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OPEN A systematic review and metaanalysis of traditional insect **Chinese medicines combined** chemotherapy for non-surgical hepatocellular carcinoma therapy

Zhaofeng Shi¹, Tiebing Song², Yi Wan³, Juan Xie¹, Yiquan Yan¹, Kekai Shi⁵, Yongping Du¹ & Lei Shang⁴

On the background of high morbidity and mortality of hepatocellular carcinoma (HCC) and rapid development of traditional Chinese medicine (TCM), we conducted a systematic review and metaanalysis of randomized clinical trials (RCTs) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to assess the clinical effectiveness and safety of traditional insect Chinese medicine and related preparation for non-surgical HCC. RCTs were searched based on standardized searching rules in mainstream medical databases from the inception up to May 2016. Ultimately, a total of 57 articles with 4,651 patients enrolled in this meta-analysis. We found that traditional insect Chinese medicine and related preparation combined chemotherapy show significantly effectiveness and safety in objective response rate (P < 0.001), survival time extension [12 months (P < 0.001); 18 months (P < 0.001); 24 months (P < 0.001); 36 months (P < 0.001)], amelioration for life quality [QoL scores improvement (P < 0.001); KPS improvement (P < 0.001); AFP improvement (P < 0.001)] and reduction of therapeutic toxicity [WBC decrease (P = 0.04); gastrointestinal adverse reactions (P < 0.001)]. In conclusion, traditional insect Chinese medicine and related preparations could be recommended as auxiliary therapy combined chemotherapy for HCC therapy.

Hepatocellular carcinoma (HCC), a common kind of primary liver cancer (PLC), ranks as the sixth most common neoplasm and the third most frequent reason for cancer death¹. A report by the World Health Organization (WHO) showed that HCC has become a major health problem nowadays, and the incidence of HCC is increasing as time goes on². It was estimated that 748,300 new liver cancer cases and 695,900 liver cancer deaths occurred worldwide in 2008³. The morbidity and mortality of HCC reached a new peak in 2012 with 782,000 new cases and 745,000 death cases all over the world⁴. The East and South-East Asia along with the Middle and Western Africa have the highest HCC rates compared with other places around the world⁵. Moreover, the rate of HCC in developed countries, such as the United States, has increased rapidly in recent vears⁶.

HCC is the major cause of death among patients who had been diagnosed with cirrhosis⁷. It is estimated that the combined effectiveness of the chronic hepatitis C virus (HCV) and the hepatitis B virus (HBV) infections takes up over 80% of liver cancer cases around the world⁸. With respect to HCC diagnosis, if tumor (lesions \geq 10mm) shows the typical feature on computed tomography (CT) or magnetic resonance images

¹Department of Traditional Chinese Medicine, Xijing Hospital Affiliated to Fourth Military Medical University, Xi'an, 710032, China. ²Department of Orthopaedics, Xi'an City Hospital of Traditional Chinese Medicine, Xi'an, 710021, China. ³Department of Health Services, the Public Health Faculty of Fourth Military Medical University, Xi'an, 710032, China. ⁴Department of Health Statistics, the Public Health Faculty of Fourth Military Medical University, Xi'an, 710032, China. ⁵Department of Engineering, Carnegie Mellon University, Pittsburgh, PA15213, United States. Zhaofeng Shi, Tiebing Song and Yi Wan contributed equally to this work. Correspondence and requests for materials should be addressed to L.S. (email: shanglei@fmmu.edu.cn)

(MRI), no further investigation will be required. If not, the biopsy specimen is required⁹. The measurement of alpha-fetoprotein (AFP) may not be useful in clinical practice and will not affect the formulation of final treatment strategy¹⁰.

Although HCC has a poor prognosis so far, ultrasonography surveillance can diagnose HCC at early stage (single tumors or as many as 3 nodules \leq 3 cm) when the tumor could be cured by resection, liver transplantation, or ablation, and the 5-year survival rate can exceed 50%¹⁰. For the patients at the intermediate or end stage of HCC, palliative methods such as transcatheter hepatic arterial chemoembolization (TACE) or intravenous chemotherapy are appropriately approaches¹¹. Those methods are limited by their toxicities, drug resistance, and miscellaneous adverse effects for end stage patients, meanwhile the survival benefits are still not proven¹². Given this limitation of therapy on HCC, complementary and alternative medicine (CAM) has been increasingly applied to it over the past few decades. Physicians are trying to find more adjunctive or auxiliary therapies to improve patients' quality of life or survival time and reduce side effects caused by chemotherapy.

Traditional insect Chinese medicine is an old ancient Chinese medical concept that is still used today in China. It can be recognized as the Chinese animal species medicines, including the dried medical animal bodies, the medical animal bodies without entrails, secretions and excretions of medical animals and the processing products of insects¹³. Owing to the various versions of the translation for TCM, we could not even find a precise translation for traditional insect Chinese medicine from a number of Chinese-English dictionaries of TCM. As a result, we adopted the word "insect" that has the same literary meaning of "animal" to replace it. The traditional insect Chinese medicine is a broad concept, while the narrow definition of it is only confined to the insect or worm drugs. It has been originally recorded in medical book named Fifty-two patients side for the medical interpretation and practice in the Warring States period of China (475-221BC)¹⁴. And Shennong's herbal classic, one of the earliest Chinese herbal collections of TCM, deeply introduced the effects of traditional insect Chinese medicine¹⁵. Another Chinese herbal masterpiece, Compendium of materia medica, written by Shizhen Li, collected nearly 500 kinds of traditional insect Chinese medicines and classified them meticulously, promoting traditional insect Chinese medicine to a new peak. The modern experimental researches of traditional Chinese insect medicine have been gradually focussing on anti-tumor properties by inhibiting the proliferation of cancer cells, inducing tumor cell apoptosis and improving the immune function of the human body¹⁶.

Traditional insect Chinese medicine, as an essential component of TCM, has been widely applied in the treatment of the non-surgical HCC (at the intermediate stage and the advanced stage) for a long time with side effects a rare occurance. Although a great number of published clinical studies have evaluated different kinds of traditional insect Chinese medicines and the related preparations combined chemotherapy for HCC¹⁷⁻¹⁹, the clinical efficacy and pharmacological mechanism remain unclear. No article of systematic review or meta-analysis has been conducted based on considering the traditional insect Chinese medicines as an integral part to evaluate the efficiency and safety for HCC treatment. Therefore, we conducted a systematic review and meta-analysis to investigate the evidence about traditional insect Chinese medicine and the related preparation combined chemotherapy for the clinical effectiveness and safety of non-surgical HCC.

Materials and Methods

This systematic review and meta-analysis was conducted by order of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement²⁰.

Search strategies. Literatures were extracted from the main electronic databases including PubMed, Embase, Medline, Science Direct (SD), Web of Science, ProQuest, the Cochrane Central Register of Controlled Trials, Springerlink, Wiley Library Online, Chinese Biological Medicine Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Medical Citation Index (CMCI), WanFang Database, Chinese Scientific Journal Database (VIP), and Japan Medical Abstracts Society from their inception up to May 2016. In addition, there were no language restrictions on the literature searching.

The searching terms were performed as follows: "liver cancer," "hepatocellular carcinoma," "liver neoplasm," "primary liver carcinoma," "traditional insect Chinese medicine," "insect drugs," "cinobufatalin," "huachansu," "centipede," "scorpion," "leech," "earthworm," "cantharides," "gecko," "snake venom," "grand beetle," "aspongopus," "gadfly," "honeycomb," "chemotherapy," "interventional therapy" and "random clinical trials". No other restrictions were performed and the free text strategy and Medical Subject Headings (MeSH) terms were conducted in the term searching process. Categories of traditional insect Chinese medicine on literature searching were derived from the classification of MeSH term in CBM database. The searching language in Chinese, English and Japanese was slightly changed based on the situation for different databases adaptation.

Study selection. The study selection was conducted by two reviewers (Z.F.Shi, Y.Q.Yan) independently and disagreements were resolved by the common strategy or a third reviewer (J.Xie). Eligible studies that suited for the following criteria were included in this systematic review and meta-analysis: (1) randomized clinical trials (RCTs); (2) patients were diagnosed as non-surgical HCC (TNM stage II or above; BCLC stage B or above) by pathological results or imaging examinations; (3) participants received traditional insect Chinese medicine and related preparation combined chemotherapy in the treatment group, meanwhile chemotherapy alone in the control group; (4) evaluated outcomes including at least one of the following variables: (a) complete response rate (CR), partial response rate (PR) and CR + PR as a proportion of objective response rate; (b) quality of life (QoL) scores or Karnofsky performance scores (KPS); (c) the Child-Pugh scores; (d) major side effects resulting from traditional insect Chinese medicines or chemotherapy; (5) survival time rate (the number of participants in the treatment and the control group who were alive at 6, 12, 18, 24, 36 months). The studies were excluded if they met

these following criteria: (a) received the Chinese herbal medicine in the control group; (b) received the irrelevant TCM therapies or western medical methods in experimental group; (c) the clinic pathologic types of liver cancer were not compatible with the HCC criteria; (d) severe clinical illnesses (such as liver or kidney disease) or infections; (e) absence or inconsistency of methods, evaluation criteria or results; (f) non-randomized clinical trials (comments, case reports, reviews, editorials, letters, *et al.*), articles unrelated with the topic, or duplicated articles.

Particularly, the clinical stage of HCC was identified according to the TNM staging system of the American Joint Committee on Cancer (AJCC) obtained from the National Comprehensive Cancer Network (NCCN) guideline 2015²¹ (T refers to the size of the original tumor and whether it has invaded nearby tissue; N represents nearby lymph nodes that are involved; M can be recognized as distant metastasis) or the Barcelona Clinical Liver Cancer (BCLC) system coming from the European Association for the Study of the Liver (EASL)²². For the reason of diversity and complexity of TCM therapy, traditional insect Chinese medicine and the related preparation can be obtained from some Chinese herbs that have the synergistic effects without interfering with the major function of traditional insect Chinese medicine. The imaging examination includes the methods of computed tomography (CT) or magnetic resonance imaging (MRI), showing the lesions \geq 10mm at least. Also, CT or MRI can evaluate the CR or PR: CR means all targeted lesions disappear and pathological lymph nodus must reduce to less than 10mm at least, and PR means targeted lesions decrease 30% in the sum of diameters at least. This solid tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor (RECIST) guideline (version 1.1), which has been updated and revised by the European Cancer Organization (ECCO) in 2009²³. The side effects (the chemotherapy related toxicity and TCM adverse effects) included as the follows: bone marrow suppression including leukopenia, thrombocytopenia or anemia; gastrointestinal side effects including nausea, emesis, anorexia, or diarrhea; liver or kidney injury; pyrexia; and pain. The dosage of traditional insect Chinese medicine and chemotherapy in experimental groups and control groups of trials was discrepant. There was no limitation for the dosage in the study searching and including.

Data extraction and quality analysis. Two reviewers (Z.F.Shi, Y.Q.Yan) extracted data independently, assessing the inclusion and exclusion criteria before based on the standardized collection. All disagreements were discussed between two reviewers mentioned before, and the final conclusion was reached after deliberation over with a third reviewer (J.Xie). The extracted characteristics comprised the following items: (1) the name of author and the year of publication; (2) sample size; (3) study design; (4) study performed areas; (5) the baseline characteristics of patients; (6) approaches and duration of treatments; (7) outcome evaluation and trials quality assessment.

The quality analysis was performed by two investigators independently (Z.F.Shi, Y.Q.Yan), using the Cochrane Collaboration's tools for assessing the risk of bias²⁴. This tool was conducted to evaluate the bias of studies across six domains: (1) the method of random allocation; (2) the concealment of allocation; (3) the blinding method; (4) the integrity of outcome data; (5) the outcome data of selective reports; (6) other bias sources. Every domain mentioned above was assessed by the criterion of "yes", "no" or "unclear". The article had 3 or more "yes" could be recognized as high quality and less than 3 "yes" should be considered as low quality. High quality studies had the low bias risk while the low ones had the high bias risk. The related data was analyzed by the software named the Review Manager (RevMan; version 5.2 the Nordic Cochrane Center, the Cochrane Collaboration, 2012 Copenhagen, Denmark), with the outcomes illustrated by images or tables efficiently and conveniently.

Statistical analysis. The RevMan (version 5.2) was applied to pool and analyze data. The reviewer (Z.F.Shi) calculated the risk ratio (RR) with 95% confidence interval (CI) for the dichotomous outcomes and the standard mean difference (Std.MD) or mean difference (MD) with 95% confidence interval (CI) for the continuous outcomes respectively. Statistical heterogeneity was tested through studies by the method of I^2 statistic. It was a quantitative tool for inconsistency and could provide an estimate of variation resulted from heterogeneity. Results of I^2 statistic between 25 and 50% were regarded as low heterogeneity, 50 and 75% were moderate heterogeneity, and above 75% were high heterogeneity. It should be noted that the Cochrane Handbook (version 5.1.0) indicates the value of I^2 statistic above 50% was considered to have considerable heterogeneity²⁵. The subgroup analysis was performed to find the source of heterogeneity. A fixed effects model (applying Mantel-Haenszel method²⁶) was conducted to pool data when the heterogeneity did not exist or moderate, while a random effects model (applying Der Simonian-Laired method²⁷) was performed when there was obvious heterogeneity. Additionally, sensitivity analysis was further conducted to assess the stability of results and evaluate the variation of pooled data. Publication bias was assessed visually by funnel plots and calculated in Egger's test/Begg's test through the software named Stata (version 14.0, StataCrop LP, College Station, US)^{28, 29}. P values lower than 0.05 were judged as statistically significant for the results, representing that the study has publication bias.

Results

The flowchart of article search and selection in the meta-analysis is presented in Fig. 1. Of a total of 358 potentially relevant articles identified from 15 different electronic databases, one hundred and ninety-one studies of them were ruled out for the reason of duplication. Ninety-three publications were further excluded, after detailed screening and analyzing, for the following reasons: (a) thirty-five studies were confirmed unrelated to article topics or could not find the full-text papers even after contacting with authors; (b) ten studies were found to be systematic reviews and meta-analyses; (c) Thirty-two studies were non-clinical trials or non-randomized clinical trials; (d) Sixteen articles were unrelated to hepatocellular carcinoma or traditional insect Chinese medicine. Seventy-four full-text articles were eligible and then reviewed independently. Of 17 publications further

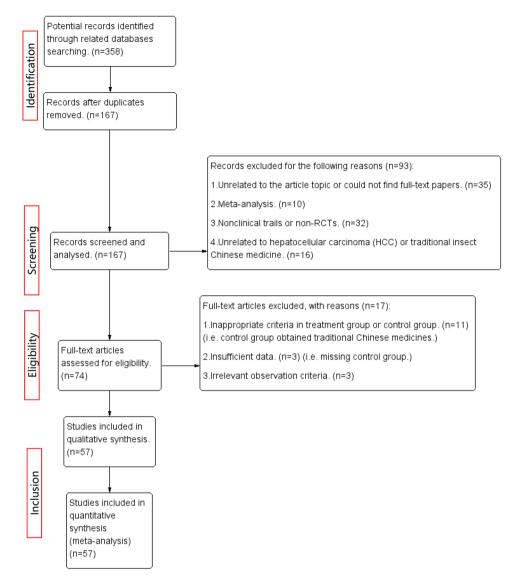


Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

excluded, 11 publications were excluded because the inappropriate criteria of experimental or control group, for instance, the control group contains TCM therapy. Three publications missed sufficient data (i.e. Control group), which made the report outcomes untrustworthy. Three publications obtained irrelevant observation criteria, which seemed inconsistent with the criteria mentioned before. Overall, a total of 57 articles with 4,651 patients were enrolled in this meta-analysis^{30–86}. (Table 1)

Included articles characteristics and quality evaluation. A total of 57 publications met with the final eligibility criteria. All studies were randomized clinical trials (RCTs) and carried out in the hospitals in China. All trials were single-center studies except one performed in 3 different areas' hospitals in China⁴⁵. Published year of articles was between 1999 and 2015. These trials were conducted among men and women between 18 and 85 years old. There were eighteen articles clearly introduce the stage of HCC^{30, 32, 35, 39, 40, 45, 46, 55–57, 59, 60, 65, 68, 69, 74, 80, 85}. The most common stage of HCC was the stage II-III based on the National Comprehensive Cancer Network (NCCN) guidelines 2015²¹ except for 2 publications including stage I hepatocellular carcinoma^{45,74}. (Table 1) Seventeen articles clearly reported the Child-Pugh grades included class A and B^{31, 32, 37, 39, 41, 44, 45, 49–51, 53, 58, 64–67, 73} However, Child-Pugh class C was extra included in 5 articles mentioned before^{39, 44, 50, 51, 64} and Child-Pugh class A was only included in 1 article⁷³. The traditional insect Chinese medicine and the related preparation are diversified in included articles: the major insect related medicines contained as follow: cinobufotalin injection, Aidi injection, sodium cantharidinate and vitamin B6 injection, sodium norcantharidate injection, jinlong capsule, and compound cantharides capsule. (Table 1) The major chemotherapy plan in studies was transcatheter hepatic arterial chemoembolization (TACE), while some articles reported additional chemotherapy regimens, which included FAP (5-fluorouracil + doxorubicin + cisplatin), FAM (5-fluorouracil + doxorubicin + mitomycin), FOLFOX4 (oxaliplatin + calcium folinate + 5-fluorouracil) and 5-fluorouracil^{30, 31, 35, 55, 59, 62, 65}. Drug types of chemotherapy for included trials were listed as follows: oxaliplatin, epirubicin, 5-fluorouracil, pirarubicin,

	Experimental group	Control group	Sex(M/F)	Age	Disease stage	Child-Pugh scores	KPS score	Treatment group	Control group		
											1. Clinical effectiveness
Huang	41	41	44/26	48.54 ± 4.16	II, III	_	>60	Cinobufotalin injection + TACE	TACE (OXA,	3 weeks	2. Life quality
W.K. ³⁰ 2013		11	11/20	years old	11, 111		200	(OXA, EPI)	EPI,)	5 Weeks	3. Blood routine examination
				$\begin{array}{c} \text{E:55.2} \pm 7.4 \\ \text{years old} \end{array}$							1. Clinical effectiveness
Cao Y. ³¹	68	68 78/58	A and B	>50	Compound cantharis capsule $+$ FAP (5-FU,	FAP (5-FU,	10 days	2. Life quality			
2014	00	00	10,00	$\begin{array}{c} \text{C:57.8} \pm 6.9 \\ \text{years old} \end{array}$		T und D	250	EPI, DDP)	EPI, DDP)	10 uuys	3. Complication
					1						4. Economic evaluation
				E:51.65±6.92 years old							1. Clinical effectiveness
					1			Jinlong			2. AFP
Zeng C.S. ³² 2012	30	30	19-Nov	$\begin{array}{c} \text{C:53.20} \pm 9.24 \\ \text{years old} \end{array}$	II, III	A and B	-	capsule + TACE (THP, DDP, 5-FU)	TACE (THP, DDP, 5-FU)	60 days	3. Liver function
					1						4. Complication
					1						5. Life quality
				E:48.65±16.12 years old							1. AFP
Deng Z.Y. ³³	25		20/20		1			Cinobufotalin	TACE (THP,	4 weeks	2. Clinical effectiveness
2015	25	24	29/20	C:48.30 ± 16.24 years old		_	-	injection + TACE (THP, DDP)	DDP)		3. TCM symptoms scores + KPS
											4. Complication
Dong M.E. ³⁴				E:median age 55 years				Cinobufotalin injection + TACE	TACE (GEM,		1. Clinical effectiveness
2014	60	60	76/44	C:median age 53 years		_	-	(GEM, DDP, 5-FU, CF)	DDP, 5-FU, CF)	4 weeks	2. Complication
				E:52.6±11.7 years old						3	1. Clinical effectiveness
Feng X.M. ³⁵ 2012	38	32	44/26	C:53.2 \pm 11.4 years old	11 111	_	>60	Cinobufotalin injection + FOLFOX4	FOLFOX4 (OXA, 5-FU,	rounds (2 days	2. Life quality
					-			(OXA, 5-FU, CF)	CF)	per round)	3. Blood routine examination
				E:median age 58 years				Cinobufotalin			1. Clinical effectiveness
Fu Z.L. ³⁶ 2010	78	78	119/37	C:median age 56 years	-	_	>60	injection + TACE (5- FU, DDP, MMC)	TACE (5-FU, DDP. MMC)	3 months	2. Life quality
					1						3. Complication
											1. Clinical effectiveness
								Cinchufatalia			2. MST and TTP
He S.L. ³⁷ 2012	26	25	37/14	58.8 years old	-	A and B	-	Cinobufotalin injection + TACE (OXA, 5-FU, THP)	TACE (OXA, 5-FU, THP)	2 weeks	3. VEGF, HIF-1α and AFP
								()			4. KPS
											5. Complication
											1. Clinical effectiveness
											2. Survival at 6/12/24 months
								Cinobufotalin	TACE (DDP,	4-5	3. Life quality
i J.F. ³⁸ 2015	25	22	36/11	62.3 years old	-	—	-	injection + TACE (DDP, 5-FU, DOX)	5-FU, DOX)	weeks	4. Comparison of
											WBC,TBIL and ALT 5. Immunological
				E:54.2±6.4				linlana			function 1. Clinical effectiveness
lia C.H. ³⁹ 2008	30	30	44/16	years old C:51.5±7.0	I, II, III	A, B and C	>60	Jinlong capsule + TACE (MMC)	TACE (MMC)	3 months	2. Immunological
				years old E:median						2	function. 3. Life quality 1. Clinical effectiveness
liang C.Y. ⁴⁰ 2013	30	33	36/27	age:57 years C:median	II, III	_	≥60	Jinlong capsule + TACE (5-	TACE (5-FU, THP)	rounds (8 days	2. CBR
-				age:53 years	-			FU, THP)	,	per round)	3. Complication
Continued											2. Complication

	Experimental group	Control group	Sex(M/F)	Age	Disease stage	Child-Pugh scores	KPS score	Treatment group	Control group		
				E:58.32±11.59 years old							1. Clinical effectiveness
				C:57.09 ± 11.77 years old						3	2. Life quality
Ke J. ⁴¹ 2011	38	40	69/9		_	A and B	>60	Cinobufotalin injection + TACE (5- FU, DDP, DOX)	TACE (5-FU, DDP, DOX)	rounds (20 days per	3. Comparison of WBC, TBIL, ALT and AFP
										round)	4. Survival at 6/12 months
]						5. Complication
				E:40.5 years old							1. Clinical effectiveness
				C:41 years old				Cinobufotalin	TACE		2. QoL scores
Kou C.Y. ⁴² 2011	31	31	40/22		i —	-	>60	injection + TACE	(HCPT, DDP,	4 weeks	3. Complication
								(HCPT, DDP, DOX)	DOX)		4. Survival at 12/24/36 months
										2	1. Clinical effectiveness
				1.0				Jinlong	TACE (5-FU,	2 rounds	2. Life quality
Li B. ⁴³ 2013	74	73	97/50	Median age:56.4 years	_	_	>60	capsule + TACE (5-FU, EPI, DDP, MMC, CF)	EPI, DDP, MMC, CF)	(28 days per round)	3. Comparison of Child- pugh, Classification and WBC
				$E:45.2 \pm 4.8$ years old							1. Life quality
Li j. ⁴⁴ 2013	43	62	76/29	C:45.7 ± 6.4 years old	_	A, B and C	_	Aidi injection + TACE (5-FU, THP, DDP,	TACE (5-FU, THP, DDP,	10 days	2. Survival at 6/12/24/36 months
								MMC)	MMC)		3. AFP
											4. TACE times
											1. Clinical effectiveness
											2. Life quality
Li Q. ⁴⁵ 2008	50	46	84/12	50.2 years old	I, II, III	A and B	≥ 60	Cinobufotalin injection + TACE	TACE (5-FU, HCPT, DOX, MMC)	4 weeks	3. Survival at 6/12/24 months
LI Q. 2008	50	40	04/12	50.2 years old	1, 11, 111	A and b	200	(5-FU, HCPT, DOX, MMC)		4 weeks	4. Comparison of WBC, TBIL and ALT
											5. Immunological function
Li Q.M. ⁴⁶								Qining	TACE		1. Clinical effectiveness
2003	20	18	28-Oct	29–65 years old	II, III	-	≥ 60	injection + TACE	(HCPT, 5-FU,	7 days	2. Complication
											1. Life quality
											2. Clinical effectiveness
Li W.H. ⁴⁷	19	19	28-Oct	45 years old	_	_		Cinobufotalin injection + TACE (5-	TACE (5-FU,	2	3. Comparison of WBC and AFP
2006	17	17	20-001	+5 years old				FU, DDP, MMC)	DDP, MMC)	rounds	4. Survival at 12/24 months and median survival time
											5. Complication
Liang B.L. ⁴⁸ 2010	20	20	30-Oct	E:59 \pm 6 years old C:55 \pm 8 years old		_	≥50	Sodium Cantharidinate and vitamin B6 + TACE (MMC, 5-FU, EPI)	TACE (MMC, 5-FU, EPI)	4weeks	Comparison of liver function and blood routine examination
				E:median age 53 years				Sodium Cantharidinate and	TACE (5-FU,	3–4 rounds	1. Clinical effectiveness
Liang C.X. ⁴⁹ 2015	30	30	34/26	C:median age 52 years	_	A and B	>80	Vitamin B6 + TACE (5-FU, DDP, OXA,	DDP, OXA, EPI)	(15 days per	2. Comparison of WBC and AFP
					1			EPI)		round)	3. QoL scores
				E:52.1±9.7 years old				Jinlong			1. Survival at 6/12/24/36 months
Liang.T.J. ⁵⁰ 2005	116	108	187/37	$\begin{array}{c} \text{C:50.4} \pm 8.5 \\ \text{years old} \end{array}$	-	A, B and C	-	capsule + TACE (EPI, MMC, CBP)	TACE (EPI, MMC, CBP)	\geq 3 years	2. Clinical effectiveness
					1						3. QoL scores
											1. Clinical effectiveness
								Cinobufotalin	TACE (EPI,	2	2. Live quality
					1	1	1	injection + TACE	I TUE (EFI,	1	1 /
Liang Y. ⁵¹ 2008	48	48	72/24	Median age:44.5 years	_	A, B and C	\geq 70	(EPI, DDP, 5-FU) and IFN	DDP, 5-FU) and IFN	rounds (4 weeks)	3. Comparison of 6/12/18 months

	Experimental group	Control group	Sex(M/F)	Age	Disease stage	Child-Pugh scores	KPS score	Treatment group	Control group		
	J	0 P	()	0					5 T		1. Clinical effectiveness
								Cinobufotalin		2–3 rounds	2. Survival at 12/24/36 months
Liu X.H. ⁵² 2009	42	42	70/14	48.5 years old	_	_	_	injection + TACE (5-FU, DDP, EPI)	TACE (5-FU, DDP, EPI)	(4 weeks per round)	3. Comparison of immune function and liver function
											4. Complication
				$\begin{array}{c} \text{E:54.21} \pm 10.32 \\ \text{years old} \end{array}$						2-3	1. Lipiodol deposition after TACE
Liu Y.Q. ⁵³	38	44	72/10			A and B	>60	Cinobufotalin injection + TACE	TACE (THP,	rounds (3weeks	2. Clinical effectiveness
2010	50	11	/2/10	$\begin{array}{c} \text{C:55.32} \pm 11.62 \\ \text{years old} \end{array}$			200	(THP, DDP, MMC)	DDP, MMC)	per round)	3. Comparison of TTP
											4. Complication
				E:46.5 years old							1. Clinical effectiveness
1 0 1 54 2014	20	20	22/15	C:47.3 years old				Cinobufotalin injection + THM and	TACE (DDP,	20.1	2. Life quality
Lu S.J. ⁵⁴ 2014	30	30	33/17		_	-	_	TACE (DDP, DOX, 5-FU)	DOX, 5-FU)	30 days	3. Survival at 6/12/24 months
											4. Complication
				$E:45.0 \pm 13.5$ years old							1. Clinical effectiveness
Peng W.D. ⁵⁵ 2011	40	40	43/37	$\begin{array}{c} \text{C:}44.0\pm13.9\\ \text{years old} \end{array}$	II, III	_	\geq 50	Compound cantharis capsule + FAP (5-FU, EPI, DDP)	FAP (5-FU, EPI, DDP)	10 days	2. Life quality
											3. Immunological function
Qu J.R. ⁵⁶				E:median age 54 years				Secretio bufonis	TACE (CBP,		1. Complication
2012	40	40	64/16	C:median age 56 years	II, III	_	≥60	injection + TACE (CBP, 5-FU, MMC,DOX)	5-FU, MMC, DOX)	28 days	2. Comparison of liver function and blood routine examination
Shen J.J. ⁵⁷	23	24	36/11	52.2±7.4 years	II, III	_	_	Cinobufotalin injection + TACE (5-	TACE (5-FU,	4 weeks	1. Complication 2. Comparison of liver Function and AFP
2009				old				FU, DDP, MMC)	DDP, MMC)		3. Life quality
											4. Solid tumor variation
Shen J.J. ⁵⁸ 2015	18	18	23/13	E:57.5 years old		A and B	\geq 60	Cinobufotalin injection + TACE	TACE (Lobaplatin,	2 weeks	 Clinical effectiveness Comparison of HIF-1α
2015				C:54.7 years old				(Lobaplatin, DDP,	DDP, MMC)		and VEGF 1. Clinical effectiveness
ol w 11 59								Cinobufotalin		1–2 rounds	2. The degree of pain
Shu X.H. ⁵⁹ 2004	29	29	48/10	Median age: 51 years	II, III	-	≥ 60	injection + 5-fluoro- uracil	5-fluorouracil	(5 days	relief
								uracii		per round)	3. Life quality
				F 52 2 0 7							4. Complication
				E:53.2±8.7 years old				Cinobufotalin injection + TACE	TACE (5-FU,		1. Clinical effectiveness
Su Y. ⁶⁰ 2013	33	30	53/10	$\begin{array}{c} \text{C:52.7} \pm 7.9 \\ \text{years old} \end{array}$	II, III	-	>60	(5-FU, HCPT, DOX, MMC)	HCPT, DOX, MMC)	4 weeks	2. Life quality
											3. Complication
											1. Clinical effectiveness
See 7 16								Cinobufotalin	TACE (EDI	2 rounds	2. Survival at 12/24/36 months
Sun Z.J. ⁶¹ 2002	118	118	197/39	51.4 years old	_	_	-	injection + TACE (EPI, MMC, CBP)	TACE (EPI, MMC, CBP)	(4 weeks per round)	3. Immunological function
										round)	4. Liver function and complication
Tang L C 62				E:49 years old				Cinobufotalin	DAM (5 DI		1. Complication
Tang J.G. ⁶² 1999	46	42	67/21	C:48 years old	_	-	-	injection + FAM (5-	FAM (5-FU, DOX, MMC)	1 month	2. AFP
								FU, DOX, MMC)			3. Life quality
				$\begin{array}{c} \text{E:53.4} \pm 10.5 \\ \text{years old} \end{array}$						2-3	1. Clinical effectiveness
Tian X.L. ⁶³ 2006	36	36	53/19	C:52.5±9.6 years old	Aiyishu TACE rounds	70 injection + TACE	2. QoL scores				
2000								DDP)	5-FU, DDP)	per	3. Life quality
										round)	4. Survival at 6/12/18/24 months

	Experimental group	Control group	Sex(M/F)	Age	Disease stage	Child-Pugh scores	KPS score	Treatment group	Control group		
											1. Improvement of
											clinical symptom
											2. Complication
Wang C.J. ⁶⁴								Cinobufotalin	TACE (DOX,		 Child-pugh level Serum levels of hepatic
2001	30	30	-	48 years old	—	A,B and C	\geq 30	injection + TACE (DOX, CBP, MMC)	CBP, MMC)	-	fibrosis
								(DOX, CDI, MINC)			5. AFP
											6. Clinical effectiveness
											7. Survival at 12/24/36
				D (0.5 11							months
				E:62.5 years old						2 rounds	1. Clinical effectiveness
Wang L.J. ⁶⁵ 2007	72	70	117/25	C:64.1 years old	II, III	A and B	\geq 50	Aidi injection + FAP (5-FU, EPI, DDP)	FAP (5-FU, EPI, DDP)	(30 days	 2. Life quality 3. Child-pugh level
					-			,		per round)	4. AFP
				E:median age				TIM (to a day on and			1.7111
Wang Q.C. ⁶⁶	24	24	41/7	55 years		A and B	_	THM (toad venom, Salvia miltiorrhiza,	TACE(MMC,	3 days	Comparison of
2013	24	24	41/7	C:median age		A and D	_	and matrine) + TACE (MMC, THP, OXA)	THP, OXA)	5 days	T-lymphocyte subsets
				57.2 years				(WINC, IIII, OAA)			1. Clinical effectiveness
MA.: N. F. 67				50 6 1 6 0				Sodium cantharidinate and	TACE (5 EU	3 rounds	
Wei Y.F. ⁶⁷ 2015	48	44	61/31	58.6 ± 6.8 years old	—	A and B	\geq 70	vitamin B6 + TACE	TACE (5-FU, EPI, MMC)	(30 days per	 Complication Survival at 12/24/36
								(5-FU, EPI, MMC)		round)	months
				E:52.4±7.2 years old							1. Clinical effectiveness
				<i>years</i> or <i>a</i>	-					2	2. AFP
Wu H.M. ⁶⁸	26	44	60/11	C:50.5 ± 8.7	11 111			Cinobufotalin	TACE (5-FU,	rounds	3. Comparison of tumor
200	36	44	69/11	years old	II, III	- injection + TACE (5 FU, MMC, DDP)	injection + TACE (5- FU, MMC, DDP)	MMC, DDP)	(10 days per	metastasis	
										round)	4. Survival at 3/6/12 months
											5. Complication
Wu J.Y. ⁶⁹	30	30	53/7	E:50 years old	III	_	_	Cinobufotalin	TACE	25 days	1. Clinical effectiveness
2006				C:50 years old				injection + TACE	(HCPT, THP)		2. Complication
Wu J.S. ⁷⁰ 2015	15	15	26-Apr	44–68 years old	_	_	\geq 70	Sodium cantharidinate and	TACE (5-FU, EPI, MMC)	3 rounds	1. Comparison of WBC, ALT and AST
								vitamin B6 + TACE	. ,		2. Complication
											1. Clinical effectiveness
Wu Z.M. ⁷¹			======	Median age 45				Sodium cantharidinate and	TACE (5-FU,		2. Comparison of liver function and AFP
2010	41	41	50/32	years old	_	_	_	vitamin B6 + TACE (5-FU, EPI, DDP)	EPI, DDP)	2 weeks	3. Comparison of new vessel and portal vein tumor thrombosis
Xiao X.S. ⁷²				E:65.4 years old				Cinobufotalin	TACE	2	
2011	25	25	35/15	C:63.6 years old	_	—	-	injection + TACE	(MMC, 5-FU,	rounds	Clinical effectiveness
				E:58.09±11.67 years old							1. Numbers of TACE
Xie J. ⁷³ 2015	50	50	89/11	C:58.32±11.55 years old	_	A	_	Scorpion and earthworm + TACE	TACE (5-FU,	2	2. AFP
) curo ora	-			(5-FU, MMC, EPI)	MMC, EPI)	months	3. Liver function
					-						4. Lung metastasis
											1. Clinical effectiveness
								linlong			2. Life quality
Xie Y.F. ⁷⁴ 2003	31	31	49/13	Median age	I, II, III	_	>60	Jinlong capsule + TACE (5-	TACE (5-FU, DDP, MMC)	21 days	3. Comparison of WBC
2005				53.5 years				FÛ, DDP, MMC)			4. Immunologic function
											5. AFP
											1. Clinical effectiveness
X X C 75								Sodium	TACE (DDD	1–3 rounds	2. Survival at 12/24/36
Xu Y.S. ⁷⁵ 2011	64	64	84/44	50.25 years old	-	_	>60	norcantharidate (SNCTD) + TACE	TACE (DDP, 5-FU, DOX)	(15 days	months
								(DDP, 5-FU, DOX)	,,	per round)	3. KPS
								1			4. Complication

	Experimental group	Control group	Sex(M/F)	Age	Disease stage	Child-Pugh scores	KPS score	Treatment group	Control group		
				E:45.75±11.40 years old							1. Clinical effectiveness
Xue Q. ⁷⁶				C:45.45 \pm 10.70 years old				Cinobufotalin	TACE (DDD	1–3 rounds	2. Survival at 6/12/24/36 months
2010	32	30	45/17		-	_	>60	injection + TACE (DDP, 5-FU, DOX)	TACE (DDP, 5-FU, DOX)	(28 days per	3. Comparison of clinical symptoms
										round)	4. KPS
											5. Complication
											1. Clinical effectiveness
											2. Comparison of ALT, TBIL and ALB
Yang P.Y. ⁷⁷ 2013	34	36	48/22	55.1 ± 8.2 years	_	A and B	≥ 60	Jinlong capsule + TACE (EPI,	TACE (EPI,	42	3. KPS scores
2013				old			-	5-FU, DDP)	5-FU, DDP)	weeks	4. TCM clinical symptom
											5. TH1 and TH2
											6. Safety analysis
				$E:49 \pm 3$ years old				Cinobufotalin			1. Clinical effectiveness
You S.Y. ⁷⁸ 2006	25	25	32/18	$\begin{array}{c} C:\!48\!\pm\!9 \text{ years} \\ \text{old} \end{array}$	_	_	-	injection + TACE (5-FU, DDP, EPI)	TACE (5-FU, DDP, EPI)	2 rounds	2. Survival at 12/24/36 months
											3. Complication
				E:49.7 years old							1. Clinical effectiveness
Yu J.G. ⁷⁹	30	30	29-Nov	C:50.8 years old	_	_	>60	Cinobufotalin injection + TACE	TACE (DDP, DOX, MMC,	60 days	2. Clinical symptom improvement
2013			2, 10,					(DDP, DOX, MMC, 5-FU)	5-FU)		3. Comparison of blood routine examination, liver function and AFP
				E:52.3±3.5 years old							1. Clinical effectiveness
Yuan C.Y. ⁸⁰			20 D	$\begin{array}{c} \text{C:53.2} \pm 3.4 \\ \text{years old} \end{array}$]			Cinobufotalin	TACE (5-FU, DDP, EPI)	2 rounds	2. AFP
2007	20	20	28-Dec		II, III	-	-	injection + TACE (5-FU, DDP, EPI)			3. Life quality
											4. Immunological function
											5. Complication
				E:54.3 years old							1. Clinical effectiveness
Zhang B. ⁸¹				C:50.1 years old				Sodium cantharidinate and			2. Life quality
2007	51	49	76/24		_	_	>80	vitamin B6 + TACE (THP)	TACE (THP)	4 weeks	3. Clinical symptom improvement
											4. Complication
71 0.08				$\begin{array}{c} \text{E:52.1} \pm 9.7 \\ \text{years old} \end{array}$				Jinlong			1. Survival at 6/12/24/36 months
Zhang C.Q. ⁸² 2005	116	108	187/37	$\begin{array}{c} \text{C:50.4} \pm 8.5 \\ \text{years old} \end{array}$	_	A, B and C	-	capsule + TACE (EPI, MMC, CBP)	TACE (EPI, MMC, CBP)	3 years	2. Clinical effectiveness
											3. QoL scores
				$\begin{array}{c} \text{E:53.99} \pm 2.43 \\ \text{years old} \end{array}$							1. Clinical effectiveness
Zhang M.J. ⁸³				$\begin{array}{c} \text{C:55.02} \pm 2.16 \\ \text{years old} \end{array}$				Sodium cantharidinate and	TACE	4-6	2. Clinical symptom improvement and weight
2011	38	38	$38/38$ — — — ≥ 60 $\begin{pmatrix} cantharidinate a \\ vitamin B6 + TA \end{pmatrix}$	vitamin B6+TACE	(MMC, DOX)	weeks	3. Life quality				
		(MMC, DOX)	(MMC, DOX)	2 011)		4. Immunological function					
											5. Complication
				E:52 years old							1. Clinical effectiveness
Thong T C 84				C:51 years old	1			Cinobufotalin	TACE (DOV	1.6	2. AFP
Zhang T.S. ⁸⁴ 2011	32	32	53/11		_	—	>60	injection + TACE	TACE (DOX, CBP, MMC)	4–6 weeks	3. Complication
					1			(DOX, CBP, MMC)			4. Survival at 6/12/24/36 months

	Experimental group	Control group		Age	Disease stage	Child-Pugh scores	KPS score	Treatment group	Control group		
											1. Clinical effectiveness
		1 22						Cinobufotalin injection + TACE (5- FU, DDP, MMC)	TACE (5-FU, DDP, MMC)	4 rounds (4 weeks per round)	2. Liver function
Zhou J.S. ⁸⁵	21		34/9		II, III	A, B and C	50- 70				3. Clinical symptom improvement
2006	21		54/9	60.08 years old	11, 111	A, D allu C					4. Life quality
											5. Survival at 18/24 months
											6. AFP and KPS
											1. Complication
Zhu W.Q. ⁸⁶	48			Sodium cantharidinate and			2. Liver function, Child- Pugh scores				
2014	40	50	71/27	47.5 years old	_	_	_	vitamin B6 + TACE (-)	TACE (-)	20 days	3. Serum hepatic fibrosis markers
											4. Clinical effectiveness

Table 1. General Characteristics of Included Randomized Clinical Trials Note: E: Experimental group; C: Control group; M: Male; F: Female; KPS: Karnofsky performance score; RCT: Randomized clinical trial; TACE: Transcatheter hepatic arterial chemoembolization; THM: Traditional herb medicine; AFP: Alphafetoprotein; Th1: Helper T cell type 1; Th2: Helper T cell type 2; HIF-1 α : Hypoxia inducible factor-1 α ; MST: Median survival time; TTP: Time to progression; QoL: Quality of life; VEGF: Vascular endothelial growth factor; WBC: White blood cell; TBIL: Total bilirubin; ALT: Alanine aminotrnsferase; ALB: Albumin; MTTP: Median time to progression; CBR: Clinical beneficial rate; IFN: Interferon; OXA: Oxaliplatin; EPI: Epirubicin; 5-FU: 5-fluorouracil; THP: Pirarubicin; DDP: Cisplatin; CF: Calcium folinate; GEM: Gemcitabine; DOX: Doxorubicin; MMC: Mitomycin; HCPT: Hydroxycamptothecine; CBP: Carboplatin.

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cisplatin, calcium folinate, gemcitabine, doxorubicin, mitomycin, hydroxycamptothecine and carboplatin. (Table 1) As for the duration of therapy, all included studies except one⁶⁴ clearly reported although the range of treating duration was various obviously. All included trials except one⁸⁶ clearly introduce the dosage of chemotherapy drugs.

For the included articles, all of them expect 7 studies (12%) were only mentioned the allocation sequence generation without showing the specific random method. However, of the 7 articles, three used shuffling envelopes method^{36, 45, 74} and 4 used the random number table method^{31, 32, 48, 49}. Only 3 articles (5%) mentioned the allocation concealment from the included studies: the sealed envelope method was the way they chosen^{36, 45, 74}. All articles did not report the blinding method, excepted 1 article which was a single-blind randomized clinical trial⁷⁰. Most of studies (92%) were ranked as low risk of outcome integrity data, while 5 articles (8%) reported participants' dropout reason^{51, 63, 67, 82, 84}. None of the articles clearly illustrated the reporting bias and only 2 studies (3%) were rated as low risk for no other bias^{31, 32}. (Table 2, Figs 2, 3).

Meta-analysis. Objective response rates (CR + PR). Figure 4 illustrated the clinical effects (objective response rate) of traditional insect Chinese medicine in advanced hepatocellular carcinoma (HCC) therapy. There were 46 articles including 3,659 participants analyzed in the forest plot^{31-42,45-47,49-55,57-61,63-65,67-72,74-81,83-86}. We conducted subgroup analysis on the condition of the pervasive low quality (high bias risk) of included studies. We extracted the high quality articles (5 papers, 510 participants) from the 46 papers based on the Cochrane Collaboration's tools for assessing risk of bias mentioned before ^{31, 32, 36, 45, 74}, making meta-analysis to compare with the rest low quality articles (41 papers, 3,149 participants). The meta-analysis reported that the objective response rate (CR + PR) of high quality group, low quality group and overall group all revealed traditional insect Chinese medicine combined chemotherapy was superior to single chemotherapy method for the non-surgical HCC (Low quality: RR = 1.21, 95% CI = 1.01 to 1.45, P = 0.04 < 0.05; High quality: RR = 1.32, 95% CI = 1.23 to 1.42, P < 0.001; Overall: RR = 1.31, 95% CI = 1.22 to 1.40, P < 0.001). The results showed that the objective response rate for the treatment group and the control group has statistical difference. The heterogeneity did not exist in the trials (Low quality: P = 0.92, $I^2 = 0\%$; High quality: P = 0.78, $I^2 = 0\%$; Overall: P = 0.88, $I^2 = 0\%$) and the fixed effects model was performed to calculate combined data by Mantel-Haenszel test.

Survival time. Five kinds of survival time were assessed in the meta-analysis including 6 months, 12 months, 18 months, 24 months and 36 months. (Fig. 5). Twelve articles including 1,206 participants analyzed the 6 months survival time^{38, 41, 44, 45, 50, 51, 54, 63, 71, 76, 82, 84}. The meta-analysis showed the 6 months survival time for the experimental group (used traditional insect Chinese medicine combined chemotherapy) and the control group (used chemotherapy alone) was irrelevant (RR = 1.04, 95% CI = 0.99 to 1.10, P = 0.14å 0.05). The heterogeneity was moderately high (P = 0.14, $I^2 = 31\%$), which might be due to a particular trial⁵⁴ included in the meta-analysis. So we performed the sensitivity analysis and if this trial was excluded, the I^2 value would be down to 0%. The fixed effects model was performed to pool data. Twenty articles including 1,831 participants assessed the 12 months survival time compared with the control group (RR = 1.42, 95% CI = 1.32 to 1.53, P < 0.001). The heterogeneity was moderately high (P = 0.02, $I^2 = 43\%$) while the I^2 value was lower than 50%. The fixed effects

Article names	Random collection method	Allocation concealment	The blinding method	Outcome data integrity	The outcome data of selective report	no other bias sources	The level of bias risk
Huang W.K. ³⁰ 2013	U	U	U	Y	U	U	High
Cao Y. ³¹ 2014	Y	U	U	Y	U	Y	Low
Zeng C.S. ³² 2012	Y	U	U	Y	U	Y	Low
Dong M.E. ³⁴ 2014	N	U	U	Y	U	U	High
Feng X.M. ³⁵ 2012	U	U	N N	Y	U	U	High
Fu Z.L. ³⁶ 2010	Y	Y	U	Y	U	N N	Low
He S.L. ³⁷ 2012	U	I U	U	Y Y	U	N N	
	U					U U	High
Ji J.F. ³⁸ 2015	-	U	U	Y	U	-	High
Jia C.H. ³⁹ 2008	N	U	U	Y	U	U	High
Jiang C.Y. ⁴⁰ 2013	U	U	U	Y	U	U	High
Ke J. ⁴¹ 2011	U	U	U	Y	U	U	High
Kou C.Y. ⁴² 2011	U	U	U	Y	U	U	High
Li B. ⁴³ 2013	U	U	U	Y	U	U	High
Li J. ⁴⁴ 2013	U	U	U	Y	U	U	High
Li Q. ⁴⁵ 2008	Y	Y	U	Y	U	U	Low
Li Q.M. ⁴⁶ 2003	U	U	U	Y	U	U	High
Li W.H. ⁴⁷ 2006	U	U	N	Y	U	U	High
Liang B.L. ⁴⁸ 2010	Y	U	U	Y	U	U	High
Liang C.X. ⁴⁹ 2015	Y	U	U	Y	U	U	High
Liang T.J. ⁵⁰ 2005	N	U	U	Y	U	U	High
Liang Y. ⁵¹ 2008	U	U	N	N	U	U	High
Liu X.H. ⁵² 2009	U	U	N	Y	U	U	High
Liu Y.Q. ⁵³ 2010	U	U	U	Y	U	U	High
Lu S.J. ⁵⁴ 2014	U	U	U	Y	U	U	•
							High
Peng W.D. ⁵⁵ 2011	U	U	U	Y	U	U	High
Qu J.R. ⁵⁶ 2012	U	U	U	Y	U	U	High
Shen J.J. ⁵⁷ 2009	U	U	U	Y	U	U	High
Shen J.J. ⁵⁸ 2015	U	U	U	Y	U	U	High
Shu X.H. ⁵⁹ 2004	U	U	U	Y	U	U	High
Su Y. ⁶⁰ 2013	U	U	U	Y	U	U	High
Sun Z.J. ⁶¹ 2002	U	U	U	Y	U	U	High
Tang J.G. ⁶² 1999	U	U	U	Y	U	U	High
Tian X.L. ⁶³ 2006	U	U	U	N	U	U	High
Wang C.J. ⁶⁴ 2001	U	U	U	Y	U	U	High
Wang L.J. ⁶⁵ 2007	U	U	N	Y	U	U	High
Wang Q.C. ⁶⁶ 2013	U	U	U	Y	U	U	High
Wei Y.F. ⁶⁷ 2015	U	U	Y	N	U	U	High
Wu H.M. ⁶⁸ 2000	U	U	U	Y	U	U	High
Wu J.Y. ⁶⁹ 2006	U	U	U	Y	U	U	High
Wu J.S. ⁷⁰ 2015	U	U	U	Y	U	U	High
Wu Z.M. ⁷¹ 2010	U	U	U	Y	U	U	High
Xiao X.S. ⁷² 2011	N	U	N N	Y	U	U	High
							•
Xie J. ⁷³ 2015	U	U	N	Y	U	U	High
Xie Y.F. ⁷⁴ 2003	Y	Y	U	Y	U	U	Low
Xu Y.S. ⁷⁵ 2011	U	U	U	Y	U	U	High
Xue Q. ⁷⁶ 2010	U	U	U	Y	U	U	High
Yang P.Y. ⁷⁷ 2013	U	U	U	Y	U	U	High
You S.Y. ⁷⁸ 2006	U	U	Ν	Y	U	U	High
Yu J.G. ⁷⁹ 2013	U	U	U	Y	U	U	High
Yuan C.Y. ⁸⁰ 2007	U	U	U	Y	U	U	High
Zhang B. ⁸¹ 2007	U	U	U	Y	U	U	High
Zhang C.Q. ⁸² 2005	U	U	U	N	U	U	High
Zhang M.J. ⁸³ 2011	U	U	U	Y	U	U	High
Zhang T.S. ⁸⁴ 2011	U	U	U	N	U	U	High
Zhu W.Q. ⁸⁵ 2014	U	U	U	Y	U	U	High
	U	U	U	Y	U	N N	High
Deng Z.Y.33 2015							

Table 2. The Risk Bias Evaluation of Articles Note: Y refers to "yeas"; N refers to "no"; U refers to "unclear".

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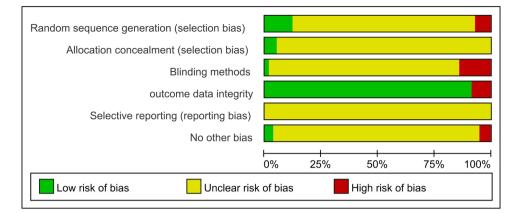


Figure 2. The risk of bias graph.

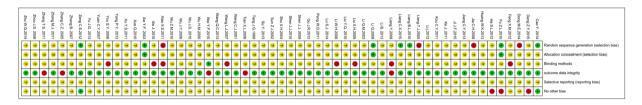


Figure 3. The risk of bias summary.

model was performed to pool data. Only four articles including 289 participants analyzed the 18 months survival time $5^{1,63,71,85}$. The meta-analysis illustrated the experimental group significantly improved the 18 months survival time compared with the control group (RR = 2.62, 95% CI = 1.70 to 4.05, P < 0.001). There was no heterogeneity in these four articles (P = 0.44, $I^2 = 0\%$), so the fixed effects model was performed to pool data. Nineteen articles including 1,825 participants analyzed the 24 months survival time $3^{8,42,44,45,47,50,52,54,61,63,64,67,71,75,76,78,82,84,85}$. The meta-analysis illustrated the experimental group significantly improved the 24 months survival time compared with the control group (RR = 1.70, 95% CI = 1.50 to 1.91, P < 0.001). The heterogeneity was low among the included articles ($P = 0.24, I^2 = 17\%$) and the fixed effects model was performed to pool data. Twelve articles including 1,381 participants analyzed the 36 months survival time $4^{2,44,52,61,64,67,75,76,78,82,84}$. The meta-analysis illustrated the experimental group significantly improved the 36 months survival time compared with the control group (RR = 1.93, 95% CI = 1.55 to 2.39, P < 0.001). There was no heterogeneity in these 4 articles (P = 0.86, $I^2 = 0\%$) and the fixed effects model was performed to pool data. We did not find any valid articles that had analyzed the 5 years survival time, and only one article analyzed 3 months survival time 6^{8} .

Indexes improvement for QoL scores, KPS, and AFP. Eighteen trials including 1,337 patients reported data on quality of life (QoL) scores improvement^{31, 35, 38, 42, 45, 47, 51, 54, 55, 59, 60, 63, 65, 76, 80, 81, 83, 85}. No obvious heterogeneity was found in the included articles (P = 0.22, $I^2 = 19\%$), so that the fixed effects model was conducted to pool data. The meta-analysis showed that the QoL scores improvement in the experimental group was superior to the control group (RR = 1.74, 95% CI = 1.53 to 1.97, P < 0.001). Only 4 trials including 318 patients reported data on Karnofsky performance scores (KPS) improvement^{33, 36, 37, 74}, and 9 trials including 608 patients on AFP improvement^{32, 33, 62, 65, 68, 78-80, 84}. Both heterogeneities of the two indexes were not notable (KPS: P = 0.56, $I^2 = 0\%$; AFP: P = 0.35, $I^2 = 11\%$) and the statistical model was fixed effects model. The meta-analysis showed both the two indexes (KPS and AFP) were significantly improved in experimental group compared with the control group (KPS: RR = 1.84, 95% CI = 1.42 to 2.39, P < 0.001; AFP: RR = 1.57, 95% CI = 1.32 to 1.87, P < 0.001). (Fig. 6).

Side effects. This part of meta-analysis included 6 kinds of side effects, which contained bone marrow depression, gastrointestinal adverse reactions, liver damage, kidney damage, fever and pain. As for bone marrow depression, two laboratory indexes including white blood cell (WBC) decrease (13 articles, 1058 patients)^{30, 32, 37, 40, 43, 46, 51, 53, 63-65, 67, 68} and hemoglobin (HB) decrease (7 articles, 563 patients)^{30-32, 37, 53, 64, 67} were applied as random effects model (the heterogeneity of WBC decrease: P < 0.001, $I^2 = 85\%$; HB decrease: P = 0.04, $I^2 = 54\%$); one laboratory index named the platelets (PLT) decrease (only 3 articles, 193 patients)^{32, 37, 53} was applied fixed effects model (heterogeneity: P = 0.6, $I^2 = 0\%$). The subgroup analysis (seen in the Supplementary Information of the article) of WBC decrease was performed based on the drugs classification, literature publication years and experimental areas, but the source of heterogeneity was still unclear. However, the subgroup analysis of HB decrease found that the heterogeneity came from experimental areas (North of China: P = 0.27, $I^2 = 23\%$; South of China: P = 0.13, $I^2 = 46\%$). The incidence rates of HB decrease and PLT decrease in experimental group were irrelevant to control group

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1.1 High quality	00			00	0.00/	4 47 10 70 4 701	
Cao Y. 2014	28	68	24	68	3.2%	1.17 [0.76, 1.79]	
Fu Z.L.2010	32	78	26	78	3.4%	1.23 [0.82, 1.86] 1.10 [0.78, 1.56]	
Li Q.2008 Xie Y.F. 2003	30 17	50 31	25 14	46 31	3.5% 1.9%	1.21 [0.73, 2.01]	_ _
Zeng C.S.2012	25	30	14	30	2.4%	1.39 [1.00, 1.94]	
Subtotal (95% CI)	20	257	10	253	14.3%	1.21 [1.01, 1.45]	◆
Total events	132		107				
Heterogeneity: Chi ² =		(P = 0.9)		%			
Test for overall effect:							
1.1.2 Low quality							
Deng Z.Y.2015	9	25	8	24	1.1%	1.08 [0.50, 2.33]	
Dong M.E.2014	15	60	12	60	1.6%	1.25 [0.64, 2.44]	
Feng X.M.2012	9	38	3	32	0.4%	2.53 [0.75, 8.55]	
He S.L.2012	17	26	16	25	2.2%	1.02 [0.68, 1.53]	
Ji J.F.2015	19	25	10	22	1.4%	1.67 [1.01, 2.78]	
Jia C.H.2008	17	30	10	30	1.3%	1.70 [0.94, 3.08]	
Jiang C.Y.2013	10	30	10	33	1.3%	1.10 [0.53, 2.27]	
Ke J. 2011	18	38	19	40	2.5%	1.00 [0.62, 1.59]	
Kou C.Y.2011	21	31	12	31	1.6%	1.75 [1.06, 2.90]	
Li Q.M.2003 Li W.H.2006	13 3	20 19	6 2	18 19	0.8% 0.3%	1.95 [0.94, 4.04]	
Liang C.X.2015	19	30	10	30	1.3%	1.50 [0.28, 7.99] 1.90 [1.07, 3.38]	
Liang T.J.2005	73	104	53	90	7.5%	1.19 [0.96, 1.48]	
Liang Y.2008	28	48	22	48	2.9%	1.27 [0.86, 1.88]	+ -
Liu X.H.2009	35	40	24	42	3.2%	1.46 [1.09, 1.96]	
Liu Y.Q. 2010	16	38	14	44	1.7%	1.32 [0.75, 2.34]	
Lu S.J. 2014	9	30	6	30	0.8%	1.50 [0.61, 3.69]	
Peng W.D.2011	15	40	13	40	1.7%	1.15 [0.63, 2.10]	
Shen J.J.2015	5	18	3	18	0.4%	1.67 [0.47, 5.96]	
Shu X.H.2004	12	29	10	29	1.3%	1.20 [0.62, 2.33]	_ _
Su Y. 2013	17	33	10	30	1.4%	1.55 [0.84, 2.83]	+
Sun Z.J.2002	97	118	68	118	9.0%	1.43 [1.20, 1.70]	-
Tian X.L.2006	16	35	12	33	1.6%	1.26 [0.71, 2.24]	-
Wang C.J.2001	21	30	23	30	3.0%	0.91 [0.67, 1.24]	
Wang L.J.2007	30	72	25	70	3.4%	1.17 [0.77, 1.77]	
Wei Y.F.2015	30	48	22	44	3.0%	1.25 [0.87, 1.81]	+
Wu H.M.2000	17	36	9	44	1.1%	2.31 [1.17, 4.54]	
Wu J.Y.2006	16	30	10	30	1.3%	1.60 [0.87, 2.94]	
Wu Z.M.2010	23	41	15	41	2.0%	1.53 [0.94, 2.49]	
Xiao X.S.2011	18	25	12	25	1.6%	1.50 [0.93, 2.41]	
Xu Y.S.2011	53	64	36	64	4.8%	1.47 [1.15, 1.88]	
Xue Q.2010	23	32	20	30	2.7%	1.08 [0.77, 1.50]	
Yang P.Y. 2013	9	34	7	36	0.9%	1.36 [0.57, 3.25]	
You S.Y. 2006	14	25 30	15	25 30	2.0%	0.93 [0.58, 1.50]	
Yu J.G. 2013 Yuan C X 2007	8 11	30 20	5 12	30 20	0.7% 1.6%	1.60 [0.59, 4.33]	
Yuan C.Y.2007 Zhang B. 2007	19	20 51	12	20 49	1.6% 2.2%	0.92 [0.54, 1.56] 1.14 [0.67, 1.95]	_
Zhang M.J. 2007	19	38	14	49 38	2.2% 1.9%	1.07 [0.60, 1.90]	_ _
Zhang T.S. 2011	20	30	14	30	2.6%	1.02 [0.69, 1.50]	<u> </u>
Zhou J.S. 2006	11	21	7	22	0.9%	1.65 [0.79, 3.43]	+
Zhu W.Q.2014	33	48	21	50	2.7%	1.64 [1.12, 2.39]	 -
Subtotal (95% CI)	00	1584	- 1	1565	85.7%	1.32 [1.23, 1.42]	♦
Total events	864		641				
Heterogeneity: $Chi^2 = 3$ Test for overall effect:	32.80, df =	`	0.78); l² =	= 0%			
Total (95% CI)		1841		1818	100.0%	1.31 [1.22, 1.40]	•
Total events	996		748				
Heterogeneity: Chi ² = 3	34.05, df =	45 (P =	0.88); l² =	= 0%			+ + + + + + + + + + + + + + + + + + +
Test for overall effect:	Z = 7.98 (F	° < 0.000	001)				0.05 0.2 1 5 20 rours [experimental] Favours [control]
Test for subaroup diffe	erences: Ch	i² = 0.83	8. df = 1 (P = 0.3	6). I ² = 0%	n i dv	

Test for subaroup differences: $Chi^2 = 0.83$. df = 1 (P = 0.36). l² = 0%

Figure 4. The forest plot of subgroup analysis based on the article's quality for the objective response rate of traditional insect Chinese medicine and the related preparation combined chemotherapy versus chemotherapy alone (*M*-*H*: Mantel-Haenszel estimates; *CI*: Confidence Interval).

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with corresponding Risk Ratio (*RR*) and 95% *CI* were (0.84, 0.62to 1.12, P = 0.23å 0.05), and (0.97, 0.75 to 1.26, P = 0.84å 0.05), respectively. The incidence rate of WBC decrease in the experiment group was lower than in control: (0.74, 0.55 to 0.99, P = 0.04 < 0.05). (Fig. 7). Red blood cell (RBC) decrease, another important component of bone marrow depression, was excluded owing to only one trial analyzing it³⁰.

	Experime	ental	Contro	5I		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events		Weight		
1.2.1 6 months							1
Ji J.F.2015 Ke J. 2011	18 27	25 38	15 21	22 40	3.3% 4.3%	1.06 [0.73, 1.54] 1.35 [0.95, 1.94]	—
Li j.2013	38	43	54	63	9.2%	1.03 [0.89, 1.20]	+
Li Q.2008	37	50	35	46	7.6%	0.97 [0.77, 1.22]	t
Liang T.J.2005 Liang Y.2008	104 47	116 48	90 46	108 48	19.5% 9.6%	1.08 [0.97, 1.19] 1.02 [0.95, 1.10]	E Constantino de Cons
Lu S.J. 2014	5	30	19	30	4.0%	0.26 [0.11, 0.61]	
Tian X.L.2006	33	35	29	33	6.2%	1.07 [0.92, 1.25]	t
Wu Z.M.2010 Xue Q.2010	35 23	41 32	28 21	41 30	5.9% 4.5%	1.25 [0.98, 1.60]	
Zhang C.Q.2005	104	116	21	108	4.5%	1.03 [0.75, 1.41] 1.08 [0.97, 1.19]	+
Zhang T.S. 2011	32	32	30	31	6.5%	1.03 [0.95, 1.13]	t
Subtotal (95% CI)		606		600	100.0%	1.04 [0.99, 1.10]	1
Total events Heterogeneity: Chi ² = 1	503	11 (P =	478 0 14): l ² =	31%			
Test for overall effect: 2				3176			
1.2.2 12 months							
Ji J.F.2015	15	25	2	22	0.4%	6.60 [1.69, 25.71]	
Ke J. 2011	16	38	9	49	1.6%	2.29 [1.14, 4.61]	
Kou C.Y.2011 Li j.2013	22 35	31 43	14 46	31 63	2.8% 7.6%	1.57 [1.00, 2.46] 1.11 [0.91, 1.37]	-
Li Q.2008	32	50	19	46	4.0%	1.55 [1.04, 2.32]	
Li W.H.2006	12	19	9	19	1.8%	1.33 [0.74, 2.39]	<u>+-</u>
Liang T.J.2005	90 40	116 48	70 22	108 48	14.7% 4.5%	1.20 [1.01, 1.42]	·
Liang Y.2008 Liu X.H.2009	40 33	48 42	22 20	48 42	4.5% 4.1%	1.82 [1.30, 2.54] 1.65 [1.16, 2.35]	
Lu S.J. 2014	15	30	11	30	2.2%	1.36 [0.76, 2.46]	+
Sun Z.J.2002	94	118	56	118	11.4%	1.68 [1.36, 2.07]	
Tian X.L.2006	24	35 30	18	33 30	3.8% 2.0%	1.26 [0.86, 1.85]	T
Wang C.J.2001 Wei Y.F.2015	19 37	30 48	10 29	30 44	2.0% 6.2%	1.90 [1.07, 3.38] 1.17 [0.90, 1.52]	+
Wu Z.M.2010	28	40	16	41	3.3%	1.75 [1.13, 2.71]	 -
Xu Y.S.2011	50	64	30	64	6.1%	1.67 [1.25, 2.23]	
Xue Q.2010 You S.Y. 2006	18 16	32 25	13 15	30 25	2.7% 3.1%	1.30 [0.78, 2.16]	Ŧ
Zhang C.Q.2005	90	25 116	70	25 108	3.1%	1.07 [0.69, 1.65] 1.20 [1.01, 1.42]	+
Zhang T.S. 2011	17	32	14	31	2.9%	1.18 [0.71, 1.95]	
Subtotal (95% CI)		983		982	100.0%	1.42 [1.32, 1.53]	•
Total events Heterogeneity: Chi ² = 3	703	10 /D -	493	420/			
Test for overall effect: 2				4370			
1.2.3 18 months							
Liang Y.2008	20	48	5	48	22.7%	4.00 [1.64, 9.79]	_ _
Tian X.L.2006	12	35	4	33	18.7%	2.83 [1.01, 7.90]	— •–
Wu Z.M.2010	17	41	10	41	45.4%	1.70 [0.89, 3.26]	+∎-
Zhou J.S. 2006 Subtotal (95% CI)	9	21 145	3	22 144	13.3% 100.0%	3.14 [0.98, 10.04] 2.62 [1.70, 4.05]	•
Total events	58	145	22	144	100.070	2.02 [1.70, 4.03]	-
Heterogeneity: Chi ² = 2				%			
Test for overall effect: 2	Z = 4.37 (P	< 0.000)1)				
1.2.4 24 months							
Ji J.F.2015	9	25	2	22	0.8%	3.96 [0.96, 16.40]	
Kou C.Y.2011 Li j.2013	15 28	31 43	10 37	31 63	3.9% 11.7%	1.50 [0.80, 2.81] 1.11 [0.82, 1.50]	Ţ.
Li Q.2008	20	50	10	46	4.0%	1.93 [1.02, 3.66]	
Li W.H.2006	9	19	6	19	2.3%	1.50 [0.66, 3.39]	
Liang T.J.2005	55	116	36	108	14.5%	1.42 [1.02, 1.98]	
Liu X.H.2009 Lu S.J. 2014	28 10	42 30	14 0	42 30	5.4% 0.2%	2.00 [1.24, 3.23] 21.00 [1.29, 342.93]	
Sun Z.J.2002	80	118	38	118	14.8%	2.11 [1.58, 2.81]	-
Tian X.L.2006	5	35	0	33	0.2%	10.39 [0.60, 180.84]	
Wang C.J.2001	10	30	7	30	2.7%	1.43 [0.63, 3.25]	
Wei Y.F.2015 Wu Z.M.2010	16 12	48 41	10 7	44 41	4.1% 2.7%	1.47 [0.75, 2.88] 1.71 [0.75, 3.91]	
Xu Y.S.2011	42	64	21	64	8.2%	2.00 [1.35, 2.96]	
Xue Q.2010	14	32	7	30	2.8%	1.88 [0.88, 4.00]	
You S.Y. 2006 Zhang C O 2005	11 55	25 116	8 37	25 108	3.1% 14.9%	1.38 [0.67, 2.83]	
Zhang C.Q.2005 Zhang T.S. 2011	55 14	32	37	31	14.9% 3.6%	1.38 [1.00, 1.91] 1.51 [0.77, 2.96]	+
Zhou J.S. 2006	3	21	Ő	22	0.2%	7.32 [0.40, 133.66]	
Subtotal (95% CI)	107	918		907	100.0%	1.70 [1.50, 1.91]	•
Total events Heterogeneity: Chi ² = 2	437 1.81, df =	18 (P =	259 0.24); l ² =	17%			
Test for overall effect: 2							
1.2.5 36 months							
Kou C.Y.2011	14	31	7	31	7.0%	2.00 [0.94, 4.27]	—
Li j.2013	17	43	21	63	17.0%	1.19 [0.71, 1.97]	
Liang T.J.2005 Liu X.H.2009	23 15	116 42	11 6	108 42	11.4% 6.0%	1.95 [1.00, 3.80] 2.50 [1.07, 5.82]	
Sun Z.J.2009	42	118	17	42 118	17.0%	2.47 [1.50, 4.08]	
Wang C.J.2001	8	25	5	25	5.0%	1.60 [0.61, 4.22]	+
Wei Y.F.2015	9	48	5	44	5.2%	1.65 [0.60, 4.55]	
Xu Y.S.2011 Xue Q.2010	22 5	64 32	9 4	64 30	9.0% 4.1%	2.44 [1.22, 4.89] 1.17 [0.35, 3.96]	
You S.Y. 2006	9	32 25	4 5	30 25	4.1% 5.0%	1.80 [0.70, 4.62]	+
Zhang C.Q.2005	23	116	11	108	11.4%	1.95 [1.00, 3.80]	
Zhang T.S. 2011	5	32	2	31	2.0%	2.42 [0.51, 11.57]	
Subtotal (95% CI) Total events	192	692	103	689	100.0%	1.93 [1.55, 2.39]	•
Heterogeneity: Chi ² = 6	.24, df = 1	1 (P = 0	.86); I ² = ()%			
Test for overall effect: 2	z = 5.99 (P	< 0.000	001)				
							+ + + + + +
						-	0.02 0.1 1 10 50
						F	avours [experimental] Favours [control]

Figure 5. The forest plot of survival time for traditional insect Chinese medicine and the related preparation combined chemotherapy versus chemotherapy alone (*M*-*H*: Mantel-Haenszel estimates; *CI*: Confidence Interval).

Twenty articles including 1,529 patients reported data on gastrointestinal adverse reactions^{31-34,40,46,53,58,59,64,} 65,67,69,75,78-81,83,86. The random effects model was conducted to pool data because the heterogeneity (P < 0.001, $I^2 = 62\%$) was obvious. We made the subgroup analysis based on the drugs categories, publication years and experimental areas. The outcome of subgroup analysis showed that the variation among the different experimental areas was the source of heterogeneity (North of China: P = 0.34, $I^2 = 11\%$; South of China: P = 0.18, $I^2 = 28\%$). The meta-analysis showed the gastrointestinal adverse reactions in the experimental group were significantly fewer than the control group (RR = 0.63, 95% CI = 0.51 to 0.77, P < 0.001).

	F		0			Dist. Datis	Diele Detie
01 1 0 1	Experim		Contr		187-1-1-6	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	lotal	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
1.3.1 QoL improemen		~~~	10	~~~	00 404	4 00 14 07 4 001	-
Cao Y. 2014	56	68	42	68	20.4%	1.33 [1.07, 1.66]	
Feng X.M.2012	7	38	4	32	2.1%	1.47 [0.47, 4.58]	
Ji J.F.2015	6	25	1	22	0.5%	5.28 [0.69, 40.53]	
Kou C.Y.2011	19	31	10	31	4.9%	1.90 [1.06, 3.40]	
Li Q.2008	9	50	1	46	0.5%	8.28 [1.09, 62.84]	
Li W.H.2006	6	19	4	19	1.9%	1.50 [0.50, 4.48]	
Liang Y.2008	28	48	12	48	5.8%	2.33 [1.35, 4.02]	
Lu S.J. 2014	19	30	12	30	5.8%	1.58 [0.95, 2.65]	
Peng W.D.2011	15	40	10	40	4.9%	1.50 [0.77, 2.93]	
Shu X.H.2004	21	29	6	29	2.9%	3.50 [1.66, 7.39]	
Su Y. 2013	19	33	8	30	4.1%	2.16 [1.11, 4.18]	
Tian X.L.2006	21	35	9	33	4.5%	2.20 [1.18, 4.09]	
Wang L.J.2007	29	72	18	70	8.9%	1.57 [0.96, 2.55]	
Xue Q.2010	28	32	20	30	10.0%	1.31 [0.99, 1.75]	
Yuan C.Y.2007	9	20	3	20	1.5%	3.00 [0.95, 9.48]	· · ·
Zhang B. 2007	39	51	22	49	10.9%	1.70 [1.21, 2.41]	<u> </u>
Zhang M.J. 2011	18	38	14	38	6.8%	1.29 [0.75, 2.19]	-
Zhou J.S. 2006	13	22	7	21	3.5%	1.77 [0.88, 3.56]	
Subtotal (95% CI)	000	681		656	100.0%	1.74 [1.53, 1.97]	•
Total events	362		203	100/			
Heterogeneity: Chi ² = 2				= 19%			
Test for overall effect:	Z = 8.58 (P	< 0.000	001)				
1.3.2 KPS improveme	ant						
Deng Z.Y.2015	22	25	12	24	25.3%	1.76 [1.15, 2.69]	
Fu Z.L.2010	42	78	22	78	25.3 <i>%</i> 45.4%	1.91 [1.27, 2.87]	
He S.L.2012	42	26	11	25	43.4 % 23.1%	1.40 [0.82, 2.39]	+ - -
Xie Y.F. 2003	10	31	3	31	6.2%	3.33 [1.01, 10.96]	
Subtotal (95% CI)	10	160	5	158	100.0%	1.84 [1.42, 2.39]	
Total events	90	100	48	150	100.070	1.04 [1.42, 2.00]	•
Heterogeneity: $Chi^2 = 2$		$(\mathbf{P} - 0)$		0/			
Test for overall effect:				/0			
	2 = 4.50 (F	< 0.000	501)				
1.3.3 AFP improveme	ent						
Deng Z.Y.2015	15	25	7	24	6.6%	2.06 [1.02, 4.15]	—
Tang J.G.1999	31	36	16	28	16.7%	1.51 [1.07, 2.13]	
Wang L.J.2007	32	72	11	70	10.3%	2.83 [1.55, 5.16]	
Wu H.M.2000	21	36	16	44	13.3%	1.60 [0.99, 2.59]	
You S.Y. 2006	13	25	12	25	11.1%	1.08 [0.62, 1.89]	- + -
Yu J.G. 2013	21	30	18	30	16.7%	1.17 [0.80, 1.70]	+ -
Yuan C.Y.2007	13	20	8	20	7.4%	1.63 [0.87, 3.04]	+
Zeng C.S.2012	7	30	6	30	5.6%	1.17 [0.44, 3.06]	_
Zhang T.S. 2011	19	32	13	31	12.2%	1.42 [0.86, 2.34]	+
Subtotal (95% CI)		306			100.0%	1.57 [1.32, 1.87]	♦
Total events	172		107				
Heterogeneity: Chi ² = 8	3.96, df = 8	(P = 0.3	35); l² = 1	1%			
Test for overall effect:	Z = 5.04 (P	< 0.000	001)				
							0.01 0.1 1 10 100
						Fa	avours [experimental] Favours [control]

Figure 6. The forest plot of QoL scores, KPS and AFP improvement for traditional insect Chinese medicine and the related preparation combined chemotherapy versus chemotherapy alone (QoL: Quality of life; KPS: Karnofsky performance scores; AFP: Alpha fetoprotein; *M-H*: Mantel-Haenszel estimates; *CI*: Confidence Interval).

Eleven articles including 815 patients and 5 articles including 340 participants gathered information on liver damage^{33, 34, 40, 51, 53, 67, 73, 78, 80, 81, 83} and kidney damage^{53, 67, 78, 80, 83} respectively. The random effects model was performed to collect data for the liver damage group because the heterogeneity was high (P < 0.001, $I^2 = 92\%$). The subgroup analysis based on the drugs categories, publication years and experimental areas didn't reveal the source of heterogeneity. The fixed effects model was conducted to collect data for kidney damage group because no obvious heterogeneity was found in the included articles (P = 0.97, $I^2 = 0\%$). The meta-analysis demonstrated that the liver damage and kidney damage in the experimental group were irrelevant to control group (liver damage: RR = 0.56, 95% CI = 0.31 to 1.02, P = 0.06 > 0.05; kidney damage: RR = 0.55, 95% CI = 0.24 to 1.27, P = 0.16 > 0.05).

Ten articles including 621 patients^{30,37,46,51,53,57,67,69,70,85} and eight articles including 490 patients^{30,37,42,53,64,67,70,87} reported fever and pain respectively. They all used the random effects model for the reason of the obvious heterogeneity (P < 0.001, $I^2 = 72\%$; P < 0.001, $I^2 = 80\%$). We also didn't find the source of heterogeneity through the subgroup analysis. The meta-analysis also showed both these two indexes in the treatment group and the

	Experime	ontal	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Woight	M-H, Random, 95% C	
1.4.1 WBC decrease	LVCIILS	Total	LVCIIIS	Total	Height	m-n, Kanuoni, 35% C	
He S.L.2012	23	26	21	25	10.4%	1.05 [0.84, 1.31]	+
Huang W.K.2013	23 16	20 41	21	25 41	8.4%	0.80 [0.49, 1.31]	
Jiang C.Y.2013	5	30	20 14	30	8.4 <i>%</i> 5.5%		
Li B. 2013	34	30 74	49	73		0.36 [0.15, 0.87]	-
Li Q.M.2003	34 7	19	49 16	19	9.9% 7.4%	0.68 [0.51, 0.92] 0.44 [0.24, 0.81]	
Liang Y.2008	43	48	13	48	7.4% 8.6%	3.31 [2.06, 5.31]	
Liu Y.Q. 2010	43 34	40 41	37	40	10.6%	0.92 [0.77, 1.09]	1
Tian X.L.2006	5 5	35	15	33	5.5%		
Wang C.J.2000	0	30	8	30	5.5% 1.0%	0.31 [0.13, 0.77] 0.06 [0.00, 0.98]	←
•							
Wang L.J.2007	12	72	39	70	7.9%	0.30 [0.17, 0.52]	
Wei Y.F.2015	15	48	20	44	8.1%	0.69 [0.40, 1.17]	-
Wu H.M.2000	28	36	31	44	10.2%	1.10 [0.85, 1.43]	
Zeng C.S.2012	8	30 530	11	30 528	6.4%	0.73 [0.34, 1.55]	
Subtotal (95% CI)	000	530	294	520	100.0%	0.74 [0.55, 0.99]	•
Total events	230	70.00			0004) 12	050/	
Heterogeneity: Tau ² = (,	P < 0.0	0001); 1* =	85%	
Test for overall effect: 2	Z = 2.02 (P	= 0.04)					
1.4.2 HB decrease							
Cao Y. 2014	6	68	14	68	8.4%	0.43 [0.18, 1.05]	
He S.L.2012	10	26	9	25	11.7%	1.07 [0.52, 2.18]	_ _ _
Huang W.K.2013	29	41	35	41	30.9%	0.83 [0.66, 1.05]	-
Liu Y.Q. 2010	36	41	35	41	34.0%	1.03 [0.87, 1.22]	_
Wang C.J.2001	0	30	6	30	1.0%	0.08 [0.00, 1.31]	← − − − +
Wei Y.F.2015	10	48	12	44	11.3%	0.76 [0.37, 1.59]	_ _
Zeng C.S.2012	2	30	3	30	2.7%	0.67 [0.12, 3.71]	
Subtotal (95% CI)	2	284	3		100.0%	0.84 [0.62, 1.12]	•
Total events	93	204	114	210	100.070	0.04 [0.02, 1.12]	ľ
Heterogeneity: $Tau^2 = 0$		- 13 12		- 0.04	· 12 - 54%		
Test for overall effect: 2				- 0.04), 1 - 34 /0)	
	2 – 1.20 (F	- 0.23)					
							0.01 0.1 1 10 100
						Fa	avours [experimental] Favours [control]
	Experim	ental	Con	trol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Tota	Events	<u>Tota</u>	<u> Weight</u>	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.5.1 PLT decrease							
He S.L.2012	8	26	8	25	6 16.6%	0.96 [0.43, 2.17]	_ + _
Liu Y.Q. 2010	31	41					· · · · · · · · · · · · · · · · · · ·
Zeng C.S.2012	9	30					
Subtotal (95% CI)	3	97		. 96			
Total events	48	51	49		100.07		1
Heterogeneity: Chi ² =		$\rho = \rho$					
		`		U 70			
Test for overall effect:	z = 0.21 (ł	0.84	9				
							0.01 0.1 1 10 100
						Fav	vours [experimental] Favours [control]

Figure 7. The forest plots of bone marrow depression (WBC decrease, HB decrease and PLT decrease) for traditional insect Chinese medicine and the related preparation combined chemotherapy versus chemotherapy alone (PLT: Platelets, WBC: White blood cell, HB: Hemoglobin, *M-H*: Mantel-Haenszel estimates; *CI*: Confidence Interval).

control group were irrelevant (RR = 0.82, 95% CI = 0.58 to 1.15, P = 0.24 > 0.05; RR = 0.82, 95% CI = 0.53 to 1.29, P = 0.40 > 0.05). (Fig. 8).

Immune function. Immune function after tumor therapy was measured by continuous laboratory data as follows: CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺ and Natural Killer cell (NK). As the difference of standard deviation (SD) in the same article laboratory indexes was obvious, Standard Mean Difference (Std.MD) was conducted as combined statistics. Significant improvement of CD3⁺ (7 studies, 662 patients)^{38, 45, 52, 55, 61, 80, 83}, CD4⁺ (7 studies, 659 patients)^{38, 45, 52, 55, 61, 80, 83}, CD4⁺ (7 studies, 721 patients)^{38, 45, 52, 55, 61, 74, 80, 83} and NK (6 studies, 565 patients)^{38, 45, 52, 61, 74, 80} in the experimental group were found in the forest plot compared with the control group with associated Std.MD (95% *CI*) were 1.55 (1.01 to 2.08, P < 0.001), 2.49 (1.34 to 3.64, P < 0.001), 1.70 (0.69 2.70, P < 0.001) and 1.79 (0.49 to 3.09, P = 0.007). But CD8⁺ (3 studies, 240 patients)^{52, 55, 83} in the experimental group was irrelevant to control group with associated Std.MD (95% *CI*) was 0.93 (-0.66 to 2.52, P = 0.25 > 0.05). All heterogeneity that was high (P < 0.001, $I^2 = 88\%$; P < 0.001, $I^2 = 97\%$; P < 0.001, $I^2 = 97\%$; P < 0.001, $I^2 = 97\%$) might be attributed to the differences in the measurement time, measurement areas or the ingredient of traditional insect Chinese medicine. The random effects models were conducted to pool data and so any conclusions need to be made with caution (Fig. 9).

	Experime	ental	Contro	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% C	
1.6.1 Gastrointestinal		eaction					
Cao Y. 2014	18	68	34	68	6.9%	0.53 [0.33, 0.84]	
Deng Z.Y.2015 Dong M.E.2014	3 23	25 60	10 35	24 60	2.5% 7.7%	0.29 [0.09, 0.92] 0.66 [0.45, 0.97]	
Jiang C.Y.2013	6	30	13	33	3.9%	0.51 [0.22, 1.17]	
Li Q.M.2003	4	20	7	18	2.9%	0.51 [0.18, 1.47]	
Liu Y.Q. 2010	11	38	17	44	5.4%	0.75 [0.40, 1.40]	
Shen J.J. 2009 Shu X.H.2004	10 3	23 29	9 2	24 29	4.8% 1.3%	1.16 [0.58, 2.32] 1.50 [0.27, 8.32]	
Wang C.J.2004	3	30	10	30	2.4%	0.30 [0.09, 0.98]	
Wang L.J.2007	26	72	47	70	8.1%	0.54 [0.38, 0.76]	
Wei Y.F.2015	11	48	18	44	5.4%	0.56 [0.30, 1.05]	
Wu J.S. 2015	1	15 64	8	15 64	1.0% 5.4%	0.13 [0.02, 0.88]	
Xu Y.S.2011 You S.Y. 2006	10 21	25	32 22	25	5.4% 9.3%	0.31 [0.17, 0.58] 0.95 [0.76, 1.19]	
Yu J.G. 2013	9	30	15	30	5.2%	0.60 [0.31, 1.15]	
Yuan C.Y.2007	17	20	18	20	9.2%	0.94 [0.75, 1.19]	
Zeng C.S.2012	10	30	12	30	5.0%	0.83 [0.43, 1.63]	
Zhang B. 2007 Zhang M.J. 2011	8 14	51 38	9 24	49 38	3.7% 6.7%	0.85 [0.36, 2.03] 0.58 [0.36, 0.94]	
Zhu W.Q.2014	5	48	24 14	50	3.3%	0.37 [0.15, 0.94]	
Subtotal (95% CI)	-	764		765	100.0%	0.63 [0.51, 0.77]	
Total events	213		356				
Heterogeneity: Tau ² =				P = 0.0	002); l² = 6	52%	
Test for overall effect: 2	2 = 4.41 (P	< 0.000	1)				
1.6.2 Liver damage							
Deng Z.Y.2015	9	25	16	24	9.8%	0.54 [0.30, 0.98]	
Dong M.E.2014	6	60	13	60	8.7%	0.46 [0.19, 1.13]	
Jiang C.Y.2013	11	30	24	30	10.1%	0.46 [0.28, 0.76]	
Liang Y.2008	47	48 38	45 16	48	10.8%	1.04 [0.96, 1.14]	
Liu Y.Q. 2010 Wei Y.F.2015	8 5	38 48	16 9	44 44	9.4% 8.3%	0.58 [0.28, 1.20] 0.51 [0.18, 1.40]	
Xie J. 2015	12	25	9	25	9.6%	1.33 [0.69, 2.59]	
You S.Y. 2006	4	25	20	25	8.7%	0.20 [0.08, 0.50]	
Yuan C.Y.2007	2	20	15	20	7.1%	0.13 [0.03, 0.51]	
Zhang B. 2007	20	51	20	49	10.2%	0.96 [0.59, 1.55]	
Zhang M.J. 2011 Subtotal (95% CI)	4	38 408	5	38 407	7.4% 100.0%	0.80 [0.23, 2.75] 0.56 [0.31, 1.02]	
Total events	128	100	192		1001070	0.00 [0.0.1, 1.02]	-
Heterogeneity: Tau ² =	0.87; Chi ² =			(P < 0.	00001); l²	= 92%	
Test for overall effect: 2	Z = 1.90 (P	= 0.06)					
1.6.3 Fever							
He S.L.2012	7	26	19	25	10.7%	0.35 [0.18, 0.69]	
Huang W.K.2013	34	41	35	41	17.2%	0.97 [0.80, 1.17]	
Li Q.M.2003	4	20	5	18	5.9%	0.72 [0.23, 2.27]	
Liang Y.2008	25	48	2	48	4.6%	12.50 [3.13, 49.87]	
Liu Y.Q. 2010	20	38	25	44	14.6%	0.93 [0.62, 1.38]	
Shen J.J. 2009 Wang C.J.2001	8 3	23 30	8 18	24 30	9.2% 6.2%	1.04 [0.47, 2.31] 0.17 [0.05, 0.51]	
Wei Y.F.2015	15	48	16	44	12.0%	0.86 [0.48, 1.52]	
Wu J.S. 2015	12	15	13	15	15.7%	0.92 [0.67, 1.27]	
Zhou J.S. 2006	2	21	5	22	3.9%	0.42 [0.09, 1.93]	
Subtotal (95% CI)		310		311	100.0%	0.82 [0.58, 1.15]	•
Total events Heterogeneity: Tau ² = 0	130 17: Chiž -	- 22.00	146 df = 0./P	- 0.00	02)-12 - 71	20/	
Test for overall effect: 2			ui = 9 (P	= 0.00	02); 1- = 72	270	
	(.	0					
1.6.4 Pain							
He S.L.2012	11	26	23	25	15.6%	0.46 [0.29, 0.73]	
Huang W.K.2013 Kou C.Y.2011	36 25	41 30	34 10	41 28	18.2% 15.0%	1.06 [0.88, 1.27] 2.33 [1.38, 3.93]	
Liu Y.Q. 2010	12	38	15	44	13.8%	0.93 [0.50, 1.73]	
Wang C.J.2001	2	26	8	26	6.3%	0.25 [0.06, 1.07]	
Wei Y.F.2015	10	48	11	44	12.3%	0.83 [0.39, 1.77]	
Wu J.S. 2015	10	15	9	15	14.7%	1.11 [0.64, 1.92] 0.08 [0.01, 0.56]	
Zhou J.S. 2006 Subtotal (95% CI)	1	21 245	13	22 245	4.1% 100.0%	0.08 [0.01, 0.56] 0.82 [0.53, 1.29]	
Total events	107		123			[0.00, 1.20]	
Heterogeneity: Tau ² =	0.28; Chi² =			< 0.00	01); l² = 80	0%	
Test for overall effect: 2	Z = 0.85 (P	= 0.40)					
							++
						-	0.01 0.1 1 10 100
						F	avours [experimental] Favours [control]
	Experim		Cont			Risk Ratio	Risk Ratio
Study or Subgroup 1.7.1 Kidney damage	Events	Total	Events	Tota	l Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.7.1 Kidney damage Liu Y.Q. 2010	2	38	6	44	38.0%	0.39 [0.08, 1.80]	
Wei Y.F.2015	2	38 48	2	44			
You S.Y. 2006	1	25	2				
Yuan C.Y.2007	1	20	2				
Zhang M.J. 2011	2	38	3			0.67 [0.12, 3.77]	
Subtotal (95% CI)		169		171	100.0%	0.55 [0.24, 1.27]	
Total events Heterogeneity: Chi ² = 0	8 0.54 df = /	1/0 - 0	15 1 = 12 - 1	n %			
Test for overall effect:				<i>o</i> 70			
		5.10	,				
							0.01 0.1 1 10 100
						Fa	vours [experimental] Favours [control]

Figure 8. The forest plots of other side effects (gastrointestinal adverse reaction, liver damage, fever, pain and kidney damage) for traditional insect Chinese medicine and the related preparation combined chemotherapy versus chemotherapy alone (*M*-*H*: Mantel-Haenszel estimates; *CI*: Confidence Interval).

Network contribution graphs of included studies. Figure 10 was the network contribution graph of the experimental group and the control group. This figure illustrated the treating method numbers in orders: cinobufotalin injection plus TACE versus TACE contained 26 studies, sodium cantharidinate vitamin B_6 injection plus TACE versus TACE contained 7 studies, Jinlong capsule plus TACE versus TACE contained 6 studies, and both Aidi injection plus TACE and sodium demethylcantharidate (SNCTD) plus TACE versus TACE contained 1 study, respectively. Five treating methods contributed 20% respectively to the entire network graph.

		erimen			ontrol			Std. Mean Difference		d. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	:I IV	/, Random, 95% Cl	
1.8.1 CD3+											
Ji J.F.2015	43.98	6.2	25		5.6	25	13.6%	1.26 [0.65, 1.87]			
Li Q.2008	46.65	5.4	50	40.41	4.8	46	14.9%	1.21 [0.77, 1.65]			
Liu X.H.2009	43.1	7.2	42	37.8	10.1	42	14.9%	0.60 [0.16, 1.04]		•	
Peng W.D.2011	58.9	1.2	40	57.1	1.2	40	14.5%	1.49 [0.99, 1.98]			
Sun Z.J.2002	52.17	6.65	118	36.09		118	15.6%	2.40 [2.06, 2.73]			
Yuan C.Y.2007	47.6	10.7	20	30.3	8.7	20	12.6%	1.74 [1.00, 2.48]			
Zhang M.J. 2011 Subtotal (95% CI)	69.94	5.03	38 333	60.11	3.98	38 329	13.9% 100.0%	2.15 [1.58, 2.72] 1.55 [1.01, 2.08]		•	
Heterogeneity: Tau ² = 0.45; Chi ² = 49.81, df = 6 (P < 0.00001); l ² = 88%											
Test for overall effect: Z = 5.68 (P < 0.00001)											
1.8.2 CD4+											
Ji J.F.2015	34.27	4.8	25	28.49	3.6	22	14.5%	1.33 [0.69, 1.97]		-	
Li Q.2008	33.19	3.6	50	29.22	3.5	46	14.9%	1.11 [0.68, 1.54]		-	
Liu X.H.2009	28.8	8.8	42	18.7	7.2	42	14.8%	1.24 [0.78, 1.71]		-	
Peng W.D.2011	35.5	0.2	40	33.9	0.1	40	11.6%	10.02 [8.37, 11.67]			>
Sun Z.J.2002	35.02	3.72	118	23.44	3.21	118	14.9%	3.32 [2.93, 3.72]		-	
Yuan C.Y.2007	35.6	6.4	20	27.5	7	20	14.4%	1.18 [0.51, 1.86]		-	
Zhang M.J. 2011	46.74	7.65	38		8.04	38	14.8%	0.79 [0.32, 1.26]		-	
Subtotal (95% CI)			333			326	100.0%	2.49 [1.34, 3.64]		•	
Heterogeneity: Tau ² =	2.27; Cł	ni² = 19	0.43, c	lf = 6 (P	< 0.00	0001); I	² = 97%				
Test for overall effect:	Z = 4.23	6 (P < 0	.0001)	``		,.					
1.8.3 CD8+											
Liu X.H.2009	26.1	5.7	42	21.4	5.3	42	33.6%	0.85 [0.40, 1.29]		•	
Peng W.D.2011	31.2	0.8	40	29.2	0.8	40	32.9%	2.48 [1.89, 3.06]		*	
Zhang M.J. 2011	30.02	4.79	38	32.64	5.36	38	33.5%	-0.51 [-0.97, -0.05]		•	
Subtotal (95% CI)			120			120	100.0%	0.93 [-0.66, 2.52]		-	
Heterogeneity: Tau ² =	1.91; Cł	ni² = 62	.24, df	= 2 (P •	< 0.000	001); I²	= 97%				
Test for overall effect:	Z = 1.14	(P = 0	.25)								
1.8.4 CD4+/CD8+											
Ji J.F.2015	1.53		25		0.21	22	12.3%	1.56 [0.90, 2.22]		-	
Li Q.2008	1.47	0.29	50		0.25	46	12.7%	1.10 [0.67, 1.53]		-	
Liu X.H.2009	1.27	0.28	42		0.23	42	12.6%	1.74 [1.23, 2.25]		-	
Peng W.D.2011	1.2	0.1	40	1.1	0.1	40	12.6%	0.99 [0.52, 1.46]		· · · · ·	
Sun Z.J.2002	1.72	0.14	118		0.12	118	12.5%	5.12 [4.59, 5.65]			
Xie Y.F. 2003	1.31	0.24	31	1	0.12	31	12.4%	1.61 [1.04, 2.19]			
Yuan C.Y.2007	1.6	0.2	20	1.4	0.2	20	12.3%	0.98 [0.32, 1.64]		-	
Zhang M.J. 2011	1.5	0.46	38	1.3	0.37	38	12.6%	0.47 [0.02, 0.93]		~	
Subtotal (95% CI)			364			357	100.0%	1.70 [0.69, 2.70]			
Heterogeneity: Tau ² =					< 0.00	0001); I	² = 97%				
Test for overall effect:	Z = 3.31	(P = 0	.0009)								
1.8.5 NK											
	00 70		05	05.00			10 50/	4 50 50 05 0 40		-	
Ji J.F.2015	32.73	4.6		25.63	4.7	22	16.5%	1.50 [0.85, 2.16]			
Li Q.2008	32.8	4.2	50	27.5	5.2	46	16.9%	1.12 [0.69, 1.55]			
Liu X.H.2009	27.9	7.2	42	19.2	1.8	42	16.8%	1.64 [1.14, 2.14]			
Sun Z.J.2002	32.06	5.16	118	12.91		118	16.8%	4.72 [4.22, 5.22]			
Xie Y.F. 2003	12.4	5.22	31	11.05		31	16.8%	0.26 [-0.24, 0.76]		[_	
Yuan C.Y.2007	31.5	4.8	20	24.8	4.1	20	16.4%	1.47 [0.76, 2.18]		-	
Subtotal (95% CI)	0.50		286	u _ c / ~	- 0.00	279	100.0%	1.79 [0.49, 3.09]		-	
Heterogeneity: Tau ² = 2.56; Chi ² = 179.42, df = 5 (P < 0.00001); l ² = 97% Test for overall effect: Z = 2.70 (P = 0.007)											
i est for overall effect:	2 = 2.70	v (P = 0	.007)								
									++		+
									-10 -5	0 5	10
									Favours [experi	mental] Favours [contr	ol]

Figure 9. The forest plots of immune function (CD3+, CD4+, CD8+, CD4+/CD8+, NK) for traditional insect Chinese medicine and the related preparation combined chemotherapy versus chemotherapy (*M-H*: Mantel-Haenszel estimates; *CI*: Confidence Interval; NK: Natural Killer cells).

Funnel plot characteristics. We applied the pooled odds ratio (OR) as the midpoint to draw the funnel plot (Fig. 11). The publication bias was evaluated in the funnel plot by comparing the symmetry of included studies on objective response rate. The funnel plot was symmetrical in visual while the images (Fig. 12) and calculating results of Egger's test (t = -2.96, P = 0.005) and Begg's test (z = 1.96, P = 0.092) indicated the potential publication bias did exist.

Discussion

Hepatocellular carcinoma (HCC) is a worldwide serious disease, causing serious health problems to human beings. The treating methods of western medicine, which include liver transplantation, liver resection, radiofrequency ablation (RFA), transcatheter hepatic arterial chemoembolization (TACE) and molecular targeted drugs, have already been used on HCC therapy for a long time. As for non-surgical hepatocellular carcinoma, the effective clinical evidence is insufficient and the heated debate also was aroused for the selection of optimal treating methods^{88, 89}. The current chemotherapy performed to end-stage HCC has been proved many side effects: bone

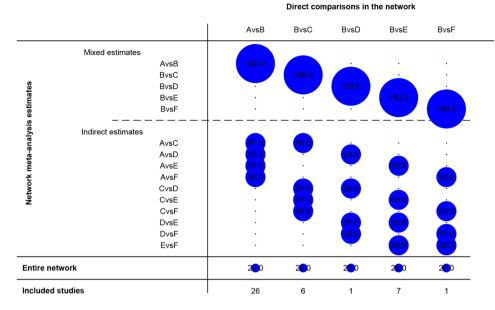


Figure 10. Network Contribution Graph: as for A vs B, for example, the contribute proportion of "A vs B" for "A vs B" is 100%, and for "A vs C", "A vs D", "A vs E" and "A vs F" was 50% respectively. The contribute proportion for entire network was 20% and 26 clinical studies included. Note: (**A**) cinobufotalin injection + TACE; (**B**) TACE; (**C**) Jinlong capsule + TACE; (**D**) Aidi injection + TACE; (**E**) Sodium Cantharidinate and Vitamin B6 Injection + TACE; F: Sodium Demethylcantharidate (SNCTD) + TACE.

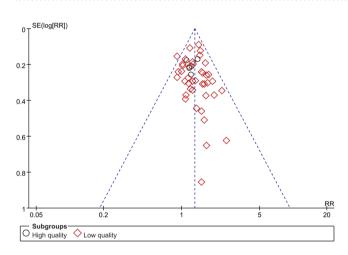


Figure 11. The funnel plot of objective response rate (CR+PR) Note: CR: Complete response rate. PR: Partial response rate.

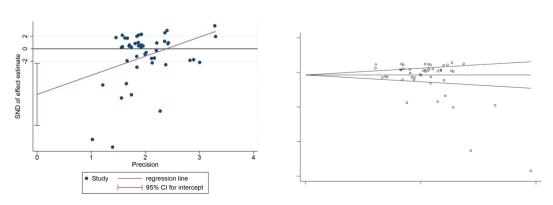


Figure 12. The Egger's and Begg's test of objective response rate (CR+PR).

marrow depression, gastrointestinal adverse reactions, liver damage, kidney damage, fever, pain, hair loss, dizziness, et al. These complications also become a huge burden for HCC patients. Based on this serious context, various complementary and alternative medicine (CAM) treatments have been administered for HCC in clinical practice. The traditional insect Chinese medicine, as an essential part of TCM, has been utilized to treat HCC as an auxiliary method (or CAM methods) for a long time. The effective and safe evaluation of traditional insect Chinese medicine for non-surgical HCC treatment is urgent and necessary. To the best of our knowledge, this article is the first PRISMA compliant systemic reviews and meta-analysis to evaluate the effects and safety of traditional insect Chinese medicine combined chemotherapy for non-surgical HCC. Fifty-seven articles, all of which were conducted in China, included 4,651 participants in the meta-analysis. Even with strong cultural and population bias, seven obvious advantages still need to be emphasized: (a) fourteen medical databases were utilized and the publication language was English, Chinese and Japanese; (b) the article quality was strictly accessed and evaluated by three cooperated reviewers (T.B.Song, Y.Wan and L. Shang); (c) we performed a comprehensive analysis for different categories of the including traditional insect Chinese medicine and the subgroup analysis and sensitivity analysis was both well conducted to seek the source of heterogeneity; (d) we contacted authors on whether the included articles could receive on full-text; (e) Egger's test, Begg's test and funnel plot was performed to confirm whether the publication bias existed in the studies; (f) the contribution network plot graph was strictly designed to evaluate the mutual effectiveness among the included traditional insect Chinese medicines as clearly exhibited as graphs; (g) the Cochrane risk of bias tool was performed to assess the study quality. The studies' outcomes showed good qualities were still insufficient for the reason of the high risk on blinding methods bias, selective reporting bias, and other bias.

The meta-analysis was carried out in 46 articles to evaluate the objective response rate (CR + PR), showing the significantly effectiveness in the experimental group (traditional insect Chinese medicine combined chemotherapy) compared with the control group (chemotherapy) alone. The subgroup analysis based on the articles' quality difference also provided the same result. These results suggest that the short-term effects of traditional insect Chinese medicine as auxiliary method combined chemotherapy are superior to chemotherapy alone. It is important to note that the publication bias on objective response rate indicates inconformity between funnel plot in visual appearance and Egger's/Begg's test results. Involved studies showed that experimental groups significantly improve the survival time at 12 months, 18 months, 24 months and 36 months compared with control groups, revealing that traditional insect Chinese medicine combined chemotherapy might prolong the survival time of non-surgical HCC patients. However, no statistical difference was found in 6 months survival time. The meta-analysis contained quality of life (QoL) scores, Karnofsky performance scores (KPS) and AFP improvement, all showing significant improvement in the experimental group compared with the control group. We did not observe large heterogeneity among these studies and the results indicated an excellent improvement of patients' life quality for the the utilization oftraditional insect Chinese medicine. The meta-analysis evaluated the side effects ratio after therapy, clearly showing the obvious reduction of gastrointestinal adverse reaction and WBC decrease in the experimental group compared to the control group. The liver damage, kidney damage, fever, pain, HB decrease and PLT decrease did not show significantly statistically difference although all of them indicated the same conclusion that side effects ratio of traditional insect Chinese medicine combined chemotherapy lower than chemotherapy alone. Although we found that the obvious heterogeneity in WBC decrease, HB decrease, gastrointestinal adverse reactions, liver damage, fever and pain was obvious, most of them did not show the source of heterogeneity except the HB decrease and gastrointestinal adverse reactions. The heterogeneity of HB decrease and gastrointestinal adverse reactions both came from the variation among the different experimental areas. The meta-analysis showed that the improvement of immune function in the experimental group was higher than the control group although the heterogeneity was obvious. We did not find the source of heterogeneity of them. So we could not give the firmly conclusion on the effectiveness of immune function improvement except we could include more relevant articles in the future meta-analysis. For forty-six included trials focused on objective response ratio, all experimental groups utilized traditional insect Chinese medicine related preparation as auxiliary therapy combined chemotherapy for the advanced HCC therapy.

The included traditional insect Chinese medical preparations contained cinobufotalin injection (28 trials, 62%), Jinlong capsule (6 trials, 13%), sodium cantharidinate and vitamin B6 injection (7 trials, 15%), Aidi injection (1 trial, 2%), sodium demethylcantharidate (SNCTD) (1 trial, 2%), compound cantharis capsule (1 trial, 2%), Aiyishu injection (1 trial, 2%) and Qining injection (1 trial, 2%). It has been clearly revealed that the cinobufotalin injection contributes as the major adjuvant therapy choice for non-surgical HCC. Transcatheter hepatic arterial chemoembolization (TACE) was ranked as the most frequently way of chemotherapy both in experimental groups and control groups (43 trials, 93%). Chemotherapy drugs, applied in HCC patients' therapy through the way of TACE with 1-4 of them, were diversified, such as OXA (oxaliplatin), DDP (cisplatin), CBP (carboplatin), lobaplatin, EPI (epirubicin), DOX (doxorubicin), THP (pirarubicin), MMC (mitomycin) and HCPT (hydroxycamptothecine). The dosage of traditional insect Chinese medicine and chemotherapy drugs had their own differences.

The publication bias for objective response rate did exist in this meta-analysis after Egger's and Begg's test. It might be derived from (a) some authors tended to deliver positive results of articles to editors while prejudiced negative results⁹⁰; (b) some magazine editors or reviewers had a preference to positive results of articles while caviled to negative results to some extent⁸⁷; (c) trials that received government funding had more possibility to publish on some magazines than received private or company funding⁹¹. The meta-analysis would overstate the degree of association between treating effects and risk factors because of the publication bias, which would bring mistakes for clinical patient's therapy or health decision-making.

Limitation. There are several potential limitations of current data and results that should be interpreted with caution. Firstly, included clinical studies all conducted in different centers in China, which may bring the regional and cultural bias and influence the widely application of traditional insect Chinese medicine in the future. Secondly, for the reason of varied medical development in different regions of China, clinical centers in China conducting the trials have different clinical levels of tumor diagnosis and treatment, which could result in a bias of the reported incidence rate. Thirdly, the included randomized clinical trials have many flaws caused by human baseline risk factors (all patients were Chinese), incomplete methodological design of trials, small sample trials (some studies have less than 30 patients per group) and index criteria deficiency (the information of the clinical stage of HCC or Child-Pugh scores deficiency). Fourthly, some results showed significantly heterogeneity among the included studies, which may be due to the sample size, different experimental region in China, medicine application and dose, publication years, as well as duration of treatment. However, we need to understand that establishing the random-effects model to pool data cannot give exact and stable conclusion in this situation. Fifthly, the application of traditional insect Chinese medical preparations varied in included articles. For example, some insect medical preparations were used through the way of injection (i.e. cinobufotalin injection, sodium cantharidinate and vitamin B6 injection, Aidi injection, et al.) and some were administrated through the oral way (i.e. Jinlong capsule, compound cantharis capsule, et al.). The time of applying medicines was unsynchronized, which also might exert potential time bias.

Conclusion

This system review and meta-analysis offers a practical and beneficial result for the effectiveness and safety of traditional insect Chinese medicine combined chemotherapy on non-surgical hepatocellular carcinoma (HCC). This combined therapy can provide assistance for improving the objective response rate (CR + PR) of HCC, prolonging long term survival time (12, 18, 24, 36 months), enhancing life quality (QoL scores and KPS) of patients, increasing some laboratory index (AFP) and immune functions (CD3⁺, CD4⁺, CD4⁺, CD8⁺, NK) and reducing some adverse effects (WBC decrease, gastrointestinal adverse effects). However, some results (6 months survival time, PLT decrease, HB decrease, liver damage, kidney damage, pain, fever and CD8⁺) cannot support a convincing conclusion because they cannot obtain the statistical difference. We should make the conclusion cautiously that this combined therapy can be applied as an auxiliary clinical treating method on non-surgical HCC treatment because many included publications' low quality increases risk and bias and affects the reliability of study to some extent. So the traditional insect Chinese medicine and related preparation still need further standard, multicenter, double-blind randomized clinical trials (RCTs) to provide more clinical evidences in the future.

Data Availability Statement. All data in this article are fully available without restriction.

References

- Ferlay, J., Shin, H. R., Bray, F. & Forman, D. et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer. 127, 2893–2917 (2010).
- 2. WHO. World Health Organization Mortality Database http://apps.who.int/healthinfo/statistics/mortality/whodpms/(2015) (2015).
- 3. Jemal, A., Bray, F., Cente, M. M. & Ferlay, J. et al. Global cancer statstics, 2008. CA: A Cancer Journal for Clinicians. 61, 69-90 (2011).
- 4. Torre, L. A., Bray, F. & Siegel, R. L. et al. Global cancer statstics, 2012. CA: A Cancer Journal for Clinicians. 00, 11-13 (2015).
- siegel, R., Ward, E., Brawley, O. & Jemal, A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA: A Cancer Journal for Clinicians. 61, 212–236 (2011).
- Maluccio, M. & Covey, A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. CA:A Cancer Journal for Clinicians. 62(no. 6), 394–399 (2012).
- Alazawi, W., Cunningham, M., Dearden, J. & Foster, G. R. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. *Alimentary Pharmacology & Therapeutics*. 32, 344–355 (2010).
- Bosch, F. X., Ribes, J., Diaz, M. & Cléries, R. Primary liver cancer: world-wide incidence and trends. Gastroenterology. 127, 5–16 (2004).
- 9. Jordi, B., Maria, R. & Morris, S. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology.* **150**, 835–853 (2016).
- 10. Alejandro, F., Josep, M. L. & Jordi, B. Hepatocellular carcinoma. Lancet. 379, 1245-1246 (2012).
- 11. EI-Serag, H. B. Hepatocellular carcinoma. The New England Journal of Medicine 365, 1118-1127 (2011).
- 12. Andres, P., Michael, M. & Joachim, D. Liver cancer: targeted future options. World Journal of Hepatology 3, 34-44 (2011).
- Gao, X. Prospects and research situation of insect-drugs. China Journal of Traditional Chinese Medicine and Pharmacy. 25, 807–809 (2010).
- 14. Yan, J. M. The Annotation of Fifty-two patients side (ed. Wu, B. Y.) 251-257 (TCM Ancient Books Publishing House 2005).
- 15. Gu, G. G. Shennong's herbal classic (ed. Chen, H.) 11-303 (The Academy Press House 2007).
- 16. Zhu, L. C. The application of insects-drugs (ed. Zhang, K.) 13-564 (People's Health Publishing House 2016).
- Zeng, C. S., Cai, M. L. & Li, J. W. et al. Influence of Jinlong capsule combined with transarterial chemo-embolization on quality of life of patients with primary liver cancer. *Chinese Journal of Clinical Oncology*. 39, 1839–1842 (2012).
- Chen, T. S., Wu, S. B. & Wu, X. X. *et al.* Clinical observation of 16 patients with primary liver cancer treated by TACE with continuous infusing Huachansu injection in portal vein. *China Journal of Traditional Chinese Medicine and Pharmacy.* 25, 792–794 (2010).
- 19. Xu, Y. S., Meng, Q. S. & Su, F. *et al.* Clinical study of sodium norcantharidin combined with transcatheter hepatic arterial chemoembolization as treatment for advanced liver cancer. *Medical Recapitulate.* **17**, 2058–2059 (2011).
- Mother, D., Liberati, A. & Tetzlaff, J. et al. Preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement. British Medical Journal. 339, 2535 (2009).
- NCCN. The NCCN hepatobiliary cancer clinical practice guidelines in oncology (version 3. 2015) https://www.nccn.org/ professionals/physician_gls/f_guidelines_nojava.asp#hepatobiliary Cancers (2016).
- 22. Reig, M., Darnell, A. & Forner, A. *et al.* Systemic therapy for hepatocellular carcinoma: the issue of treatment stage migration and registration of progression using the BCLC-refined RECIST. *Seminars Liver Disease.* **34**, 444–455 (2014).
- Eisenhauera, E. A., Therasse, P. & Bogaerts, J. et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45, 228–247 (2009).
- 24. Higgins, J. P. T. & Green, S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. *The Cochrane Collaboration*, http://handbook.cochrane.org (2011).

- Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. British Medical Journal. 327, 557–560 (2003).
- Donald, A. & Donner, A. Adjustments to the Mantel-Haenszel chi-square statistic and odds ratio variance estimator when the data are clustered. Statistics in Medicine. 6, 491–499 (1987).
- 27. Bohning, D., Malzahn, U. & Dietz, E. et al. Some general points in estimating heterogeneity variance with the DerSimonian–Laird estimator. *Biostatistics.* **3**, 445–457 (2002).
- Sterne, J. A. C. & Egger, M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. Journal of Clinical Epidemiology. 54, 1046–1055 (2001).
- 29. Egger, M., Smith, G. D., Schneider, M. & Minder, C. Bias in meta-analysis detected by a simple, graphical test. British Medical Journal. 315, 629-634 (1997).
- 30. Huang, W. K., Liu, D. Y. & You, L. *et al.* Jinlong capsule decreases adverse reactions after transcatheter arterial chemoembolization(TACE) in patients with hepatocellular carcinoma. *Oncology and Translational Medicine.* **1**, 87–91 (2015).
- Cao, Y. Efficacy and safety of compound cantharis capsules in treatment of primary liver cancer and cost-effectiveness evaluation. Evaluation and Analysis of Drug-use in Hospitals of China. 14, 711–713 (2014).
- Zeng, C. S., Cai, L. M. & Li, J. W. et al. Influence of Jinlong capsule combined with transarterial chemoembolization on quality of life of patients with primary liver cancer. *Chinese Journal of Clinical Oncology*. 39, 1839–1842 (2012).
- Deng, Z. Y. & Duan, H. B. Clinical observation of Cinobufacini injection combined with TACE in the treatment of hepatocellular carcinoma. *Tianjin Journal of Traditional Chinese Medicine* 32, 275–278 (2015).
- Dong, M. E. The clinical observation of Huachansu injection in combination with small dose of arterial perfusion chemotherapy treatment in middle and advanced stages of hepatocellular carcinoma. *Journal of Emergency in Traditional Chinese Medicine*. 32, 350–351 (2014).
- Feng, X. M., Fu, F. X. & Han, W. Q. et al. The clinical observation of FOLFOX4 program combined with Huachansu injection for 52 cases middle and advanced stages of hepatocellular carcinoma. Journal of Chinese Community Physicians. 14, 78–79 (2012).
- Fu, Z. L., Qu, Z. H. & Wang, Y. The clinical research of Huachansu injection combined with interventional therapy for middle and advanced stages of hepatocellular carcinoma. *China Practical Medical*. 5, 107–108 (2010).
- He, S. L., Liu, L. M. & Sun, X. J. et al. Effect of huachansu injection sequence TACE including oxaliplatin regimen for advanced hepatocellular carcinoma. Chinese Journal of Clinicians (Electronic Edition). 6, 3880–3883 (2012).
- Ji, J. F., Deng, X. L. & Xiao, Q. J. et al. Percutaneous cinobufotalin injection under ultrasonography combined with transcatheter arterial chemoembolization on treating portal vein tumor thrombus. *Journal of Changchun University of Chinese Medicine*. 31, 1059–1062 (2015).
- Jia, C. H., Wang, W. Y. & Kang, Y. Clinical studies on combination therapy of jinlong capsule and transarterial chemoembolization in treatment of primary hepatic carcinoma. *Chinese Journal of Cancer Prevention and Treatment.* 15, 1416–1418 (2008).
- 40. Jiang, C. Y., Cao, J. J. & Cheng, Q. The clinical evaluation of Jinlong capsule combines with transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma. *Medical Innovation of China*. **10**, 110–111 (2013).
- Ke, J., Lu, K. & Li, Y. Clinical observation of patients with primary liver cancer treated by Cinobufagin Injection combined with transcatheter arterial chemoembolization(TACE). *China Practical Medical* 6, 1–2 (2011).
- Kou, C. Y. & Xu, Z. The clinical analysis of Huachansu injection combines with transcatheter arterial chemoembolization for middle and advanced stages of hepatocellular carcinoma treatment. *Chinese Journal of Mis-diagnostics.* 11, 6151–6152 (2011).
- Li, B., Zhao, L. X. & Liu, Z. W. et al. Jinlong capsule combined with interventional therapy for primary hepatocellular carcinomas: a clinical analysis on 150 patients. Chinese Journal of Hepatobiliary Surgery. 19, 530–533 (2013).
- Li, J. & Qi, C. H. Clinical efficiency of transcatheter arterial chemoembolization combined Traditional Chinese Medicine foe the treatment of primary liver cancer. *Chinese Imaging Journal of Integrated Traditional and Western Medicine*. 11, 627–629 (2013).
- Li, Q., Sun, B. M. & Peng, Y. H. *et al.* Clinical Study on the Treatment of Pr imary Liver Cancer by Cinobufotain Combined with Transcatheter Arterial Chemoembolization. *Acta Universitatis Traditionis Medicalis Sinensis Pharmacologiaeque Shanghai.* 22, 32–34 (2008).
- Li, Q. M. & Zhao, Y. L. The clinical observation of Qining injection combined interventional therapy for hepatocellular carcinoma. Sichuan Journal of Cancer Control 16, 160–161 (2003).
- Li, W. H., Yin, J. P. & Wang, X. H. The clinical observation of Huachansu injection combined interventional therapy for middle and advanced stages of hepatocellular carcinoma. World clinical drugs. 27, 304–306 (2006).
- Liang, B. L., Nan, Y. M. & Liu., S. M. et al. The influence of Cantharis acid sodium vitamin B6 for liver function and blood picture of hepatocellular carcinoma artery Perfusion chemotherapy embolism. *Chinese Medicine*. 5, 701–702 (2010).
- 49. Liang, C. X. The clinical observation of Cantharis acid sodium injection combined interventional therapy for hepatocellular carcinoma. *Chinese Journal of Clinical Research* 28, 742–744 (2015).
- Liang, T. J., Qin, C. Y. & Zhang, C. Q. et al. Clinical studies on the combination therapy with Jinlong capsule and chemotherapy plus embolization by hepatic artery catheterization on primary hepatic carcinoma. *Chinese Journal of Clinical Oncology.* 32, 641–643 (2005).
- Liang, Y., Long, J. Z. & Liu, H. *et al.* Study of cinobufotalin and interferon combined with transcatheter hepatic arterial chemoembolization on primary hepatocellular carcinoma. *Modern Journal of Integrated Traditional Chinese and Western Medicine*. 17, 1628–1630 (2008).
- Liu, X. H., Fu, H. & Zhu, Q. H. et al. The clinical study of cinobufotalin injection combined with transcatheter hepatic arterial chemoembolization on hepatocellular carcinoma. Chinese Journal of Modern Drug Application. 3, 134–135 (2009).
- Liu, Y. Q., Yu, Z. H. & Shao, Z. H. et al. The clinical study of cinobufotalin injection combined with transcatheter arterial chemoembolization for hepatocellular carcinoma treatment. Chinese Rural Health Service Administration. 30, 402–404 (2010).
- Lu, S. J. Thirty cases of patients with advanced liver cancer treated with TCM syndrome differentiation combined with cinobufotalin injection. *Henan traditional Chinese Medicine*. 34, 2348–2349 (2012).
- 55. Peng, W. D. The clinical observation of compound cantharis capsule combined with chemotherapy for advance primary hepatocellular carcinoma treatment. *Guiding Journal of Traditional Chinese Medicine Pharmacy.* **17**, 39–40 (2011).
- Qu, J. R., Wang, Q. S. & Dai., J. et al. The preventive effect for adverse effect of Secretio bufonis injection on primary hepatocellular carcinoma after intervention. Chinese Journal of Difficult and Complicated Cases. 11, 294–295 (2012).
- Shen, J. J. The clinical effect of cinobufotalin injection by transcatheter arterial chemoembolization combined with intravenous on treating primary liver cancer. *Chinese Journal of Clinical Hepatology.* 25, 207–209 (2009).
- Shen, J. J. & Tan, S. Z. The cinobufotalin injection combined with transcatheter arterial chemoembolization for advance hepatocellular carcinoma treatment. *Jilin Journal of Traditional Chinese Medicine*. 35, 678–680 (2015).
- Shu, X. H. & Tan, B. X. The short term clinical observation of cinobufotalin injection combined with 5-fluorouracil for advanced hepatocellular carcinoma treatment. *The Journal of Sichuan oncology prevention*. 17, 88–89 (2004).
- 60. Su, Y., Yang, J. Q. & Guo, C. Q. The cinobufotalin injection in combination with transcatheter arterial chemoembolization for advance hepatocellular carcinoma treatment. *Journal of Basic and Clinical Oncology.* **26**, 245–246 (2013).
- 61. Sun, Z. J., Pan, C. E. & Wang, G. J. The clinical study by cinobufotalin injection in combination with transcatheter arterial chemoembolization. *Cancer Research on Prevention and Treatment.* **29**, 67–68 (2002).

- Tang, J. G., Wei, Z. X., Yin, J. F. & Guan, L. R. 46 cases of end-stage hepatocellular carcinoma treatment by cinobufotalin injection in combination with transcatheter arterial chemoembolization. *Chinese Journal of Integrated Traditonal and Western Medicine on Liver Disease* 9, 54 (1999).
- Tian, X. L. The clinical effects analysis of Aiyishu injection combined with interventional therapy on 36 cases advanced hepatocellular carcinoma therapy. *Central Plains Medical Journal.* 33, 32–34 (2006).
- Wang, C. J., Chen, Q. Q. & Deng, L. et al. Hepatic artery infusion of cinobufotalin for treating advanced hepatocellular carcinoma. Chinese Journal of Integrated Traditonal and Western Medicine on Liver Diseases. 11, 5–7 (2001).
- Wang, L. J., Ii, X. D., Ma, M. & Zhang, H. Z. Efficacy of Banmao complex injection in chemotherapy of primary hepatic carcinoma. Modern Oncology. 15, 1812–1813 (2007).
- 66. Wang, Q. C., Chen, W. & Chen, D. Q. et al. Influence of toad venom, salvia miltiorrhiza and matrine combined with transcatheter arterial chemoembolization on the immune function of the patients with hepatocellular carcinoma. Chinese Journal of Gastroenterology and Hepatology. 22, 632–634 (2013).
- 67. Wei, Y. F., Wu, J. S. & Huo, Z. G. *et al.* The clinical evaluation of disodium cantharidinate and vitamin B6 injection combined with interventional embolization chemotherapy for 48 cases end-stage hepatocellular carcinoma. *China Pharmaceuticals.* **24**, 72–74 (2015).
- Wu, H. M., Zhu, Z. D., Ling, C. Q. & Chen, Z. The clinical observation for hepatocellular carcinoma treatment by cinobufotalin combined interventional embolization chemotherapy. *Liaoning Journal of Traditional Chinese Medicine*. 27, 127–128 (2000).
- Wu, J. Y. Clinical observation for interventional embolization chemotherapy by arterial infusion of cinobufotalin injection combined with transcatheter arterial chemoembolization. *Modern Journal of Integrated Traditional Chinese and Western Medicine* 15, 1313–1314 (2006).
- Wu, J. S., Wei, Y. F. & Huo, Z. G. et al. The side effect evaluation of Aiyishu injection combined with half amount of transcatheter arterial chemoembolization for hepatocellular carcinoma. Neimenggu Traditional Chinese Medicine. 7, 66–67 (2015).
- Wu, Z. M., Liu, Q. & Qi, X. H. Efficacy of cantharidin combined with transcatheter arterial embolization for primary hepatocellular carcinoma. *Journal of Southern Medical University*. 30, 2774–2776 (2010).
- 72. Xiao, X. S. Fifty cases clinical observation for the advanced liver cancer by cantharidin combined with transcatheter arterial embolization. *China Foreign Medical Treatment.* 25, 88–89 (2011).
- Xie, J., Wang, Z. R. & Ma, J. et al. Fifty cases clinical study of Xifeng Chinese medicine combined transcatheter arterial embolization for liver cancer treatment. Jiangsu Traditional Chinese Medicine. 47, 32–33 (2015).
- Xie, Y. F., Tan, X. F. & Ma, Q. H. et al. Clinical observation: Jinlong capsule combined transcatheter arterial embolization for liver cancer treatment. Chinese Journal of Clinical Oncology. 30, 297–298 (2003).
- Xu, Y. S., Meng, Q. S., Su, F. & Zhao, T. B. Clinical study of sodium norcantharidin combined with transcatheter hepatic arterial chemoembolization as treatment for advanced liver cancer. *Medical Recapitulate*. 17, 2058–2059 (2011).
- Xue, Q., Lu, L. Q., Yuan, G. R. & Zhao, T. W. Thirty-two cases clinical study for middle and end-stage primary liver cancer across cantharidin combined with transcatheter arterial embolization. *Jiangsu Traditional Chinese Medicine*. 42, 22–24 (2010).
- 77. Yang, P. Y., Sun, Y. Y. & Zhang, Y. C. *et al.* Effectiveness of early intervention with Jin-long capsules and transarterial chemoembolization for the treatment of primary liver cancer. *Chinese Journal Clinical Oncology.* **40**, 45–49 (2013).
- You, S. Y., Fan, H. & Huan, Z. G. et al. Clinical study of cantharidin injection combined with transcatheter arterial embolization for middle and end-stage liver cancer. *Hebei Medicine*. 12, 1096–1100 (2006).
- Yu, J. G. Clinical observation for primary hepatocellular carcinoma by cantharidin injection combined with transcatheter arterial embolization. Modern Digestion & Intervention 18, 32–33 (2013).
- Yuan, C. Y., Xie, Q. & Xie, B. R. et al. Twenty cases clinical observation of cantharidin injection combined with transcatheter arterial embolization by primary liver cancer. Guiding Journal of Traditional Chinese Medicine and Pharmacy. 17, 16–17 (2011).
- Zhang, B. Clinical observation of Aiyishu injection combined with transcatheter arterial embolization for primary liver cancer. *China Medical Herald.* 4, 48–49 (2007).
- Zhang, C. Q., Liang, T. J. & Yuan, M. B. Clinical studies of the combination therapy with Jinlong capsule and chemical therapy and embolization by hepatic artery catheterization on primary hepatic carcinoma. *Beijing Medical Journal.* 27, 357–359 (2005).
- Zhang, M. J. & Zuo, C. F. Clinical efficacy of sodium cantharidate vitamin B6 injection combined with chemotherapy in treatment of liver cancer. *Journal of Practical Oncology.* 26, 50–52 (2011).
- Zhang, T. S. & Shan, G. Z. Continuous transarterial infusion with cinobufotain combined with transhepatic arterial embolism in the treatment of 32 cases with primary hepatocellular carcinoma. *Journal of China Oncology.* 17, 557–558 (2011).
- Zhou, J. S., Lu, H., Wu, X. D. & Xu, X. Clinical observation of Huachansu injection combined transarterial infusion therapy for primary liver cancer. *Chinese Journal of Primary Medicine and Pharmacy*. 13, 571–572 (2006).
- Zhu, W. Q. Sodium cantharindinate and vitamin B6 injection in combination with TACE for p rim ary liver cancer. *International Medicine and Health Guidance News.* 20, 2130–2132 (2014).
- 87. Angell, M. Negative studies. New England Journal of Medicine 321, 464-466 (1989).
- Germani, G. et al. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: a Meta-analysis. Journal of Hepatology. 52, 380–388 (2010).
- Yang, J. D. & Roberts, L. R. Hepatocellular carcinoma: A global view. Nature Reviews Gastroenterology & Hepatology. 7, 448–458 (2010).
- 90. Begg, C. B. A measure to aid in the interpretation of published clinical trials. Statistical in Medicine. 4, 1-9 (1985).
- Dickersin, K., Min, Y. I. & Meinert, C. L. Factors influencing publication of research results: follow-up of applications submitted to two institutional review boards. JAMA. 267, 374–378 (1992).

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Author Contributions

All authors have contributed to this article. The databases were searched and data were extracted by Z.F.S., J.X., Y.Q.Y. The statistical analysis was conducted by Z.F.S. and modified by L.S. and Y.W. The study tables and figures were conducted by Z.F.S. and T.B.S. The article language was edited and revised by K.K.S. and Y.W. The basic knowledge of TCM was guided by Y.P.D.

Additional Information

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