

Chinese Herbal Medicine and Chemotherapy in the Treatment of Hepatocellular Carcinoma: A Meta-analysis of Randomized Controlled Trials

Xiaojuan Shu, MPH (candidate), Michael McCulloch, LAc, MPH, Hang Xiao, MPH, PhD, Michael Broffman, LAc, and Jin Gao, MD, PhD

Background: Hepatocellular carcinoma (HCC), one of the most common malignancies worldwide, is highly resistant to standard therapy. It is unclear whether chemotherapy, arterial embolization, or arterial chemoembolization improve survival advantage enough to justify their high toxicity. Treatment with Chinese herbal medicine has been explored, combining herbs that stimulate host immune response with those that have cytotoxic activity against HCC cells. The authors sought to evaluate the effectiveness of Chinese herbal medicine combined with chemotherapy. The hypothesis was that Chinese herbal medicine added to chemotherapy for the treatment of HCC would improve survival and tumor response, when compared to treatment with chemotherapy alone. **Methods:** The authors searched the databases TCMLARS, PubMed, and EMBASE as well as the bibliographies of studies identified in the systematic search for potentially relevant titles or abstracts of studies in any language. They retained those that (1) treated only HCC patients, (2) were described as randomized or reported that there was no statistical difference between treatment groups, (3) gave patients either Chinese herbal medicine therapy combined with chemotherapy in the treatment group or chemotherapy alone in the control group, and (4) provided data on the number of enrolled subjects and responders and nonresponders for tumor response and survival. The authors used random effects meta-analysis to combine data. **Results:** Twenty-six studies representing 2079 patients met the inclusion criteria. Chinese herbal medicine combined with chemotherapy, compared to chemotherapy alone, improved survival at 12 months (relative risk [RR], 1.55; 95% confidence interval [CI], 1.39-1.72; $P < .000$), 24 months (RR, 2.15; 95% CI, 1.75-2.64; $P < .000$), and 36 months (RR, 2.76; 95% CI, 1.95-3.91; $P < .000$). Tumor response increased (RR, 1.39; 95% CI, 1.24-1.56; $P < .000$). **Conclusions:** These findings provide promising evidence that combining Chinese herbal medicine with chemotherapy may benefit patients with HCC. Because of the low quality of these studies, these findings should be confirmed through conducting high-quality, rigorously controlled trials.

Keywords: *hepatocellular carcinoma (HCC); chemotherapy; Chinese herbal medicine; randomized, controlled trials (RCTs); quasi-randomized, controlled trials (quasi-RCTs); survival; tumor response (TR)*

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer worldwide, with increasing incidence.¹ The incidence ranges from 1 to 4 cases per 100 000 population in Western Europe and North America to 50 to 150 cases per 100 000 population in parts of Asia and Africa, where HCC is responsible for a large proportion of cancer deaths.² Its treatment remains a controversial issue, despite the progress that has been made during the past decades, as most HCC patients are diagnosed at late stages and receive only palliative treatments not intended to extend survival.¹ Untreated patients with advanced disease have a 1-year survival rate of 29%, a 2-year survival rate of 16%, and a 3-year survival rate of 8%.³

Arterial embolization, chemoembolization, and arterial chemotherapy are the major procedures in chemotherapy. Arterial embolization or chemoembolization is a technique combining intra-arterial chemotherapy and selective ischemia and was developed as an alternative to conventional systemic or intra-arterial chemotherapy. It is intended to induce tumor necrosis through administration of chemotherapy and an embolizing agent directly into the tumor by way of the feeding artery. The cytotoxic effect of arterial occlusion can be potentiated by labeling the infusion with radioactive isotopes or by adding cytotoxic drugs. Arterial embolization or chemoembolization includes

XS, MM, and MB are at the Pine Street Foundation, San Anselmo, California. MM and JG are at the Institute of Biophysics, Chinese Academy of Sciences, Beijing P.R. China. XS and HX are in the School of Public Health, Nanjing Medical University, Nanjing, P.R. China.

Correspondence: Michael McCulloch, LAc, MPH, Pine Street Foundation, 124 Pine Street, San Anselmo, CA 94960. E-mail: mcculloch@pinestreetfoundation.org.

procedures such as transcatheter arterial chemoembolization, transarterial embolization, hepatic arterial chemoembolization, and hepatic arterial embolization. Arterial chemotherapy is not aimed to achieve arterial occlusion. It includes procedures such as transarterial infusion, hepatic arterial infusion, and intravenous chemotherapy. However, these procedures are associated with their own potentially life-threatening toxicities and complications, such as severe postembolization syndrome, hepatic insufficiency, abscess, or infarction.⁴ In addition, they have shown only slightly improved survival or no survival advantages in previous studies.⁵⁻⁷ Meta-analysis of randomized controlled trials of treatment with chemoembolization or embolization has shown only a modest advantage in 2-year survival for patients with unresectable HCC, compared with conservative management.⁸ The same meta-analysis revealed that tamoxifen provided no advantage in 1-year survival.⁸ Since the prognosis with existing therapy is so poor, we sought to evaluate the clinical evidence for effectiveness of Chinese herbal medicine in combination with systemic chemotherapy for the treatment of HCC.

In China, herbal medicine is frequently combined with chemotherapy in the treatment of liver cancer, usually in formulas that combine various Chinese herbs into one treatment strategy. In this meta-analysis, we sought to assess the effectiveness of this therapy for HCC by analyzing data from studies that compared treatment with Chinese herbal medicine combined with chemotherapy to treatment with chemotherapy alone.

Methods

Systematic Search

Retrieval of studies in all languages was performed through systematic searching of the databases TCMLARS (1984-August 2004; www.cintcm.com), PubMed (1966-August 2004; www.pubmed.gov), and EMBASE (1974-August 2004; www.embase.com) using the keywords *liver cancer*, *chemotherapy*, *Chinese medicine*, and *randomized controlled trials*. We also searched the bibliographies of review papers and published randomized controlled trials identified in our systematic search.

Criteria for Inclusion

To be included in this meta-analysis, a study had to fulfill the following criteria: (1) only patients with HCC were included, (2) studies were described as randomized or had the design elements of quasi-randomized studies (studies did not mention adoption of randomization but reported there was no statistical difference

between 2 groups), (3) HCC patients were given either Chinese herbal medicine therapy in combination with chemotherapy in the treatment group or chemotherapy alone in the control group, and (4) authors provided necessary data on the number of responders and nonresponders for the end points of tumor response and survival sufficient to calculate relative risks (RRs) and 95% confidence intervals (CIs).

Criteria for Exclusion

Randomized controlled trials were excluded if they (1) were not described as randomized or quasi-randomized, (2) did not provide information concerning survival or tumor response, (3) included patients with cholangiocellular carcinomas or liver metastases of primary cancers other than liver, (4) did not contain an experimental arm treated with Chinese medicine combined with chemotherapy and control arm treated with chemotherapy alone, or (5) were duplicate publications of other studies previously identified in our systematic search. Decisions on whether to include or exclude trials and how to group studies for analysis by end points reported were made before conducting the meta-analysis.

Criteria for Combinability

Since there is no successful standard treatment for HCC, there are few published trials using exactly the same chemotherapy treatments and same Chinese herbal formula. As has been done in previous meta-analyses of chemotherapy for HCC, we combined studies in which patients in the treatment group were treated with the new therapy being evaluated and those in the control group were treated with standard chemotherapy alone.⁷⁻⁹ We also sought to separately meta-analyze any subgroups of studies that all used the same herbal combination.

Data Collection and Abstraction

Two reviewers (X.S. and M.M.) independently reviewed the retained studies. Since prior work has shown that blinding during study selection and data extraction does not result in either a clinically or a statistically significant effect on the summary effect measure of a meta-analysis,¹⁰ we chose a nonblinded design for data extraction.

Analysis of Outcomes

The primary outcome of interest was the proportion of patients surviving at 6, 12, 24, and 36 months. The secondary outcome of interest was tumor response.

Survival. We calculated survival using the proportion of subjects surviving among the total number of

subjects, separately for each treatment group. The ratio for improvement in survival at each time point was calculated as the proportion of subjects alive in the Chinese herbal medicine combined with chemotherapy group divided by the proportion of subjects alive in the chemotherapy-only group.

Objective tumor response. We selected studies that reported tumor response using the World Health Organization scale.¹¹ Following a method used in a previous meta-analysis of studies treating HCC patients with chemotherapy,¹² we calculated tumor response as any response (complete response plus partial response) divided by the total (complete response plus partial response plus no change plus progressive disease), separately for each treatment group. The RR of tumor response was calculated as the probability of any tumor response in the herbal medicine combined with chemotherapy group divided by the probability of any tumor response in the chemotherapy-only group.

Pooled analysis. We used the Stata statistical software package (version 8.0; Stata Corp, College Station, Tex) for data management and analysis. All analyses were performed on an intention-to-treat basis. We used the random effects method to calculate pooled treatment effects.¹³ An RR value greater than 1.0 was considered to be consistent with a beneficial effect of Chinese herbal medicine combined with chemotherapy (vs chemotherapy alone) in the treatment of patients with HCC.

Qualitative Analysis

Study quality. To evaluate study quality, we used the Jadad scale, a validated 5-point scale developed to evaluate the quality of reporting in studies included in a meta-analysis.^{14,15} The scale assigns a score of 0 or 1 for each of the following quality criteria, whether (1) the study was described as randomized, (2) the authors reported the method of randomization, (3) the use of blinding was reported, (4) the method for concealment of allocation was reported, and (5) authors accounted for withdrawals and dropouts. Thus, a highest-quality study would receive a score of 5 and a lowest-quality study a score of 0.

Results

Selection of Trials

After an initial screening of titles and abstracts, 385 potentially relevant clinical trials of HCC were identified. We then performed a second screening of these 385

studies and retained 126 published full papers, which were randomized controlled trials assessing Chinese herbal medicine in the treatment of HCC. After further evaluation, we excluded 9 studies because of nonrandomization, 13 studies because they lacked relevant end points, 24 studies because other cancers were included, 51 studies because they were missing either a qualified experimental group or controlled group, and 3 studies because they were duplicate publications of other studies previously identified in our systematic search. This yielded a total of 24 randomized controlled trials and 2 quasi-randomized controlled trials, which were identified as meeting protocol-specified inclusion criteria, totaling 2079 patients (Tables 1 and 2).

Treatment Effectiveness

Chemotherapy combined with Chinese herbal medicine, compared with chemotherapy alone, significantly improved survival at 12 months (RR, 1.55; 95% CI, 1.39-1.72; $P < .000$; Figure 1), 24 months (RR, 2.15; 95% CI, 1.75-2.64; $P < .000$; Figure 2), and 36 months (RR, 2.76; 95% CI, 1.95-3.91; $P < .000$; Figure 3). Tumor response was also significantly improved (RR, 1.39; 95% CI, 1.24-1.56; $P < .000$; Figure 4). There were no reliable data indicating significant survival improvement at 6 months since there was significant between-study heterogeneity (Table 3; figure not shown).

We identified 2 studies that used the exact same herbal formula (Hua Chan Su) and conducted a separate meta-analysis.^{16,17} The result also showed survival benefits of Hua Chan Su at 12 months (RR, 1.67; 95% CI, 1.38-2.02; $P < .000$; Table 3; figure not shown). It should be noted that Hua Chan Su contains bufotoxin, a digoxin-like substance that must be provided in carefully measured dosages to avoid cardiac glycoside toxicity.

A Chinese-English translation table is provided as an appendix, which identifies the original names of herbal formulas as identified in included studies and the names as translated into English.

Conclusions

Our meta-analysis data suggest promising evidence that Chinese herbal medicine in the treatment of HCC may have potential therapeutic value. Herbal medicine combined with chemotherapy for the treatment of HCC can improve survival at 12, 24, and 36 months when compared with chemotherapy alone. There is additional evidence that 6-month survival may also be improved; however, this finding is limited by the presence of between-study heterogeneity. Tumor response was also improved by the addition of Chinese herbal medicine to chemotherapy.

Table 1. Characteristics of Eligible Trials for This Meta-analysis

Study	No. Patients Enrolled		Mean Age (Median), y		Stage (Average size in cm ³)	Enrollment Interval, y	Jadad	Statistical Comparison	KPS		Comparison Treatment vs Control
	Treatment	Control	Treatment	Control					Treatment	Control	
Cao and Tang, 2003 ²⁰	29	38	50.0	51.0	II, III	2000-2002	0	Yes			TAE-herbs vs TAE
Chen et al, 2001 ²¹	42	41	49.0	49.0	II, III	1998-2000	1	Yes			TAE-herbs vs TAE
Feng, 2002 ²²	35	33	50.5	51.0	II, III	1997-2001	1	Yes	>60	>60	TACE-herbs vs TACE
Gao, 2004 ²³	20	20	53.5	54.7	I, II	1998-2003	1	Yes	70	71	HACE-herbs vs HACE
Jia et al, 2003 ²⁴	34	32			T3-4MOMO	2000-2002	1	Yes	>60	>60	TACE-herbs vs TACE
Li et al, 1998 ²⁵	34	31			II, III	1993-?	3	Yes	60-90	60-90	HAI-herbs vs HAI
Li, 2001 ²⁶	62	44	46.0	48.0	II, III	1997-2000	1	No			TACE/TAI-herbs vs TACE/TAI
Li and Li, 2001 ²⁷	45	20	54.5	55.3	II, III	1994-?	1	Yes	≥40	≥40	IVC-herbs vs IVC
Liu and Zhu, 2002 ²⁸	32	38	(47.0)	(48.0)	II, III	1996-1999	1	No			TACE-herbs vs TACE
Shao et al, 2001 ²⁹	30	30	48.6	51.3	II, III	1994-2000	1	Yes			HACE-herbs vs HACE
Sun et al, 2002 ¹⁶	118	118	51.4	51.4	II, III	1998-?	1	Yes	60-80	60-80	TACE-herbs vs TACE
Tian et al, 2001 ³⁰	23	20	52.8	51.6	I, II, III	1993-1996	1	Yes			HACE-herbs vs HACE
Wang, 1998 ³¹	36	36	48.3	46.5	II, IV	1997-?	0	Yes			HACE-herbs vs HACE
Wang et al, 2001 ³²	63	44	48.0	49.0	II, III	1996-1997	1	Yes			TACE-herbs vs TACE
Wu et al, 2000 ¹⁷	36	44	52.4	50.5	II, III	1994-1998	1	Yes			TAE-herbs vs TAE
Wu, 1999 ³³	13	12	55.0	56.0	II	1994-1998	1	Yes			TACE-herbs vs TACE
Wu et al, 2001 ³⁴	25	25	53.1	49.3	I, II, III	1998-2000	1	Yes	≥60	≥60	TACE-herbs vs TACE
Wu et al, 2002 ³⁵	30	30	51.5	52.3	II, III (56)	2000-?	1	Yes	64.5	64.5	TAE-herbs vs TAE
Xie et al, 2004 ³⁶	42	34	48.3	43.6	II, III	1999-?	1	Yes			IVC-herbs vs IVC
Yu, 2002 ³⁷	29	31	(40.3)	(40.3)	II, III (56)	1999-?	1	No			TACE-herbs vs TACE
Zhang and Zhang, 1998 ³⁸	30	28	60.0	61.0	III, IV		1	Yes			HAI-herbs vs HAI
Zhang et al, 1996 ³⁹	30	27	51.0	49.0	I, II		1	No			TAI + TAE-herbs vs TAI + TAE
Zhang, 1998 ⁴⁰	80	80	54.5	53.3	II, III		1	Yes	>60	>60	HAI-herbs vs HAI
Zhou et al, 2002 ⁴¹	26	20	50.0	49.5	II, III		1	No			TAE-herbs vs TAE
Zhou et al, 2002 ⁴²	118	110	(48.0)	(47.5)	II, III	1990-1999	2	No			TACE-herbs vs TACE
Zhou et al, 1999 ⁴³	15	16	57.7	57.7		1995-1997	1	No			IVC-herbs vs IVC

TACE/TAE = transcatheter arterial chemoembolization or transcatheter arterial embolization; TAI = transcatheter arterial infusion; HACE = hepatic arterial infusion; HAI = hepatic arterial chemoembolization; IVC = intravenous chemotherapy.

a. For specific definitions of the staging system used, see the respective reference(s).

Table 2. Chinese Herbal Medicines and Chemotherapy Drugs Used in Included Studies

Study	Chemotherapy Drugs	TCM Formula	Ingredients ^a
Cao and Tang, 2003 ²⁰	Epi-ADM or THP-ADM, CBP, MMC, lipiodol	Ai Di Zhu She Ye	Panax ginseng, Astragalus membranaceus, Eleutherococcus senticosus, Mylabris cichorii
Chen et al, 2001 ²¹	ADM, DDP, 5-Fu, MMC, lipiodol, gelatin sponge	Pei Yuan Gu Ben Kang Ai Jiao Nang	Panax ginseng, Corydalis bulbosa, Curcuma phaeocaulis, Salvia miltiorrhiza, Momordica charantia, Euphorbia japonica, Astragalus membranaceus, Ganoderma lucidum, Platycladus orientalis, Polyporus umbellatus, Houttuynia cordata, Poria cocos, Bupleurum chinense, Crataegus cuneata, Angelica polymorpha, Sargassum siliquastrum, Eleutherococcus senticosus, Scutellaria barbata, Hedyotis diffusa, Ziziphus spinosa, Rabdosia rubescens, Buthus martensii, Strychnos nux-vomica, Mylabris cichorii, Cremastra variabilis, Cervus elaphus
Feng, 2002 ²²	CPT, DDP, 5-Fu, lipiodol	Xiao Yao San + Liu Jun Zi Tang/Yi Guan Jian/Ge Xia Zhu Yu Tang ^b	
Gao, 2004 ²³	DDP, 5-Fu, MMC, lipiodol	Gan Ai Jian Ji	Astragalus membranaceus, Atractylodes macrocephala, Coix lacryma-jobi, Akebia trifoliata, Actinidia chinensis, Crataegus cuneata, Corydalis tuber, Bupleurum chinense, Curcuma aromatica, Artemisia scoparia
Jia et al, 2003 ²⁴	ADM, DDP, MMC (or 5-Fu), lipiodol, gelatin sponge	Brucea javanica oil	Brucea javanica oil
Li et al, 1998 ²⁵	ADM (or MMC), DDP (or CBP), 5-Fu	Gan Kang Chong Ji	Pseudostellaria heterophylla, Atractylodes macrocephala, Astragalus membranaceus, Angelica polymorpha, Panax notoginseng, Actinidia chinensis, Akebia trifoliata, Trionyx sinensis, Manis pentadactyla
Li, 2001 ²⁶	THP-ADM, 5-Fu, MMC, lipiodol	Ge Xia Zhu Yu Tang/Xiao Yao San/Yi Chen Wu Ling San/Zi Shui Qing Gan Yin	Prunus persica, Paeonia suffruticosa, Cyperus rotundus, Carthamus tinctorius, Citrus aurantium, Salvia miltiorrhiza, Plicorhiza scrophulariifolia, Hedyotis diffusa, Bupleurum chinense, Melia toosendan, Paeonia lactiflora, Angelica polymorpha, Poria cocos, Atractylodes macrocephala, Astragalus membranaceus, Hedyotis diffusa, Scutellaria barbata, Artemisia scoparia, Rheum officinale, Gardenia jasminoides, Poria cocos, Alisma orientalis, Polyporus umbellatus, Atractylodes macrocephala, Phellodendron amurense, Hedyotis diffusa, Scutellaria barbata, Rehmannia glutinosa, Cornus officinalis, Dioscorea opposita, Poria cocos, Paeonia suffruticosa, Ligustrum lucidum, Eclipta prostrata, Hedyotis diffusa
Li and Li, 2001 ²⁷	5-Fu, CF	Fu Zheng Yi Liu Tang	Astragalus membranaceus, Cinnamomum cassia, Polygonatum chinense, Rehmannia glutinosa, Pseudostellaria heterophylla, Atractylodes macrocephala, Coix lacryma-jobi, Angelica polymorpha, Paeonia lactiflora, Sparganium stoloniferum, Curcuma phaeocaulis, Hedyotis diffusa, Ligusticum chuanxiong, Salvia miltiorrhiza
Liu and Zhu, 2002 ²⁸	ADM, DDP, 5-Fu, lipiodol	Yan Shu Zhu She Ye	Sophora flavescens, Euphorbia fischeriana, Angelica polymorpha, Smilax glabra
Shao et al, 2001 ²⁹	ADM, DDP, 5-Fu, MMC, lipiodol or gelatin sponge	Gan Ai Yi Hao	Astragalus membranaceus, Codonopsis pilosula, Poria cocos, Ganoderma lucidum, Stephania tetrandra, Rehmannia glutinosa, Ligustrum lucidum, Eclipta prostrata, Salvia miltiorrhiza, Ligusticum chuanxiong, Buthus martensii, Curcuma phaeocaulis, Dioscorea opposita, Cremastra variabilis, Coix lacryma-jobi, Bupleurum chinense, Hedyotis diffusa, Scutellaria barbata, Paris polyphylla var. chinensis, Akebia quinata, Curcuma aromatica, Crataegus cuneata.
Sun et al, 2002 ¹⁶	Epi-ADM, CBP, MMC, lipiodol	Hua Chan Su	Bufotoin
Tian et al, 2001 ³⁰	DDP, 5-Fu, THP, lipiodol	Fu Zheng Jie Du Tang	Codonopsis pilosula, Astragalus membranaceus, Dioscorea opposita, Coix lacryma-jobi, Bupleurum chinense, Polygonum cuspidatum, Akebia trifoliata, Ligustrum lucidum, Eclipta prostrata
Wang, 1998 ³¹	ADM, CBP, MMC, iophendylate	Combination	Astragalus membranaceus, Poria cocos, Lycium barbarum, Ligustrum lucidum, Glycyrrhiza glabra var. glandulifera

(continued)

Table 2 (continued)

Study	Chemotherapy Drugs	TCM Formula	Ingredients ^a
Wang et al, 2001 ³²	ADM, 5-Fu, MMC, lipiodol	Fu Zheng Hua Ji Jie Du Fang	Armeniaca mume, Crataegus cuneata, Panax ginseng, Atractylodes macrocephala, Trionyx sinensis, Sophora japonica, Poria cocos, Cornus officinalis, Coix lacryma-jobi, Scutellaria barbata, Cremastra variabilis, Smilax glabra
Wu et al, 2000 ¹⁷	DDP, 5-Fu, MMC, lipiodol, gelatin sponge	Hua Chan Su	Bufotoxin
Wu, 1999 ³³	CBP, 5-Fu, MMC	Yi Guan Jian Jia Wei	Adenophora verticillata, Codonopsis pilosula, Lycium barbarum, Melia toosendan, Angelica polymorpha, Ophiopogon japonicus, Rehmannia glutinosa, Hedyotis diffusa, Atractylodes macrocephala, Polyporus umbellatus, Solanum nigrum, Prunella vulgaris, Pinellia ternata, Cirsium spicatus, Ostrea cucullata, Salvia miltiorrhiza
Wu et al, 2001 ³⁴	DDP, 5-Fu, MMC (or ADM), lipiodol, gelatin sponge	Ping Xiao Jiao Nang	Curcuma species, Agrimonia eupatoria, Citrus aurantium
Wu et al, 2002 ³⁵	ADM (or CBP), 5-Fu, MMC, lipiodol, gelatin sponge	Hu Gan Ruan Jian Fang	Codonopsis pilosula, Astragalus membranaceus, Poria cocos, Hedyotis diffusa, Rabdosia serra, Atractylodes macrocephala, Curcuma aromatica, Bupleurum chinense, Trionyx sinensis, Alisma orientalis, Salvia miltiorrhiza, Scolopendra subspinipes
Xie et al, 2004 ³⁶	ADM, 5-Fu, MMC	Ruan Gan Jian	Trionyx sinensis, Manis pentadactyla, Placenta hominis, Polygonatum chinense, Astragalus membranaceus, Sparganium stoloniferum, Curcuma phaeocaulis, Solanum nigrum, Paeonia lactiflora, Hedyotis diffusa, Paris polyphylla var. chinensis
Yu, 2002 ³⁷	ADM, DDP, 5-Fu, lipiodol	Combination	Melia toosendan, Corydalis bulbosa, Saussurea lappa, Curcuma aromatica, Paris polyphylla var. chinensis, Curcuma phaeocaulis, Prunus persica, Carthamus tinctorius, Panax notoginseng, Ranunculus ternatus, Pinellia ternata, Bulbostemma paniculatum, Papaver somniferum, Artemisia scoparia, Rheum officinale, Lobelia radicans, Cynanchis paniculata, Panax quinquefolium, Ophiopogon japonicus, Schisandra chinensis, Poria cocos, Dioscorea opposita
Zhang and Zhang, 1998 ³⁸	ADM + 5-Fu or DDP + MMC	Zi Ni Fu Gan Tang	Astragalus membranaceus, Polygonatum chinense, Codonopsis pilosula, Atractylodes macrocephala, Poria cocos, Ligustrum lucidum, Citrus reticulata, Ophiopogon japonicus, Cornus officinalis, Hedyotis diffusa, Glycyrrhiza glabra var. glandulifera
Zhang et al, 1996 ³⁹	ADM, DDP, MMC	AC-III Zhu She Ye	Not specified
Zhang, 1998 ⁴⁰	ADM, 5-Fu, MMC, lipiodol	Bu Gan Ruan Jian Tang	Manis pentadactyla, Asparagus species, Trionyx sinensis, Dendrobium moniiforme, Ostrea cucullata, Agrimonia eupatoria, Codonopsis pilosula, Scutellaria barbata, Sargassum siliquastrum, Lagenaria siceraria var. microcarpa, Ganoderma lucidum, Buthus martensii, Panax notoginseng
Zhou et al, 2002 ⁴¹	ADM, 5-Fu, MMC, lipiodol, gelatin sponge	Ping Xiao Jiao Nang + Sophora japonica injection	Curcuma species, Agrimonia eupatoria, Citrus aurantium, Sophora japonica
Zhou et al, 2002 ⁴²	ADM, DDP, 5-Fu, MMC, lipiodol (or gelatin sponge)	Liu Jun Zi Tang	Pseudostellaria heterophylla, Atractylodes macrocephala, Poria cocos, Glycyrrhiza glabra var. glandulifera, Pinellia ternata, Citrus reticulata, Astragalus membranaceus, Coix lacryma-jobi, Gallus gallus domesticus, Crataegus cuneata, Massa fermentata, Mantis pentadactyla, Trionyx sinensis
Zhou et al, 1999 ⁴³	ADM, 5-Fu, MMC	Fu Zheng Xiao Liu He Ji	Panax ginseng, Astragalus membranaceus, Ligustrum lucidum, Xanthium sibiricum, Cremastra variabilis, Smilax glabra, Fritillaria thunbergii, Sophora japonica, Curcuma phaeocaulis, Manis pentadactyla, Hirudo nipponica, Scolopendra subspinipes

TCM = traditional Chinese medicine; ADM = Adriamycin; THP-ADM = pirarubicin hydrochloride; CBP = carboplatin; MMC = Mitomycin; 5-Fu = fluorouracil; DDP = cisplatin; CPT = Camptosar.

a. We use the term *Chinese herbal medicine* broadly to designate the traditional formulas or their modern revisions, as some of the products included in this review are animal in origin.

b. Because more than 30 individual herbs were combined in this study, we have noted here the names of the combination formulas in which they are found.

Table 3. Results

End Point	No. of Studies	No. of Patients	Relative Risk	95% Confidence Interval	Significance	Publication Bias	Heterogeneity
6-mo survival							
All studies combined	13	974	1.25	1.11, 1.40	$P < .000^a$	$P < .000$	$P = .03$
12-mo survival							
All studies combined	17	1480	1.55	1.39, 1.72	$P < .000^a$	$P = .03$	$P = .94$
Hua Chan Su	2	316	1.67	1.38, 2.02	$P < .000^a$		$P = .90$
24-mo survival							
All studies combined	11	1082	2.15	1.75, 2.64	$P < .000^a$	$P = .45$	$P = .77$
36-mo survival							
All studies combined	8	818	2.76	1.95, 3.91	$P < .000^a$	$P = .94$	$P = .63$
Tumor response							
All studies combined	18	1369	1.39	1.24, 1.56	$P < .000^a$	$P = .01$	$P = 1.00$

a. Significant treatment effect.

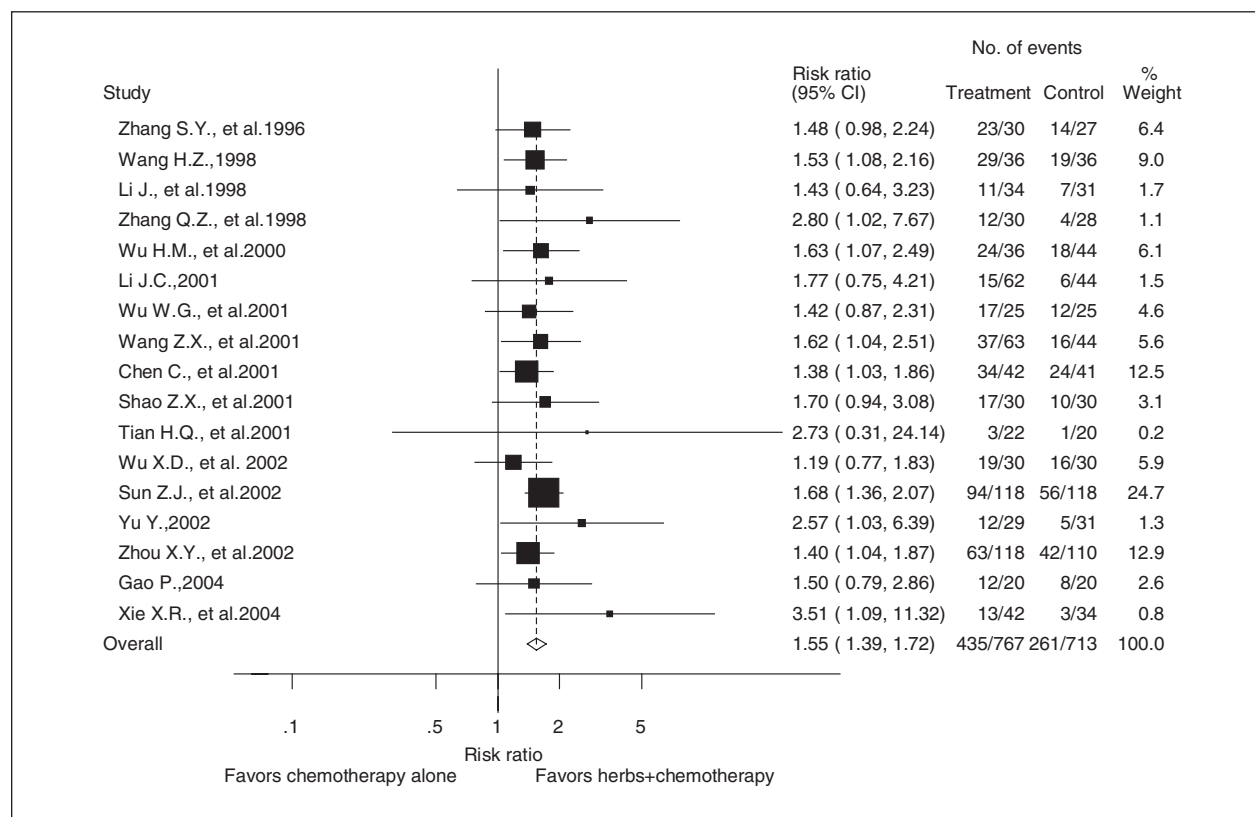


Figure 1 Twelve-month survival: herbs + chemotherapy versus chemotherapy alone.

In a separate meta-analysis of the only 2 studies using the exact same herbal medicine, Hua Chan Su, we found that 12-month survival was also increased.^{16,17}

Limitations

Publication bias. We found evidence for publication bias in the data for meta-analysis of survival at 6 and 12 months for all herbal formulas combined. We also found evidence for publication bias in the data for meta-analysis of tumor response.

Research techniques used in Chinese studies. Because the studies we found were of generally poor quality, we are unable to make definite conclusions from our data. Published studies from China were found to be more highly condensed than typical articles published in the Western literature, with key details of study design omitted, especially details concerning blinding of subjects and clinicians. In addition, since most studies did not describe subject withdrawals or dropouts, it is not possible to adjust the analysis for censoring, and therefore pooled estimates of survival should be interpreted with caution. However, inadequate reporting

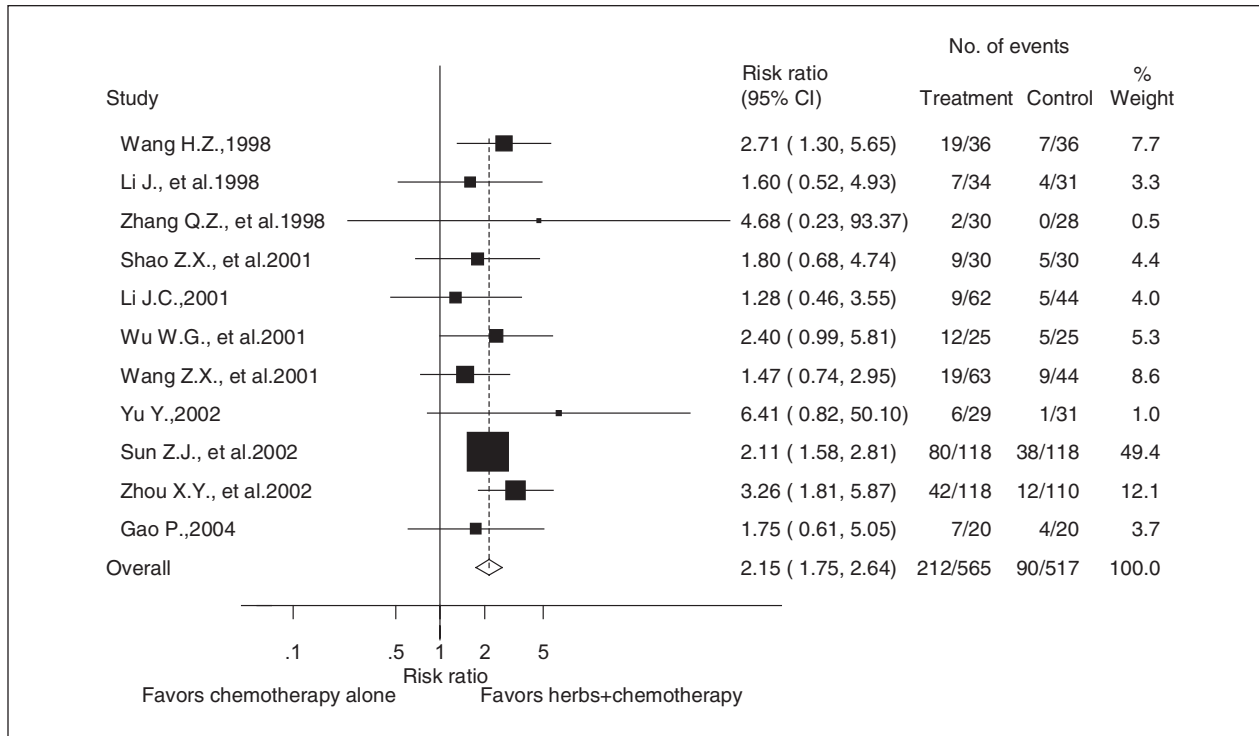


Figure 2 Twenty-four-month survival: herbs + chemotherapy versus chemotherapy alone.

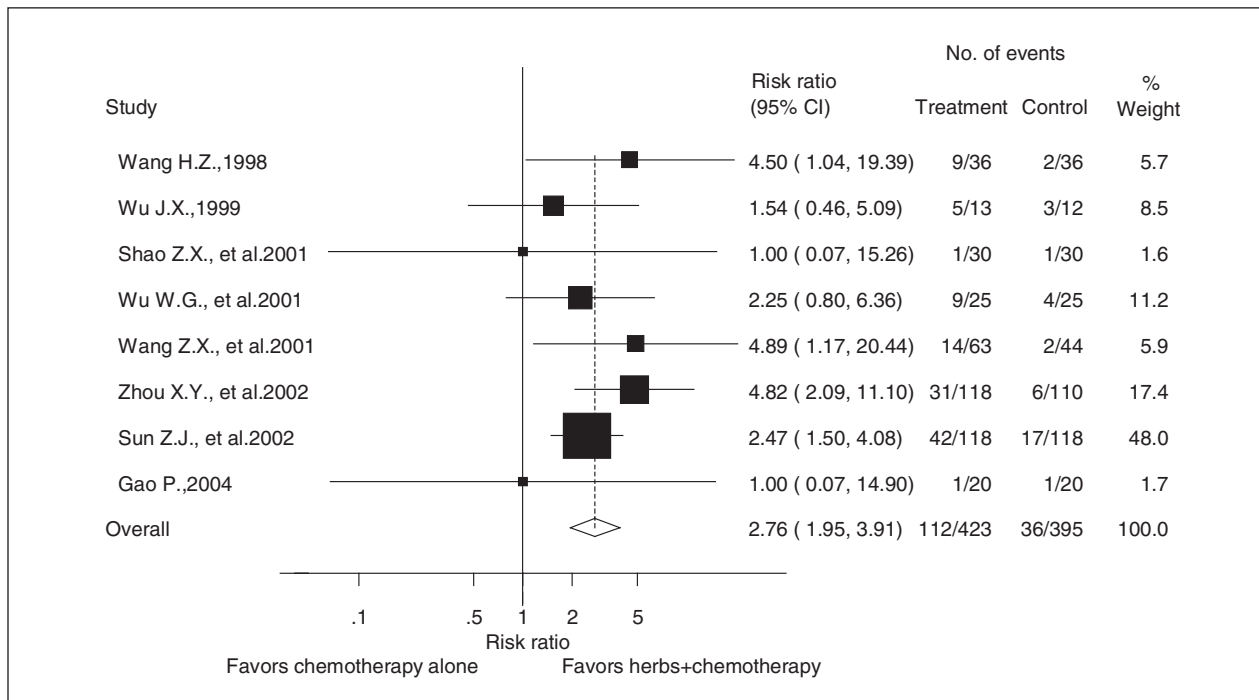


Figure 3 Thirty-six-month survival: herbs + chemotherapy versus chemotherapy alone.

of specific details of randomization is also found in many Western medical journals. In 2004, 8 years after publication of the CONSORT Statement (intended to

improve the quality of reporting of results in randomized controlled trials), more than 40% of trials published in Western medical journals failed to use

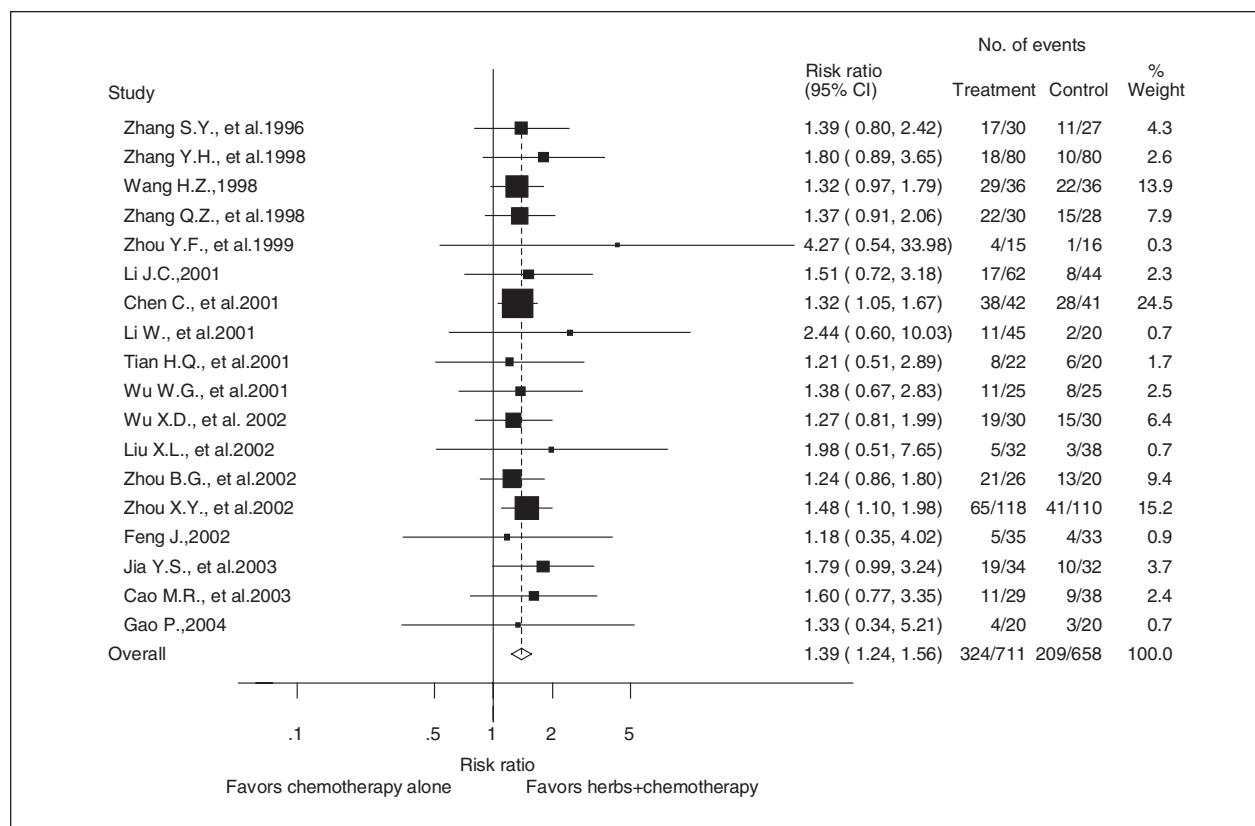


Figure 4 Tumor response: herbs + chemotherapy versus chemotherapy alone.

adequate randomization methods or failed to report the method for concealment of allocation.¹⁸ In 1994, this figure was as high as 70% to 80%.¹⁹

An additional comment on the issue of blinding in these studies is warranted. Most of the studies (20 of 26) assessed in this meta-analysis provided the treatment group with orally administered Chinese herbal medicine combined with intravenous chemotherapy and the control group only intravenous chemotherapy. Therefore, blinding of subjects and clinicians was not possible. In such a study design setting, blinding could be achieved only if the treatment and control groups received both oral and intravenous trial medications (ie, the treatment group was given true orally administered herbal medicine and intravenous chemotherapy and the control group was given placebo orally administered herbal medicine and intravenous chemotherapy).

In future trials, we propose that Chinese investigators employ relatively simple measures such as random number-generating software for use in

randomization and placebo trial drugs for use in comparing different therapies or in evaluating new and emerging extracted active components of Chinese herbal medicines. More thorough reporting of patients' characteristics and accounting for patient withdrawals and dropouts would also be helpful.

Standardized herbal formulas. Since there is no standard Chinese formula for the treatment of HCC, it is hard to identify the active components in the treatments. Further investigation is needed on effects of Chinese herbal medicine on HCC, on the identity of active components of Chinese herbal medicine, and on the therapeutic mechanisms underlying possible survival benefits of combining Chinese herbal medicine with chemotherapy for HCC.

Acknowledgments

Administrative and methodological support provided by the Pine Street Foundation (San Anselmo, Calif; www.pinestreetfoundation.org).

APPENDIX
English-Chinese Table of Herbal Formula Names

English	Chinese
AC-III Zhu She Ye	AC-III 注射液
Ai Di Zhu She Ye	艾迪注射液
Brucea javanica oil	鸦胆子油乳
Bu Gan Ruan Jian Tang	补肝软坚汤
Combination	中医辨证治疗
Fu Zheng Hua Ji Jie Du Fang	扶正化积解毒方
Fu Zheng Jie Du Tang	扶正解毒汤
Fu Zheng Xiao Liu He Ji	扶正小瘤合剂
Fu Zheng Yi Liu Tang	扶正抑瘤汤
Gan Ai Jian Ji	肝癌煎剂
Gan Ai Yi Hao	肝癌一号
Gan Kang Chong Ji	肝康冲剂
Ge Xia Zhu Yu Tang	膈下逐瘀汤
Hu Gan Ruan Jian Fang	护肝软坚方
Hua Chan Su	华蟾素
Liu Jun Zi Tang	刘君子汤
Pei Yuan Gu Ben Kang Ai Jiao Nang	培元固本抗癌胶囊
Ping Xiao Jiao Nang	平消胶囊
Ruan Gan Jian	软肝煎
Sophora japonica injection	苦参素
Xiao Yao San	逍遥散
Yan Shu Zhu She Ye	岩舒注射液
Yi Guan Jian	一贯煎
Yi Guan Jian Jia Wei	一贯煎加味
Yin Chen Wu Ling San	茵陈五苓散
Zi Ni Fu Gan Tang	自拟复肝汤
Zi Shui Qing Gan Yin	滋水清肝饮

References

- Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003;362:1907-1917.
- Bosch FX, Ribes J, Borrás J. Epidemiology of primary liver cancer. *Semin Liver Dis*. 1999;19:271-285.
- Llovet JM, Bustamante J, Castells A. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology*. 1999;29:62-67.
- Chan ES, Chow PK, Tai B, Machin D, Soo K. Neoadjuvant and adjuvant therapy for operable hepatocellular carcinoma. *Cochrane Database Syst Rev*. 2000(2):CD001199.
- Llovet JM. Treatment of hepatocellular carcinoma. *Curr Treat Options Gastroenterol*. 2004;7:431-441.
- De Maio E, Fiore F, Daniele B, et al. Transcatheter arterial procedures in the treatment of patients with hepatocellular carcinoma: a review of literature. *Crit Rev Oncol Hematol*. 2003;46:285-295.
- Geschwind JF, Ramsey DE, Choti MA, Thuluvath PJ, Huncharek MS. Chemoembolization of hepatocellular carcinoma: results of a metaanalysis. *Am J Clin Oncol*. 2003;26:344-349.
- Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003;37:429-442.

9. Mathurin P, Raynard B, Dharancy S, et al. Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. *Aliment Pharmacol Ther.* 2003;17:1247-1261.
10. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. *Lancet.* 1997;350:185-186.
11. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment.* Vol offset publication no. 40. Geneva, Switzerland: World Health Organization; 1979.
12. Kountouras J, Zavos C, Chatzopoulos D, Zavos N, Boura P, Safioleas M. Locoregional immunochemotherapy in primary and metastatic liver disease: meta-analysis and review of literature. *Hepatology.* 2003;50:1506-1510.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177-188.
14. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1-12.
15. Clark HD, Wells GA, Huet C, et al. Assessing the quality of randomized trials: reliability of the Jadad scale. *Control Clin Trials.* 1999;20:448-452.
16. Sun ZJ, Pan CE, Wang GJ. Clinical observation of Hua Chan Su combined with TACE in the treatment of hepatocellular carcinoma. *Zhong Liu Fang Zhi Yan Jiu.* 2002;29:67-68.
17. Wu HM, Zhu DZ, Ling CQ, Chen Z. Clinical observation of hepatic artery intubation with Hua Chan Su infusion chemotherapy in treatment of liver cancer. *Liaoning Journal of Traditional Chinese Medicine.* 2000;27:127-128.
18. Hewitt C, Hahn S, Torgerson DJ, Watson J, Bland JM. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. *BMJ.* 2005;330:1057-1058.
19. Williams DH, Davis CE. Reporting of assignment methods in clinical trials. *Control Clin Trials.* 1994;15:294-298.
20. Cao MR, Tang HL. Observation of the effectiveness of Ai Di Zhu She Ye combined with hepatic artery infusion chemotherapy in the treatment of mid- and late-stage hepatocellular carcinoma. *Zhong Guo Zhong Xi Yi Jie He Za Zhi.* 2003;23:713-714.
21. Chen C, Zhou JG, Huang HC, Ruan SH, Zhang QS. Hepatic artery lipiodol infusion chemotherapy combined with Pei Yuan Gu Ben Kang Ai Jiao Nang in the treatment of 42 cases of mid- and late-stage hepatocellular carcinoma. *Zhong Xi Yi Jie He Gan Bing Za Zhi.* 2001;11:183-184.
22. Feng J. Chinese medicine and interventional therapy in the treatment of 35 cases of hepatocellular carcinoma. *Guang Xi Zhong Yi Xue Yuan Xue Bao.* 2002;5:51-52.
23. Gao P. Clinical study of Gan Ai Jian Ji combined with hepatic artery infusion chemoembolization in the treatment of hepatocellular carcinoma. *Zhongguo Yi Yao Xue Bao.* 2004;19:28-30.
24. Jia YS, Wu SQ, Qin ZQ, Lu LQ. Clinical analysis of Ya Dan Zi oil combined with interventional chemotherapy in treatment of primary hepatocellular carcinoma. *Zhong Guo Zhong Yao Za Zhi.* 2003;28:683-684.
25. Li J, Sun GZ, Pu BK, Chen CH, Song L. Clinical study of Gan Kang Chong Ji combined with hepatic artery interventional chemotherapy in the treatment of hepatocellular carcinoma. *Yi Xue Li Lun Yu Shi Jian.* 1998;11:341-343.
26. Li JC. Clinical study of Chinese medicine differential diagnosis combined with interventional therapy in the treatment of hepatocellular carcinoma. *GuangDong Yi Xue.* 2001;22:263-264.
27. Li W, Li XL. Clinical study of Fu Zheng Yi Liu Tang in reducing toxicity and increasing effectiveness of chemotherapy in mid- and late-stage primary hepatocellular carcinoma chemotherapy. *Zhong Guo Zhong Yi Yao Xin Xi Za Zhi.* 2001;8:52-53.
28. Liu XL, Zhu XQ. Clinical study in Yanshu in the treatment of hepatocellular carcinoma. *Journal of Ningxia Medical College.* 2002;24:105-106.
29. Shao ZX, Chen ZG, Yin XE, et al. Clinical observation of hepatic artery infusion chemotherapy combined with Chinese medicine Gan Ai I and II in the treatment of mid- and late-stage hepatocellular carcinoma. *Zhong Guo Zhong Xi Yi Jie He Za Zhi.* 2001;21:168-170.
30. Tian HQ, Liang GW, Tao Y, Huang ZQ, Yu SY, Ye WY. Clinical study of Chinese medicine combined with interventional therapy in the treatment of hepatocellular carcinoma. *Henan Zhong Yi Yao Xue Kan.* 2001;16:47-48.
31. Wang HZ. Clinical study of immune and Chinese medicine in post-treatment of liver cancer with infusion chemotherapy. *Zhong Guo Zhong Xi Yi Jie He Za Zhi.* 1998;18:411-413.
32. Wang ZX, Wu XH, Chen SQ, Fu Zheng Hua Ji Jie Du Fang and hepatic artery infusion chemotherapy in treatment of primary hepatocellular carcinoma. *Henan Traditional Chinese Medicine.* 2001;21:48-49.
33. Wu JX. Observation of long-term effectiveness of Yi Guan Jian Jia Wei combined with TACE in the treatment of hepatocellular carcinoma. *Zhejiang Zhong Xi Yi Jie He Za Zhi.* 1999;9:100-101.
34. Wu WG, Guo WJ, Lin JH. Ping Xiao capsule combined with hepatic artery infusion in the treatment of 25 cases of primary hepatocellular carcinoma. *Zhong Xi Yi Jie He Gan Bing Za Zhi.* 2001;11:50-51.
35. Wu XD, Wang YD, Liu SM, Wu ZS, Ye AN. Observation of Hu Gan Ruan Jian Fang in increasing effectiveness and reducing toxicity of hepatic artery chemoembolization in stage II and III hepatocellular carcinoma. *Zhong Xi Yi Jie He Gan Bing Za Zhi.* 2002;12:43-44.
36. Xie XR, Li JK, Zhan GQ. Ruan Gan Jian combined with chemotherapy in the treatment of 42 cases of mid- and late-stage hepatocellular carcinoma. *Zhong Xi Yi Jie He Gan Bing Za Zhi.* 2004;14:110-111.
37. Yu Y. Observations of the effect of hepatic artery chemoembolization combined with Chinese medicine in the treatment of mid- and late-stage hepatocellular carcinoma. *Xian Dai Zhen Duan Yu Zhi Liao.* 2002;13:1-3.
38. Zhang QZ, Zhang CL. Hepatic artery intubation embedding drug pump combined with Chinese medicine in the treatment of 30 cases of mid- and late-stage primary hepatocellular carcinoma. *Practical Journal of Integrating Chinese With Modern Medicine.* 1998;11:242.
39. Zhang SY, Geng NZ, Liu YE, Jiang W, Jiang LF. Clinical study of hepatic artery infusion chemotherapy combined with AC-III Zhu She Ye in the treatment of hepatocellular carcinoma. *Information on Traditional Chinese Medicine.* 1996(4):29-31.
40. Zhang YH. Clinical study of anti-tumor effect of Bu Gan Ruan Jian Tang. *Hubei Zhong Yi Za Zhi.* 1998;20(1):21-22.
41. Zhou BG, Sun JZ, Jing SH, Fan YZ, Huang YN. Observation of combined Chinese and Western medicine in the treatment of 26 cases of mid- and late-stage hepatocellular carcinoma. *Xin Zhong Yi.* 2002;34:37-38.
42. Zhou XY, Wu XD, Zuo X, Ge R, Xue YB. Clinical research of TACE combined with Chinese medicine in the treatment of 118 cases of mid- and late-stage hepatocellular carcinoma. *Jiangsu Zhong Yi Yao.* 2002;23:15-17.
43. Zhou YF, Jiao ZH, Song MM, et al. Fu Zheng Xiao Liu He Ji combined with chemotherapy in the treatment of 15 cases of primary hepatocellular carcinoma. *Shandong Zhong Yi Yao Da Xue Xue Bao.* 1999;23:123-125.