Efficacy of *Cordyceps sinensis* as an adjunctive treatment in kidney transplant patients: A systematic-review and meta-analysis

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**Abstract**

Objectives: *Cordyceps sinensis* (cordyceps) is a fungus used in traditional Chinese medicine as adjuvant immunosuppressive agent in patients with kidney transplant. This review evaluates current evidence on the efficacy and safety of natural and fermented cordyceps preparations in patients with kidney transplant.

Methods: English and Chinese electronic databases including The Cochrane Central Register of Controlled Trials, EMBASE, MEDLINE, and CNKI (China National Knowledge Infrastructure) were searched up to December 2015 for relevant randomized controlled trials. Journals and conference proceedings were also searched. Two review authors independently selected trials for inclusion, extracted data, and assessed methodological quality. The primary outcome measures were incidence of acute graft rejection in the first year post-transplantation, one-year graft survival rate (defined as the percentage of patients with functioning grafts) and patient survival rate (or all-cause mortality).

Results: Nine studies were eligible for inclusion. These studies were considered to be at moderate risk of bias due to poor reporting of methods. Four studies that compared cordyceps-based therapy with azathioprine-based therapy gave comparable acute rejection rates, and graft and patient survival. The cordyceps-treated group however showed better kidney function and lower incidences of hyperuricemia, hyperlipidemia, hyperglycemia and liver injury. Cordyceps used with different combinations of immunosuppressant therapy showed significant reduction in proteinuria after 6–12 months. Compared to the group receiving cyclosporine A monotherapy, treatment with a combination of cordyceps and cyclosporine A showed less treatment-induced nephrotoxicity. Adverse events were either not monitored or poorly documented in most trials.

Conclusions: Current evidence shows that cordyceps as an adjuvant to routine immunosuppressant therapy may benefit kidney transplant patient, however, better quality evidence is still required.

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**Contents**

1. Introduction ........................................................................................................................................ 85
2. Materials and methods ..................................................................................................................... 85
   2.1. Selection of studies .................................................................................................................... 85
   2.2. Search strategy ......................................................................................................................... 85
   2.3. Data extraction and assessment of risk of bias ......................................................................... 85
   2.4. Data synthesis ......................................................................................................................... 86
3. Results ................................................................................................................................................ 86
   3.1. Description of studies ............................................................................................................. 86
   3.2. Risk of bias ............................................................................................................................ 86
   3.3. Effects of interventions ....................................................................................................... 86

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1. Introduction

End-stage renal disease (ESRD) is the final stage of chronic kidney disease when the glomerular filtration rate (GFR) drops to below 15 ml/min/1.73 m² and dialysis is required. 1 Kidney transplantation is cost-effective and is the preferred treatment in ESRD patients primarily due to effective immunosuppressive therapy. 2 An early study 1 reported that patients who received a kidney transplant had a 54% lower death rate and an estimated 17.19 years of life expectancy compared to only 5.84 years in dialysis patients.

In the early 1980s, the introduction of cyclosporine A and tacrolimus significantly improved the short-term outcome of kidney transplantation. These calcineurin inhibitors (CNI) reduce allograft rejection, improved allograft half-life and patient survival. 3 An early report suggested that cyclosporine A improved the one-year graft survival rate by 5.1 percentage points using transplants from living donors and by 12.0 percentage points with transplants from deceased donors. 4 In more recent years, the use of combination immunosuppressant therapy, consisting of a CNI and either an antimetabolite such as azathioprine or mycophenolate mofetil (MMF), or a proliferation signal inhibitor (TOR-I) such as sirolimus or everolimus with or without prednisolone has markedly reduced the incidence of early loss of graft. 5 Yet, the frequency of late loss of graft has remained virtually unchanged due to chronic allograft nephropathy (CAN). 6 Additionally, chronic use of these drugs has been associated with various side effects including dose-dependent CNI nephrotoxicity, hepatotoxicity, new-onset diabetes, dyslipidemia, hypertension and cardiovascular related death. 7,8 Thus, exploring the CNI-free regimens or adjuvant therapies with high efficacy and low toxicity is still a challenge in the kidney transplantation field.

Recently, there has been considerable interest in the use of traditional Chinese medicine in kidney transplantation. In China, the immunoregulating, Cordyceps sinensis has been widely used following kidney transplantation. 9,10 C. sinensis is a rare Ascomycetes fungus found in the high altitude regions of Tibet and China. 11 The fungus is known as dong chong xia cao or “winter worm, summer grass” in China. 12 It contains many potentially bioactive constituents, such as polysaccharides, adenosine, cordycepin, cordycepic acid, and ergosterol. 13,14 The polysaccharides have been reported to have anti-inflammatory, antioxidant, hypoglycemic, hypolipidemic and bidirectional immunomodulatory effects. 15-18 In view of the limited supply of wild cordyceps, various cultured and fermented mycelia products with similar active constituents are now in use. 19,20 Several studies have shown that the immunosuppressive effect of cordyceps was weaker than cyclosporine A, but as an adjuvant, it reduces graft lesions, prolongs graft survival and reduces the dose of cyclosporine A. 21,22 Use of cordyceps in kidney transplant patients is confined to China. 11 There are several randomized controlled trials (RCTs) evaluating the efficacy of cordyceps as adjuvant immunosuppressive agent. 22-24 The aim of this systematic review was to examine current evidence on the efficacy and safety of natural and fermented C. sinensis preparations in kidney transplant recipients.
urea nitrogen), change in proteinuria (measured by 24-h urinary protein), difference in the dosage and trough concentration of cyclosporine A, and complications (for instance, hyperuricemia, infections, liver injury). All reported adverse events were also extracted. Authors of trials were contacted for missing data and additional information.

The methodological quality of included studies was assessed using the Cochrane risk of bias tool. Discrepancies at the stages of selection of studies, data extraction and assessment of risk of bias were resolved through discussion between the two review authors.

2.4. Data synthesis

Information from eligible studies was aggregated to produce a quantitative summary of the results using Review Manager (RevMan) version 5.3. Risk ratio (RR) was calculated for dichotomous outcomes (graft rejection and survival rate, hepatotoxicity, nephrotoxicity, infections and adverse events). For continuous outcomes (measurement of kidney and liver functions, 24-h urinary protein, serum uric acid, lipid profile, blood glucose level, and cyclosporine dosage and concentration), results were expressed as weighted mean difference (WMD) with 95% confidence intervals (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. If the heterogeneity was deemed high, the results from studies were not pooled.

3. Results

3.1. Description of studies

The process applied for study selection is shown in Fig. 1. Of the 195 records identified through electronic databases, eight trials22,24,26–31 met our inclusion criteria, while one additional trial23 was identified through cited reference in the articles we reviewed. All these trials were included in the quantitative analysis. Another 11 trials11,19,20,32–39 were excluded for a variety of reasons (Fig. 1).

All nine trials were conducted in China and were published between 1991 and 2012 (Table 1). Six trials22,24,27,28,30 were published in Chinese while three trials26,29,31 were in English. Of the nine included trials, seven22,24,26–29 evaluated the efficacy of cordyceps in patients receiving kidney transplants, while two trials26,31 included only transplant patients with CAN. Overall, 449 patients received cordyceps and 458 patients received the control. Most studies had two treatment arms, but one study26 had four treatment arms. In this study,26 two comparison groups were separated based on use of enalapril and were separately analyzed in the meta-analysis. Bailing66 oral capsule which is made by fermented C. sinensis was administered in all trials, and the daily dose ranged from 3 to 12 g. The patients were followed from 15 days to 2 years and were treated concomitantly with different combinations of immunosuppressive agents.

3.2. Risk of bias

The study methodology was mostly incompletely reported in the trials (Fig. 2). Two studies26,28 used a random number table to generate random allocation while the other studies did not describe the method used for randomization. None of the trials described allocation concealment, and blinding of participants, personnel or outcome assessors. Only one trial23 was judged to have a high risk of attrition bias as completeness of outcome data was not adequately addressed. Because study protocols were not available, we considered those studies which reported on all the pre-specified outcomes mentioned in their method section as free of selective reporting bias. Thus, seven trials23,24,26,28–31 were considered to have low risk of bias for selective reporting. Two other potential sources of bias considered in this review were baseline comparability and financial support received for the trial. All except one study22 were deemed to have low risk of bias as there were no significant differences in patient characteristics and baseline laboratory data between the treatment and control groups. Information on possible financial bias was unclear in eight studies22,24,27–31 as information on sponsorship or its absence was not specifically given. Only one study26 was non-industry sponsored and therefore was judged to have low risk of financial bias.

3.3. Effects of interventions

Outcome measures relevant to our review questions are as shown in Table 1. Concomitant immunosuppressant therapy used between trials varied making it necessary to subcategorize the studies for a meta-analysis. Thus, we classified and pooled the effects of interventions according to the concomitant immunosuppressant therapy used. Within each of this group, we presented the results separately for the different outcomes.

3.3.1. Cordyceps-based immunosuppressant therapy versus azathioprine-based immunosuppressant therapy

Four studies22,23,27,28 involving 265 patients compared cordyceps-based immunosuppressant therapy with azathioprine-based immunosuppressant therapy. The dosage used in these studies ranged from 3 to 12 g/day for cordyceps and 50 to 150 mg/day for azathioprine. In all studies, the immunosuppressant therapy consisted of cyclosporine A and prednisolone.

3.3.1.1. Primary outcomes: acute graft rejection, 1-year graft survival and patient survival rates

The incidence of acute rejection was reported in three trials involving 197 patients.22,23,28. The pooled estimates did not show any statistically significant difference between the cordyceps group and the azathioprine group (Fig. 3A).

Four trials22,23,27,28 reported the incidence of graft loss after one year of transplantation. Again, the difference between the two groups was not statistically significant (Fig. 3B). Only one trial23 reported on survival rate. The proportion of patients who survived in the first year after kidney transplantation in the cordyceps group did not differ significantly from that of the azathioprine group (RR 1.00; 95% CI 0.90–1.12) (Fig. 3C).

3.3.1.2. Secondary outcome: kidney function

In one study,28 kidney function was expressed as mean serum creatinine (Scr) and blood urea nitrogen (BUN) levels at one year after intervention. Patients in the cordyceps-based immunosuppressant therapy had significantly lower Scr (n = 121; MD −15.00 μmol/L; 95% CI −27.25 to −2.75) and BUN (MD −1.80 mmol/L; 95% CI −2.51 to −1.09) than those in the azathioprine-based immunosuppressant therapy. In another study,23 Scr was reported as ordinal data. Therefore, data from both studies could not be combined.

3.3.1.3. Secondary outcome: complications

Sun et al.28 reported on disease complications and on side-effects of treatment including hyperuricemia, hyperlipidemia, hyperglycemia, liver injury and infection rate. Compared with the azathioprine-based therapy, treatment with cordyceps-based therapy significantly increased the HDL-cholesterol level (n = 121; MD 0.40 mmol/L; 95% CI 0.31–0.49) and significantly decreased serum uric acid (MD −255.00 μmol/L; 95% CI −293.66 to −216.34), total cholesterol (MD −1.70 mmol/L; 95% CI −2.02 to −1.38), alanine transaminase (MD
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Participants</th>
<th>Mean age in years (SD)</th>
<th>Study design (Country)</th>
<th>Intervention</th>
<th>Cordyceps</th>
<th>Study period</th>
<th>Outcomes reported</th>
<th>Note:</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al.24</td>
<td>56 kidney transplant patients with proteinuria (24 h Upro &gt;0.5 g)</td>
<td>T: 40.1 (8.2), C: 38.5 (7.4)</td>
<td>Open-label RCT (China)</td>
<td>Cordyceps + Irbesartan + Pred + (CsA/TAC) + MMF (n = 30)</td>
<td>Oral Bailing (1 g thrice daily)</td>
<td>6 months</td>
<td>No, No, No, Yes, Yes, No, No, Yes</td>
<td>Graft rejection, Graft survival, Patient survival, Kidney function, 24 h Upro, CsA dose &amp; level, Complications, ADR</td>
<td></td>
</tr>
<tr>
<td>Li et al.26</td>
<td>202 kidney transplant patients with 194 having primary kidney transplantation</td>
<td>T: 37.4 (10.8), C: 34.8 (11.2)</td>
<td>Open-label RCT (China)</td>
<td>CsA + MMF + Pred (n = 93)</td>
<td>Oral Bailing (1 g thrice daily)</td>
<td>12 months</td>
<td>Yes, Yes, Yes, Yes, Yes, Yes, No, No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun et al.28</td>
<td>121 kidney transplant patients with 116 having primary kidney transplantation</td>
<td>T: 42.9 (NR), C: 40.5 (NR)</td>
<td>Open-label RCT (China)</td>
<td>AZA + CsA + Pred (n = 57)</td>
<td>Oral Bailing (3 g daily)</td>
<td>12–24 months</td>
<td>Yes, Yes, No, No, No, No, No, Yes</td>
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<td></td>
</tr>
<tr>
<td>Wang27</td>
<td>68 kidney transplant patients</td>
<td>T: 45.0 (NR), C: 47.0 (NR)</td>
<td>Open-label RCT (China)</td>
<td>Cordyceps + CsA + Pred (n = 36)</td>
<td>Oral Bailing (12 g daily)</td>
<td>12 months</td>
<td>No, Yes, No, No, No, No, No, Yes</td>
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</tr>
<tr>
<td>Wang28</td>
<td>42 cadaveric kidney transplant patients with 38 having primary kidney transplantation</td>
<td>T: 34.2 (NR), C: 35.2 (NR)</td>
<td>Open-label RCT (China)</td>
<td>Cordyceps + CsA + Pred (n = 21)</td>
<td>Oral Bailing (First year: 6 g daily Second year: 3 g daily)</td>
<td>12 months</td>
<td>Yes, Yes, No, No, No, No, No, Yes</td>
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<tr>
<td>Xu et al.29</td>
<td>69 patients with stable transplant kidney function for ≥3 months</td>
<td>NR</td>
<td>Parallel RCT (China)</td>
<td>Placebo (oral glucose) + CsA (n = 30)</td>
<td>Oral Bailing (3 g daily)</td>
<td>15 days</td>
<td>No, No, No, Yes, No, Yes, No, No</td>
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<tr>
<td>Yu et al.30</td>
<td>34 cadaveric kidney transplant patients with 30 having primary kidney transplantation</td>
<td>T: 34.2 (NR), C: 35.2 (NR)</td>
<td>Open-label RCT (China)</td>
<td>Cordyceps + CsA + Pred (n = 17)</td>
<td>Oral Bailing (5.2 g daily)</td>
<td>12 months</td>
<td>Yes, Yes, Yes, Yes, No, No, Yes, No</td>
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<tr>
<td>Zhang et al.31</td>
<td>84 CAN patients with cadaveric transplant (n = 72) and live-donor transplants (n = 12)</td>
<td>T: 34.3 (15.5)</td>
<td>Open-label RCT (China)</td>
<td>T1: Cordyceps + Enalapril + *triple drugs (n = 22) T2: Cordyceps + *triple drugs (n = 21)</td>
<td>Oral Bailing (2 g thrice daily)</td>
<td>9 months</td>
<td>No, No, No, Yes, Yes, No, No, Yes</td>
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<tr>
<td>Zhang et al.32</td>
<td>231 CAN patients with cadaveric transplants (n = 161) and live-donor transplant (n = 70)</td>
<td>T: 41.4 (13.6), C: 42.2 (13.8)</td>
<td>Open-label RCT (China)</td>
<td>Cordyceps + (AZA/MMF) + Pred (n = 122)</td>
<td>Oral Bailing (2 g thrice daily)</td>
<td>6 months</td>
<td>No, No, No, Yes, Yes, No, No, Yes</td>
<td></td>
<td></td>
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</table>

Note: T: treatment; C: control; SD: standard deviation; NR: not reported; RCT: randomized controlled trial; ADR: adverse drug reaction; n: number; g: gram; 24 h Upro: 24-h urinary protein; CAN: Chronic allograft nephropathy; *triple drugs: (CsA/TAC) + (AZA/MMF) + Pred; CsA: cyclosporine A; Pred: prednisolone; AZA: azathioprine; TAC: tacrolimus; MMF: mycophenolate mofetil.
3.3.1.4. Secondary outcome: adverse effects. One study \cite{27} reported that no obvious adverse effects were associated with cordyceps treatment. None of the other studies reported adverse events.

3.3.2. Cordyceps-based immunosuppressant therapy versus control (immunosuppressant therapy only)

Four different types of cordyceps-based immunosuppressant therapy were used \cite{24,26,30,31}. The therapy consisted of cyclosporine A plus MMF \cite{25}, cyclosporine A plus (azathioprine or MMF) \cite{31}, MMF plus (cyclosporine A or tacrolimus) \cite{24}, and (cyclosporine A or tacrolimus) plus (azathioprine or MMF) \cite{30}. In all studies, prednisolone was also given to patients. The data are presented separately for each of these four studies. Of these, only that of Zhang et al. \cite{30} had four treatment arms with two arms receiving additional enalapril co-therapy.

3.3.2.1. Primary outcomes: acute graft rejection, 1-year survival and patient survival rates. Of the four trials, only one trial \cite{25} reported on acute graft rejection, graft loss and patient mortality at one year. This trial \cite{25} showed that there was no statistically significant difference in incidence of acute graft rejection between the treatment and control arms (RR 0.76; 95% CI 0.37–1.54). The time to occurrence of an acute rejection episode were 23.48 ± 7.22 and 22.27 ± 8.03 days in cordyceps and control groups respectively. Similarly, the results on both graft (RR 1.03; 95% CI 0.96–1.11) and patient survival rates (RR 1.02; 95% CI 0.98–1.06) showed no statistically significant difference between the two groups.

3.3.2.2. Secondary outcomes: kidney function and proteinuria. All four studies reported on Scr and BUN for kidney function (Table 2). Li et al. \cite{25} reported that the combination of cordyceps and low-dose cyclosporine A did not produce any significant difference in Scr and BUN levels compared to standard-dose cyclosporine A. When cordyceps was combined with any of the CNIs and antimetabolites, its use with enalapril led to a significant reduction in Scr level after 9-month of therapy (MD −45.62; 95% CI −90.96 to −0.29). \cite{30} However, this reduction was not found with BUN level over the same study period. This study \cite{30} also indicated that cordyceps could reduce Scr level effectively even without the incorporation of enalapril (MD −96.89; 95% CI −124.05 to −69.73). But, this effect was not seen with BUN level. Another study \cite{24} which incorporated irbesartan into the cyclosporine A/tacrolimus regimen used in both study arms reported similar results for Scr (MD −8.87; 95% CI −16.34 to −1.40) and BUN (MD −0.65; 95% CI −1.35 to 0.05). In contrast to these findings, the combination of cyclosporine A and

Fig. 1. Flow chart of result of searches, studies identified and included in this review.
azathioprine/MMF in another study showed significant reductions in both Scr (MD: -57.12; 95% CI: -64.44 to -49.80) and BUN concentration (MD: -1.38; 95% CI: -2.68 to -0.08) in favor of cordyceps.

Two trials evaluating the benefits of cordyceps for CAN reported creatinine clearance (CrCl). Zhang et al. reported that cordyceps-treated arms failed to increase CrCl significantly compared to the control arms regardless of the use of enalapril (Table 2). However, a significant elevation in CrCl (MD: 10.84; 95% CI: 8.08–13.60) was found after 6-month of treatment in another study. Proteinuria was measured as the 24-h urinary protein excretion in all the four trials. All studies showed significant reductions in 24-h proteinuria favoring the cordyceps-treated arms (Table 2).

3.3.2.3. Secondary outcomes: dosage and trough concentration of cyclosporine A. Li et al. compared the changes in cyclosporine A dosage and concentration over 6 months of therapy. Trend analyses demonstrated an approximately linear decrease in cyclosporine A dosage and whole-blood trough concentration with cordyceps-
based immunosuppressant therapy. This study reported that changes in the cyclosporine A dosage were statistically significant from two to six months after transplantation (n = 167; MD –0.27 mg/kg/day; 95% CI –0.37 to –0.17; I² = 93%) compared to control group. Similarly, the whole-blood trough concentration of cyclosporine A in cordyceps-treated arm was significantly lower than those in the control group from the third month onwards (MD –21.77 μg/L; 95% CI –29.27 to –14.27; I² = 28%).

3.3.2.4. Secondary outcome: complications. Li et al.26 reported that common complications were hyperuricemia, nephrotoxicity, hepatotoxicity and chronic allograft nephropathy. The addition of cordyceps to the basic immunosuppressant therapy significantly reduced the uric acid concentration (n = 202, MD –63.34 μmol/L; 95% CI –94.06 to –32.62). Cordyceps adjuvant therapy was associated with less hepatotoxicity, nephrotoxicity and chronic allograft nephropathy than the control.

3.3.2.5. Secondary outcome: adverse effects. Two studies reported no apparent adverse effects with cordyceps preparations.30,31 Another study did not report adverse events.26 Only Chen et al.24 described an extraordinary increase in SCR in one participant in the control arm. However, the elevation in SCR did not exceed 30% above the baseline value. Thus, the participant continued to receive the conventional treatment and no other adverse effects were noted.

3.3.3. Cordyceps + CNI versus placebo + CNI

Only one trial25 that examined concurrent administration of cordyceps with cyclosporine A at the dose of 5 mg/kg/day. Participants in the control arm received placebo and cyclosporine A. Kidney function was assessed by Scr and BUN levels together with cyclosporine A trough concentrations on days 5, 10 and 15 of treatment. In this trial, cordyceps exerted a significant protective effect against cyclosporine nephrotoxicity by reducing the Scr and BUN levels. The longer cordyceps was given, the larger the differences in Scr (n = 69, MD –28.34 μmol/L; 95% CI –37.96 to –18.71; I² = 36%) and BUN (n = 69, MD –4.22 mmol/L; 95% CI –5.23 to –3.21; I² = 30%) levels between the treatment arms.

4. Discussion

Our review found that the existing evidence is not convincing enough to make definitive statements about the efficacy and safety of cordyceps as adjuvant immunosuppressive agent in kidney transplant patients. Data from most of the published studies could not be pooled because of the clinical heterogeneity between trials particularly for the different combination of immunosuppressive regimens employed. Additionally, because of inadequate reporting in almost all studies, these studies were judged to have unclear risk of bias.

In this review, cordyceps as adjunct to six different types of immunosuppressant therapy were assessed and compared. All study participants received Bailing8 oral capsule which have similar bioactive constituents and pharmacological activities as the
wild cordyceps. Four studies that compared cordyceps-based therapy with azathioprine-based therapy gave comparable acute rejection rates, and graft and patient survival between the two groups. Consistent with our findings, a retrospective study in China found that cordyceps-based therapy had the same immunosuppressive activity as the azathioprine-based therapy. Furthermore, cordyceps-based therapy was associated with better recovery of kidney function, less hepatic toxicity and less reduction in lymphocyte count. In our review, only Sun et al. reported better kidney function and lower incidences of hyperuricemia, hyperlipidemia, hyperglycemia, liver injury and infection rate in the cordyceps-treated group. However, this result needs to be interpreted with caution as the trial had unknown allocation concealment and was an open-label trial. It has been shown that trials with inadequate allocation concealment yielded 40% larger estimates of treatment effects than trials with adequate allocation concealment.

In one trial, participants in the intervention arm received cordyceps with cyclosporine A while those in the control arm received glucose pill (placebo) with cyclosporine A. Since cordyceps was given as capsules, the use of glucose pill as placebo was considered inappropriate as this could unblind the study, particularly since the authors did not clearly state who was blinded and how blinding was achieved.

When compared with immunosuppressant therapy, the addition of cordyceps to different combinations of immunosuppressant therapy in the four included studies failed to produce a consistent result in kidney function parameters, namely SCR, BUN and CrCl. Nevertheless, all four studies showed significant reductions in 24-h proteinuria after 6–12 month of cordyceps-based immunosuppressant therapy. This finding is of great interest as proteinuria is an important risk factor for chronic rejection after one year of kidney transplantation. Researchers have shown that transplant patients with persistent proteinuria above 1500 mg/day had 14.3 times increased risk of graft loss compared to proteinuria-free grafts. In addition, proteinuria plays an important role in the pathogenesis of CAN. Two included trials that assessed patients with CAN found that cordyceps-treated group had significantly lower proteinuria compared to the control group. This finding is in agreement with one observational study which compared cordyceps with standard therapy (traditional immunosuppressive agents only) in patients diagnosed with CAN in accordance with the Banff 97 scheme. This study reported that treatment with cordyceps significantly improved SCR, CrCl and 24-h proteinuria compared with standard therapy.

The effects of cordyceps in reducing CNI-induced nephrotoxicity have been identified in two included studies. Li et al. showed that cordyceps augmented the anti-rejection effect of cyclosporine A and reduced its use and trough concentration with a consequential reduction in side-effects. Whereas, another study found that treatment with a combination of cordyceps and cyclosporine A showed less treatment-induced nephrotoxicity than cyclosporine A monotherapy with significant reductions in SCR and BUN levels. However, the research methodology of both studies was either questionable or poorly documented, thus limiting the validity of the results. In most studies, data on cordyceps-related adverse effects were lacking. Therefore, the current evidence is insufficient to determine whether the benefits of taking cordyceps outweighed the harms.

In general, our findings are in consistent with one recently published systematic review which examined the benefits and adverse effects of cordyceps in kidney transplant recipients. The results of this meta-analysis are slightly different to those of our systematic review because we included an additional four randomized studies assessing the adjunctive effects of cordyceps in the amelioration of cyclosporine-induced nephrotoxicity, chronic allograft nephropathy, and proteinuria after kidney transplantation. Additionally, there were two duplicate studies. The previous systematic-review included both studies whereas we only included Li et al. as it provided complete data for all outcome measures and detailed information on how patient randomization was done.

The quality of the available evidence restricted our findings and interpretations. The methodological quality of the trials is generally suboptimal. Most trials did not describe the methods of randomization, allocation concealment and blinding procedures, thus limiting the internal validity of the results. Studies have shown that poorly reported RCTs yields biased results and are likely to overestimate treatment effects. On the other hand, nearly all studies had unclear sources of funding. Since industry-sponsored studies may bias results in favor of sponsors’ products, study authors should disclose the sources of their funding and other financial interests. We made attempts to contact authors for details of study methods and missing data. Unfortunately, the authors did not respond to our request and consequently, we were not able to analyze some relevant outcome data. In addition, all studies were conducted in China and involved only Chinese participants. Hence, our meta-analysis may not be generalizable to the global population of kidney transplant patients. Furthermore, research originating in China had been shown to produce unusually high proportions of positive results favoring the test treatment. The positive findings could be due to lack of methodological rigor in conducting the studies. For example, the method of allocation concealment, blinding of outcome assessors were unclear for all studies. Finally, all the included studies were of short-duration. Thus the long-term effects of cordyceps are still unknown.

5. Conclusions

The results of the available trials did not provide strong evidence to support the inclusion of cordyceps in routine immunosuppressive regimen even though some beneficial effects on graft survival, kidney function, and disease or treatment-related complications have been consistently reported in kidney transplant recipients. Future studies should be large-scale RCTs with longer follow-ups and high-quality design to confirm our findings of possible effectiveness.

Conflicts of interest

None declared.

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