Traditional Chinese medicines in the treatment of hepatocellular cancers: a systematic review and meta-analysis

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CRD summary
The review concluded that there was compelling evidence for treatment of hepatocellular cancers with Chinese traditional medicine. The review was generally well conducted. The poor quality of the studies and potential for publication bias indicate the conclusions should be treated with caution.

Authors’ objectives
To assess the evidence that traditional Chinese medicines provide treatment for hepatocellular cancer.

Searching
MEDLINE, AMED, Alt HealthWatch, CINAHL, Nursing and Allied Health Collection: Basic, Cochrane Database of Systematic Reviews and CNKI were searched without language restrictions between 1966 to February 2009. Wanfang database was searched. Search terms were not reported.

Study selection
Randomised controlled trials (RCTs) that involved adults (18 years old and above) with liver cancer and treated with active traditional Chinese medicine formulation were eligible for inclusion in the review. Eligible comparators were placebo or no treatment. Studies that reported laboratory values were excluded and direct comparisons of traditional Chinese medicine formulations were excluded.

Outcomes were disease stage, Karnofsky performance, Child-Pugh score, response evaluation criteria in solid tumours (RECIST), complete response, partial response, stable disease, progressive disease, response rate (complete response and partial response), improvement of symptoms and survival rates.

All studies were performed in China and most were published in Chinese languages. Median intervention groups size was 32 participants, median control group size was 31. Most participants had stage II disease or more advanced cancer.

Interventions were predominantly combinations of different herbal medicines or animal/insect extracts (astragalus, Panax ginseng, toad skin secretions, beetle extracts, Atractylodes, Bupleurum, Curcuma).

Three reviewers selected studies for inclusion in the review. Disagreements were resolved by consensus or a third reviewer.

Assessment of study quality
Trial quality was assessed according to sequence generation, allocation concealment, blinding, withdrawal, language of article and exposure to chemotherapy.

Three reviewers performed the validity assessment.

Data extraction
Three reviewers independently extracted data using a standard pre-piloted form. Disagreements were resolved by consensus or a third reviewer.

Methods of synthesis
Meta-regression was used to assess the effect of different traditional Chinese medicine formulations on the treatment outcomes. DerSimonian-Laird random-effects meta-analysis was used to synthesis risk ratios (RR) and 95% confidence intervals (CIs). Heterogeneity was assessed using the I² statistic. Publication bias was measured using Forest plots, Begg-
Mazumdar, Egger and Horbold-Egger tests.

Results of the review
Forty-five RCTs (n=3,236) were included in the meta-analysis. Reporting of methodological issues of included studies was generally poor, but no further details on trial quality were reported.

Traditional Chinese medicines significantly improved the complete response effects score compared to controls (RR 1.26, 95% CI 1.04 to 1.52; 23 trials) and the partial response effects score (RR 1.27, 95% CI 1.17 to 1.38; 37 trials, n=unclear). A significantly increased progressive disease rate was found in control groups compared to treatment (RR 0.54, 95% CI 0.45 to 0.64; 37 trials, n=unclear). There was no significant heterogeneity measured between trials. Traditional Chinese medicines did not significantly influence stable disease.

Traditional Chinese medicines significantly improved survival rates compared to controls at six-month outcomes (RR 1.10, 95% CI 1.04 to 1.15; 15 trials), 12 months (RR 1.26, 95% CI 1.17 to 1.36; 22 trials), 18 months (RR 1.71, 95% CI 1.002 to 2.91; four trials), 24 months (RR 1.72, 95% CI 1.40 to 2.03; 15 trials) and 36 months (RR 2.40, 95% CI 1.65 to 3.49; eight trials). Significant heterogeneity between trials was found only at 18 months (I^2=70%).

Traditional Chinese medicines significantly improved abdominal pain (RR 1.50, 95% CI 1.09 to 2.07; six trials), fatigue (RR 1.54, 95% CI 1.17 to 2.01; four trials) and appetite (RR 1.53, 95% CI 1.14 to 2.05; four trials). There was no significant heterogeneity measured between trials.

Meta-regression indicated products that contained ginseng, astragalus and Mylabris had a larger treatment effect in terms of complete response (OR 1.34, 95% CI, 1.04 to 1.71) and products that contained astragalus had this effect (OR 1.35, 95% CI, 1.001 to 1.80). There was no statistical evidence of publication bias, but the authors reported that the funnel plots could not rule out publication bias (the funnel plots were not presented).

Authors' conclusions
There was compelling evidence that traditional Chinese medicine was effective for treating hepatocellular cancers and should be evaluated in further high-quality and transparent clinical trials.

CRD commentary
This review addressed a clear research question supported by clear inclusion criteria. The authors searched several relevant databases without language restrictions, which reduced the chances of language bias. Unpublished studies were not systematically sought, so relevant trials may have been missed. A validity assessment was used, but not reported clearly. Trial quality was deemed poor. Adequate steps were taken throughout the review process to minimise errors and bias. Data were analysed using appropriate statistical techniques. Concerns about the quality of the studies and potential for publication bias indicate that the authors' conclusions should be treated with caution.

Implications of the review for practice and research
The authors did not state any recommendations for practice.

Research: The authors stated that further high-quality RCTs based in Western academic settings were required.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.