

# INPLASY PROTOCOL

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None declared.

## Cordyceps preparations for preventing contrast-induced nephropathy: A protocol of systematic review of randomized controlled trials

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**Review question / Objective:** To systematically evaluate the efficacy and safety of cordyceps preparations as a complementary preventive therapy for Contrast-induced nephropathy (CIN).

**Condition being studied:** At present, contrast agents are widely used in diagnostic and interventional radiology examinations worldwide. However, they can affect kidney function and cause a risk of renal impairment. Contrast-induced nephropathy (CIN) is defined as a rise in serum creatinine (SCr) levels by  $\geq 25\%$  of baseline or  $44 \mu\text{mol/l}$  from the pre-contrast value within 72 h of intravascular administration of a contrast agent in the absence of an alternative etiology. The incidence of CIN varies widely among studies depending on study population and baseline risk factors, as for high-risk groups such as pre-existing renal insufficiency, diabetes, advanced age, or receiving nephrotoxic agents, the incidence is up to 30–50%. To date, CIN has been the third most common cause of hospital-acquired renal failure, after impaired renal perfusion and nephrotoxic medications, which can lead to longer hospital stay, increased costs and higher mortality.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 June 2022 and was last updated on 24 June 2022 (registration number INPLASY202260098).

### INTRODUCTION

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complementary preventive therapy for Contrast-induced nephropathy (CIN).

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## METHODS

**Participant or population:** All patients irrespective of age or presence of kidney disease, who received intravascular injection of contrast agent.

**Intervention:** Cordyceps is a genus of entomopathogenic ascomycetes that grows by infecting insect larvae or mature insects, where ascomycetes indicate that this is a fungus that produces spores internally in sacs, including *Ophiocordyceps sinensis* (*O. sinensis*), *Cordyceps militaris*, and *C. cicadae*. The most famous and historically influential species of Cordyceps is *O. sinensis*, a precious tonic Chinese medicine, along with ginseng and deer antler, which was first recorded in the 8th century AD in Somaratsa. Some studies have shown that *O. sinensis* contains a variety of bioactive components such as cordycepin, cordycepic acid, adenosine, exopolysaccharides, polysaccharides, ergosterol, Sterols, Amino acids, etc. These components have various physiological properties, such as anti-inflammatory, anti-oxidative, anti-fibrogenic, anti-diabetic, hypolipidemic, anti-tumor, anti-thrombotic, increasing immunity. Due to its scarcity and technical limitations, scientific

organisations use mycelium produced by fermentation or *C. militaris* of similar composition as a substitute for natural *O. sinensis*.

**Comparator:** As there is no definitive treatment for CIN, the most effective strategy remains prevention. It is essential to take effective measures in the perioperative period of the contrast, such as hydration, selection of the appropriate contrast agent and dose control, discontinuation of nephrotoxic drugs, application of nephroprotective drugs like antioxidants (N-acetylcysteine, ascorbic acid) or statins. Current evidence suggests that hydration represents the gold standard of the preventive therapy of CIN. However, a randomized controlled trial published in The Lancet in 2017 came to a different conclusion: the difference in the incidence of CIN in the intravenous hydration group (2.7%) compared to the non-hydrated control group (2.6%) was not statistically significant. Besides, “bicarbonate-based hydration is absolutely superior to physiological saline” is still under debate. Currently, due to insufficient evidence, N-acetylcysteine, ascorbic acid and high-dose statins are not recommended as routine preventive strategies in Italy and Japan. Therefore, there is a strong need to further optimize the prevention strategies for CIN.

**Study designs to be included:** In recent years, a number of systematic reviews of clinical trials have confirmed the efficacy of cordyceps preparations to treat certain kidney diseases. However, there is yet no systematic review evaluating whether Cordyceps preparations have the preventive effect against CIN.

**Eligibility criteria:** Original studies will be included when they meet the following inclusion criteria:(1)Participants: all patients irrespective of age or presence of kidney disease, who received intravascular injection of contrast agent; (2)Intervention: Cordyceps preparations alone or combined with control group, which included raw herb, Cordyceps extracts, any mycelial products that contain pharmacologically-

active components similar to wild *O. sinensis*. Other *Cordyceps* species, such as *C. militaris*, were also included; (3)Comparators: no intervention or any intervention that aimed to reduce contrast induced nephropathy(CIN); (4)Outcomes: primary: the incidence of CIN, eGFR, Scr; secondary: need for dialysis, BUN, IL-18, KIM-1, adverse events. (5) Studies: Randomized controlled trials.

**Information sources:** The PubMed, the Cochrane Library, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), SinoMed, and WanFang Data were searched from inception to June 2022. We also explored the World Health Organization International Clinical Trials Registry Platform (<https://www.who.int/clinical-trials-registry-platform>), ClinicalTrials.gov (<http://www.clinicaltrials.gov/>), and the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/index.aspx>) for ongoing or unpublished trials to June 2022. Mesh terms and entry terms are determined based on published systematic reviews, clinical practice guidelines, ICD-10, ICD-11, MeSH terms, and Emtree in Supplementary materials.

**Main outcome(s):** To evaluate the efficacy and safety of *Cordyceps* preparations as a complementary preventive therapy for CIN, we will present a synthesis of evidence from relevant randomized controlled trials.

**Quality assessment / Risk of bias analysis:** The Cochrane Collaboration's RoB2 tool will be used to assess risk of bias for included studies by two authors (YQW and CMT). This revision tool includes the following six aspects: randomization process, deviation from established interventions, outcome measures, missing outcome data, selective reporting of results, and overall bias. The included studies will be assessed for low risk of bias, some concern, or high risk of bias in each area. The GRADE evidence grading system will be used to evaluate the

evidence quality of the main outcome indicators.

**Strategy of data synthesis:** This study will use STATA (version 15.0, Stata SE) for Statistical analysis. Dichotomous data are expressed by risk ratio (RR) with 95% confidence interval (CI), and continuous data are expressed by weighted mean difference (WMD) with 95%CI. The standard mean difference (SMD) are used for results reported by various measurement methods or different measurement scales. Heterogeneity is determined by the Q-statistical test and I<sup>2</sup>-statistical test. According to the Cochrane Handbook of Heterogeneity Analysis, I<sup>2</sup> values between 50% and 90% may represent substantial heterogeneity; 75% to 100% means considerable heterogeneity. A fixed-effects model is adopted if I<sup>2</sup> < 50%; otherwise, a random-effects model will be applied. If ten or more studies are included in the meta-analysis, the publication bias in these studies will be assessed using Egger's test and funnel plots.

**Subgroup analysis:** Post-subgroups analysis will be performed on the indicators with significant heterogeneity (I<sup>2</sup> > 50%). If there is significant heterogeneity in the study and post-subgroups (characteristics) fail to find the source of heterogeneity, then a meta-regression analysis will be further performed using Stata 15.0 software.

**Sensitivity analysis:** Sensitivity analysis should be performed on the outcomes whose heterogeneity are significant.

**Country(ies) involved:** China/Centre for Evidence Based Chinese Medicine, Beijing University of Chinese Medicine.

**Keywords:** *Cordyceps*; *Ophiocordyceps sinensis*; Chinese medicine; Contrast-induced nephropathy; CIN; Acute kidney injury; AKI; systematic evaluation; Meta-analysis.

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