Efficacy of Cordyceps sinensis as an adjunctive treatment in hemodialysis patients: a systematic review and Meta-analysis

Bee Yean Ong, Zoriah Aziz

Abstract

OBJECTIVE: To evaluate current evidence on the efficacy and safety of Cordyceps sinensis (cordyceps) or its fermented products used as an adjunctive treatment in patients undergoing maintenance hemodialysis.

METHODS: The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, China National Knowledge Infrastructure (CNKI) and Wanfang Database were searched for relevant randomized controlled trials up to March 2016. Two review authors independently selected trials for inclusion, extracted data, assessed the methodological quality and rated the quality of evidence with the Grading of Recommendations, Assessment, Development and Evaluation approach.

RESULTS: Twelve studies involving 655 participants were included. Evidence of low to moderate-quality showed that cordyceps plus conventional treatment compared to conventional treatment alone significantly improved C-reactive protein [standardized mean difference (SMD) – 0.61; 95% confidence intervals (CI) – 1.00 to – 0.22], high-sensitivity C-reactive protein [weighted mean difference (WMD) – 3.44 mg/L; 95% CI – 3.89 to – 2.99], serum albumin (WMD 3.07 g/L; 95% CI 1.59 to 4.55), malondialdehyde (WMD – 1.95 nmol/L; 95% CI – 2.24 to – 1.66), and hemoglobin (WMD 9.56 g/L; 95% CI 3.65 to 15.47) levels. However, there was no significant improvement for serum creatinine and low-density lipoprotein cholesterol. Overall, most trials either did not monitor adverse events or poorly documented them.

CONCLUSION: Given the small number of trials included, the unclear methodological quality of the included trials, and the high heterogeneity in pooled analyses, the evidence obtained in this review is insufficient to recommend the use of cordyceps as adjunctive treatment in hemodialysis patients.

INTRODUCTION

End-stage renal disease (ESRD) is a growing health problem worldwide and it is associated with debilitating medical, social and economic consequences. Although maintenance dialysis has successfully prolonged survival in patients with ESRD, mortality remains high. The adjusted mortality rate per 1000 patient-years for hemodialysis patients in 2013 was 172 deaths, of which 41% were attributed to cardiac disease.
Malnutrition-inflammation complex syndrome is highly prevalent in hemodialysis patients and it is strongly associated with accelerated atherosclerosis. The degree of chronic inflammation and the nutritional status of dialysis patients is reflected by the circulating levels of inflammatory and nutritional biomarkers such as C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), albumin and prealbumin. These biomarkers are potent predictors of cardiovascular and all-cause mortality in hemodialysis patients. Malnutrition is a consequence of chronic inflammatory processes in patients with ESRD. Both of these conditions correlate with poor dialysis outcomes in hemodialysis patients including erythropoietin hypo-responsiveness, diminished quality of life, increased hospitalization and mortality rate. In addition, patients undergoing hemodialysis are subjected to oxidative stress which promotes endothelial dysfunction and atherosclerosis. Studies have shown that elevated CRP or hs-CRP levels increased oxidative production while hypoalbuminemia reduced antioxidant defense. Since malnutrition, inflammation and oxidative stress are interrelated in the pathogenesis of cardiovascular disease, drug treatments with antioxidant and anti-inflammatory properties could be beneficial to reduce the mortality rate.

In China and other Asian countries, Traditional Chinese Medicines (TCM) are frequently used as an adjunct to western medicine for the treatment of chronic kidney disease (CKD). Cordyceps sinensis (cordyceps) is one of the most common TCM used in China for the treatment of kidney diseases. In addition, cordyceps has been claimed to be therapeutically effective in treating lung and heart ailments, male and female sexual dysfunction, cancer, fatigue, and to promote longevity. Cordyceps is a rare Ascomycetes fungus, growing on the larvae of a small moth, Hepialus armoricanus. In nature, it is found in the high mountainous regions of Tibet, China and Nepal. Laboratory and clinical studies showed that polysaccharides in cordyceps possess antioxidant, anti-inflammatory, immunomodulatory and anti-fibrotic activities. It has been shown that taking cordyceps could decrease the levels of CRP and low-density lipoprotein cholesterol (LDL-C), and increase the albumin and hemoglobin levels. Cordyceps sinensis has been widely used for many centuries in Asian countries as a medicine and health supplements. In view of the limited supply of wild cordyceps, modern cultivation techniques have made cultured cordyceps mycelia products such as Bailing® and Jin Shui Bao® oral capsules more readily available at a lower cost.

Several systematic reviews have examined the therapeutic effects of Cordyceps sinensis in people with all stages of CKD. However, none of these reviews specifically addressed the clinical benefits of cordyceps in patients undergoing maintenance hemodialysis. Therefore, this systematic review aims to systematically evaluate the existing evidence regarding the efficacy and safety of wild cordyceps or its fermented products used as adjuvants in hemodialysis patients receiving conventional treatment.

METHODS

This systematic review was conducted following the guideline of Preferred reporting items for systematic review and Meta-analysis (PRISMA) statement.

Eligibility criteria

We included all accessible randomized controlled trials (RCTs) that compared the effects of wild Cordyceps sinensis or its fermented products with placebo or no treatment in patients receiving conventional treatment. There were no restrictions on language, date of trials or publication status of the trials. Studies involving patients of any age and sex, with any causes of ESRD were eligible for inclusion. To be included, all trials had to report one of the following outcome measures: inflammatory and nutritional markers (serum CRP, hs-CRP, and albumin levels), oxidative stress marker [serum malondialdehyde (MDA)], antioxidant enzyme activities [superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px)], anemia (serum hemoglobin), hyperlipidemia (serum total cholesterol, triglycerides and LDL-C), and kidney function parameters [serum creatinine (SCR) and blood urea nitrogen (BUN)]. Trials that reported clinical symptom improvement in hemodialysis patients were also included in this review. Any drug-related adverse events were considered as safety outcome measures for inclusion. Animal studies, in-vitro-studies, articles with abstracts only and review articles were excluded as were studies that included cordyceps as a component of compounded preparations or as part of a combined regimen with other herbal or complementary medicines.

Outcome measures

The primary outcomes were changes in the serum levels of inflammatory, malnutrition and oxidative stress biomarkers before and after the intervention. Secondary outcomes included: (a) changes in the serum levels of kidney function, anemia and lipid parameters from baseline to post-intervention; (b) changes in symptom scores; and (c) adverse effects.

Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, CINAHL via EBSCOhost, China National Knowledge Infrastructure (CNKI), Wanfang Database, and China Science and Technology Journal Database (VIP) Information/Chinese Scientific Journals database were searched. An electronic search of the databases was performed from their inception up to March 2016, using a comprehensive search strategy. The following search terms were used: (Cordyceps OR Cordyceps sinensis OR Ophio-
cordyceps sinensis OR dongchongxiacao OR chongcao OR bailing capsule OR corbin capsule OR jinshuibao jiao nang) AND ("hemodialysis" OR "haemodialysis" OR "renal dialysis"). We also hand searched conference abstracts and theses that were not identified by other searches. Reference lists of all retrieved articles and reviews were screened for additional potential studies. Study authors and local manufacturers marketing cordyceps products were also contacted to identify any unpublished or ongoing trials. We limited the literature search to RCTs on human subjects. No language restrictions were used. Search strategies used for Medline database were as follows:

#1 Cordyceps.mh.
#2 (Cordyceps or "Cordyceps sinensis" or "Ophiocordyceps sinensis" or dongchongxiacao or "dong chong xia cao" or chongcao or "chong cao" or "Bailing capsule" or "Corbin capsule" or "jinshuibao jiao nang").ti,ab.
#3 #1 or #2
#4 ("renal dialysis" or "Hemodialysis Units, Hospital" or "Hemodialysis, Home").mh.
#5 (hemodialysis or haemodialysis).ti,ab.
#6 (ESRD or ESKD or ESRF or ESKF).ti,ab.
#7 ("end-stage renal disease" or "end-stage kidney disease" or "end-stage renal failure" or "end-stage kidney failure").ti,ab.
#8 (uremia or uraemia).mh.ti,ab.
#9 #4 or #5 or #6 or #7 or #8
#10 ("Randomized controlled trial" or "controlled clinical trial" or "placebo-controlled").pt.
#11 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
#12 #10 or #11
#13 (animals not humans).sh.
#14 (#3 and #9 and #12) not #13

**Study selection and data extraction**

Two review authors independently screened abstracts and titles identified from the searches. Full texts of potentially relevant papers were then retrieved and assessed in detail against the review inclusion and exclusion criteria. Data from each primary paper including authors, participants, settings, study design, interventions, comparators, study period, outcomes and results were extracted by the first reviewer using a uniform data extraction form. All the extracted data were summarized into a table and checked by the second reviewer. Authors of trials were contacted for missing data and additional information. Any disparities between the two reviewers were discussed and resolved by consensus.

**Quality assessment**

The methodological quality of included studies was assessed using the Cochrane risk of bias tool. This tool consists of seven domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias such as baseline comparability and sponsorship. Critical assessment on the risk of bias was done and the degree of bias was categorized as "high", "low" or "unclear" risk for each domain. We considered a trial as having low risk of bias if all domains were adequately addressed. Whereas, a trial was considered as having high risk of bias if one or more domains were assessed as inadequate or unclear. Results were tabulated into a "risk of bias graph" and a "risk of bias summary table” which detailed all judgements made for the included trials. Any disagreements at this stage were resolved through discussion between the two reviewers.

Meanwhile, the quality of the evidence for selected outcomes was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. The GRADE approach classifies the quality of evidence into four levels: high, moderate, low or very low. Evidence from RCTs was assumed to be high quality at the outset, but it was then down rated if the trials demonstrated one of the following: serious risk of bias, inconsistency of results, indirectness of evidence, imprecision of estimated effect and potential publication bias. Conversely, the quality of evidence would have been increased if there was a large magnitude of effect, a dose-response gradient, or when all plausible confounders increased our confidence in the estimated effect. Two individual evaluation reports were prepared by the reviewers and discrepancies were resolved by discussion.

**Data synthesis**

Meta-analysis was used to combine results from the individual studies that compared similar treatment and control interventions using Review Manager (RevMan) version 5.3. Risk ratio (RR) was calculated for dichotomous outcomes (symptom remission rates and adverse events). For continuous outcomes (measurement of inflammatory, oxidative stress and nutritional biomarkers, kidney function, anemia, lipid parameters and total symptom scores), results were expressed as mean difference (MD) or weighted mean difference (WMD) with 95% confidence intervals (CI). If different units of measurement were used in different trials, we reported the continuous outcomes as the standardized mean difference (SMD) and 95% CI. Statistical significance was set at P < 0.05 for all outcomes. A fixed-effect model was used if pooling seemed appropriate in view of clinical and methodological similarities between studies where I² statistic was below 25%. Otherwise, data were pooled using a random effects model. Subgroup analysis was performed to explore the treatment effect of different types of cordyceps preparations if there were enough studies included.
RESULTS

Results of the search
The process applied for study selection is shown in Figure 1. Of the 288 records identified through electronic databases, 22 were considered potentially relevant and subjected to full text review. After review, 10 trials were excluded for a variety of reasons (Figure 1). Only 12 trials met the inclusion criteria and of these, 11 trials provided quantitative data and were therefore included in the quantitative analysis.

Description of included studies
Table 1 summarizes the characteristics of the included studies. All included trials were conducted in China between 1999 and 2015. All the trials had a two-arm parallel group design that compared cordyceps plus conventional treatment versus conventional treatment alone. The conventional treatment consisted of blood pressure and blood glucose control, anemia correction, maintenance of calcium-phosphate balance, dietary restriction and other symptomatic treatment. However, the details of the medication prescribed as part of the conventional treatment were not clearly stated. All trials examined mycelia fermentation products of Cordyceps sinensis. Of the 12 trials, two trials studied cordyceps oral capsules (contain 0.2 g or 0.5 g cordyceps)33,34,41 and six studied Jin Shui Bao oral capsules (contain 0.33 g cordyceps).33,34,37,38,41 The remaining one trial did not dis-close the product brand name. The daily dose of cordyceps varied across studies. Overall, patients were followed from 2 to 8 months.

Risk of bias and grades of evidence
Study methodologies were incompletely described in all the trials (Figure 2). All the trials were found to be of low methodological quality (Figure 3). Only two trials described the method of randomization. One used a random number table to generate random allocation while another used simple random sampling by drawing of lots. None of the trials described allocation concealment and blinding of participants, personnel or outcome assessors. Details of drop-outs and withdrawals were not provided in three trials which were therefore judged to have unclear risk of attrition bias. We considered 10 trials as free of selective reporting bias as these trials reported all the pre-specified outcomes mentioned in their method section. Meanwhile, selective outcome reporting was found in one trial that did not report the non-significant finding. Two other potential sources of bias considered in this review were baseline comparability and financial support received for the trial. Ten trials were deemed to have a low risk of bias for baseline comparability as there were no significant differences in baseline between the treatment and control groups. The risk of this bias was not clear for the other two trials. Information on possible financial bias was unclear since none of the trials specified their sponsorship or its absence in their reports.

Figure 1 Flow chart of result of search, studies identified and included in this review
RCT: randomized controlled trial.
### Table 1: Characteristics of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Mean age in years (SD)</th>
<th>Cordyceps (dose)</th>
<th>Intervention</th>
<th>Type of conventional treatment</th>
<th>Study period in months</th>
<th>Outcome reported</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng et al 2011&lt;sup&gt;1&lt;/sup&gt;</td>
<td>90 patients receiving 2 or 3 dialysis sessions per week.</td>
<td>43.7 (NR)</td>
<td>Oral Jin Shui Bao (1.98 g thrice daily)</td>
<td>Cordyceps + conventional treatment</td>
<td>Low protein diet, recombinant human erythropoietin, folic acid, ferrous fumarate, calcium carbonate</td>
<td>6</td>
<td>CRP, albumin, hemoglobin, hematocrit, RBC, and iron.</td>
<td>Cordyceps significantly decreased serum CRP and increased serum albumin, hemoglobin, hematocrit, RBC and iron levels.</td>
</tr>
<tr>
<td>Du et al 2015&lt;sup&gt;2&lt;/sup&gt;</td>
<td>59 uremic patients receiving MHD for ≥6 months.</td>
<td>NR</td>
<td>Oral Bailing (0.6 g thrice daily)</td>
<td>Conventional treatment only</td>
<td>Blood pressure control, anemia correction and other baseline treatment</td>
<td>8</td>
<td>hs-CRP, albumin, hemoglobin, TC, TG, LDL-C, clinical symptoms, SGA, fatigue rating, and ADR. SCr, BUN, uric acid, total protein, and symptom remission rates</td>
<td>Cordyceps significantly reduced hs-CRP, LDL-C, fatigue and SGA scores. Two patients had gastrointestinal discomfort with cordyceps treatment.</td>
</tr>
<tr>
<td>Guo 2009&lt;sup&gt;3&lt;/sup&gt;</td>
<td>64 patients receiving MHD every 2 to 3 days.</td>
<td>T: 46.3 (12.8) C: 44.6 (13.2)</td>
<td>Oral Jin Shui Bao (1.98 g thrice daily)</td>
<td>Cordyceps + conventional treatment</td>
<td>Low protein diet, blood pressure control, anemia correction, maintenance of water, electrolyte and acid-base balance and other baseline treatment</td>
<td>3</td>
<td>SCr, BUN, uric acid, total protein, hemoglobin, and symptom remission rates</td>
<td>Cordyceps showed significant improvements in SCr, BUN, uric acid and total protein, as well as higher remission rate of clinical symptoms. No significant improvement in serum hemoglobin in both groups.</td>
</tr>
<tr>
<td>Meng et al. 2000&lt;sup&gt;4&lt;/sup&gt;</td>
<td>30 patients receiving 2 or 3 dialysis sessions per week.</td>
<td>42.5 (19.8)</td>
<td>Oral Cordyceps (3 capsules thrice daily)</td>
<td>Cordyceps + conventional treatment only</td>
<td>Blood pressure control and other baseline treatment</td>
<td>NR</td>
<td>SCr, BUN, hemoglobin, and clinical symptoms (nausea, anorexia and heart failure)</td>
<td>More patients in the cordyceps group had hemoglobin level above 70 g/L (81%) than in the control group (33%). Cordyceps significantly reduced symptoms. No significant reductions in SCr and BUN.</td>
</tr>
<tr>
<td>Sun et al. 1999&lt;sup&gt;5&lt;/sup&gt;</td>
<td>60 patients receiving MHD every 2 to 3 days.</td>
<td>T: 47.0 (12.0) C: 45.0 (13.0)</td>
<td>Oral Jin Shui Bao (3 capsules thrice daily)</td>
<td>Cordyceps + conventional treatment</td>
<td>Blood pressure control, maintenance of water, electrolyte and acid-base balance and other baseline treatment</td>
<td>3</td>
<td>SCr, BUN, total protein, hemoglobin, clinical symptoms, and ADR</td>
<td>Cordyceps significantly improved SCr, BUN, total protein and hemoglobin levels. More patients in cordyceps group (66.7%) had an improvement in clinical symptoms than control group (26.7%). No ADR was reported. Cordyceps significantly improved serum albumin, hemoglobin and hematocrit levels, and reduced the weekly dosage of erythropoietin required.</td>
</tr>
<tr>
<td>Wu et al. 2010&lt;sup&gt;6&lt;/sup&gt;</td>
<td>38 anemic patients (serum hemoglobin ≤ 90 g/L, hematocrit ≤ 27%) receiving 10 dialysis sessions per month.</td>
<td>50.0 (12.0)</td>
<td>Oral Jin Shui Bao (5 caps. thrice daily)</td>
<td>Cordyceps + conventional treatment</td>
<td>Recombinant human erythropoietin, folic acid, ferrous, vitamins</td>
<td>3</td>
<td>Albumin, hemoglobin, hematocrit, and weekly dosage of erythropoietin</td>
<td>Cordyceps significantly improved serum albumin, hemoglobin and hematocrit levels, and reduced the weekly dosage of erythropoietin required.</td>
</tr>
</tbody>
</table>
### Table 1 Characteristics of included trials (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Mean age in years (SD)</th>
<th>Intervention</th>
<th>Cordyceps + conventional treatment (n)</th>
<th>Type of conventional treatment</th>
<th>Study period in months</th>
<th>Outcome reported</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. 2013</td>
<td>60 patients receiving MHD for 3 months.</td>
<td>T: 43.18 (6.23) C: 45.02 (6.78)</td>
<td>Oral Bailing’ (1 g thrice daily)</td>
<td>30</td>
<td>High quality protein diet, blood pressure and blood glucose control, anemia correction, compound α-keto acid, L-carnitine, calcitriol and other treatment.</td>
<td>3</td>
<td>CRP, albumin, prealbumin, hemoglobin, TG, TC, SCr, total symptom scores, and symptom remission rates</td>
<td>Significant results for all outcomes after treatment, but cordyceps group had higher albumin and prealbumin levels, lower total symptom scores, and higher symptom remission rates than the control.</td>
</tr>
<tr>
<td>Ye et al. 2012</td>
<td>68 diabetic nephropathy patients receiving 3 dialysis sessions per week.</td>
<td>T: 61.6 (9.3) C: 61.3 (8.8)</td>
<td>Oral Jin Shui Bao’ (1.98 g thrice daily)</td>
<td>34</td>
<td>Blood pressure and blood glucose control, anemia correction and other baseline treatment.</td>
<td>3</td>
<td>SCr, BUN, WBC, hemoglobin, IL-2, and IL-6</td>
<td>Cordyceps significantly improved SCr, BUN, WBC, hemoglobin, IL-2 and IL-6 levels.</td>
</tr>
<tr>
<td>Yi et al. 2014</td>
<td>40 patients receiving 3 dialysis sessions per week.</td>
<td>T: 74.8 (5.1) C: 72.6 (5.4)</td>
<td>Oral Bailing’ (2.5 g thrice daily)</td>
<td>20</td>
<td>Blood pressure and blood glucose control, anemia correction and other baseline treatment.</td>
<td>3</td>
<td>hs-CRP, TNF-α, MDA, SOD, and GSH-Px</td>
<td>hs-CRP, IL-6, TNF-α and MDA were markedly lower, while serum levels of SOD and GSH-Px were significantly higher in cordyceps group.</td>
</tr>
<tr>
<td>Yi et al. 2015</td>
<td>36 diabetic nephropathy patients receiving 3 dialysis sessions per week.</td>
<td>T: 56.8 (7.21) C: 56.6 (7.42)</td>
<td>Oral Jin Shui Bao’ (1.65 g thrice daily)</td>
<td>18</td>
<td>Blood pressure and blood glucose control, anemia correction and other baseline treatment.</td>
<td>3</td>
<td>hs-CRP, TNF-α, MDA, SOD, and GSH-Px</td>
<td>hs-CRP, IL-6, TNF-α and MDA were significantly lower while SOD and GSH-Px were significantly higher in cordyceps group.</td>
</tr>
<tr>
<td>Yu et al. 2002</td>
<td>65 elderly patients receiving 2 dialysis sessions per week.</td>
<td>NR</td>
<td>Oral Bailing’ (5 capsules thrice daily)</td>
<td>35</td>
<td>Low protein diet and other baseline treatment.</td>
<td>6</td>
<td>Albumin and total protein</td>
<td>Cordyceps significantly increased serum albumin and total protein levels.</td>
</tr>
<tr>
<td>Zeng 2009</td>
<td>45 patients aged 18 to 75 years receiving MHD for &gt;3 months.</td>
<td>T: 54.43 (11.11) C: 56.55 (12.79)</td>
<td>Oral Bailing’ (4 capsules thrice daily)</td>
<td>33</td>
<td>Anemia correction, maintenance of calcium and phosphate balance, and other baseline treatment.</td>
<td>2</td>
<td>hs-CRP, SCr, and total symptom scores</td>
<td>Cordyceps significantly reduced serum hs-CRP and total symptom scores. No significant reduction in SCr in both groups.</td>
</tr>
</tbody>
</table>

Notes: ADR: adverse drug reaction; BUN: blood urea nitrogen; CRP: C-reactive protein; C: control; g: gram; GSH-Px: glutathione peroxidase; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; LDL-C: low-density lipoprotein cholesterol; MDA: malondialdehyde; MHD: maintenance hemodialysis; NR: not reported; RBC: red blood cell; SCr: serum creatinine; SD: standard deviation; SGA: Subjective Global Assessment; SOD: superoxide dismutase; T: treatment; TC: total cholesterol; TG: triglycerides; TNF-α: tumor necrosis factor-α; WBC: white blood cell.
Since all the included studies had an unclear risk of bias in most domains, application of the GRADE approach led to the quality of evidence for all reported outcomes being downgraded for risk of bias (Table 2). In addition, we also rated down the quality of evidence for indirectness, inconsistency and imprecision. The overall quality of evidence was not upgraded because none of the trials yielded a very large magnitude of effect or showed a dose-response gradient. There was also no evidence that the influence of all plausible confounders would increase our confidence in the estimated effect.

**Inflammatory biomarkers (CRP and hs-CRP)**

Two included trials\(^{17,38}\) showed that the serum CRP level decreased significantly in the cordyceps-treated group compared with that of the control group (SMD -0.61; 95% CI -1.00 to -0.22), with acceptable statistical heterogeneity (Figure 4A). Another four trials\(^{33,40,41,43}\) utilized a more sensitive CRP test, called hs-CRP assay to detect small amount of CRP in the blood. The pooled estimates showed a statistically significant reduction in hs-CRP level favoring the cordyceps-treated group (WMD -3.44 mg/L; 95% CI -3.89 to -2.99) (Figure 4B).

**Nutritional marker (serum albumin)**

Five trials\(^{17,33,37,38,42}\) provided data for serum albumin levels and the data were pooled for analysis. Subgroup analysis showed that both Jin Shui Bao and Bailing oral capsules significantly increased serum albumin level compared with the control (WMD 4.83 g/L; 95% CI 3.43 to 6.24 and WMD 1.96 g/L; 95% CI 0.91 to 3.01) (Figure 5).

**Oxidative stress biomarkers (MDA, SOD and GSH-Px)**

Two trials\(^{40,41}\) analyzed the effects of cordyceps on oxidative stress biomarkers. The pooled result of these trials indicated a significant reduction in MDA level favoring the cordyceps-treated group (WMD -1.95 nmol/L; 95% CI -2.24 to -1.66) (Figure 6A). Additionally, both trials reported that activities of the plasma antioxidant enzymes SOD and GSH-Px were significantly increased in patients treated with cordyceps, and there was evidence of heterogeneity (Figures 6B and 6C).
Table 2 Summary of findings for the main comparison

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Illustrative comparative risks' (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (CRP) -follow-up: 3-6 months High-sensitivity</td>
<td>Mean CRP was 11.09 lower (4.3 to 0.95 lower)</td>
<td>150 (2)</td>
<td>+++-- moderate1</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (hs-CRP) -follow-up: 2-8 months</td>
<td>Mean hs-CRP ranged from 6.18 to 14.97 mg/L lower (3.89 to 2.99 lower)</td>
<td>174 (4)</td>
<td>+++-- low11</td>
<td></td>
</tr>
<tr>
<td>Albumin -follow-up: 3-8 months</td>
<td>Mean albumin was 3.07 higher (1.59 to 4.55 higher)</td>
<td>312 (5)</td>
<td>+++-- moderate1</td>
<td></td>
</tr>
<tr>
<td>Malondialdehyde (MDA) -follow-up: 3 months</td>
<td>Mean MDA was 6.55 nmol/L lower (2.24 to 1.66 lower)</td>
<td>76 (2)</td>
<td>+++-- low11</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (SCr) -follow-up: 3 months</td>
<td>Mean SCr ranged from 364.25 to 890.4 µmol/L lower (47.42 lower to 30.86 higher)</td>
<td>238 (4)</td>
<td>+++-- very low3,4</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin -follow-up: 3-8 months</td>
<td>Mean hemoglobin was 9.56 higher (3.65 to 15.47 higher)</td>
<td>425 (7)</td>
<td>+++-- low11</td>
<td></td>
</tr>
<tr>
<td>Adverse effects -follow-up: 3-8 months</td>
<td>See commentb</td>
<td>See commentb</td>
<td>Not estimable</td>
<td>119 (2)</td>
</tr>
</tbody>
</table>

Notes: 'The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Most studies were of unclear risk of bias regarding sequence generation, allocation concealment and blinding: 'Indirectness in study population because one study involved diabetic nephropathy patients which may not be of relevance to the wider population; 'Significant statistical heterogeneity between studies; 'Sample size is not adequate (n < 300) and the pooled effect estimate is not precise with a confidence interval that includes the null value "0". CI: confidence interval. 'One trial reported that cordyceps was associated with mild gastrointestinal disturbances while another trial reported no apparent adverse events.

A

<table>
<thead>
<tr>
<th>Study</th>
<th>Cordyceps Mean (SD)</th>
<th>Total</th>
<th>Control Mean (SD)</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng &amp; Hu [17]</td>
<td>7.88 (3.79)</td>
<td>45</td>
<td>11.09 (4.31)</td>
<td>45</td>
<td>36.2%</td>
<td>-0.78 [-1.21, -0.35]</td>
</tr>
<tr>
<td>Yang [36]</td>
<td>3.81 (1.88)</td>
<td>30</td>
<td>3.75 (1.83)</td>
<td>30</td>
<td>43.8%</td>
<td>-0.38 [-0.89, 0.13]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>75</td>
<td>75</td>
<td>100.0%</td>
<td>-0.61 [-1.00, -0.22]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z=15.24 (P< 0.00001)

B

<table>
<thead>
<tr>
<th>Study</th>
<th>Cordyceps Mean(SD)</th>
<th>Total</th>
<th>Control Mean(SD)</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Jin Shui Bao8</td>
<td>6.44(0.95)</td>
<td>18</td>
<td>10.17(0.42)</td>
<td>18</td>
<td>45.8%</td>
<td>-3.73 [-4.21, -3.25]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>18</td>
<td>18</td>
<td>45.8%</td>
<td>-3.73 [-4.21, -3.25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=15.24 (P&lt; 0.00001)</td>
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</tr>
</tbody>
</table>

| ii) Bailing8 | 8.15(1.15) | 30 | 14.97(14.35) | 29 | 0.5% | -6.84 [-13.49, -0.19] |
| Yi et al [40] | 6.98(0.81) | 20 | 10.14(0.55) | 20 | 51.2% | -3.16 [-3.59, -2.73] |
| Zeng [43] | 3.07(2.81) | 28 | 6.18(4.37) | 11 | 2.6% | -3.11 [-5.89, -0.33] |
| Subtotal (95% CI) | 78 | 60 | 54.2% | -3.17 [-3.60, -2.75] |
| Test for subgroup differences: Ch2 = 2.90, df= 1 (P = 0.09), I2 =65.6% |

| Total (95% CI) | 96 | 78 | 100.0% | -3.44 [-3.89, -2.99] |
| Test for overall effect: Z=14.70 (P< 0.00001) |

Figure 4 Comparison of cordyceps and conventional treatment versus conventional treatment alone (control) A: C-reactive protein; B: high-sensitivity C-reactive protein (mg/L).
However, subgroup analyses to explore the potential sources of heterogeneity were not possible due to the small number of studies.

**Kidney function (SCr and BUN)**

Data regarding the effect of cordyceps on kidney function were available from four trials.\cite{17,34,36,38,39} The meta-analysis showed that there was no statistically significant reduction in SCr level in the cordyceps-treated groups (WMD = -8.28 µmol/L; 95% CI = -47.42 to 30.86), with significant heterogeneity ($I^2 = 90\%$) (Figure 7A). Subgroup analysis showed that no difference was found for the change of SCr level among trials that used Jin Shui Bao\textsuperscript{®} and Bailing\textsuperscript{®} oral capsules (Figure 7A). Meanwhile, the pooled result for BUN also indicated no significant favorable effects of cordyceps in reducing BUN level when compared with the control group (Figure 7B).

**Anemia parameter (serum hemoglobin)**

Serum hemoglobin level was reported in seven trials.\cite{17,33,34,36-39} High statistical heterogeneity ($I^2 = 85\%$) was found. Subgroup analysis showed no significant favorable effects of cordyceps in increasing hemoglobin concentration when compared with the control group (Figure 7A).
found in the meta-analysis, indicating large variations in the intervention effects observed across these trials. In the subgroup analysis, participants who received Jin Shui Bao® oral capsules had a significantly higher serum hemoglobin level than those in the control group (WMD 8.42 g/L; 95% CI 1.36 to 15.47) (Figure 8). However, this treatment effect was not significant in two studies which used Bailing® oral capsules as their intervention (WMD 12.66 g/L; 95% CI −2.02 to 27.34) (Figure 8).

### Lipid parameters (serum total cholesterol, triglycerides and LDL-C)

Two trials reported on lipid parameters and overall, no significant differences in serum total cholesterol, triglycerides and LDL-C were found between cordyceps and control groups (Figure 9).

### Clinical symptom improvement

The results from three trials suggested that cordyceps significantly reduced the total symptom scores as

<table>
<thead>
<tr>
<th>Study</th>
<th>Cordyceps Mean (SD)</th>
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<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo [34]</td>
<td>614.4 (109.7)</td>
<td>25</td>
<td>739.6 (176.2)</td>
<td>25</td>
<td>14.4%</td>
<td>-125.2 [-206.56, -43.84]</td>
<td></td>
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<tr>
<td>Sun et al [36]</td>
<td>397.13 (26.3)</td>
<td>30</td>
<td>364.25 (17.39)</td>
<td>30</td>
<td>36.7%</td>
<td>32.88 [21.53, 44.23]</td>
<td></td>
</tr>
<tr>
<td>Ye et al [39]</td>
<td>575.69 (29.97)</td>
<td>34</td>
<td>581.17 (30.21)</td>
<td>34</td>
<td>36.0%</td>
<td>-5.58 [-19.88, 8.72]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>89</td>
<td>89</td>
<td>87.1%</td>
<td></td>
<td></td>
<td>-9.80 [-52.88, 33.28]</td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.45 (P = 0.66)

### Lipid parameters (serum total cholesterol, triglycerides and LDL-C)

Two trials reported on lipid parameters and overall, no significant differences in serum total cholesterol, triglycerides and LDL-C were found between cordyceps and control groups (Figure 9).

### Clinical symptom improvement

The results from three trials suggested that cordyceps significantly reduced the total symptom scores as
defined in the Chinese Drug Clinical Research Guide- line (Trial)\(^4\) (WMD 2.0; 95% CI = 2.68 to 1.46) and improved symptom remission rates (RR 1.35; 95% CI 1.07 to 1.72) (Figure 10).

**Adverse effects**

Du \textit{et al}\(^3\) reported that two participants in the cordyceps-treated group had nausea, abdominal distention and other symptoms of gastrointestinal discomfort at the beginning of treatment. These symptoms diminished when treatment was continued. Meanwhile, no participants experienced hepatotoxicity, leukopenia or allergic reactions due to cordyceps preparation being used.\(^5\) One trial\(^6\) reported no apparent adverse effects with cordyceps and none of the other studies reported adverse events.

**DISCUSSION**

A total of 12 RCTs involving 655 patients examined whether cordyceps had an effect on the main abnormalities resulting from ESRD in hemodialysis patients.

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**Table 9** Comparison of cordyceps and conventional treatment versus conventional treatment alone (control)

A: total cholesterol (mmol/L); B: triglycerides (mmol/L); C: low-density lipoprotein cholesterol (mmol/L).

**Figure 9** Comparison of cordyceps and conventional treatment versus conventional treatment alone (control)

A: total cholesterol (mmol/L); B: triglycerides (mmol/L); C: low-density lipoprotein cholesterol (mmol/L).

**Figure 10** Comparison of cordyceps and conventional treatment versus conventional treatment alone (control)

A: total symptom scores; B: symptom remission rates.
Pooled data showed a tendency for improvement of inflammation, nutrition status, oxidative stress, anemia, and symptom remission rates. However, there is no evidence that cordyceps can improve kidney function or hyperlipidemia in hemodialysis patients. Poor reporting of methods and results was common among the studies included in this review. Whilst cordyceps products have been heavily promoted for hemodialysis patients, our review has highlighted a relative lack of high-quality evidence to support the routine use of cordyceps in the clinical care of these patients.

Published studies indicate that CRP is a stronger overall predictor of cardiovascular disease and stroke than is LDL-C. A level of CRP less than 1 mg/L reflects low cardiovascular risk, 1 to 3 mg/L indicates moderate risk and value greater than 3 mg/L is considered as high risk. In this review, the mean hs-CRP in the cordyceps-treated arms was 3.44 mg/L lower than the control arms, but it did not reach the optimal range for cardiovascular risk reduction after 2 to 8 months of treatment with cordyceps. We rated this evidence as low quality due to a serious risk of bias and indirectness because one study involved diabetic nephropathy patients which may not be of relevance to the wider population. Malnutrition is another common cause of mortality in the dialysis population. Studies have shown that for every 10 g/L decrease in serum albumin, mortality increases by 137%. Evidence from five RCTs that were judged to be of moderate-quality demonstrated a significant improvement in mean serum albumin levels, with 3.07 g/L higher in the cordyceps-treated arms compared with the control arms. As for other outcomes relating to the efficacy of treatment, it is difficult to draw a conclusion that cordyceps alleviates oxidative stress and improves anemia or kidney function in hemodialysis patients. We found the quality of evidence for the outcome oxidative stress and anemia to be low primarily due to serious risk of bias, high statistical heterogeneity or inconsistency and indirectness of the evidence. Most of the included trials were highly heterogeneous particularly for the types of drugs used in conventional treatment, types of cordyceps products and the dose used, frequency of dialysis sessions, and study duration. Together with these factors, serious imprecision was noted for the outcome SCr as the study population was small and the confidence intervals were large and consequently, the evidence was downgraded to very low quality. We did not grade the quality of evidence for treatment-related adverse events since this outcome was either not monitored or poorly documented in most trials.

To our knowledge, this review remains the only systematic review of RCTs that investigated the clinical effects of cordyceps in a hemodialysis population. There have been several other reviews that have focused on the use of cordyceps in people with all stages of CKD. In a recent review of 22 studies that involved 1746 participants, the combined use of cordyceps and conventional treatment had significantly decreased SCr, increased creatinine clearance and reduced proteinuria in non-dialysis CKD patients. A similar treatment effect was reported in another review of eight studies (involving 710 CKD patients) that compared the treatment effects of cordyceps plus conventional treatment versus conventional treatment alone in all CKD patients who were not receiving dialysis or kidney transplant. Meanwhile, another review of six studies that involved patients with earlier stages of CKD concluded that patients treated with cordyceps had a significantly higher response rate and total effective rate than patients receiving no treatment. Our review involved hemodialysis patients and we did not find any significant difference between the cordyceps and control groups in SCr and BUN levels reduction. This seems to indicate that people with earlier stages of CKD may have gained a greater improvement in kidney function with cordyceps compared with people on hemodialysis. Even though the effects of cordyceps were promising in these published reviews, the overall quality of the evidence for the outcomes reported was unknown. The GRADE approach was not applied in any of these reviews.

There are several limitations of this review. First, due to inadequate reporting in the published reports, the risk of bias assessment may not reflect the true quality of the trials. Littlewood et al suggested that reasonable attempts to contact study authors should be made in order to obtain more information about the study methodology. We had tried to seek clarification from the authors upon the methodological issues, but none responded. On the other hand, the influence of sponsorship on the effects of intervention was unclear as none of the included trials provided information on whether their trials received any sponsorship. It has been shown that studies funded by product manufacturers were four times more likely to produce positive results favoring the sponsor’s product than were studies sponsored by other sources. Since participants in all the included trials were administered with the commercial products of cordyceps, study authors should disclose the sources of their funding and other financial interests. Second, this review could have missed some relevant unpublished trials. We contacted the authors and local manufacturers to request for unpublished RCTs, but none of them responded to our request. It has been found that published trials were more likely to contain statistically significant results than unpublished trials. Therefore, the findings of these 12 included trials may have overestimated the true treatment effect of cordyceps for the outcomes reported. Third, though the patients included in most of the trials were similar in their characteristics at baseline, statistical heterogeneity was apparent in our pooled analyses. As recommended by Deeks et al., we used the random effects model and did subgroup analyses. Finally, our meta-analysis may not be generalizable to the glob-
al population of hemodialysis patients as all the included trials were conducted in China and involved only Chinese participants.

In conclusion, the overall quality of evidence for the treatment of cordyceps in hemodialysis patients was low. Given the small number of trials included, the unclear methodological quality of the included trials, and the high heterogeneity in pooled analyses, the evidence obtained in this review is insufficient to recommend the use of cordyceps as adjunctive treatment in hemodialysis patients. Future trials should have adequate sample size, longer follow-ups and trials should be adequately reported and use the hard end-points such as hospitalization and mortality to elucidate the clinical efficacy of cordyceps as an additional therapeutic option for hemodialysis patients more effectively.

ACKNOWLEDGEMENTS

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