 tal (95% CI) terogeneity: Tau ² = st for overall effect: 2 st for suboroup diffe utdv or Suboroup 3.1 FZHY 0.2015 1 2020a	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) reences: Chi ² = 0.37, df = 2 (F Experimental Mean SD Total Me 42.4 10.2 31 62 41.02 2.28 44 53.	5 (P < 0.00001); I ² = = 0.83). I ² = 0% Control In <u>SD Total V</u> .8 14.1 31 26 5.58 44	Mean Differen Velaht IV. Random. J 6.3% -20.40 [-26.53, - 7.5% -12.24 [-14.02, -	-200 -100 0 Favours [experimental] Favo & Cl IV. Random. 9: 127]	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: Z Test for suboroup differe Study or Subgroup 2.4.1 FZHY Jiang 2019 Liu 2020a	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000 ences: Chi ² = 6.37. Experimental <u>Mean SD Tot</u> 44.2 11.25 4 35.63 5.19 4	df = 15 (P < 0.00001 1) df = 2 (P = 0.04). I ^a = Control <u>ial Mean SD T</u> 41 68.17 14.11 14 45.26 5.63); P = 77% = 68.6% = <u>fotal Weight</u> = 41 = 6.8% = 44 = 7.4%	Mean Difference IV. Random. 95% Cl -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37]	Favours [experimental] F	Favours [control]
st for overall effect: 2 tal (95% Cl) terogeneily: Tau ^s = st for overall effect: 2 st for suboroup diffe udy or Suboroup 3.1 FZHY so 2015 J 2020a U 2012	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) arences: Chi ² = 0.37. df = 2 (F Experimental Mean SD Total Me 41.02 2.28 44 53. 40.5 8.2 40 51	5 (P < 0.00001); I ² = = 0.83). I ² = 0% Control III SD Total V 8 14.1 31 26 5.58 44 .5 10.1 40	Mean Differen Veiaht IV. Random. J 6.3% -20.40 [-26.53, - 7.5% -12.24 [-14.02, - 7.0% -1.1.00 [-15.03,	200 100 0 Favcurs (experimental) Favc Mean Differe X. Cl IV. Random 31 (27)	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: Zi Test for subaroup differe Study or Subgroup 2.4.1 FZHY Jiang 2019 Liu 2020a Wu 2012	1.01; Ch ² = 65.34, = 6.88 (P < 0.0000 Inces: Ch ² = 6.37. Experimental Mean SD Tol 44.2 11.25 4 35.63 5.19 4 36.6 6.3 4	df = 15 (P < 0.0001 1) df = 2 (P = 0.04). I ^a = Control al Mean SD T 41 68.17 14.11 14 45.26 5.63 40 41.8 5.2); P = 77% : 68.6% <u>Total Weight</u> 41 6.8% 44 7.4% 40 7.4%	Mean Difference IV. Random. 95% Cl -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37] -5.20 [-7.73, -2.67]	Favours [experimental] F	Favours [control]
st for overall effect : tal (95% CI) terogeneity: Tau ² = st for overall effect : st for suboroup diffe udv or Suboroup diffe udv or Suboroup - 3.1 FZHY ao 2015 1.2020a u 2012 = 2012	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) srences: Chi ² = 0.37. df = 2 (F Experimental Mean SD Total Me 42.4 10.2 31 62 41.02 2.28 44 53. 40.5 8.2 40 51 33 5 15	5 (P < 0.0001); P = = 0.83). P = 0% Control in <u>SD Total V</u> .8 14.1 31 26 5.58 44 .5 10.1 40 18 9 14	Mean Differen Veleht IV. Random. J 6.3% -20.40 [-26.53, - 7.5% -12.24 [-14.02, - 7.0% -11.00 [-15.03, 6.6% -5.00 [-10.35	200 100 0 Faxcurs (experimental) Faxcurs (exp	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect. Z Test for subaroup differe Study or Subgroup 2.4.1 FZHY Jiang 2019 Liu 2020a Wu 2012 Xia 2012	1.01; Ch ² = 65.34, = 6.88 (P < 0.0000 nces: Ch ² = 6.37. Experimental <u>Mean SD Tof</u> 44.2 11.25 4 35.63 5.19 4 36.6 6.3 4 46 6	df = 15 (P < 0.0001 1) df = 2 (P = 0.04). I ^a = <u>Control</u> al <u>Mean SD J</u> 41 68.17 14.11 14 45.26 5.63 10 41.8 5.2 15 54 8); P = 77% 68.6% <u>fotal Weight</u> 41 6.8% 44 7.4% 40 7.4% 14 6.8%	Mean Difference IV. Random. <u>95% Cl</u> -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37] -5.20 [-7.73, -2.67] -8.00 [-13.17, -2.83]	Favours [experimental] F	Favours [control]
st for overall effect: 2 tal (95% CI) terogeneity: Tau ² = st for overall effect: 2 st for suboroup diffe udv or Suboroup diffe udv or Suboroup diffe 1,1 F2HY so 2015 J 2020a U 2012 a 2012 a 2012 a 2012 a 2012	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001) intences: Chi ² = 0.37. df = 2 (F Experimental Mean SD Total Me 42.4 10.2 31 66 41.02 2.28 44 53 40.5 8.2 40 51 33 5 15 44.67 18.23 60 66.	5 (P < 0.0001); P = = 0.83). P = 0% Control in SD Total V 8 14.1 31 26 5.58 44 .5 10.1 40 18 9 14 18 9 14	Mean Differen Neicht IV. Random. : 6.3% -20.40 [-26.53, 7.5% -12.24 [-14.02, - 7.0% -11.00 [-15.03, 6.6% -5.00 [-10.35 5.6% -2.17 [-29.63, -	200 100 Fexcurs (experimental) Favo	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: Z Test for subarous differe 2.4.1 F2HY Jiang 2019 Liu 2020a Wu 2012 Xiang 2012 Zhang 2014	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000 inces: Chi ² = 6.37. Experimental Mean SD Tol 44.2 11.25 4 35.63 5.19 4 36.6 6.3 4 46 6 45.8 19.3 3	df = 15 (P < 0.0001 1) ff = 2 (P = 0.04). P = Control al Mean SD T 41 68.17 14.11 14 45.26 5.63 40 41.8 5.2 15 54 8 10 47.5 21.3); P = 77% 68.6% (otal Weight 41 6.8% 44 7.4% 40 7.4% 14 6.8% 30 5.3%	Mean Difference IV. Random. 95% Cl -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37] -5.20 [-7.73, -2.67] -8.00 [-13.17, -2.83] -1.70 [-11.99, 8.59]	Favours [experimental] F	Favours [control]
at (or overall effect: 2 al (95% CI) erogeneity: Tau ² = it for overall effect: 2 it for subgroup diffe udv or Subgroup 1.1 F2HY o 2015 12020a 12012 2012 2012 2012 2012 2012 2	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001)	5 (P < 0.0001); P = = 0.83). P = 0% Control m SD Total V 8. 14.1 31 26 5.58 44 .5 10.1 40 88 9 14 15 25.12 60 44 10.6 65	Mean Differen Velaht IV. Randsm. 1 6.3% -20.40 [-26.53, - 7.5% -12.24 [-14.02, - 7.6% -1.100 [-15.03, 6.6% -5.00 [-10.35 5.6% -21.76 [-29.63, - 7.1% -20.20 [-23.84, -	200 100 Fescus [sxperimental] Favc	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: 2 Test for subcroup differe Study or Subgroup 2.4.1 F2HY Jiang 2019 Liu 2020a Wu 2012 Zhang 2014 Subtotal (95% CI)	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000 inces: Chi ² = 6.37. I Experimental Mean SD Tol 44.2 11.25 4 35.63 5.19 4 36.6 6.3 4 46.6 6 45.8 19.3 3	df = 15 (P < 0.0001 1) df = 2 (P = 0.04), P = Control al Mean SD T 41 68.17 14.11 44 45.26 5.63 10 41.8 5.2 15 54 8 30 47.5 21.3 10); P = 77% 68.6% Cotal Weight 41 6.8% 44 7.4% 40 7.4% 14 6.8% 14 6.8% 16.9 33.7%	Mean Difference IV. Random. <u>95% Cl</u> -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37] -5.20 [-7.73, -2.67] -8.00 [-13.17, -2.83]	Favours [experimental] F	Favours [control]
t for overall effect: 2 al (95% CI) erogeneity: Tau ² = t for overall effect: 2 t for subaroun diffe idv or Subaroun diffe t for subaroun diffe 2020a 2015 2020a 2015 2020a 2012 2012 ag 2017 g 2017 g 2012 2014	629 183.34; Chi ² = 145.79, df = 1 Z = 7.30 (P < 0.00001)	5 (P < 0.0001); P = = 0.83i. P = 0% Control in <u>SD Total V</u> 8 14.1 31 26 5.58 44 15 25.12 60 48 9 14 15 25.12 60 4 10.6 65 2 23.4 30	Mean Differen Velaht IV. Randsm. 1 6.3% -20.40 [-26.53, - 7.5% -12.24 [-14.02, - 7.6% -1.100 [-15.03, 6.6% -5.00 [-10.35 5.6% -21.76 [-29.63, - 7.1% -20.20 [-23.84, -	200 100 0 Fexcurs (experimental) Favc % Cl IV. Random 3 271	burs [control]	Total (B5% CI) Hoterogeneity: Tau's 41 Test for overall effect 2 Test for subgroup 2.4.1 F2HY Jiang 2019 Liu 2020a Wu 2012 Zhang 2014 Zutang 2014 Subtoal (S5% CI) Hoterogeneity: Tau's 43	1.01; Ch ² = 65.34, = 6.88 (P < 0.0000 inces: Ch ² = 6.37. Experimental Mean SD Tof 44.2 11.25 4 35.63 5.19 4 36.6 6.3 4 46 6 45.8 19.3 : 1 2.71; Ch ² = 39.18,	df = 15 (P < 0.0001 1) df = 2 (P = 0.04), P = Control al Mean SD T 41 68.17 14.11 14 45.26 5.63 15 54 8 30 47.5 21.3 70 df = 4 (P < 0.0001); P = 77% 68.6% Cotal Weight 41 6.8% 44 7.4% 40 7.4% 14 6.8% 14 6.8% 16.9 33.7%	Mean Difference IV. Random. 95% Cl -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37] -5.20 [-7.73, -2.67] -8.00 [-13.17, -2.83] -1.70 [-11.99, 8.59]	Favours [experimental] F	Favours [control]
at for overall effect: 2 tai (95% CI) terogeneity: Tau ² = to roverall effect: 2 to roverall effect: 2 to roverall effect: 2 to 2014 a 2012 a 2012 b 2014 b b total (95% CI) terogeneity: Tau ² =	629 183.34; Chi ² = 145.79, df = 145.79, df = 245.79, df = 245.70, df = 245.70, df = 245.70, df = 245.70, df = 10.37, df = 245.70, df = 10.37, df = 245.70, df = 10.37, df = 1	5 (P < 0.0001); P = = 0.83). P = 0% Control in <u>SD Total V</u> 8 14,1 31 26 5.58 44 .5 10.1 40 83 9 14 83 9 14 83 9 14 85 25.12 60 .4 10.6 65 .2 23.4 30 284	Mean Differen Weicht U. Random. 1 6.3% 2040 (2653) 7.5% 12.24 [-14.02, 7.5% 12.24 [-14.02, 7.5% 21.78 [-29.63, 7.1% 20.20 [-23.84, -1.0% 21.0% [-18.04, 4.5% 2.06 [-18.04, 4.5% 2.06 [-18.04, 2.06 [-18.04, 2	200 100 0 Fexcurs (experimental) Favc % Cl IV. Random 3 271	burs [control]	Total (95% CI) Heterogeneity: Tau ² = 41 Test for overall effect: 2 Test for subcroup differe Study or Subgroup 2.4.1 F2HY Jiang 2019 Liu 2020a Wu 2012 Zhang 2014 Subtotal (95% CI)	1.01; Ch ² = 65.34, = 6.88 (P < 0.0000 inces: Ch ² = 6.37. Experimental Mean SD Tof 44.2 11.25 4 35.63 5.19 4 36.6 6.3 4 46 6 45.8 19.3 : 1 2.71; Ch ² = 39.18,	df = 15 (P < 0.0001 1) df = 2 (P = 0.04), P = Control al Mean SD T 41 68.17 14.11 14 45.26 5.63 15 54 8 30 47.5 21.3 70 df = 4 (P < 0.0001); P = 77% 68.6% Cotal Weight 41 6.8% 44 7.4% 40 7.4% 14 6.8% 14 6.8% 16.9 33.7%	Mean Difference IV. Random. 95% Cl -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37] -5.20 [-7.73, -2.67] -8.00 [-13.17, -2.83] -1.70 [-11.99, 8.59]	Favours [experimental] F	Favours [control]
t for overall effect: 2 al (95% CI) strogeneity: Tau ² = t for overall effect; t for subarous diffe udv or <u>Subarous</u> diffe diffect 2020a 2020a 2020a 2020a 20212 2020a 20212 2020a 20212	533 Cb ²⁺ 145.76, df = 1 183.34, Cb ²⁺ 145.76, df = 1 1 27.30 (* 0.0000; cl = 2 if if 1 2 Experimental Mass 50 Total Ma 42.4 10.2 31 67 41.02 2.28 44 35 15 40.5 8.2 4.0 5 32 60 66 37.2 10.6 65 52 4.0 5 2.2 44 30 5 42.4 10.2 34 51 5 2.2 44 30 5 42.2 14.3 5 2.2 42 30 5 2.2 44 30 5 2.2 2.20, Ch ²⁺ 39.44, df = 6 5.2 2.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.4 3.5 3.2 3.2 2.2 2.2 3.4 3.5 3.2 3.2 3.2 3.2 3	5 (P < 0.0001); P = = 0.83). P = 0% Control in <u>SD Total V</u> 8 14,1 31 26 5.58 44 .5 10.1 40 83 9 14 83 9 14 83 9 14 85 25.12 60 .4 10.6 65 .2 23.4 30 284	Mean Differen Weicht U. Random. 1 6.3% 2040 (2653) 7.5% 12.24 [-14.02, 7.5% 12.24 [-14.02, 7.5% 21.78 [-29.63, 7.1% 20.20 [-23.84, -1.0% 21.0% [-18.04, 4.5% 2.06 [-18.04, 4.5% 2.06 [-18.04, 2.06 [-18.04, 2	200 100 0 Fexcurs (experimental) Favc % Cl IV. Random 3 271	burs [control]	Total (195% CI) Hoterogeneity: Tar's 4 / Test for overail effect. 2 Test for averail effect. 2 Test for automus differe 2.4.1 F2HY Jaing 2019 Liu 2020a Wu 2012 Xing 2019 Subtotal (95% CI) Heterogeneity: Tar's 3 2.4.2 FFBJRG	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000 nnces: Chi ² = 6.37. Experimental Mean SD Tof 44.2 11.25 4 36.6 6.3 4 46 6 45.8 19.3 5; 11 2.71; Chi ² = 39.18, = 3.55 (P = 0.0004	df = 15 (P < 0.0001 1) df = 2 (P = 0.04). P = Control al Mean SD T 41 68.17 14.11 44 45.26 5.63 10 41.8 5.2 15 54 8 30 47.5 21.3 70 16 = 4 (P < 0.0001 8)); P = 77% : 68.6% : 68.6%	Mean Difference IV. Random. 95% Cl -23.97 [-29.49, -18.45] -9.63 [-11.89, -7.37] -5.20 [-7.73, -2.67] -8.00 [-13.17, -2.83] -1.70 [-11.99, 8.59]	Favours [experimental] F	Favours [control]
t for overail effect: 2 al (95% CI) srogeneity: Tau* = the overail effect: the subarous diffe very subarous diffe very subarous diffe very subarous diffe very subarous diffe very subarous diffect very subarous diffect ve	E23 E23 183.34; Cli ^a = 146.76; dl = 1 183.76; dl = 1 183.34; Cli ^a = 146.76; dl = 1 120 183.34; Cli ^a = 1.66; dl = 1.67 120 Experimental Mean 50 4427 142.2 31 4102 2.8 44.53 31 51 53 344.67 162.3 66 37.2 10.6 65 342 19.4 30.5 242 20.5 20.5 =26.20; Cli ^b = 39.41; dl = 6. 2.4	5 (P < 0.0001); P = = 0.83). P = 0% Control m <u>SD Total V</u> .8 14.1 31 6 5.58 44 .5 10.1 40 15 25.12 60 .4 10.6 65 .2 23.4 30 .2 23.4 30 P < 0.00001); P = 8	Mean Differen Veloht IV. Random, 1 6.3% 20.40 [-26.53, - 7.5% 1-2.24 [-14.02, - 7.5% - 7.5% - 7.5% - 7.5% - 5.5% 2.71 [-2.84, - 4.5% - 2.00]-12.88 4.4.5% - 13.65 [-16.81, - 5%	200 100 Fescus [sxperimental] Favc	burs [control]	Total (195%, CI) Helerogeneity, Tar 4 Fest for ownel inelfect 2 Test for subarous differe Study or Subarous differe Liu 2020 Jung 2019 Liu 2020 Wu 2012 Xia 2012 Zuang 2014 Subtoal (S% CI) Helerogeneity: Tar 4 - 3 Test for overall effect 2 2.4.2 FFBJRG A 12021	1.01; Chi ² = 65.34, = 6.88 (P < 0.0000 nnces: Chi ² = 6.37.1 Experimental Mean SD Tol 44.2 11.25 4 36.6 6.3 4 46.6 6 45.8 19.3 1 12.71; Chi ² = 39.18, = 3.55 (P = 0.0004 26.35 6.28 4	df = 15 (P < 0.0001 1) df = 2 (P = 0.04), P = Control ial Mean SD T 11 68.17 14.11 14 45.26 5.63 10 41.8 5.2 15 54 8 30 47.5 21.3 10 df = 4 (P < 0.0001 1) 13 54.14 10.15); P = 77% 68.6% 10 68.6% 11 6.8% 44 7.4% 40 7.4% 14 6.8% 30 5.3% 169 33.7% ; P = 90% 43 7.2%	Mean Difference IV. Random. 95% CI 23.97 (29.49, -18.45) -9.83 (+14.86, -7.37) -5.20 (+7.73, -2.67) -1.70 (+11.99, 5.59) -10.04 (-15.59, -4.49) -27.79 (-31.36, -24.22)	Favours [experimental] F	Favours [control]
t for overall effect: 2 al (35% CI) progenetic; Tou* = for overal effect: for subaroun diffe dv or Subaroun 1 FZHY 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2014 stotal (85% CI) mogenety; Tau* = 1 for overall effect: 2 FFBJRG n 2019	E33 Clip* = 145.76, dl = 1 183.34; Clip* = 145.76, dl = 1 2 183.34; Clip* = 13.07, dl = 2 (F 1 menoac: Clip* = 0.37, dl = 2 (F 1 Experimental 41.02 23 41.02 2.28 45.33 5 15 5 44.07 18.23 60 37.2 10.6 65 44.07 18.23 60 37.2 10.6 65 49.2 19.4 30 28.20; Clip* = 38.41, df = 6. 2.2 2.44, 67 8.23 2.42; Clip* = 3.84, df = 6. 2.2 2.20; Clip* = 3.84, df = 6. 2.2 2.20; Clip* = 3.84, df = 6. 10	5 (P < 0.00001); P = = 0.83); P = 0% Control m SD Total V 8. 14.1 31 8. 558 44 5 558 44 5 558 44 5 558 44 5 558 24 2 24 4 106 65 2 23.4 30 2 24 P < 0.0001); P = 8 3 15.3 37	Mean Differen Weight IV. Random. J 6.3% 20.40 (2653). 7.5% 12.22 (1-4.02, - 7.5% 12.24 (1-4.02, - 7.5% 21.76). 7.1% 20.20 (22.84, - 4.5% 20.16). 7.1% 20.20 (22.84, - 4.5% 20.20). 7.1% 20.20 (22.84, - 5% 21.10). 5.5% -11.10 (-18.40, - 5.5% -11.10).	200 100 0 Fescus (experimental) Favc Mean Difference X CI IV. Random 21 IV. IV. IV. IV. IV. IV. IV. IV. IV. IV.	burs [control]	Total (195% CI) Hoterogeneity: Tar's 4 / Test for valential effect. Z Test for subarous differe 24.1 F2HY Jang 2019 Liu 2020a Wu 2012 Xie 2012 Subtotal (55% CI) Heterogeneity: Tar's 3 Z 4.2 FFBJRG A 2021 Chen 2019	1.01; Chi ² = 65.34, = 68.8 (P < 0.0000 nnces: Chi ² = 6.37. Experimental Mean SD Tol 44.2 11.25 - 45.63 Chi 36.6 C - 45.8 - 45.8 Chi 2.71; Chi ² = 39.18, = 3.55 (P = 0.0004 - 26.35 C - 28.4 - 81.5 14.8 d	df = 15 (P < 0.0001 1) df = 2 (P = 0.04), P = Control ial Mean SD T 11 68.17 14.11 14 45.26 5.63 10 41.8 5.2 15 54 8 30 47.5 21.3 10 df = 4 (P < 0.0001 1) 13 54.14 10.15); P = 77% 68.6% 10 68.6% 11 6.8% 44 7.4% 40 7.4% 14 6.8% 30 5.3% 169 33.7% ; P = 90% 43 7.2%	Mean Difference IV. Random. 85% CI 23.97 (29.49, -18.45) -8.63 (+1.48, -7.37) -5.20 (+7.73, -2.67) -1.00 (+1.17, -2.83) -1.70 (+1.98, 5.59) -10.04 (-15.59, -4.49) -27.79 (-31.38, -24.22)	Favours [experimental] F	Favours [control]
t for overall effect: 2 al (95% CI) srogeneity: Tar ¹ = 1 the overall effect: 1 the subarous diffe the overall effect: 1 the subarous diffe 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2012 2014 2015 2017	E23 E23 183.34; Cli ^a = 146.76; dl = 1 183.36; dl = 1 183.34; Cli ^a = 146.76; dl = 1 127.30 (P < 0.0001)	5 (P < 0.00001); P = = 0.83\. P = 0% Control m SD Total V 8. 14.1 31 6 558 44 5 558 44 5 558 44 5 558 44 15 2512 60 4 105 655 24 P < 0.00001); P = 8 P < 0.00001; P = 8 3 15.3 37 8 15.27 28	Mean Differen VI. Bandom. J. 6.3% 20.40 (26.53. 7.5% 12.24 (14.02. 7.0% 11.00 (-16.33. 6.5% 2.02 (12.38.4.4.5) 4.5% 2.00 (12.38.4.4.5) 5.5% 1.28 (15.01,1.5%) 5.5% -11.10 (-16.8.0), 5.5%	200 100 Fescus [sxperimental] Fax	burs [control]	Total (19%). C1) Heleropeneity. Tart # test for ownel intel # C2. Test for subarous differe Study or Subarous differe Liu 2020a Wu 2012 Xia 2012 Ziang 2014 Substal (S%). C1) Heleropeneity. Tart = 3. Test for overal effect. Z 2.4.2 FFBJRG A.12021 Chen 2019	1.01; Chi ² = 65.34, = 68.8 (P < 0.0000 nnces: Chi ² = 6.37. Experimental Mean SD Tol 44.2 11.25 - 45.63 Chi 36.6 C - 45.8 - 45.8 Chi 2.71; Chi ² = 39.18, = 3.55 (P = 0.0004 - 26.35 C - 28.4 - 81.5 14.8 d	df = 15 (P < 0.00001 1) ff = 2 (P = 0.041, P = Control al Mean SD T 11 88.17 14.13 14 88.17 14.13 14 522 15 54 8 10 41.8 5.2 15 94.8 10 47.5 21.3 10 47.6 21.3 11 95.3 18 88.37 21.99); P = 77% cotal Weight 41 6.8% 44 7.4% 40 7.4% 40 7.4% 14 6.8% 30 5.3% 169 33.7%); P = 90% 43 7.2% 37 6.2% 	Mean Difference IV. Random, 95% CI 23.97 (2249, -1644) 9.63 (-1180, -7.37) -8.00 (-1317, -2.83) -1.70 (-11.99, 8.59) -10.04 (-15.59, -4.49) -27.79 (-31.36, -24.22) -13.80 (-21.16, -6.44) -5.77 (-5.42, -3.08)	Favours [experimental] F	Favours [control]
ther overall effect: 2 in (195% CI) strogeneilly: Tau's for overall effect: 2 for suboround diffe div or Suboround diffe div or Suboround diffe 1 FZHY 2 2015 2012 2015 2020 2	E33 Clip* = 145.76, dl = 1 183.34, Clip* = 145.76, dl = 1 7.30 f < 0.0000, dl = 0.16	5 (P < 0.00001); P = = 0.83). P = 0%. Control m SD Total V 8 14,1 31 6 558 44 5 25.1 26 1,1 40 18 9 14 15 25.1 26 1,1 40 18 9 14 15 25.1 26 2 23,4 30 284 24 30 284 P < 0.00001); P = 8 3 15,3 37 8 15,27 28 15 3,25 38	Mean Differen Neioht IV. Random. J 6.3% 20.40 (2653). 7.5% 1224 (1-402.) 7.5% 1224 (1-402.) 7.5% 21.76 (1-28.84.) 7.5% 21.76 (1-28.84.) 7.1% 20.20 (22.84.) 7.1% 20.20 (22.84.) 7.1% 2.14 (1-28.84.) 5.5% -11.10 [-18.40.) 5.8% -14.10 [-18.40.]	20 10 0 Fescus (experimental) Favc Mean Difference X CI IV. Random 21 IV. IV. IV. IV. IV. IV. IV. IV. IV. IV.	burs [control]	Total (195% CI) Hoterogeneity: Tar's 4 1 Test for valential effect 2: Test for subarous differe 24.1 F2HY Jaing 2019 Liu 2020a Wu 2012 Xie 2012 Zhang 2014 Subtotal (55% CI) Heterogeneity: Tau's 3: Test for overall effect 2 2.4.2 FFBJRG A 2021 Liu 2020b	1.01; Chi ² = 65.34, = 68.8 (* 0.0000 nnces: Chi ² = 6.37. Experimental Mean SD Tol 44.2 11.25 - 36.56 5.19 - 36.56 5.19 - 36.56 1.51 - 1 - 2.71; Chi ² = 39.18, = 3.55 (P = 0.000 26.35 6.28 - 8.15 14.8 - 3.55 11.8.2 -	df = 15 (P < 0.00001 1) ff = 2 (P = 0.041, P = Control al Mean SD T 11 88.17 14.11 14 4526 56.38 10 41.8 5.2 15 54 8 30 47.5 21.3 10 41 64.26 0.00001 1) 13 54.14 10.15 11 95.3 18 18 38.37 21.99 18 38.32 14.99 18 38.35 18); μ = 77% 68.6% total Weight 41 6.8% 44 7.4% 40 7.4% 40 7.4% 41 6.8% 43 7.2% 37 6.2% 28 5.7%	Mean Difference IV. Random. 95% CI -23.97 [-29.49, -18.45] -8.03 [-11.88, -7.37] -8.00 [-13.77, -2.67] -8.00 [-13.17, -2.63] -10.04 [-15.59, -4.49] -10.04 [-15.59, -4.49] -27.79 [-31.36, -24.22] -13.80 [-21.16, -6.44]	Favours [experimental] F	Favours [control]
tor overall effect: 2 it (95% CI): mogenety: Tau* = for suberound diffe- tor overall effect: for suberound diffe- tor suberound diffe- tor Suberound f F2HY 2015 2012 2012 2012 2012 2017 2015 2020 20	E23 183.34; Cli ² = 146.75; dl = 1 183.34; Cli ² = 146.75; dl = 1 183.34; Cli ² = 1.36; dl = 1.65; 183.34; Cli ² = 1.36; dl = 1.65; Experimental Mean 5D 140.2 31 410.2 23 410.2 23 31 51 32 105 33 51 4427 182.3 428 18.24 232 225 242.20; Cli ¹ = 394.1, dl = 6; 242.20; Cli ¹ = 394.1, dl = 6; 242.21; Cli 2.75; 243.22; Cli 1.75; 243.22; 243.21; 235.22; 243.21; 243.21; 244.2; 245.2; 251.11; 252.2; 253.11; 254.11; 254.11; 255.11; 255.11; 255.11; 255.11; 257.11; 257.11; 257.11; <td>5 (P < 0.00001); P = = 0.83), P = 0%. Control m SD Total V & 14.1 31 fo 5.58 44 .5 10.1 40 18 9 14 15 2512 60 .2 23.4 30 .284 P < 0.00001; P = 8 .3 15.3 37 .8 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .5 23 88 .5 23 88 .5 23 88 .5 24 88 .5 25 88 .5 28 88 .5</td> <td>Mean Differen Vicibit IV. Bandom. J. 6.3% 20.40 (26.53.1) 7.5% 12.24 (14.02 7.0% -11.00 [-16.30.6) 6.5% 20.04 (26.35.2) 7.0% -11.00 [-16.30.6) 5.6% -2.178 [-28.6]. 4.5% -2.02 (-12.88 4.45% - 5.5% -11.10 [-18.40.6] 5.5% -11.10 [-18.40.7] 5.5% -12.85 [-48.07] 5.5% -12.85 [-48.07] 5.5% -12.85 [-48.07]</td> <td>20 100 Fescus [sxperimental] Fax</td> <td>burs [control]</td> <td>Total (195% CI) Hoterogeneity: Tar's 4 1 Test for valential effect 2: Test for subarous differe 24.1 F2HY Jaing 2019 Liu 2020a Wu 2012 Xie 2012 Zhang 2014 Subtotal (55% CI) Heterogeneity: Tau's 3: Test for overall effect 2 2.4.2 FFBJRG A 2021 Liu 2020b</td> <td>1.01; Ch² = 65.34, - 6.88 (P < 0.0000</td> ncnes: Ch ² = 6.37. Experimental Mean SD Tol 44.2 11.25 36.6 6.3 44.6 11.25 36.6 6.3 44.6 11.25 36.8 19.3 2.71; Ch ² = 3.95 (P = 0.000 26.35 (S = 0.000 32.56 (S = 0.000 26.35 (S = 0.000 26.35 (S = 0.000 32.56 (S = 0.000	5 (P < 0.00001); P = = 0.83), P = 0%. Control m SD Total V & 14.1 31 fo 5.58 44 .5 10.1 40 18 9 14 15 2512 60 .2 23.4 30 .284 P < 0.00001; P = 8 .3 15.3 37 .8 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .3 15.27 28 .5 23 88 .5 23 88 .5 23 88 .5 23 88 .5 24 88 .5 25 88 .5 28 88 .5	Mean Differen Vicibit IV. Bandom. J. 6.3% 20.40 (26.53.1) 7.5% 12.24 (14.02 7.0% -11.00 [-16.30.6) 6.5% 20.04 (26.35.2) 7.0% -11.00 [-16.30.6) 5.6% -2.178 [-28.6]. 4.5% -2.02 (-12.88 4.45% - 5.5% -11.10 [-18.40.6] 5.5% -11.10 [-18.40.7] 5.5% -12.85 [-48.07] 5.5% -12.85 [-48.07] 5.5% -12.85 [-48.07]	20 100 Fescus [sxperimental] Fax	burs [control]	Total (195% CI) Hoterogeneity: Tar's 4 1 Test for valential effect 2: Test for subarous differe 24.1 F2HY Jaing 2019 Liu 2020a Wu 2012 Xie 2012 Zhang 2014 Subtotal (55% CI) Heterogeneity: Tau's 3: Test for overall effect 2 2.4.2 FFBJRG A 2021 Liu 2020b	1.01; Ch ² = 65.34, - 6.88 (P < 0.0000	df = 15 (P < 0.00001 1) Control al Mean SD 1 14 88.17 14.11 14 4528 5.63 10 418 52.2 15 54 6 10 418 52.2 13 54.14 10.15 11 95.3 18 38 38.73 21.9 38 38 37 21.9); P = 77% • 68.6% • 68.5% • 74% • 14.68% • 30.5.3% • 16.9% • 33.7% • 19.0% • 72% • 33.7% • 72% • 33.7% • 72% • 38.5.7% • 72% • 38.5% • 72% • 38.5% • 72% • 38.5% • 72% • 38.7% • 72% • 38.7% • 72% • 38.7% • 74% • 74% • 72% • 38.5% • 74% • 74% • 72% • 38.5% • 74% • 74% • 72% • 38.7% • 74% • 74% • 72% • 74% • 74% • 72% • 74% • 74% • 74% • 72% • 74% • 74% • 72% • 74% • 74% • 72% • 74% • 74% • 74% • 74% • 72% • 74% • 74%	Mean Difference IV. Random. 95% CI -23.97 (-29.49, -18.45) -8.03 (-11.48, -7.37) -5.20 (-7.73, -2.67) -5.20 (-7.73, -2.77) -8.00 (-11.57, -2.83) -1.00 (-11.98, -5.59) -10.04 (-15.59, -4.49) -27.79 (-31.36, -24.22) -13.80 (-21.16, -6.44) -6.71 (-15.42, -0.80) -2.97 (-5.09, -0.85)	Favours [experimental] F	Favours [control]
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tor overall effect: 2 (1657, correctly Carlor of the c	529 183.34; Ch ²⁺ = 145.76, dl = 1 183.34; Ch ²⁺ = 145.76, dl = 1 2 - 7.30 f ≈ 0.0007, dl = 2.66 Experimental Mean SD Total Me 424 10.2 31 4102 28 40.57 30 5 34.47 442.7 10.2.3 66 37.2 10.6 65 37.2 10.6 65 44.67 10.2.3 84.4 40.5 2.2 Ch ²⁺ = 3.03.41, df = 6 5.2 -6.14 (P < 0.00001)	5 (P < 0.00001); P = = 0.831, P = 0%. Control m SD Total V 8 14.1 31 15 558 44 5 558 44 15 558 44 15 558 45 9 14 15 25.12 60 4 106 65 22 24 30 15.3 37 8 15.27 28 15 325 38 13 5.32 58 13 5.32 58 15 325 38 15 35 35 15 35 15 35 15 35 15 35 15 35 1	Mean Differen Neinhi IV. Random. J 6.3% 20.40 (25.53.) 7.5% 12.24 (-14.02.) 7.5% 12.24 (-14.02.) 7.5% 22.178 (-29.63.) 7.1% 20.20 (22.84.) 5.6% 20.20 (22.84.) 5.6% -21.78 (-29.63.) 5.5% -11.00 (-18.40.) 5.8% -18.6 (-18.04.) 5.8% -14.1 (-3.25 (-14.38.) 5.8% -4.24 (-21.11.) 6.2% -2.29 (-2.38.) 6.2% -2.29 (-2.38.)	20 100 Fescus [sxperimental] Fax	burs [control]	Total (19%). C1) Heterogeneity. Tart = 4 Fest for oveni effect 2. Test for senial fest 2. Test for subarous differe Study or Subarous differe Liu 2020a Wu 2012 Zhing 2014 Subatel (19%). C1) Heterogeneity. Tart = 3. Test for ovenial effect. 2 2.4.2 FFBJRG A. 2021 Chen 2019 Liu 2020b Pang 2015 Liu 2020b Pang 2017 Wang 3205	101 Ch ² = 65.8 C 6.88 (P < 0.0000	af 15 (P < 0.0001) af 2 (P = 0.04), P = Centrol al Mean SD 1 11 68.17 14.11 14 4526 5.63 10 41.8 5.2 15 54 8 10 41.8 5.2 16 4.6 10 95.3 18 18 38.73 21.99 18 38.75 53 81 82.287 19 3.99 3.99 20.7 18 38.65 4.98 12 22.18 10.51 12 22.18 10.51 12 22.18 10.51 12 22.18 10.51 12 22.18 10.51 12 22.18 10.51 13 22.18 10.51 14 22.21 15 22.18 10.51 15 22.21 15 22.18 10.51 15 22.21 15 22); P = 77% - 68.6% - 701al Weight - 41 6.8% - 44 7.4% - 40 7.4% - 40 7.4% - 40 7.4% - 40 7.4% - 40 7.4% - 53% - 33.7% - 53% - 35.7% - 38 7.4% - 25 5.4% - 39 6.2% - 36 7.4% - 53% - 74% - 54% - 54%	Mean Difference IV. Random. 95% CI 23.97 (29.49, -18.45) -8.20 [-71.3, 2-87] -8.00 [-13.7, 2-87] -8.00 [-13.7, 2-87] -1.70 [-11.98, 5.9] -10.04 [-15.59, -4.49] -7.79 [-31.38, -24.22] -13.80 [-21.16, -6.44] -6.77 [-15.42, 3.08] -8.80 [-14.34, 3.74] -8.80 [-14.34, 3.74] -3.73 [6.04, -14.22] -1.88 [-6.77, 3.41]	Favours [experimental] F	Favours [control]
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FIGURE 5

Forest plot of meta-analysis of liver function (A) alkaline phosphatase; (B) gamma-glutamyl transpeptidase (C) alanine aminotransferase; and (D) aspartate aminotransferase.

3.7 Liver fibrosis

Nine trials reported the serum LN and IV-C levels, and we performed a subgroup analysis on these. The findings revealed that the LN (MD = -19.67, 95% CI: -22.73, -16.61) and IV-C (MD = -18.01, 95% CI: -20.96, -15.06) notably decreased after treatment with the combination of anti-fibrotic CMPs plus UDCA (p < 0.00001) (Figures 6A, B).

HA levels were reported in four clinical studies, and PC-III was reported as an outcome indicator in six. After testing for heterogeneity, HA was analyzed using a fixed-effects model (p = 0.22, $I^2 = 32\%$) and PC-III (p = 0.51, $I^2 = 0$) levels. The experimental group showed a greater decrease in serum HA (MD = -22.33, 95% CI: -31.69, -12.96) and PC-III (MD = -15.19, 95% CI: -19.61, -10.77) levels than the control group (p < 0.00001) (Figures 6C, D).

3.8 Immune function

3.8.1 Immunoglobulin M and immunoglobulin G

The IgG data were processed using a fixed-effects model based on the heterogeneity test (p = 0.96, $I^2 = 0\%$), and a random-effects model was used for the IgM data with high heterogeneity (p = 0.03, $I^2 = 63\%$). The MD (95% CI) of IgG and IgM were -2.86 (-3.63, -2.08) and -1.28 (-1.62, -0.94), respectively. Compared with UDCA alone, the additional use of anti-fibrosis CPMs was more effective in reducing IgG and IgM levels (Figures 7A, B).

3.9 Symptom score

Three trials reported Symptom Score Change as the main outcome. The fixed-effects model was adopted because of the



FIGURE 6

Forest plot of meta-analysis of liver fibrosis (A) laminin; (B) type IV collagen (C) hyaluronic acid; and (D) type III procollagen.



absence of heterogeneity (p = 0.62, $I^2 = 0\%$). The improvement in the Symptom Score Change was better in the experimental group than in the control group (MD = -4.89, 95% CI: -5.24, -4.54; p < 0.00001) (Figure 8).

3.10 Adverse events

Adverse events were described in seven studies. Three articles reported a total of nine patients who developed mild diarrhea and





nausea after taking CPM; however, these symptoms were not severe and did not require treatment. Four studies reported no adverse reactions.

3.11 Publication bias

An inverted funnel plot analysis of the clinical efficacy rate revealed that there may be publication bias in the asymmetric distribution of these publications (Figure 9).

4 Discussion

PBC is the most common autoimmune cirrhotic hepatic disease, occurring in all ethnic groups worldwide (Lv et al., 2020). The prognosis of patients with PBC mostly depends on the degree of liver fibrosis and its complications (Lammers et al., 2015). Patients with PBC tend to seek additional pharmacological treatments because UDCA is not uniformly effective (Lammers et al., 2015). In recent years, TCM has been widely studied and discussed as a complementary therapy. Many studies have shown that TCM plus UDCA has diverse advantages in relieving the clinical symptoms and improving the prognosis of PBC.

This meta-analysis validated the advantages of FZHY, FFBJRG, and ALHX combined with UDCA in the treatment of PBC. Compared with UDCA treatment alone, anti-fibrotic CPMs plus UDCA improved efficacy rates. Furthermore, liver function tests are widely used in clinical practice as indicators of the degree of liver damage. ALP, ALT, AST, and GGT levels decreased after combined treatment with anti-fibrotic CPMs and UDCA. LN, IV-C, PC-III, and HA are indicators for the detection of liver fibrosis, and the addition of anti-fibrosis CPMs to UDCA resulted in decreased levels of these compared with UDCA treatment alone. Moreover, immunological indicators (IgM and IgG) and clinical symptoms also notably improved with the combined treatment of anti-fibrotic CPMs and UDCA. In conclusion, anti-fibrotic CPMs combined with UDCA in the treatment of PBC effectively relieved various clinical indicators. These results provide hope for the treatment and prevention of liver fibrosis and cirrhosis in the future.

The pathobiology of PBC is characterized by inflammation, bile duct damage, and fibrosis (You et al., 2022), of which fibrosis appears in stage II. It is believed that TCM is hepatoprotective and anti-inflammatory and suppresses the activation of hepatic stellate cells, which is advantageous in the treatment of liver fibrosis. Additionally, TCM may have multilevel, multi-pathway, and multi-target pharmacological actions on the comprehensive pathogenesis of PBC. For example, P. notoginseng is an ingredient in FFBJRG and ALHX, and P. notoginseng saponins are its main active constituent, which play an immunomodulatory role by reducing the levels of pro-inflammatory cytokines (Jiang et al., 2013). Furthermore, Ophiacordyceps sinensis, as a duplicate herb in FZHY and FFBJRG, can attenuate liver inflammation and fibrosis by regulating the expression of the TGF-β/MAPK pathway (Fu et al., 2021). Moreover, a mechanistic study has revealed that FZHY can decrease the expression levels of α-SMA, CTGF, TIMP-1, TGF-β1, and Smads, thereby reducing hepatic apoptosis, acute liver injury, and liver fibrosis (Cheng et al., 2013; Xie et al., 2013). An animal experiment reported that FFBJRG ameliorates hepatic disease by reducing the serum collagen levels of LN, HA, and IV-C and downregulating TGF-β-Smad pathway fibroblast signal transduction (Yang et al., 2013). The possible mechanism of ALHX for the inhibition of hepatic fibrosis is related to enhancing MMP2 activity in liver tissue and promoting extracellular matrix degradation by hepatoprotective enzymes (Tan et al., 2010). In brief, certain evidence support the anti-inflammatory and anti-fibrosis effects of FZHY, FFBJRG, and ALHX as the appropriate CPMs for treating PBC.

However, this meta-analysis had some limitations. First, the 22 studies included had a small sample size, all were Chinese, and only a small number of studies reported several outcome indicators. Second, most publications only mentioned random assignment, and only one-third of the studies described a specific randomization method, such as a random number table. Therefore, the findings need to be further evaluated using high-quality trials. Third, different studies had different experimental periods, ranging between 12 and 48 weeks, which may be a source of heterogeneity. Fourth, although anti-fibrosis CPMs were always used in the experimental group, there were three different types—FZHY, FFBJRG, and ALHX, which could also be a source of heterogeneity. Finally, because half of the studies did not mention adverse events, the safety of CPMs as an anti-fibrosis therapy for PBC should be further evaluated, and caution is needed when drawing conclusions.

5 Conclusion

Our research shows that the combination of anti-fibrosis CPMs and UDCA is more effective than UDCA alone in treating PBC in improving clinical efficacy rate, liver fibrosis, liver function, immune function, and symptom score. This systematic review and metaanalysis provides reliable clinical evidence for PBC treatment. Antifibrotic CPMs are a promising therapeutic approach to supplement the conventional treatment of PBC. However, further evidence from high-quality and multi-center studies with larger samples is warranted to confirm the curative effect of anti-fibrosis CPMs during follow-up periods.

Data availability statement

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

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Author contributions

XW and YB designed the study. KS and JC contributed to the data collection and analysis. The results were interpreted by YB. KS drafted the original manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1159222/ full#supplementary-material

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