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Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease (Review)

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[Intervention Review]

Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

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ABSTRACT

Background

Cordyceps sinensis (Cordyceps, Dong Chong Xia Cao), a herbal medicine also known as Chinese caterpillar fungus, is one of the most commonly used ingredients in traditional Chinese medicine for the treatment of people with chronic kidney disease (CKD).

Objectives

This review aimed to evaluate the therapeutic effects and potential adverse effects of *Cordyceps sinensis* for the treatment of people with CKD.

Search methods

We searched the Cochrane Renal Group's Specialised Register to 14 April 2014 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. We also searched CINAHL, AMED, Current Controlled Trials, OpenSIGLE, and Chinese databases including CBM, CMCC, TCMLARS, Chinese Dissertation Database, CMAC and Index to Chinese Periodical Literature.

Selection criteria

Randomised and quasi-randomised trials comparing Cordyceps or its products with placebo, no treatment, or conventional treatment were considered for inclusion in the review.

Data collection and analysis

Two authors independently assessed data quality and extracted data. Statistical analyses were performed using the random-effects model and the results expressed as risk ratio (RR) for dichotomous outcomes or mean difference (MD) for continuous data with 95% confidence intervals (CI).

Main results

We included 22 studies that involved 1746 participants. Among people with CKD who were not receiving dialysis, Cordyceps preparations were found to significantly decrease serum creatinine (14 studies, 987 participants): MD -60.76 μmol/L, 95% CI -85.82 to -35.71); increase creatinine clearance (6 studies, 362 participants): MD 9.22 mL/min, 95% CI 3.10 to 15.34) and reduce 24

hour proteinuria (4 studies, 211 participants: MD -0.15 g/24 h, 95% CI -0.24 to -0.05). However, suboptimal reporting and flawed methodological approaches meant that risk of bias was assessed as high in four studies and unclear in 18 studies, and hence, these results need to be interpreted with caution.

Authors' conclusions

We found that Cordyceps preparation, as an adjuvant therapy to conventional medicine, showed potential promise to decrease serum creatinine, increase creatine clearance, reduce proteinuria and alleviate CKD-associated complications, such as increased haemoglobin and serum albumin. However, definitive conclusions could not be made because of the low quality of evidence.

PLAIN LANGUAGE SUMMARY

Cordyceps sinensis (a Chinese medicinal herb) for treating chronic kidney disease

People with chronic kidney disease (CKD) experience gradual worsening of kidney function. Cordyceps (*Cordyceps sinensis*), which is sometimes known as Chinese caterpillar fungus, is widely used in traditional Chinese medicine to treat people with CKD. We conducted this review to investigate if Cordyceps was a safe and effective treatment for people with CKD.

We searched the literature published up to April 2014 and assessed evidence from 22 studies conducted in China that involved 1746 people with CKD who received Cordyceps as part of their treatment.

We found some evidence to indicate that Cordyceps preparations given in addition to conventional Western medicine may be beneficial in improving kidney function and addressing some complications. However, evidence quality was poor, and no definitive conclusions could be made about Cordyceps for people with CKD.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a common condition in which kidney function progressively deteriorates, which may be asymptomatic until the disease is advanced. CKD aetiology has been associated with both non-communicable diseases, such as diabetes and hypertension, and infectious diseases including malaria, HIV, and hepatitis B (Nugent 2011). CKD is defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) in terms of either kidney damage (indicated by markers such as abnormalities in urine or blood tests, or on imaging), or decreased glomerular filtration rate (GFR) (< 60 mL/min/1.73 m²) with or without evidence of kidney damage, for three or more months, regardless of cause (Levey 2003; NKF 2008). People with CKD whose kidney function continues to deteriorate may require renal replacement therapy (RRT) (dialysis or kidney transplantation). Adverse effects such as high blood pressure (hypertension), too few red blood cells (anaemia), malnutrition, bone diseases, nerve damage (neuropathy), and decreased quality of life may occur concurrently with gradual loss of kidney function (NKF 2008).

CKD incidence and prevalence is increasing and is associated with escalating rates of hypertension and diabetes mellitus. Together, these diseases pose a major global healthcare challenge (Nugent 2011). In India, where incidence of diabetes and hypertension is high, it has been estimated that between 25% and 40% of the population are at risk of developing CKD (Srinath Reddy 2005). A recent systematic review reported that impaired kidney function prevalence, defined as reduced GFR (< 60 mL/min/1.73 m²), creatinine clearance (CrCl) (< 60 mL/min) or elevated serum creatinine (SCr), ranged from 1.7% in a Chinese study to 8.1% in a US study (McCullough 2012). The high cost of RRT imposes significant economic burden on society, especially in the developing world (Nugent 2011).

Description of the intervention

Laboratory and clinical studies have demonstrated that medicinal herbs traditionally used to treat people with kidney disease may offer potential therapeutic benefits for people with CKD (Wojcikowski 2006). *Cordyceps sinensis* (Cordyceps) is one of the most commonly used ingredients in traditional Chinese medicine for people with CKD (Deng 2001). Cordyceps, a unique blade-

shaped fungus that grows on caterpillars, is valued as a tonic herb in traditional Chinese medicine to treat a wide range of disorders, including respiratory, kidney, liver and cardiovascular diseases, low libido and impotence, and hyperlipidaemia. Because naturally-occurring *Cordyceps sinensis* is in limited supply, various cultured and fermented mycelial products that have similar pharmacologically active components are now used in clinical practice (Zhu 1998a; Zhu 1998b).

How the intervention might work

Clinical studies investigating the use of Cordyceps for treating people with CKD have demonstrated potential beneficial effects in decreasing progression of end-stage kidney disease (ESKD) (Jin 2004), reducing SCr levels (Yu 2003); and increasing CrCl (Wu 2007), serum albumin and haemoglobin (Jin 2004; Yang 1999b); and improving lipid metabolism (Jin 2004; Quan 2004).
Studies investigating the active mechanisms of Cordyceps for CKD have found that its observed benefits may be related to its antioxidant and immunostimulation properties (Shin 2001; Yamaguchi 2000), inhibition of mesangial proliferation (Yang 1999a; Yang 2003; Zhao 2000), anti-inflammatory effects (Liu 2005; Shahed 2001; Yin 2007), ability to decrease accumulation of extracellular matrix in the renal cortex (Ma 2008), and in reducing renal interstitial fibrosis (Min 2008).

Why it is important to do this review

Previous clinical experience and studies investigating Cordyceps have suggested that it is a promising natural substance for the treatment of people with CKD. Although a previous systematic review that investigated the therapeutic benefits of Cordyceps for people with CKD reported favourable effects, this analysis was methodologically flawed by reliance on a limited literature search, inclusion of inappropriate outcome measures, and poor quality reporting (Xu 2006). Therefore, a systematic review applying appropriate, rigorous scientific methodology will not only provide reliable evidence on the therapeutic effect of Cordyceps for people with CKD, but also identify areas for improvement if future clinical studies are to be undertaken.

OBJECTIVES

This review aimed to evaluate the therapeutic effects and potential adverse effects of *Cordyceps sinensis* for the treatment of people with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) evaluating the benefits and potential side effects of *Cordyceps sinensis* for CKD were included in the review.

Types of participants

Inclusion criteria

We included adults and children with CKD at all stages. Where possible, we applied the KDOQI definition for CKD (NKF 2008). However, we anticipated that most studies were likely to have been conducted in countries where the KDOQI definition was not applied, so we also accepted CKD definitions described by the studies.

Exclusion criteria

1. Participants with kidney impairment where baseline GFR or creatinine concentration data could be obtained from the report or through author contact
2. Kidney transplant recipients
3. Participants with diabetic nephropathy and primary nephrotic syndrome. These issues have been investigated in (Feng 2013; Liu 2007)

Types of interventions

1. Treatment group participants received Cordyceps or its products as the single treatment drug, regardless of the formulation and route of administration. These could include extracts of Cordyceps (any part of Cordyceps); or any derived, cultured, fermented mycelial products that contain pharmacologically-active components similar to wild Cordyceps
2. Control group participants received placebo, no treatment, or conventional treatment. Other herbal or complementary medicines without validated efficacy were not accepted as the control intervention
3. Studies involving Cordyceps as one of several active components in a compound or as part of a combined treatment regimen were not included in the review
4. Co-interventions were permitted where participants in all randomised arms received the same co-interventions.

Types of outcome measures

Primary outcomes

1. Time to requirement for RRT or initiation of dialysis
2. All-cause mortality
3. CKD progression, defined as increased CrCl or decreased SCr > 20% from baseline (Zheng 2002).

Secondary outcomes

1. Kidney function, measured by GFR, CrCl, or SCr levels
2. Quality of life measured by a validated scale
3. Proteinuria measured by 24 hour urinary protein excretion, protein/creatinine ratio or albumin/creatinine ratio
4. Blood pressure (systolic and diastolic)
5. Anaemia measured by haemoglobin or haematocrit levels
6. Nutritional status assessed by serum albumin, serum total cholesterol, oedema-free actual body weight, per cent standard (NHANES II) body weight, normalised protein nitrogen appearance or dietary interviews and diaries
7. Bone disease measured by serum calcium and phosphorus or bone mineral density
8. Symptoms including skin pruritus, vomiting, measured by visual analogue or other scales
9. Adverse effects.

Primary and secondary outcome measures were collected immediately after treatment and at the end of follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register to 14 April 2014 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the specialised register section of information about the Cochrane Renal Group. See Appendix 1 for search terms used in strategies for this review. We also searched the following electronic databases to July 2012.

1. CINAHL, AMED (Allied and Complementary Medicine Database), and CISCOM (Centralised Information Service for Complementary Medicine). Search strategies were adapted from the approach described for MEDLINE
2. OpenSIGLE (System for Information on Grey Literature in Europe)
3. Chinese language databases were also searched to January 2011:
   i) CBM (Chinese BioMedical Literature Database)
   ii) CMCC (Chinese Medical Current Contents)
   iii) TCMLARS (Traditional Chinese Medical Literature Analysis and Retrieval System)
   iv) Chinese Dissertation Database
   v) CMAC (China Medical Academic Conference)
   vi) Index to Chinese Periodical Literature.

The search strategies for Chinese language databases are also shown in Appendix 1.

Index to Theses and ProQuest Dissertations and Theses were also searched for relevant studies.

Searching other resources

Reference lists of nephrology textbooks, review articles and relevant studies were also checked.

Data collection and analysis

Selection of studies

The search strategies described were used to obtain titles and abstracts of studies possibly relevant to this review. Titles and abstracts were screened independently by two authors who discarded studies that were not applicable; however, studies and reviews thought to potentially include relevant data or information on studies were retained initially. Two authors independently assessed the retrieved abstracts, and if necessary the full text, to determine which satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by the same authors using a pre-tested data extraction form. Where more than one publication of one study existed, only the publication with the most recent complete data was used. When further information was required, we wrote to the first author of the article concerned.

Disagreements between authors were discussed and resolved by consensus.

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias of the included studies. Any discrepancies were resolved by discussion and conclusions made by consensus.

To detect potential selection bias, performance bias, attrition bias, detection and reporting bias, the following items were assessed using the Cochrane risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel
  - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Baseline comparability was considered as one of the other sources of bias.

We categorised the risk of bias for each outcome within and across the included studies into three levels, i.e. low, unclear and high risk of bias. Based on this, we also used the GRADE system (Higgins 2011) for evaluating the quality of evidence for each individual outcome, which involved not consideration of risk of bias (methodological quality), and directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias.

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, CKD progression), results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (kidney function, quality of life, proteinuria, blood pressure, anaemia, nutritional status, bone disease) the mean difference (MD) was calculated.

Unit of analysis issues

Analysis of outcomes was based on randomised individuals. In the case of multiple intervention groups within a study, we chose pair-wise comparisons relevant to the study objective. We did not identify any cluster RCTs, cross-over studies, or studies reporting repeated measures on the same participants.

Dealing with missing data

Available case analysis was conducted. The potential impact of missing data was considered in the risk of bias assessment and interpretation of results. Because the imbalance of missing data on treatment and control groups is suggestive of high risk of bias, two studies were excluded from our meta-analysis (Guo 2009; Yu 2003).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.1 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity, respectively.

Assessment of reporting biases

Reporting biases were investigated on a funnel plot (Higgins 2011). Possible reasons other than publication bias, such as poor methodological quality and true heterogeneity, were explored.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers. Data synthesis was restricted to studies assessed as low or unclear risk of bias. For studies at high risk of bias, results were displayed on a forest plot without pooling. A narrative, qualitative summary is also presented.

Subgroup analysis and investigation of heterogeneity

If sufficient evidence was available, we planned to conduct the following subgroup analyses to explore potential sources of heterogeneity.

- CKD stage
- CKD definition (KDOQI or other)
- Risk of bias (low or unclear)
- Cordyceps source (wild or cultivated) and preparation (whole plant or extract)
- Cordyceps use (combined with or without other treatment).

Adverse effects were to be tabulated and assessed using descriptive techniques, because they were likely to be different for the various agents used. Where possible, the risk difference (RD) with 95% CI was to be calculated for each adverse effect, either compared to no treatment or to another agent.

We were able to undertake subgroup analyses on levels of risk of bias only. There were insufficient reported data to define CKD stage; CKD definition; use, source and preparation of Cordyceps, to enable subgroup analyses to be undertaken.

Adverse effects were analysed qualitatively. There were insufficient data in the included studies to calculate risk differences (RD) with 95% CI for adverse effects.

Sensitivity analysis

There were insufficient data to conduct sensitivity analyses to explore the influence of risk of bias factors on effect estimates for adequacy of sequence generation and blinding. Likewise, sensitivity analyses were not undertaken to examine if limiting the definition of CKD to the KDOQI standard had an impact on results.

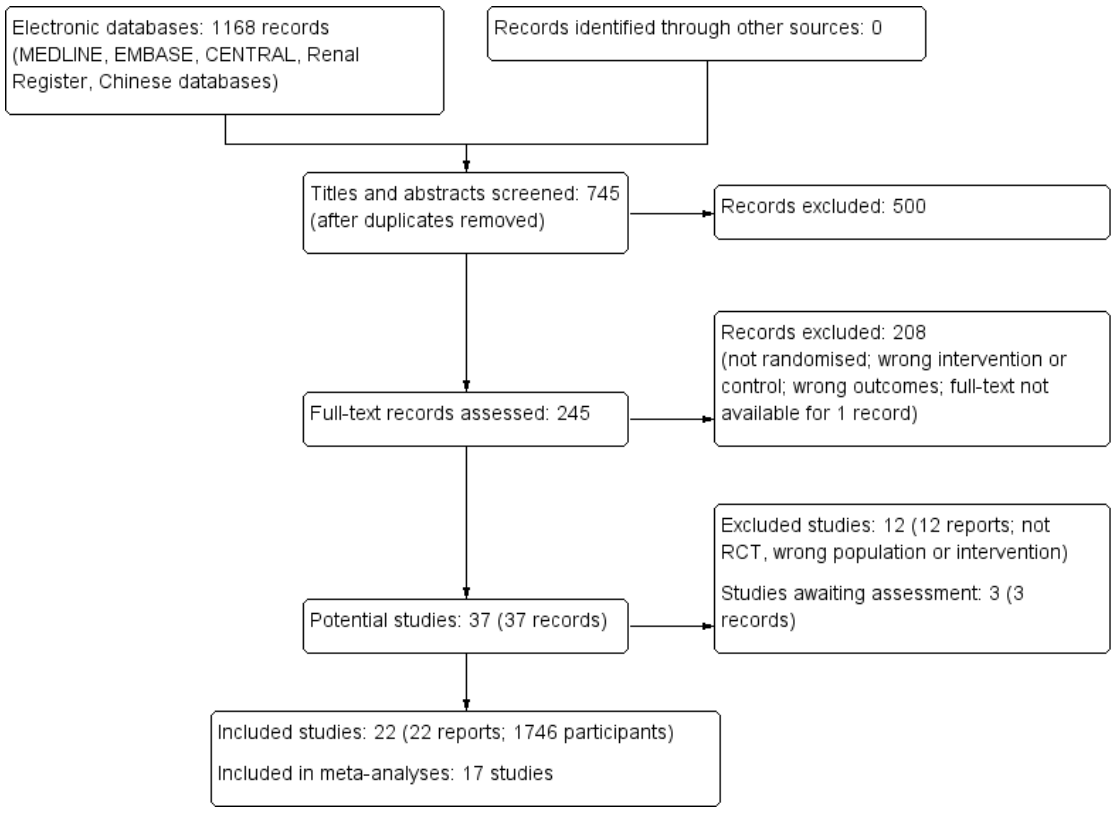
RESULTS

Description of studies

Results of the search

The search of English and Chinese language databases resulted in identification of 1168 citations (Figure 1). Two authors independently screened titles and abstracts and identified 245 studies as potentially relevant. Assessment of full-text articles resulted in identification of 25 potential studies. Three studies are awaiting assessment (Chai 2009; Jin 2006; Lin 2003). As a result, 22 studies were included in this review (Chen 2003; Chen 2006a; Fu 2009; Gao 2007; Guo 2009; Hu 2008; Huang 2008; Jin 2004; Liu 2006a; Liu 2007a; Pan 2007; Shi 2009; Sun 1999; Wang 2005a; Wei 2004; Wu 2007; Xu 2004; Yan 2005a; Yang 1999b; Yu 2002; Yu 2003; Zhang 2009).

Figure 1. Study flow diagram showing the search process and study selection



Included studies

This review included 22 studies, all published in Chinese, that were conducted in hospital settings in China involving 1746 participants (958 males (54.9%); 788 females (45.1%)). Study sample size ranged from 27 to 212 participants.

Participants in 18 studies had reported baseline SCr ranging from 135 to 820 µmol/L. Primary causes of CKD varied, but included chronic glomerulonephritis, diabetic nephropathy, arteriosclerosis of the kidney, chronic pyelonephritis, and hypertension nephropathy. Two studies dealt with aristolochic acid nephropathy (Gao 2007; Zhang 2009), and one investigated participants with hypertension nephropathy (Fu 2009).

Three studies compared Cordyceps plus conventional treatment with Western medicine plus the same conventional treatment (Gao 2007; Huang 2008; Jin 2004), and one compared Cordyceps plus traditional Chinese medicine to the same traditional Chinese medicine (Yan 2005a). The remaining 18 studies compared Cordyceps plus conventional treatment with the same conventional treatment; of these, three studies administered haemodialysis as the co-intervention (Guo 2009; Sun 1999; Yu 2002).

All studies investigated mycelial fermentation products of *Cordyceps sinensis*. Of the 22 included studies, 13 studied Jin Shui Bao capsule and nine investigated Bai Ling capsule. Jin Shui Bao capsules contain 0.33 g fermented Cordyceps and Bai Ling capsules contain 0.2 g Cordyceps. Both capsules were administered orally, and doses ranged from three to six capsules, taken three times daily. Treatment duration ranged from one to six months.

All studies included co-interventions in all treatment arms. Aside from dietary interventions, the most common co-interventions were symptomatic and supportive treatments including maintaining water, electrolyte and acid-base balance; controlling blood pressure; treating anaemia; and controlling infection when necessary. Yan 2005a reported that the compounded traditional Chinese herbal medicines administered as co-intervention to treat CKD included Cangzhu (Rhizoma Atractylodis), Baizhu (Rhizoma Atractylodis Macrocephalae), Yiyiren (Semen Coicis), Fulingpi (Poria), Zelan (Herba Lycopi), Gouqizi (Fructus Lycii), Sangjisheng (Herba Taxilli), Huainiuxi (Radix Cyathulae), Dahuang (Radix et Rhizoma Rhei), and Baihuasheshecao (Herba Hedyotidis Diffusae).

See Characteristics of included studies.

Excluded studies

The most common reasons for study exclusion were lack of control arm; no randomisation; Cordyceps was one of many components in the traditional Chinese medicine treatment; and absence of targeted outcomes. See Characteristics of excluded studies.

Studies awaiting classification

See Characteristics of studies awaiting classification

Risk of bias in included studies

Figure 2 and Figure 3 present graphical presentations of assessments of risk of bias in the included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

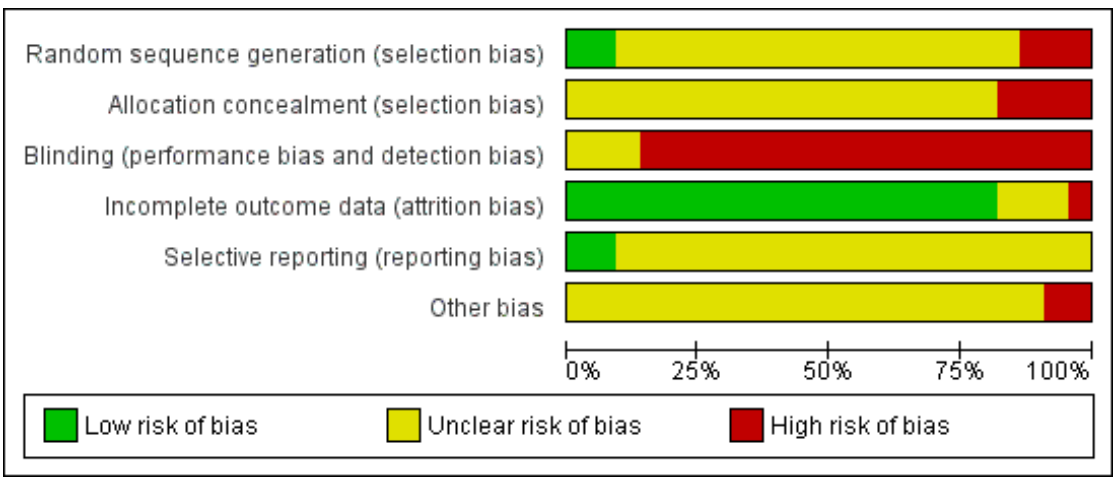
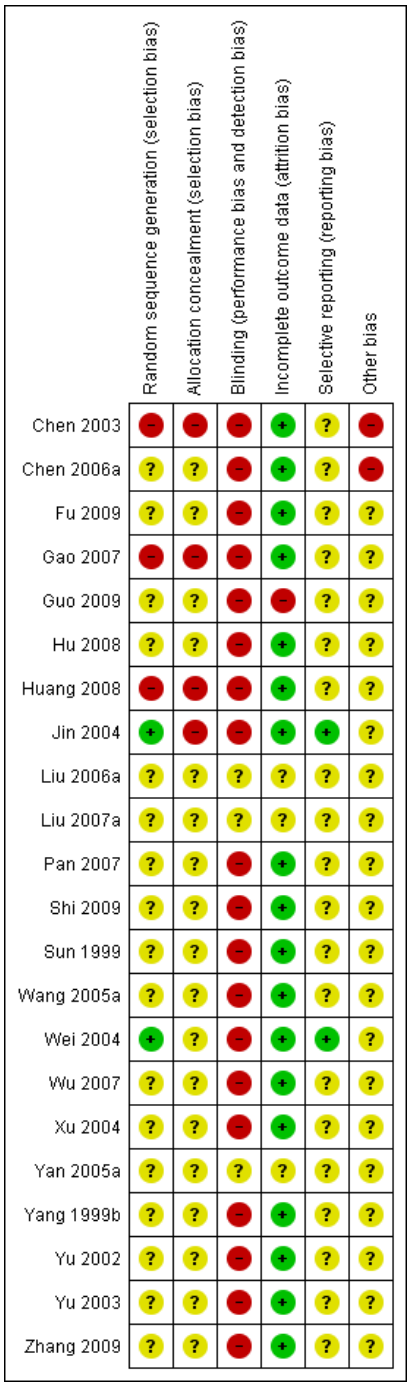


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

In most studies, random allocation was briefly mentioned, and detailed methodologies were not provided. One study used a random number table to generate allocation sequence (Wei 2004); and another used entry sequence (Huang 2008). None of the included studies reported allocation concealment.

Blinding

Blinding was unclear in three studies (Liu 2006a; Liu 2007a; Yan 2005a) and not reported in the remaining 19 studies.

Incomplete outcome data

Two studies reported on missing data. Guo 2009 and Yu 2003 reported attrition rates of 21.9% and 2.5% respectively, but reasons were not provided. Yu 2003 did not report data relating to four control arm participants; and although 34 and 30 participants respectively were enrolled into the intervention and control arms, Guo 2009 included data from 25 participants only from each arm in the analysis.

Selective reporting

Because study protocols were not available, and measurement outcomes for assessing the treatment effect were not reported consistently in the included studies, it was not possible to assess for selective reporting.

Other potential sources of bias

We considered that blinding may not have substantially influenced objective outcome measures. Our assessment found that risk of bias was unclear in most studies, except for four that were at high risk of bias (Chen 2003; Chen 2006a; Guo 2009; Yu 2003). Participant numbers did not balance after randomisation in Chen 2003 and Chen 2006a; and there were missing data from the treatment phase in Guo 2009 and Yu 2003. These four studies were therefore excluded from our quantitative analysis.

Effects of interventions

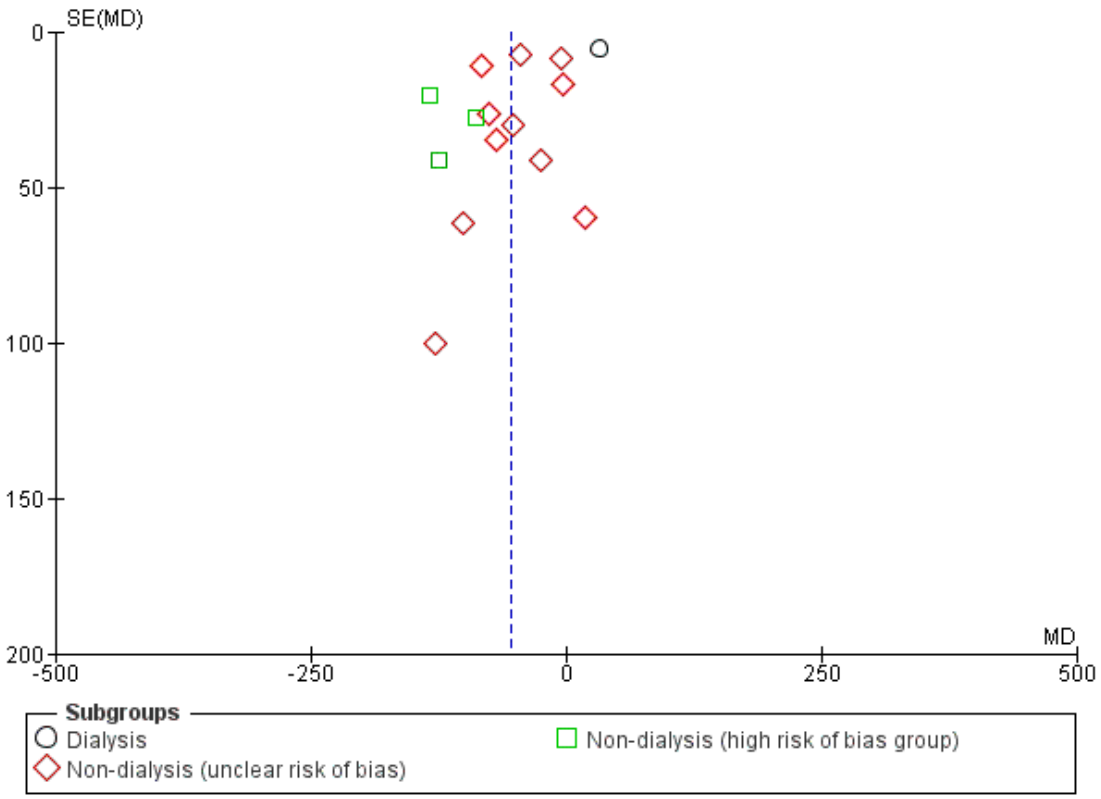
Cordyceps + conventional medicine versus conventional medicine

Kidney function measures (CKD progression, SCr, CrCl)

Overall, in studies judged to have unclear risk of bias, Cordyceps preparations did not confer significant benefits for people with CKD (defined as CrCl increase or SCr decrease greater than 20% over baseline) (Analysis 1.1.1 (5 studies, 368 participants): RR 1.09, 95% CI 0.99 to 1.21; I^2 = 23%). However, effects were significant in studies assessed as being at high risk of bias for this outcome (Analysis 1.1.2 (2 studies, 227 participants): RR 1.36, 95% CI 1.17 to 1.58; I^2 = 0%).

Overall, Cordyceps preparations significantly decreased SCr levels (Analysis 1.2 (15 studies, 1047 participants): MD -53.50 μmol/L, 95% CI -84.17 to -22.83; I^2 = 93%) in people with CKD. This was seen in both patients not on dialysis (Analysis 1.2.2 and Analysis 1.2.3 (14 studies, 987 participants): MD -60.76 μmol/L, 95% CI -85.82 to -35.71; I^2 = 82%) and in one study by Sun 1999 in patients on dialysis (Analysis 1.2.1 (1 study, 60 participants): MD -32.88 μmol, 95% CI -44.23 to -21.53). Differences in participants' CKD stages may explain some heterogeneity in treatment effects on SCr levels. Pooled SCr results also indicated greater effects in studies assessed at high risk of bias for this outcome (Analysis 1.2.3 (3 studies, 273 participants): MD -118.77 μmol, 95% CI -148.81 to -88.74). There were some differences in the pooled result for SCr between the fixed-effect model (MD -39.27 μmol, 95% CI -48.13 to -30.40) and random-effects model. There was no apparent publication bias (Figure 4).

Figure 4. Funnel plot of comparison: 1 Cordyceps + conventional treatment versus conventional treatment, outcome: 1.2 SCr



CrCl was significantly increased in participants who received Cordyceps preparations (Analysis 1.3 (6 studies, 362 participants): MD 9.22 mL/min, 95% CI 3.10 to 15.34; I^2 = 81%). A study in patients with hypertensive nephrology (Fu 2009), whose kidney function was better than participants in other studies, contributes all of the heterogeneity in this analysis. Removing this study from the analysis did not change the significance of the results (MD 6.16 mL/min, 95% CI 3.78 to 8.54). Chen 2006a, judged to be at high risk of bias for this outcome, also showed a significant increase in CrCl in patients receiving Cordyceps (Analysis 1.3.2 (1 study, 67 participants): MD 5.09 mL/min, 95% CI 0.56 to 9.62), but did not affect the significance of the result when removed (MD 6.57 mL/min, 95% CI 3.77 to 9.37).

Proteinuria

Cordyceps preparations significantly reduced 24 hour proteinuria (Analysis 1.4 (4 studies, 211 participants): MD -0.15 g/24 h, 95% CI -0.24 to -0.05; I^2 = 9%).

Blood pressure

In a study that considered treatment for people with hypertension nephrology (Fu 2009), no significant effects observed in reducing systolic or diastolic blood pressure in relation to Cordyceps (Analysis 1.5 (systolic, 1 study, 75 participants): -1.40 mm Hg, 95% CI -5.90 to 3.10); (Analysis 1.6 (diastolic, 1 study, 75 participants): 0.80 mm Hg, 95% CI -3.19 to 4.79).

Anaemia

Cordyceps significantly increased haemoglobin levels in people with CKD regardless of their haemodialysis status (Analysis 1.7 (5 studies, 283 participants): MD 10.40 g/L, 95% CI 6.22, 14.58: I^2 = 81%). The pooled results of three studies of non-dialysis patients indicated improvement in anaemia (Analysis 1.7.2 (3 studies, 173 participants): MD 8.20 g/L, 95% CI 2.39 to 14.01; I^2 = 79%). Wei 2004 reported that Cordyceps significantly increased haematocrit levels (Analysis 1.8 (1 study, 60 participants): MD 3.49%, 95% CI 1.42 to 5.56).

Nutritional status (albumin, cholesterol)

Serum albumin levels were increased among Cordyceps recipients (Analysis 1.9 (4 studies, 323 participants): MD 3.52 g/L, 95% CI 2.79 to 4.24; I^2 = 0%), but there was no significant improvement in total cholesterol (Analysis 1.10 (2 studies, 198 participants): MD 0.41 mmol/L, 95% CI 0 to 0.82; I^2 = 0%).

Bone disease (calcium, phosphorus)

Liu 2006a reported a significant increase in serum calcium (Analysis 1.11 (1 study, 66 participants): MD 0.15 mmol/L, 95% CI 0.04 to 0.26) and a significant decrease serum phosphorus (Analysis 1.12 (1 study, 66 participants): MD -0.11 mmol/L, 95% CI -0.18 to -0.04) among Cordyceps recipients.

Cordyceps + conventional medicine versus Western medicine + conventional medicine

Three studies compared Cordyceps preparations with Western medicine interventions. In consideration of the differing Western medicines used the results have not been pooled.

In a comparison of prednisone and Cordyceps for treatment of aristolochic acid nephropathy, Gao 2007 (27 participants) reported Cordyceps significantly reduced SCr (Analysis 2.2: MD -116.07 μmol/L, 95% CI -209.13 to -23.01) and significantly increased CrCl (Analysis 2.3: MD 8.07 mL/min, 95% CI 5.22 to 10.92).

In comparison to coated aldehyde oxystarch, Jin 2004 (82 participants) reported Cordyceps significantly reduced SCr (Analysis 2.2: MD -41.72 μmol/L, 95% CI -77.99 to -5.45); and increased CrCl (Analysis 2.3: MD 7.25 mL/min, 95% CI 2.29 to 12.21), haemoglobin (Analysis 2.5: MD 21.3 g/L, 95% CI 14.2 to 28.4), haematocrit (Analysis 2.6: MD 3.6%, 95% CI 1.56 to 5.64), and albumin (Analysis 2.7: MD 4.35 g/L, 95% CI 2.89 to 5.81).

Huang 2008 (86 participants) reported no significant differences between Lipo PGE1 and Cordyceps preparation on CKD progression (Analysis 2.1: RR 0.92, 95% CI 0.76 to 1.12), SCr (Analysis 2.2: MD 25.14 µmol/L, 95% CI -38.55 to 88.83), CrCl (Analysis 2.3: MD 1.61 mL/min 95% CI -3.64 to 0.42) or 24 hour proteinuria (Analysis 2.4: MD 0.31 g/24 h, 95% CI -0.06 to 0.68) in CKD patients.

Cordyceps + traditional Chinese medicine versus traditional Chinese medicine alone

Yan 2005a (65 participants) reported no significant differences when Cordyceps was administered as a co-intervention with traditional Chinese herbal medicine for the treatment of CKD for SCr (Analysis 3.1: MD -24.00 µmol/L, 95% CI -49.91 to 1.91), but significantly reduced 24 hour proteinuria (Analysis 3.2: MD -0.59 g/24 h, 95% CI -0.99 to -0.19) and significantly increased haemoglobin levels (Analysis 3.3: MD 24.00 g/L, 95% CI 16.62 to 31.38).

Adverse effects

Four studies reported that no obvious adverse effects were associated with Cordyceps preparations (Chen 2006a; Fu 2009; Sun 1999; Yan 2005a).

Hu 2008 (30 participants) reported that test results for blood chemistry, liver function, cardiographic studies and electrolytes were normal after administration of Jin Shui Bao capsule (Cordyceps 0.33 g) over two months.

Liu 2006a (66 participants) reported that two intervention arm participants (5.9%) had diarrhoea and six (17.6%) experienced constipation; three control arm participants (9.3%) developed nausea, three (9.3%) had abdominal distention, and six (18.8%) became constipated.

Huang 2008 (86 participants) reported that four (4.7%) of 86 participants experienced discomfort after taking Jin Shui Bao capsule. Symptoms were minimised when the capsule was taken after eating.

The remaining 15 included studies did not report adverse events. Therefore definitive associations between adverse effects and Cordyceps could not be derived with certainty.

Other outcomes

Several outcomes were not reported in the included studies.

- Time to requirement for RRT or initiation of dialysis (primary outcome)
- All-cause mortality (primary outcome)
- Quality of life measured by a validated scale (secondary outcome)
- Symptoms including skin pruritus, vomiting, measured by visual analogue or other scales (secondary outcome).

DISCUSSION

Summary of main results

This review included 22 studies that involved 1746 participants with CKD; all studies were undertaken in hospitals in China. Different stages of CKD were represented in the studies; baseline SCr ranged from 135 to 820 µmol/L. All studies investigated mycelial fermentation products of *Cordyceps sinensis*.

Cordyceps was administered as a co-intervention in all studies: 18/22 studies compared Cordyceps plus conventional treatment with the same conventional treatment, and of these three administered haemodialysis as the co-intervention. Three studies compared Cordyceps plus conventional treatment with Western medicine plus the same conventional treatment; and one study compared Cordyceps plus traditional Chinese medicine to the same traditional Chinese medicine.

As an adjunctive treatment to conventional medicine, Cordyceps preparation had promising effects on decreasing SCr, increasing

CrCl, reducing proteinuria and alleviating CKD-associated complications such as reduced haemoglobin and serum albumin levels. However, low methodological quality and under-reporting among the included studies meant that definitive conclusions could not be made about the possible effects of Cordyceps preparation for people with CKD.

Overall completeness and applicability of evidence

Although we intended to explore potential benefits of Cordyceps for people with CKD on aspects including CKD progression and complications, none of the included studies reported outcome data on time to requirement for RRT or initiation of dialysis, or all-cause mortality. Data on the effects of Cordyceps preparations on SCr and CrCl were reported. It is noteworthy that CrCl tends to overestimate GFR (Shemesh 1985). Lack of GFR data meant that it was difficult to clearly define degree of kidney function damage and the CKD stage.

Because all included studies were undertaken in China questions about applicability of the evidence to other settings exist. Co-interventions explored in the included studies for CKD management in China are likely to differ from other settings. It is uncertain if this aspect influenced assessment of the effects and safety of Cordyceps for people with CKD.

Quality of the evidence

Evidence quality of included studies in the review was suboptimal. Risk of bias was assessed as high in four and unclear in 18/22 included studies. Methodological flaws related to lack of clear descriptions of randomisation, allocation concealment, and binding. There was marked heterogeneity in the conventional treatment as co-interventions in some included studies. Because of no masking during the study, the possible difference in the multiple co-interventions between treatment and control group would likely introduce bias to the results.

Potential biases in the review process

Four studies were excluded from our quantitative analysis because of the absence of some essential data. However, we believe that exclusion of these studies did not bias review results because they represented similar study populations and results to the body of included studies.

Agreements and disagreements with other studies or reviews

In an earlier review that included six studies, statistically significant treatment effects were reported for Cordyceps compared with control (Xu 2006). Because information about control interventions and definitions of outcome measures were not clearly stated in Xu 2006, we did not compare our results with findings from this review.

AUTHORS' CONCLUSIONS

Implications for practice

The current evidence indicated that when used with conventional treatment, Cordyceps may offer some benefits for people with CKD by improving kidney function and alleviating complications such as anaemia and malnutrition. However, methodological quality was suboptimal, and further clinical studies are required to ascertain the potential benefits of Cordyceps for people with CKD.

Implications for research

Based on the methodological deficits identified in the available studies, we suggest that future clinical studies investigating Cordyceps for people with CKD consider the following:

1. Randomisation and allocation concealment methodology need to be undertaken and clearly reported.

2. Efforts should be made to develop placebo controls that mimic Cordyceps products to clarify its efficacy for CKD. Blinding intervention assignment to participants, clinicians and outcomes assessors needs to be undertaken and reported. In settings where it is not possible or feasible to blind participants and clinicians, outcomes assessors should be blinded, especially when subjective outcomes are involved.

3. Sample sizes should be calculated to ensure that studies have sufficient power to detect possible differences between groups.

4. Incorporating long-term outcome measures, such as need for RRT, all-cause mortality, or quality of life measures may help to confirm beneficial outcomes associated with Cordyceps for CKD.

5. Record and report all in-study adverse effects.

The elaborated CONSORT statement for reporting RCTs of herbal medicines is strongly recommended when designing and reporting clinical studies (Gagnier 2006).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chen 2003

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: Hospital • CKD patients; SCr < 442 μmol/L ○ Baseline mean SCr (μmol/L): treatment group (252.4); control group (249.72) • Number: treatment group (164); control group (48) • Mean age: 42.57 years • Sex (M/F): 130/82 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 6 capsules, 3 times/d
	  ○ Treatment duration: 2 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• High quality, low phosphate, calorie, and protein diet
	• Symptomatic treatment, including maintaining water, electrolyte and acid-base balance, controlling BP, anticoagulation treatment and infection control as needed

Outcomes	• SCr • 24 h proteinuria • Hb • Albumin
Notes	• Further information about allocation methodology was requested from the author, but no response was received at the time of drafting this review

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation claimed, but there were 164 participants in treatment group and 48 in the control group
Allocation concealment (selection bias)	High risk	Not reported

Chen 2003 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	High risk	Imbalance in the patient numbers in the treatment and control group

Chen 2006a

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients; SCr 178 to 707 μmol/L ○ Baseline mean SCr (μmol/L): treatment group (371.85); control group (389.84) • Number: treatment group (36); control group (31) • Mean age (range): 63.87 years (29 to 83) • Sex (M/F): 32/35 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 6 capsules, 3 times/d
	  ○ Treatment duration: 1 month
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Treatment of primary disease
	• High quality, low salt, lipid and protein diet
	• Symptomatic treatment, including maintaining water, electrolyte and acid-base balance, BP and infection control, anaemia resolution as needed
	• Oral medicinal charcoal: 5 tablets, 3 times/d

Outcomes	• CKD progression • SCr • CrCl
Notes	• No drop-outs or withdrawals

Risk of bias		***Risk of bias***

Chen 2006a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation methodology not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures reported
Other bias	High risk	Imbalance in participant numbers in treatment and control groups

Fu 2009

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • Diagnosis of hypertension nephrology • Number: treatment group (35); control group (30) • Mean age (range): 52.78 years (29 to 64) • Sex (M/F): 39/26 • Exclusion criteria: primary glomerular diseases; diabetes mellitus; other causes of kidney injury

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 3 capsules, 3 times/d
	  ○ Treatment duration: 3 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Oral captopril and nifedipine controlled release tablet
	• Oral hydrochlorothiazide or metoprolol tartrate tablets were administered to obtain target BP as needed

Outcomes	• SCr • CrCl • 24 h proteinuria

Fu 2009 (*Continued*)

	• BP
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation methodology not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analyses
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Gao 2007

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • History of taking Chinese medicines containing aristolochic acid; normal or slightly abnormal routine urine test; increased nocturnal urine volume, high BP, kidney function impairment that could not be explained by primary disease, or acellular interstitial fibrosis confirmed by kidney puncture biopsy; SCr ranging from 133 to 707 μmol/L • Number: treatment group (15); control group (12) • Mean age (range): 49.86 years (31 to 65) • Sex (M/F): 11/16 • Exclusion criteria: CKD caused by other primary or secondary diseases; noncompliance with dietary and treatment interventions; ESKD; cancer or other severe disease; peritoneal dialysis and haemodialysis
Interventions	Treatment group • Cordyceps ○ Oral Bai Ling: 2 g capsule, 3 times/d ○ Treatment duration: 6 months • Conventional treatment

Gao 2007 (*Continued*)

	Control group • Oral prednisone: 0.75 mg/d/kg initially, then reduced to 0.5 mg/d/kg after one month • Treatment duration: 6 months • Conventional treatment Conventional treatment • Dietary protein restricted to 0.6 g/kg/d, low salt, low lipid • Control BP • Correct anaemia • Control infection
Outcomes	• SCr • CrCl
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation methodology not reported. Sequencing according to presentation at hospital
Allocation concealment (selection bias)	High risk	Possibly quasi-randomised, based on sequencing at presentation
Blinding (performance bias and detection bias) All outcomes	High risk	Different interventions in two groups; unlikely to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Guo 2009

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients who need dialysis treatment ○ Baseline mean SCr (μmol/L): treatment group (821.7); control group (817.6)

Guo 2009 (*Continued*)

	• Number: treatment group (34); control group (30) • Age range: 16 to 78 years • Sex (M/F): 33/31 • Exclusion criteria: NR
Interventions	Treatment group • Cordyceps ○ Oral Jin Shui Bao: 6 capsules, 3 times/d ○ Treatment duration: 3 months • Haemodialysis • Conventional treatment Control group • Haemodialysis • Conventional treatment Conventional treatment • Low protein and phosphorous diet • BP control • Anaemia correction • Maintain water, electrolyte and acid-base balance
Outcomes	• CKD progression • SCr • Hb
Notes	• Drop-outs/withdrawals: Data from 9 participants in the treatment group and 5 in the control group missing

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Data from 9 and 5 participants respectively in the treatment and control arms not reported
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Hu 2008

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • Patients with CKD ○ Baseline mean SCr (μmol/L): treatment group (303.22): control group (304.88) • Number: treatment group (15); control group (15) • Mean age (range): 31.8 years (8 to 52) • Sex (M/F): 12/18 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 5 capsules, 3 times/d
	  ○ Treatment duration: 2 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• High quality, low protein diet
	• Control BP, blood lipids, and blood glucose
	• Correct water and electrolyte imbalance
	• Treat complications, such as infection

Outcomes	• SCr • 24 h proteinuria
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported

Hu 2008 (*Continued*)

Other bias	Unclear risk	Conventional treatment may differ between arms

Huang 2008

Methods	• Design: parallel quasi-RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (398.76); control group 1 (386.15); control group 2 (390.56) • Number: treatment group (43); control group 1 (43); control group 2 (43) • Age range: 31 to 81 years • Sex (M/F): 90/39 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 6 capsules, 3 times/d
	  ○ Treatment duration: 1 month
	• Conventional treatment
	Control group 1
	• Western medicine
	  ○ IV Lipo PGE1: 10 μg + 0.9% normal saline, 4 times/d
	  ○ Treatment duration: 1 month
	• Conventional treatment
	Control group 2
	• Cordyceps
	  ○ Oral Jin Shui Bao: 6 capsules, 3 times/d
	  ○ Treatment duration: 1 month
	• Western medicine
	  ○ IV Lipo PGE1: 10 μg + 0.9% normal saline, 4 times/d
	  ○ Treatment duration: 1 month
	• Conventional treatment
	Conventional treatment
	• Low protein diet
	• Treatment of primary diseases

Outcomes	• CKD progression • SCr • CrCl • UPE • 24 hour proteinuria
Notes	• No drop-outs or withdrawals

Huang 2008 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Entry sequencing used for allocation to treatment or control arms
Allocation concealment (selection bias)	High risk	Entry sequencing
Blinding (performance bias and detection bias) All outcomes	High risk	Three groups received different interventions; no placebo control
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Jin 2004

Methods	Design: parallel RCT Setting: 2 hospitals in China Power calculation: no
Participants	• Country: China • Setting: 2 hospitals • CKD patients, baseline SCr ranging from 177 to 707 μmol/L or baseline CrCl from 10 to 50 mL/min ○ Mean SCr (μmol/L): treatment group (317.76); control group 1 (318.68); control group 2 (316.78) • Number: treatment group (41); control group 1 (41); control group 2 (41) • Mean age: 50.2 years • Sex (M/F): 64/59 • ESKD (SCr > 707 μmol/L or CrCl < 10 mL/min); AKI

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 6 capsules, 3 times/d
	  ○ Treatment duration: 6 months
	• Conventional treatment
	Control group 1
	• TCM
	  ○ Individualised traditional Chinese herbal medicine orally, twice/d
	  ○ Treatment duration: 6 months
	• Conventional treatment

Jin 2004 (*Continued*)

	Control group 2 • Oral coated aldehyde oxystarch: 5 g, 4 times/d ○ Treatment duration: 6 months • Conventional treatment Conventional treatment • Symptomatic therapy for high BP, high blood glucose, gout or acidosis
Outcomes	• SCr • CrCl • Hb • HCT • Albumin • Total cholesterol
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised block design
Allocation concealment (selection bias)	High risk	The random code may easily be broken in randomised block design
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo was designed for comparisons between different interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Low risk	Some commonly used outcomes for study on CKD were reported. All results in three groups were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Liu 2006a

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (372.6); control group (369.

Liu 2006a (*Continued*)

	4) • Number: treatment group (34); control group (32) • Mean age (range): 42.06 years (24 to 69) • Sex (M/F): 39/27 • Exclusion criteria: NR
Interventions	Treatment group • Cordyceps ○ Oral Bai Ling: 5 capsules, 3 times/d ○ Treatment duration: 2 months • Conventional treatment Control group • Conventional treatment Conventional treatment • Primary disease treatment • High quality, low salt and lipid diet • Symptomatic treatment, including maintaining water, electrolyte and acid-base balance, BP and infection control, treating anaemia as needed • Oral charcoal: 5 tablets, 3 times/d
Outcomes	• CKD progression • SCr • Albumin • Total cholesterol • Calcium • Phosphorous
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported

Liu 2006a (*Continued*)

Other bias	Unclear risk	Conventional treatment may differ between arms

Liu 2007a

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (246.58); control group (248.35) • Number: treatment group (68); control group (64) • Mean age: 56.78 years • Sex (M/F): 42/26 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Bai Ling: 5 capsules,3 times/d
	  ○ Treatment duration: 1.5 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• General and symptomatic treatment
	• Dietary treatment
	• Oral Shen Shuai Ning*: 6 capsules,3 times/d

Outcomes	• Progress of CKD • SCr • Albumin • Total cholesterol
Notes	• No drop-outs or withdrawals • * Shen Shuai Ning capsule is a patent Chinese herbal formula for the treatment of CKD, mainly composed of Taizishen (Radix Pseudoxtellariae), Dahuang (Radix et Rhizoma Rhei), Honghua (Flos Carthami), Danshen (Radix Rhizoma Salviae Miltiorrhizae), Niuxi (Radix Cyathulae), Dongchongxiacao (Cordyceps), and Gancao (Radix et Rhizoma Glycyrrhiza)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported

Liu 2007a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Pan 2007

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (546); control group (561.9) • Number: treatment group (32); control group (32) • Mean age (range): 43.35 years (21 to 75) • Sex (M/F): 39/25 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Bai Ling: 5 capsules, 3 times/d
	  ○ Treatment duration: 2 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Adequate high quality protein diet
	• BP control
	• Maintain water, electrolyte and acid-base balance
	• Oral Niaoduqing granules*
	• Participants with diabetes mellitus received insulin
	• Participants with anaemia received erythropoietin 2000 U SC injection 2 to 3/wk, Shengxuening** tablet 0.5 g, and folic acid 10 mg, 3/d

Outcomes	• CKD progression • SCr • CrCl

Pan 2007 (*Continued*)

Notes	• No drop-outs or withdrawals • * Oral Niaoduqing granules* (a patent Chinese herbal formula for the treatment of uraemia, mainly composed of Huangqi (Radix Astragali), Dangshen (Radix Codonopsis), Heshouwu (Radix Polygoni Multiflori), Dahuang (Radix et Rhizoma Rhei), Baizhu (Rhizoma Atractylodis Macrocephalae), Fuling (Poria), Cheqiancao (Hegba Plantaginis Asiaticae), Banxia (Rhizoma Pinelliae Ternatae), Chuanxiong (Rhizoma Chuanxiong) and Danshen (Radix Rhizoma Salviae Miltiorrhizae) • ** Shengxuening tablet is extract of Cansha (Feculae Bombycis)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Shi 2009

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • Patients with 24 h proteinuria 0.8 to 3 g • Number: treatment group (32); control group (28) • Mean age (range): 40.93 years (19 to 76) • Sex (M/F): 36/24 • Exclusion criteria: Henoch-Schonlein purpura nephritis, lupus nephritis, or hepatitis B virus associated-glomerulonephritis; secondary glomerular diseases, such as diabetic retinopathy
Interventions	Treatment group • Cordyceps ○ Oral Bai Ling: 1 g capsule, 3 times/d

Shi 2009 (*Continued*)

	○ Treatment duration: 6 months • Conventional treatment Control group • Conventional treatment Conventional treatment • High quality low protein, low salt diet • Individualised symptomatic treatment, e.g. antihypertensives • Control infection control, diuretics, calcium or Vitamin D as needed • Valsartan 160 mg/d
Outcomes	• 24 h proteinuria
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Sun 1999

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients requiring dialysis ○ Baseline mean SCr (μmol/L): treatment group (876.60); control group (843.63) • Number: treatment group (30); control group (30) • Age range: 21 to 76 years • Sex (M/F): 36/24

Sun 1999 (*Continued*)

	• Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 4 capsules, 3 times/d
	  ○ Treatment duration: 3 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Haemodialysis
	• Conventional symptomatic treatment

Outcomes	• SCr • Hb
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment not clearly stated

Wang 2005a

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients; SCr 178 to 442 μmol/L; 24 h proteinuria < 3 g/L; SCr value constant in past 3 months • Number: treatment group (30); control group (30)

Wang 2005a (*Continued*)

	• Mean age: 41 years • Sex (M/F): 27/33 • Exclusion criteria: 24 h proteinuria > 3 g/L; serum albumin < 25 g/L; SCr > 442 μmol/L; malignant hypertension, severe heart, lung, liver or brain disease; severe haematopoietic disease; psychosis
Interventions	Treatment group • Cordyceps ○ Oral Jin Shui Bao: 3 capsules, 3 times/d ○ Treatment duration: 2 months • Conventional treatment Control group • Conventional treatment Conventional treatment • Low salt and phosphorus, high quality protein diet • BP control • Maintenance of water, electrolyte and acid-base balance • Oral coated aldehyde oxystarch:12 capsules
Outcomes	• CKD progression • SCr • CrCl • Hb
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Wei 2004

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (250.36); control group (252.52) • Number: treatment group (30); control group (30) • Mean age (range): 45.5 years (39 to 70) • Sex (M/F): 28/32 • Exclusion criteria: ESKD; severe complicated primary diseases including heart, brain, liver and hematopoietic system diseases; psychoses

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Bai Ling: 8 capsules, 3 times/d
	  ○ Treatment duration: 2 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Low protein diet
	• BP control
	• Acidosis correction

Outcomes	• SCr • CrCl • Albumin • Hb • HCT
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table used
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis

Wei 2004 (*Continued*)

Selective reporting (reporting bias)	Low risk	Some commonly used outcomes for studying CKD were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Wu 2007

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (542.04); control group (429.35) • Number: treatment group (24); control group (22) • Mean age (range): 47.60 years (34 to 69) • Sex (M/F): 24/22 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 6 capsules, 3 times/d
	  ○ Treatment duration: 1 month
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Baseline treatment, including low salt and phosphorus, high quality protein diet

Outcomes	• CKD progression • SCr • CrCl
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Wu 2007 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Xu 2004

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients requiring dialysis ○ Baseline mean SCr (μmol/L): treatment group (742); control group (725) • Number: treatment group (42); control group (40) • Mean age (range): 41.8 years (17 to 75) • Sex (M/F): 52/30 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Bai Ling: 5 capsules, 3 times/d
	  ○ Treatment duration: 2 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Low protein, high calorie, and adequate vitamin diet
	• BP control
	• Maintain water, electrolyte and acid-base balance
	• Oral coated aldehyde oxystarch: 8 to 10 tablets, 3 times/d
	• IM Testosterone propionate: 25 mg, once every 2 days
	• 20 and 18 participants respectively in the treatment and control arms received erythropoietin 2000 U SC injection 2 to 3 times/wk and were administered oral ferrous succinate 0.2 g and folic acid 10 mg, 3 times/d

Outcomes	• SCr
Notes	• No drop-outs or withdrawals

Risk of bias		***Risk of bias***

Xu 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Yan 2005a

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (135); control group (131) • Number: treatment group (33); control group (32) • Mean age (range): 48.27 years (34 to 69) • Sex (M/F): 33/32 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 4 capsules, 3 times/d
	  ○ Treatment duration: 6 months
	• TCM treatment
	Control group
	• TCM treatment
	TCM treatment
	• Traditional Chinese herbal medicine for CKD

Outcomes	• SCr • Hb • 24 h proteinuria
Notes	• No drop-outs or withdrawals

Yan 2005a (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures reported
Other bias	Unclear risk	TCM treatments may differ between arms

Yang 1999b

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (478.5); control group (456.7) • Number: treatment group (29); control group (24) • Mean age (range): 38.2 years (18.7 to 57.7) • Sex (M/F): 29/24 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Jin Shui Bao: 2 capsules, 3 times/d
	  ○ Treatment duration: 3 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment
	• Conventional symptomatic treatment, such as captopril and furosemide

Outcomes	• SCr • Hb

Yang 1999b (*Continued*)

Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment differed between arms

Yu 2002

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • Participants with uraemia at haemodialysis commencement ○ Baseline mean SCr (μmol/L): treatment group (810.34); control group (793.57) • Number: treatment group (35); control group (30) • Age: NR • Sex (M/F): 36/29 • Exclusion criteria: diseases that may cause malnutrition, such as chronic nephritis, diabetic nephropathy, hypertensive kidney disease, gout nephropathy and polycystic kidney disease

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Bai Ling: 5 capsules, 3 times/d
	  ○ Treatment duration: 6 months
	• Conventional haemodialysis with sodium bicarbonate dialysate
	Control group
	• Conventional haemodialysis with sodium bicarbonate dialysate

Yu 2002 (*Continued*)

Outcomes	• Albumin
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

Yu 2003

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting: hospital • CKD patients ○ Baseline mean SCr (μmol/L): treatment group (451.16); control group (475.25) • Number: treatment group (78); control group (82) • Mean age (range): 46.5 years (30 to 68) • Sex (M/F): 100/60 • Exclusion criteria: NR

Interventions	Treatment group
	• Cordyceps
	  ○ Oral Bai Ling: 5 capsules, 3 times/d
	  ○ Treatment duration: 3 months
	• Conventional treatment
	Control group
	• Conventional treatment
	Conventional treatment

Yu 2003 (*Continued*)

	• Low protein and phosphorus diet • Close observation on the BP and keep it in the normal range • Maintain water, electrolyte and acid-base balance
Outcomes	• CKD progression • SCr
Notes	• Data from 4 control arm participants were not reported

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data from 4 control arm participants were not reported; no reason for data omission provided
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment administered not identical in both arms

Zhang 2009

Methods	• Design: parallel RCT • Power calculation: no
Participants	• Country: China • Setting 2 hospitals • CKD patients with a history of taking medicine containing aristolochic acid; no history of taking other related medicine; normal or slightly abnormal urine routine test; anaemia not related to kidney dysfunction; acellular interstitial fibrosis; no other related diseases • Number: treatment group (28); control group (28) • Mean age: 64.2 years • Sex (M/F): 26/30 • Exclusion criteria: CKD caused by other primary or secondary diseases; non compliance with dietary and treatment interventions; ESKD; cancer or other severe disease; peritoneal dialysis or haemodialysis patients

Zhang 2009 (*Continued*)

Interventions	Treatment group • Cordyceps ○ Oral Jin Shui Bao: 1.98 g capsule, 3 times/d ○ Treatment duration: 6 months • Conventional treatment Control group • Conventional treatment Conventional treatment • Oral prednisone 1 mg/d/kg for one month, reduced by 0.1 mg/kg/d every two months, then maintained at 0.15 mg/d/kg for the study duration • High quality, low protein (0.6 g/d/kg) diet • BP control • Erythropoietin 3000 U SC, 3 times/wk for anaemia
Outcomes	• SCr • 24 h proteinuria
Notes	• No drop-outs or withdrawals

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo control and no description of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. All participants included in the analysis
Selective reporting (reporting bias)	Unclear risk	Limited outcome measures were reported
Other bias	Unclear risk	Conventional treatment may differ between arms

AKD - acute kidney injury; BP - blood pressure; CKD - chronic kidney disease; CrCl - creatinine clearance; ESKD - end-stage kidney disease; Hb - haemoglobin; HCT - haematocrit; NR - not reported; SCr - serum creatinine; TCM - traditional Chinese medicine; UPE - urinary protein electrophoresis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bao 1994	Information about the duration of aminoglycoside nephrotoxicity was not available
Huang 2008b	Ginkgo leaf tablet was used with Cordyceps preparation in the treatment group
Jiang 2008	Did not include outcomes relevant to the review
Li 1992	Wrong population: participants had respiratory infection or febrile diseases, normal kidney function, and absence of history of kidney disease
Quan 2004	Follow up periods differed for individual participants
Wu 2005	Participant allocation was not randomised
Xu 2009	Did not include outcomes relevant to the review
Yan 2005b	Participant allocation was not randomised
Yan 2007	The wording and data were similar to those in Liu 2007a to some degree, possibly duplicate report
Yang 2001	Did not include outcomes relevant to the review
Yin 2001	Did not include outcomes relevant to the review
Zhou 2002	Did not include outcomes relevant to the review

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chai 2009

Methods	• RCT
Participants	• CKD patients
Interventions	• Cordyceps + conventional treatment versus conventional treatment
Outcomes	• SCr • CrCl • ECT 20 minER
Notes	• Request was made to the authors to elicit information about the treatment information of Cordyceps and control group. No response received at the time of drafting the review.

Jin 2006

Methods	• RCT
Participants	• CKD patients
Interventions	• Chinese herb + conventional treatment versus Cordyceps + conventional medicine versus Western medicine + conventional treatment
Outcomes	• SCr • CrCl • Hb • Albumin • Total cholesterol • HCT
Notes	• Information on the evaluated number was not provided although mortality was reported. Additional information was not available upon written correspondence at the time of drafting the review

Lin 2003

Methods	• RCT
Participants	• CKD patients
Interventions	• Cordyceps + conventional treatment versus Western medicine + conventional treatment
Outcomes	• SCr • Hb
Notes	• Request was made to the authors to elicit information about numbers of participants recruited which was not available from the published report. No response received at the time of drafting the review

CKD - chronic kidney disease; CrCl - creatinine clearance; Hb - haemoglobin; HCT - haematocrit; RCT - randomised controlled trial; SCr - serum creatinine

DATA AND ANALYSES

Comparison 1. Cordyceps + conventional treatment versus conventional treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CKD progression (%)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Unclear risk of bias subgroup	6	418	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.99, 1.21]
1.2 High risk of bias subgroup	2	227	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.17, 1.58]
2 Serum creatinine	15	1047	Mean Difference (IV, Random, 95% CI)	-53.50 [-84.17, -22.83]
2.1 Dialysis	1	60	Mean Difference (IV, Random, 95% CI)	32.88 [21.53, 44.23]
2.2 Non-dialysis (unclear risk of bias)	11	714	Mean Difference (IV, Random, 95% CI)	-44.43 [-69.04, -19.83]
2.3 Non-dialysis (high risk of bias group)	3	273	Mean Difference (IV, Random, 95% CI)	-118.77 [-148.81, -88.74]
3 Creatinine clearance	6	362	Mean Difference (IV, Random, 95% CI)	9.22 [3.10, 15.34]
3.1 Unclear risk of bias subgroup	5	295	Mean Difference (IV, Random, 95% CI)	10.78 [2.54, 19.02]
3.2 High risk of bias subgroup	1	67	Mean Difference (IV, Random, 95% CI)	5.09 [0.56, 9.62]
4 Proteinuria	4	211	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.24, -0.05]
5 Systolic BP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Diastolic BP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Haemoglobin	5	283	Mean Difference (IV, Random, 95% CI)	10.40 [6.22, 14.58]
7.1 Dialysis	1	60	Mean Difference (IV, Random, 95% CI)	19.0 [14.44, 23.56]
7.2 Non-dialysis (unclear risk of bias)	3	173	Mean Difference (IV, Random, 95% CI)	8.20 [2.39, 14.01]
7.3 Non-dialysis (high risk of bias)	1	50	Mean Difference (IV, Random, 95% CI)	7.70 [2.61, 12.79]
8 Haematocrit	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Serum albumin	4	323	Mean Difference (IV, Random, 95% CI)	3.52 [2.79, 4.24]
9.1 Dialysis	1	65	Mean Difference (IV, Random, 95% CI)	3.08 [1.44, 4.72]
9.2 Non-dialysis	3	258	Mean Difference (IV, Random, 95% CI)	3.62 [2.81, 4.43]
10 Total cholesterol	2	198	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.82, 0.00]
11 Calcium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Phosphorus	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 2. Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CKD progression (%)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Serum creatinine	3	195	Mean Difference (IV, Random, 95% CI)	-37.49 [-101.43, 26.44]
3 Creatinine clearance	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Haematocrit	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Serum albumin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Total cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 3. Cordyceps + TCM versus TCM

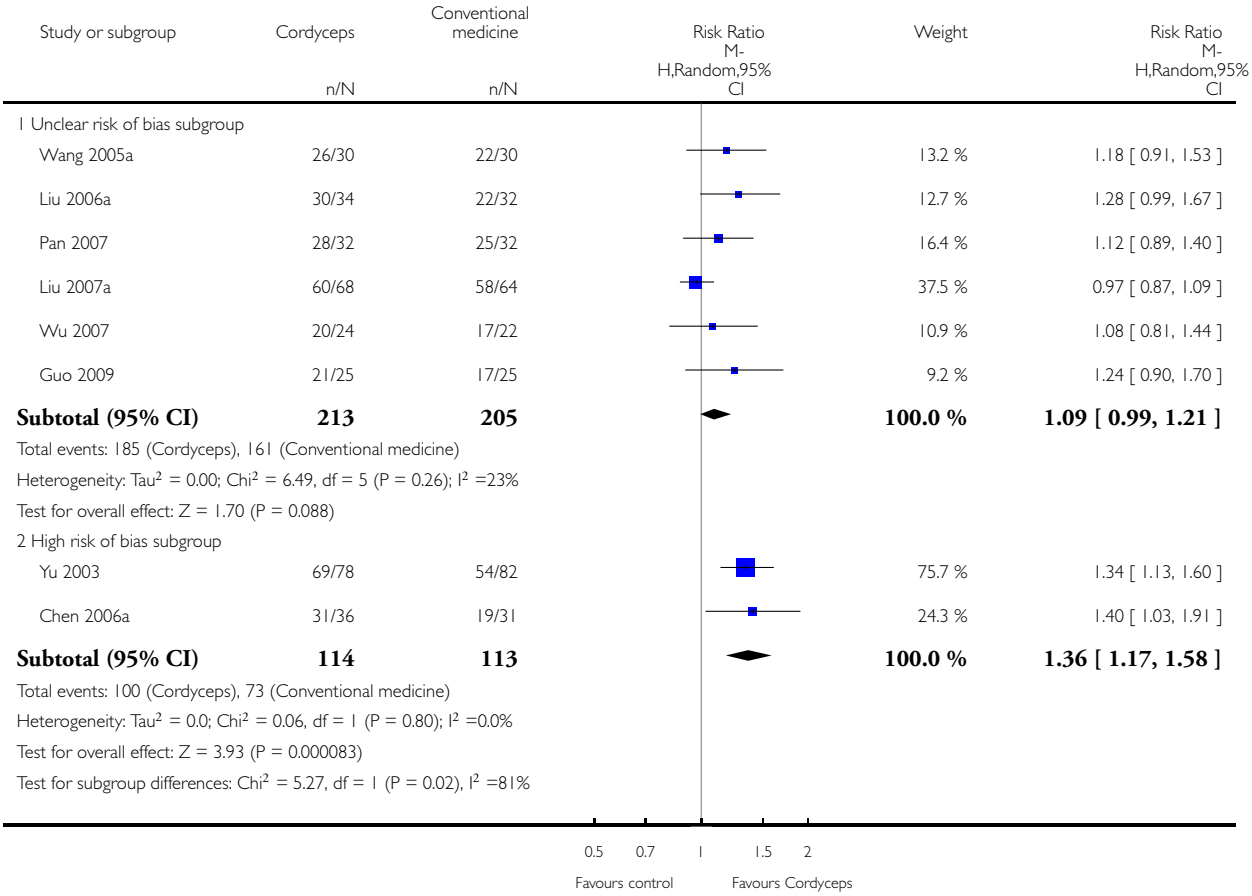
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Proteinuria	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 1 CKD progression (%).

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 1 CKD progression (%)



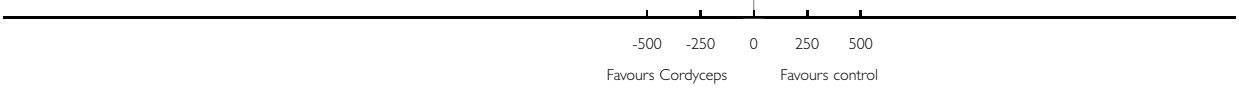
Analysis 1.2. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 2 Serum creatinine.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 2 Serum creatinine

Study or subgroup	Cordyceps N	Cordyceps Mean(SD)[mol/L]	Conventional medicine N	Conventional medicine Mean(SD)[mol/L]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Dialysis							
Sun 1999	30	397.13 (26.53)	30	364.25 (17.39)		9.0 %	32.88 [21.53, 44.23]
Subtotal (95% CI)	**30**		**30**			**9.0 %**	**32.88 [21.53, 44.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.68 (P < 0.00001)							
2 Non-dialysis (unclear risk of bias)							
Yang 1999b	29	351.7 (137.3)	24	376.9 (159.4)		5.6 %	-25.20 [-106.22, 55.82]
Wei 2004	30	180.02 (125.36)	30	248.38 (141.01)		6.3 %	-68.36 [-135.88, -0.84]
Xu 2004	42	608.3 (402.1)	40	735.8 (498.3)		1.9 %	-127.50 [-324.06, 69.06]
Wang 2005a	30	201.08 (38.99)	30	285.11 (44.21)		8.7 %	-84.03 [-105.12, -62.94]
Liu 2006a	34	268.7 (103.6)	32	345.2 (109.5)		7.3 %	-76.50 [-128.00, -25.00]
Pan 2007	32	408.2 (238.1)	32	508.7 (251.4)		3.8 %	-100.50 [-220.47, 19.47]
Wu 2007	24	419.67 (241.21)	22	401.43 (158.77)		3.9 %	18.24 [-98.87, 135.35]
Liu 2007a	68	200.36 (95.78)	64	203.45 (96.43)		8.3 %	-3.09 [-35.90, 29.72]
Hu 2008	15	254.65 (78.32)	15	306.84 (84.22)		6.9 %	-52.19 [-110.39, 6.01]
Zhang 2009	28	198.62 (33.03)	28	204.59 (30.4)		8.9 %	-5.97 [-22.60, 10.66]
Fu 2009	35	95.2 (29.5)	30	140.6 (30.1)		8.9 %	-45.40 [-59.94, -30.86]
Subtotal (95% CI)	**367**		**347**			**70.4 %**	**-44.43 [-69.04, -19.83]**
Heterogeneity: Tau^2 = 929.54; Chi^2 = 43.79, df = 10 (P<0.00001); I^2 =77%							
Test for overall effect: Z = 3.54 (P = 0.00040)							
3 Non-dialysis (high risk of bias group)							
Yu 2003	78	321.15 (98.06)	78	455.32 (154.15)		7.9 %	-134.17 [-174.71, -93.63]
Chen 2006a	36	290.68 (90.37)	31	379.85 (126.79)		7.1 %	-89.17 [-142.68, -35.66]
Guo 2009	25	614.4 (109.7)	25	739.6 (176.2)		5.6 %	-125.20 [-206.56, -43.84]
Subtotal (95% CI)	**139**		**134**			**20.6 %**	**-118.77 [-148.81, -88.74]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.75, df = 2 (P = 0.42); I^2 =0.0%							
Test for overall effect: Z = 7.75 (P < 0.00001)							



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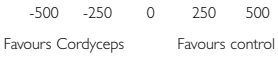
Study or subgroup	Cordyceps		Conventional medicine		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[mol/L]	N	Mean(SD)[mol/L]	IV,Random,95% CI		IV,Random,95% CI
Total (95% CI)	**536**		**511**			**100.0 %**	**-53.50 [-84.17, -22.83]**
Heterogeneity: Tau² = 2687.10; Chi² = 188.06, df = 14 (P<0.00001); I² =93%							
Test for overall effect: Z = 3.42 (P = 0.00063)							
Test for subgroup differences: Chi² = 103.92, df = 2 (P = 0.00), I² =98%							



Analysis 1.3. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 3 Creatinine clearance.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 3 Creatinine clearance

Study or subgroup	Cordyceps		Conventional medicine		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[mL/min]	N	Mean(SD)[mL/min]	IV,Random,95% CI		IV,Random,95% CI
1 Unclear risk of bias subgroup							
Fu 2009	35	90.4 (26.4)	30	50 (28.6)		10.9 %	40.40 [26.94, 53.86]
Pan 2007	32	31.26 (7.5)	32	23.51 (7.3)		21.5 %	7.75 [4.12, 11.38]
Wang 2005a	30	32.18 (16.94)	30	30.18 (18.94)		15.4 %	2.00 [-7.09, 11.09]
Wei 2004	30	34 (12.37)	30	28.25 (9.27)		19.5 %	5.75 [0.22, 11.28]
Wu 2007	24	18.52 (15.94)	22	13.12 (25.12)		12.0 %	5.40 [-6.88, 17.68]
Subtotal (95% CI)	**151**		**144**			**79.4 %**	**10.78 [2.54, 19.02]**
Heterogeneity: Tau² = 67.70; Chi² = 24.75, df = 4 (P = 0.00006); I² =84%							
Test for overall effect: Z = 2.56 (P = 0.010)							
2 High risk of bias subgroup							
Chen 2006a	36	21.24 (10.03)	31	16.15 (8.89)		20.6 %	5.09 [0.56, 9.62]
Subtotal (95% CI)	**36**		**31**			**20.6 %**	**5.09 [0.56, 9.62]**
Heterogeneity: not applicable							

(*Continued* . . .)

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Study or subgroup	Cordyceps N	Mean(SD)[mL/min]	Conventional medicine N	Mean(SD)[mL/min]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 2.20 (P = 0.028)							
Total (95% CI)	**187**		**175**			**100.0 %**	**9.22 [3.10, 15.34]**
Heterogeneity: Tau² = 41.92; Chi² = 25.89, df = 5 (P = 0.00009); I² =81%							
Test for overall effect: Z = 2.95 (P = 0.0032)							
Test for subgroup differences: Chi² = 1.41, df = 1 (P = 0.24), I² =29%							

Analysis 1.4. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 4 Proteinuria.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 4 Proteinuria

Study or subgroup	Cordyceps N	Mean(SD)[g/24 h]	Conventional medicine N	Mean(SD)[g/24 h]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Fu 2009	35	0.4256 (0.0028)	30	0.56 (0.1908)		80.5 %	-0.13 [-0.20, -0.07]
Hu 2008	15	1.84 (0.77)	15	2.04 (0.9)		2.5 %	-0.20 [-0.80, 0.40]
Shi 2009	32	1.1 (0.8)	28	1.6 (0.8)		5.3 %	-0.50 [-0.91, -0.09]
Zhang 2009	28	1.52 (0.54)	28	1.6 (0.47)		11.8 %	-0.08 [-0.35, 0.19]
Total (95% CI)	**110**		**101**			**100.0 %**	**-0.15 [-0.24, -0.05]**
Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 3 (P = 0.35); I² =9%							
Test for overall effect: Z = 3.07 (P = 0.0021)							
Test for subgroup differences: Not applicable							

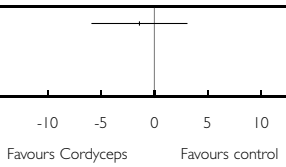
Analysis 1.5. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 5 Systolic BP.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 5 Systolic BP

Study or subgroup	Cordyceps N	Mean(SD)[mm Hg]	Conventional medicine N	Mean(SD)[mm Hg]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fu 2009	35	128.3 (9.9)	30	129.7 (8.6)		-1.40 [-5.90, 3.10]



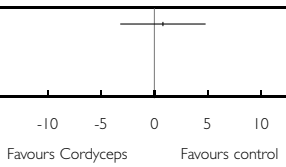
Analysis 1.6. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 6 Diastolic BP.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 6 Diastolic BP

Study or subgroup	Cordyceps N	Mean(SD)[mm Hg]	Conventional medicine N	Mean(SD)[mm Hg]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fu 2009	35	78.2 (8.5)	30	77.4 (7.9)		0.80 [-3.19, 4.79]



Analysis 1.7. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 7 Haemoglobin.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 7 Haemoglobin

Study or subgroup	Cordyceps N	Mean(SD)[g/L]	Conventional medicine N	Mean(SD)[g/L]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Dialysis							
Sun 1999	30	97.8 (9.2)	30	78.8 (8.8)		20.6 %	19.00 [14.44, 23.56]
Subtotal (95% CI)	**30**		**30**			**20.6 %**	**19.00 [14.44, 23.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.17 (P < 0.00001)							
2 Non-dialysis (unclear risk of bias)							
Yang 1999b	29	87.2 (0.44)	24	75.2 (0.37)		27.3 %	12.00 [11.78, 12.22]
Wei 2004	30	107.35 (12.19)	30	103.63 (11.22)		17.6 %	3.72 [-2.21, 9.65]
Wang 2005a	30	87.69 (17.36)	30	80.69 (10.36)		15.0 %	7.00 [-0.23, 14.23]
Subtotal (95% CI)	**89**		**84**			**59.9 %**	**8.20 [2.39, 14.01]**
Heterogeneity: Tau^2 = 20.04; Chi^2 = 9.31, df = 2 (P = 0.01); I^2 =79%							
Test for overall effect: Z = 2.77 (P = 0.0056)							
3 Non-dialysis (high risk of bias)							
Guo 2009 (1)	25	94.3 (9.8)	25	86.6 (8.5)		19.4 %	7.70 [2.61, 12.79]
Subtotal (95% CI)	**25**		**25**			**19.4 %**	**7.70 [2.61, 12.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.97 (P = 0.0030)							
Total (95% CI)	**144**		**139**			**100.0 %**	**10.40 [6.22, 14.58]**
Heterogeneity: Tau^2 = 16.66; Chi^2 = 21.14, df = 4 (P = 0.00030); I^2 =81%							
Test for overall effect: Z = 4.87 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 13.34, df = 2 (P = 0.00), I^2 =85%							

(1) Why is htis study excluded?

Analysis 1.8. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 8 Haematocrit.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 8 Haematocrit

Study or subgroup	Cordyceps		Conventional medicine		Mean Difference	Mean Difference
	N	Mean(SD)[%]	N	Mean(SD)[%]	IV,Random,95% CI	IV,Random,95% CI
Wei 2004	30	34.28 (4.68)	30	30.79 (3.38)		3.49 [1.42, 5.56]

Analysis 1.9. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 9 Serum albumin.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

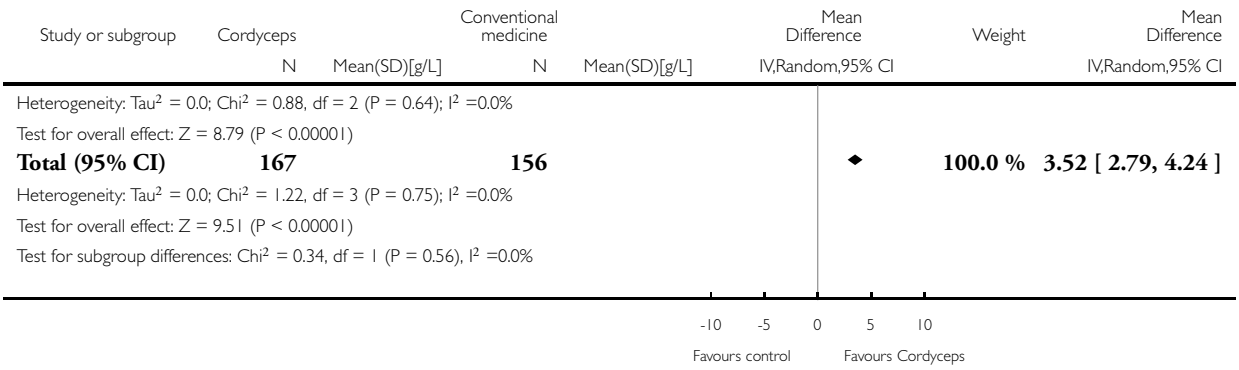
Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 9 Serum albumin

Study or subgroup	Cordyceps		Conventional medicine		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[g/L]	N	Mean(SD)[g/L]	IV,Random,95% CI		IV,Random,95% CI
1 Dialysis							
Yu 2002	35	38.31 (3.47)	30	35.23 (3.27)		19.5 %	3.08 [1.44, 4.72]
Subtotal (95% CI)	**35**		**30**			**19.5 %**	**3.08 [1.44, 4.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.68 (P = 0.00023)							
2 Non-dialysis							
Wei 2004	30	33.46 (2.39)	30	30.45 (3.52)		22.7 %	3.01 [1.49, 4.53]
Liu 2006a	34	35.26 (2.44)	32	31.32 (3.97)		20.5 %	3.94 [2.34, 5.54]
Liu 2007a	68	35.1 (3.03)	64	31.28 (3.85)		37.3 %	3.82 [2.63, 5.01]
Subtotal (95% CI)	**132**		**126**			**80.5 %**	**3.62 [2.81, 4.43]**

(*Continued* . . .)

(. . . *Continued*)

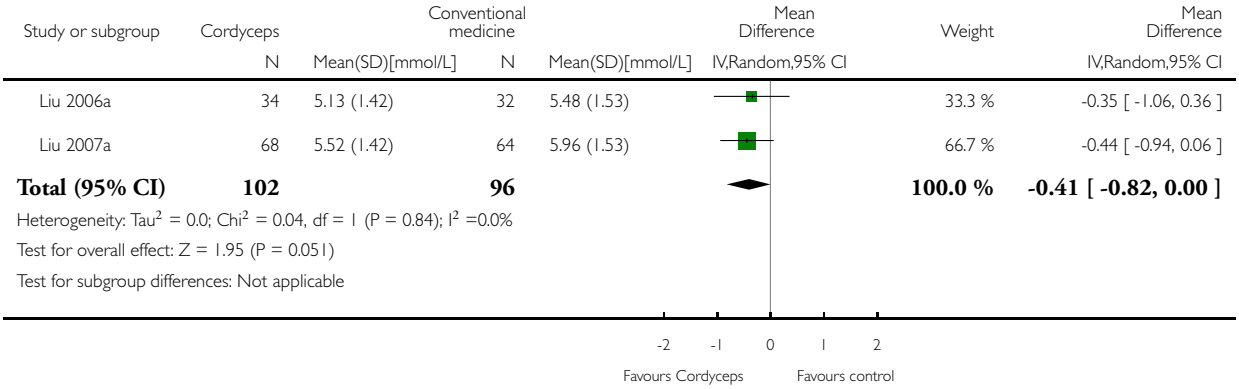


Analysis 1.10. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 10 Total cholesterol.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 10 Total cholesterol



Analysis 1.11. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 11 Calcium.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 11 Calcium

Study or subgroup	Cordyceps		Conventional medicine		Mean Difference	Mean Difference
	N	Mean(SD)[mmol/L]	N	Mean(SD)[mmol/L]	IV,Random,95% CI	IV,Random,95% CI
Liu 2006a	34	2.21 (0.23)	32	2.06 (0.24)		0.15 [0.04, 0.26]

Analysis 1.12. Comparison 1 Cordyceps + conventional treatment versus conventional treatment, Outcome 12 Phosphorus.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 1 Cordyceps + conventional treatment versus conventional treatment

Outcome: 12 Phosphorus

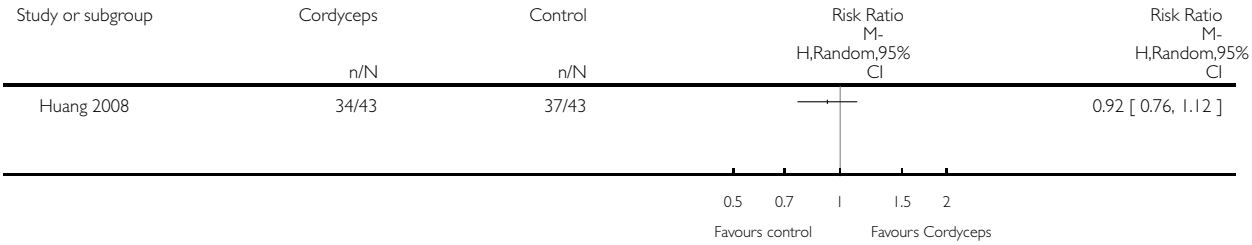
Study or subgroup	Cordyceps		Conventional medicine		Mean Difference	Mean Difference
	N	Mean(SD)[mmol/L]	N	Mean(SD)[mmol/L]	IV,Random,95% CI	IV,Random,95% CI
Liu 2006a	34	1.52 (0.12)	32	1.63 (0.15)		-0.11 [-0.18, -0.04]

Analysis 2.1. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 1 CKD progression (%).

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 1 CKD progression (%)

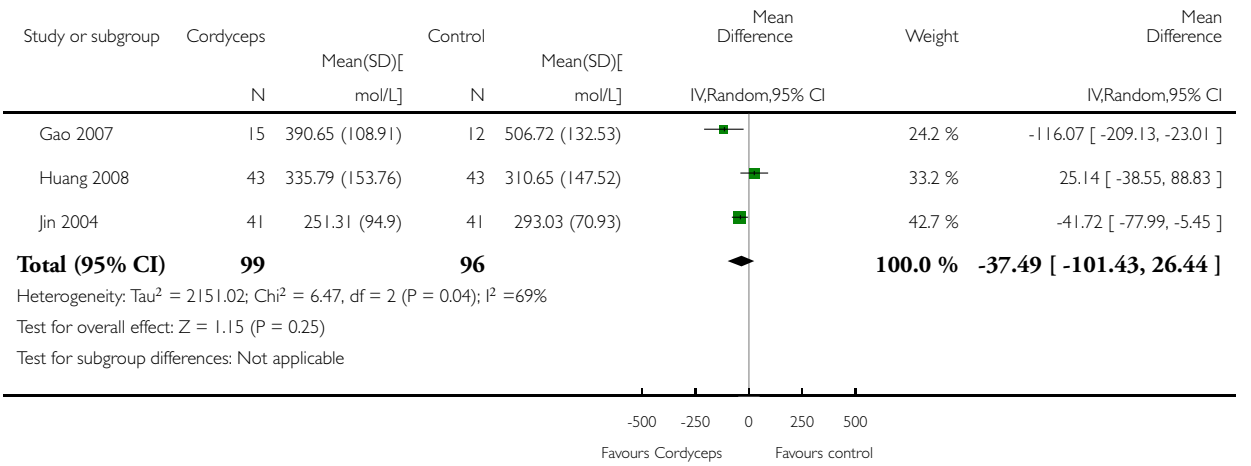


Analysis 2.2. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 2 Serum creatinine.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 2 Serum creatinine



Analysis 2.3. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 3 Creatinine clearance.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 3 Creatinine clearance

Study or subgroup	Cordyceps		Control		Mean Difference	Mean Difference
	N	Mean(SD)[mL/min]	N	Mean(SD)[mL/min]	IV,Random,95% CI	IV,Random,95% CI
Gao 2007	15	21.62 (5.02)	12	13.55 (2.28)		8.07 [5.22, 10.92]
Huang 2008	43	17.25 (5.11)	43	18.86 (4.47)		-1.61 [-3.64, 0.42]
Jin 2004	41	30.78 (13.51)	41	23.53 (8.92)		7.25 [2.29, 12.21]

Analysis 2.4. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 4 Proteinuria.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 4 Proteinuria

Study or subgroup	Cordyceps		Control		Mean Difference	Mean Difference
	N	Mean(SD)[g/24 h]	N	Mean(SD)[g/24 h]	IV,Random,95% CI	IV,Random,95% CI
Huang 2008	43	1.63 (0.86)	43	1.32 (0.88)		0.31 [-0.06, 0.68]

Analysis 2.5. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 5 Haemoglobin.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 5 Haemoglobin

Study or subgroup	Cordyceps N	Mean(SD)[g/L]	Control N	Mean(SD)[g/L]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Jin 2004	41	122.33 (14.79)	41	101.03 (17.88)		21.30 [14.20, 28.40]

Analysis 2.6. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 6 Haematocrit.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 6 Haematocrit

Study or subgroup	Cordyceps N	Mean(SD)[%]	Control N	Mean(SD)[%]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Jin 2004	41	33.92 (3.86)	41	30.32 (5.45)		3.60 [1.56, 5.64]

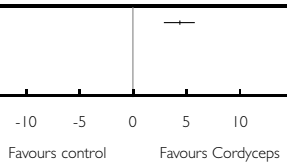
Analysis 2.7. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 7 Serum albumin.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 7 Serum albumin

Study or subgroup	Cordyceps N	Mean(SD)[g/L]	Control N	Mean(SD)[g/L]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Jin 2004	41	33.13 (2.45)	41	28.78 (4.08)		4.35 [2.89, 5.81]



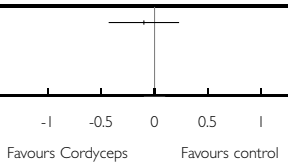
Analysis 2.8. Comparison 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment, Outcome 8 Total cholesterol.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 2 Cordyceps + conventional treatment versus Western medicine + conventional treatment

Outcome: 8 Total cholesterol

Study or subgroup	Cordyceps N	Mean(SD)[mmol/L]	Control N	Mean(SD)[mmol/L]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Jin 2004	41	6 (0.78)	41	6.1 (0.74)		-0.10 [-0.43, 0.23]



Analysis 3.1. Comparison 3 Cordyceps + TCM versus TCM, Outcome 1 Serum creatinine.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 3 Cordyceps + TCM versus TCM

Outcome: 1 Serum creatinine

Study or subgroup	Cordyceps		TCM		Mean Difference	Mean Difference
	N	Mean(SD)[mol/L]	N	Mean(SD)[mol/L]	IV,Random,95% CI	IV,Random,95% CI
Yan 2005a	33	104 (21.2)	32	128 (71.8)		-24.00 [-49.91, 1.91]

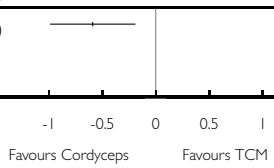
Analysis 3.2. Comparison 3 Cordyceps + TCM versus TCM, Outcome 2 Proteinuria.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 3 Cordyceps + TCM versus TCM

Outcome: 2 Proteinuria

Study or subgroup	Cordyceps		TCM		Mean Difference	Mean Difference
	N	Mean(SD)[g/24 h]	N	Mean(SD)[g/24 h]	IV,Random,95% CI	IV,Random,95% CI
Yan 2005a	33	0.62 (0.38)	32	1.21 (1.08)		-0.59 [-0.99, -0.19]



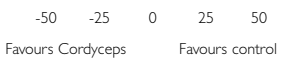
Analysis 3.3. Comparison 3 Cordyceps + TCM versus TCM, Outcome 3 Haemoglobin.

Review: Cordyceps sinensis (a traditional Chinese medicine) for treating chronic kidney disease

Comparison: 3 Cordyceps + TCM versus TCM

Outcome: 3 Haemoglobin

Study or subgroup	Cordyceps N	Mean(SD)[g/L]	TCM N	Mean(SD)[g/L]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Yan 2005a	33	140 (17.8)	32	116 (12.1)		24.00 [16.62, 31.38]



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Cordyceps, this term only 2. (cordyceps sinensis*) in Clinical Trials 3. (cordyceps*) in Clinical Trials 4. (dongchongxiacao) or (dong chong xia cao) or (dongchong xiacao) in Clinical Trials 5. (chongcao*) or chong cao* in Clinical Trials 6. (1 OR 2 OR 3 OR 4 OR 5) 7. MeSH descriptor Renal Dialysis explode all trees 8. (hemodialysis) or (haemodialysis) in Clinical Trials 9. (hemofiltration) or (haemofiltration) in Clinical Trials 10. (hemodiafiltration) or (haemodiafiltration) in Clinical Trials 11. (dialysis) in Clinical Trials 12. (PD or CAPD or CCPD or APD) in Clinical Trials 13. MeSH descriptor Renal Insufficiency, this term only 14. MeSH descriptor Kidney Failure, this term only 15. MeSH descriptor Renal Insufficiency, Chronic explode all trees 16. MeSH descriptor Kidney Diseases, this term only 17. MeSH descriptor Uremia, this term only 18. “end-stage renal” or “end-stage kidney” or “endstage renal” or “endstage kidney” in Clinical Trials

(*Continued*)

	19. (ESRF or ESKF or ESRD or ESKD) in Clinical Trials 20. "chronic kidney" or "chronic renal" in Clinical Trials 21. (CKF or CKD or CRF or CRD) in Clinical Trials 22. (ur?emi*) in Clinical Trials 23. (7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22) 24. (6 AND 23)
MEDLINE	1. Cordyceps/ 2. cordyceps sinensis.tw. 3. cordyceps.tw. 4. (dongchongxiacao or dong chong xia cao).tw. 5. (chongcao or chong cao).tw. 6. or/1-5 7. exp Renal Dialysis/ 8. (hemodialysis or haemodialysis).tw. 9. (hemofiltration or haemofiltration).tw. 10. (hemodiafiltration or haemodiafiltration).tw. 11. dialysis.tw. 12. (PD or CAPD or CCPD or APD).tw. 13. Renal Insufficiency/ 14. Kidney Failure/ 15. exp Renal Insufficiency, Chronic/ 16. Kidney Diseases/ 17. Uremia/ 18. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 19. (ESRF or ESKF or ESRD or ESKD).tw. 20. (chronic kidney or chronic renal).tw. 21. (CKF or CKD or CRF or CRD).tw. 22. ur?emi$.tw. 23. or/7-22 24. and/6,23
EMBASE	1. Cordyceps Sinensis Extract/ 2. Cordyceps/ 3. cordyceps sinensis.tw. 4. (dongchongxiacao or dong chong xia cao).tw. 5. (Chongcao or chong cao).tw. 6. or/1-5 7. exp Renal Replacement Therapy/ 8. (hemodialysis or haemodialysis).tw. 9. (hemofiltration or haemofiltration).tw. 10. (hemodiafiltration or haemodiafiltration).tw. 11. dialysis.tw. 12. (PD or CAPD or CCPD or APD).tw. 13. Kidney Disease/ 14. Chronic Kidney Disease/ 15. Kidney Failure/ 16. Chronic Kidney Failure/

(*Continued*)

	17. Uremia/ 18. (chronic kidney or chronic renal).tw. 19. (CKF or CKD or CRF or CRD).tw. 20. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 21. (ESRF or ESKF or ESRD or ESKD).tw. 22. ur?emi$.tw. 23. or/7-22 24. and/6,23
CBM	1. dong chong xia cao (Cordyceps) or chong cao (Cordycep in abbreviation) 2. jin shui bao or bai he or zhi ling or ning xin bao or xin gan bao 3. 1 or 2 4. shen bing (Kidney disease) or shen shuai (kidney failure) or shen gong neng shuai jie (kidney function failure) or shen gong neng bu quan (kidney fucntion insufficiency) or niao du zheng (uremia) or dan zhi xue zheng (azotemia) 5. 3 and 4 6. limit 5 to human
CMCC	1. dong chong xia cao (Cordyceps) or chong cao (Cordycep in abbreviation) 2. jin shui bao or bai he or zhi ling or ning xin bao or xin gan bao 3. 1 or 2
TCMLARS	1. dong chong xia cao (Cordyceps) or chong cao (Cordycep in abbreviation) 2. jin shui bao or bai he or zhi ling or ning xin bao or xin gan bao 3. 1 or 2 4. shen bing (Kidney disease) or shen shuai (kidney failure) or shen gong neng shuai jie (kidney function failure) or shen gong neng bu quan (kidney fucntion insufficiency) or niao du zheng (uremia) or dan zhi xue zheng (azotemia) 5. 3 and 4 6. limit 5 to human
Chinese Dissertation Database	1. dong chong xia cao (Cordyceps) or chong cao (Cordycep in abbreviation).abstract 2. (jin shui bao or bai he or zhi ling or ning xin bao or xin gan bao).abstract 3. 1 or 2 4. (shen bing (Kidney disease) or shen shuai (kidney failure) or shen gong neng shuai jie (kidney function failure) or shen gong neng bu quan (kidney fucntion insufficiency) or niao du zheng (uremia) or dan zhi xue zheng (azotemia)).abstract 5. 3 and 4
CMAC	1. dong chong xia cao (Cordyceps) or chong cao (Cordycep in abbreviation) 2. jin shui bao or bai he or zhi ling or ning xin bao or xin gan bao 3. 1 or 2
Index to Chinese Periodical Literature	1. dong chong xia cao (Cordyceps) or chong cao (Cordycep in abbreviation) 2. shen gong neng (kidney function) 3. 1 and 2

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement

(*Continued*)

Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

(*Continued*)

	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft protocol: HWZ, ZXL
2. Study selection: HWZ, FC, YFH
3. Extract data from studies: HWZ, FC, YFH
4. Enter data into RevMan/check data entry: HWZ, FC
5. Carry out the analysis: HWZ
6. Interpret the analysis: HWZ, ZXL, CL, LSC
7. Draft the final review: HWZ, ZXL
8. Disagreement resolution: ZXL,
9. Update the review: HWZ, ZXL

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- School of Chinese Medicine, The Chinese University of Hong Kong, China.
- Yan Oi Tong, Hong Kong, China.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Diabetic nephropathy and primary nephrotic syndrome, which will be covered in other reviews (Feng 2013; Liu 2007), were excluded from this review after discussion with the Cochrane Renal Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cordyceps; Creatine [metabolism]; Creatinine [blood]; Phytotherapy [*methods]; Proteinuria [prevention & control]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*drug therapy; metabolism]

MeSH check words

Humans