

# Acute kidney injury related to *Cordyceps militaris*: A case series

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**Research Article**

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# Abstract

## Background

*Cordyceps sinensis* is an ancient traditional Chinese medicine, known as caterpillar fungus, that is one of the most commonly used ingredients to treat people with chronic kidney disease or to facilitate post-kidney transplant health. Unfortunately, due to unavailability and heavy metal contamination, *Cordyceps militaris* has been substituted instead and incorporated into over 400 dietary supplements sold in Thailand. This is the first case series report to inform health care providers about nephrotoxicity related to *C. militaris* supplements.

## Case presentation

Eleven patients had acute kidney injury (AKI) related to dietary supplements of *C. militaris*, which mainly contained cordycepin. Most of these patients from central Thailand (2018–2021) were elderly and five patients had chronic kidney disease stage 3 to 5. Two patients developed AKI requiring dialysis. The causality of AKI related to *C. militaris* was assessed by the modified Naranjo algorithm and a probable relationship was found between *C. militaris* and AKI (range from 6–8 scores). Two potential mechanisms of nephrotoxicity from *C. militaris* were cyclooxygenase-2 inhibition and direct toxicity at kidney tubule.

## Conclusions

Patients with kidney insufficiency and elderly should avoid using health products containing *C. militaris* until further clinical research determines such supplementation safe and effective.

# Background

*Cordyceps sinensis* (*C. sinensis*), called 'Dong Chong Xia Cao' in Chinese, is an ancient traditional Chinese medicine made from caterpillar fungus that is one of the most commonly used ingredients to treat people with chronic kidney disease or to maintain post-kidney transplant health [1]. Unfortunately, due to unavailability and heavy metal contamination [2], *Cordyceps militaris* has been substituted instead and incorporated into over 400 dietary supplements sold in Thailand.

The main different compound between these two species - *C. sinensis* and *C. militaris* is adenosine, which is the main compound of cultivated *C. sinensis*, but cordycepin (3'-deoxyadenosine) is the main compound of cultivated *C. militaris* [3, 4]. The natural product of *C. sinensis* contains a very low content of cordycepin [4]. There is a lack of clinical trials to demonstrate that *C. sinensis* and *C. militaris* have similar benefits to health and to determine if *C. militaris* does not cause adverse reactions[3].

Animal studies often precede human clinical trials in drug development, and Zhou and Yao's (2013) 28-day repeated toxicity test in rats found that *C. militaris* powder orally at 0 (control), 1, 2, and 3 g/kg per day resulted in increments of serum aspartate and alanine aminotransferase (AST and ALT) levels suggestive of weak hepatic toxicity [5]. Nephrotoxicity characterized by tubular epithelium degeneration and necrosis was observed at the high dose. *C. militaris* treatment significantly decreased superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities. They concluded that dietary contamination with *C. militaris* may have renal toxicity potentials, at least in part by causing oxidative damage to the kidney[5]. Suwannasaroj's study (2021) in Thailand also tested sub-chronic (90 days) oral toxicity of *C. militaris* in rats and found that freshly mixed with distilled water at 20 mg/kg/day resulted in an increase in serum creatinine [6].

In Vietnam there was one report of 60 cases of toxicity following the ingestion of *Cordyceps* fungus found in infected cicada nymphs ("cicada flowers") utilized in traditional Chinese medicine[7]. Within 60 minutes of ingestion, symptoms occurred including dizziness, vomiting, salivation, mydriasis, jaw stiffness, urinary retention, seizures, agitated delirium, hallucinations, somnolence and coma. None of the patients suffered liver or kidney injury. There was one fatality. The researchers attributed the toxicity to Cicada infected with *Ophiocordyceps heteropoda* that contains ibotenic acid.

The anti-inflammatory effect of *C. militaris* and cordycepin is from cyclooxygenase-2 (COX) inhibition while this effect of *C. sinensis* is from nitric oxide, tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-12 inhibitions [3, 8, 9]. The effect of COX-2 inhibition is well demonstrated, that it causes vasoconstriction and decreases blood flow in kidneys [10].

Despite the lack of safety studies, scientists in Thailand developed the technology to cultivate *C. militaris*, including plant-based media technology, and launched a new cordycepin in powder and tea product since 2015 [11, 12]. There are various types of culture media to cultivate *Cordyceps* spp. and some media contain magnesium sulfate, dipotassium phosphate and peptone, which are able to contaminate in cordyceps products and may damage kidneys [13]. The Thai Food and Drug Administration (FDA) has approved manufacturers to cultivate *Cordyceps* spp. for a dietary supplement ingredient in 2019 [14]. Subsequently, many products containing *C. militaris* on the market.

Nevertheless, more than 400 dietary supplements of *C. militaris* are currently being sold in Thailand in various forms, for example cordyceps powder, tea, coffee, energy drink, and an extract of *C. militaris*, and cordycepin. Cordyceps products sold in Thailand are available as 50 – 1,000 milligrams (mg)/capsules. A recommended dose of *C. sinensis* and *C. militaris* is 1–3 gram(s)/day and 4 grams/day, respectively, and it appears to be safe in the general population [15, 16]. The amount of cordyceps in coffee is 20–600 mg/cup. The usage of products containing cordyceps has been increasing in the last few years advertising on television, radio and social media. Although the Criteria for Food Advertisement B.E.2561 in Thailand does not permit the claim that dietary supplements can treat or alleviate diseases, most cordyceps dietary supplements are advertised, claiming that they do have benefits to health such as controlling diabetes or slowing the progression of kidney disease [17]. The pharmacologic effects of *C. militaris* have been shown in *in vitro* and *in vivo* studies, but there are limited clinical trials to prove its benefits to health [18].

To the best of our knowledge, the nephrotoxicity related to *C. sinensis* and *C. militaris* in clinical studies has never been reported. This study is a preliminary report of patients who developed acute kidney injury (AKI) related to legal products containing *C. militaris* advertised on television and social media in Thailand.

## Methods

The documentation of case reports adheres to the CARE checklist 2013 [<https://www.care-statement.org/checklist>]. These case reports were collected at Sena hospital, HRH Princess Maha Chakri Sirindhorn Medical Center, the Clinic Banaobaoon at Bang Khu Wat, the Mithmitree Clinic at Bua Thong Housing, Duangkaew, Kraitsadanakorn, Sao Thong Hin and Khlong Rangsit one between 2018–2021. Doctors, pharmacists and nurses working at kidney units, an inpatient ward or primary care clinics identified patients who had the inclusion criteria of 1) consumed a dietary supplement containing *C. militaris* or cordycepin extract in four provinces of central Thailand from 2018–2021, and 2) suffered from an AKI.

AKI in this study was defined as an estimated glomerular filtration rate (eGFR) declined at least 25% compared to eGFR at baseline or diagnosed by a physician [19]. Exclusion criteria included patients suffering from AKI who took both a *C. militaris* containing product and non-steroidal anti-inflammatory drugs (NSAIDs) because NSAIDs may cause AKI. Relevant patients' health data was collected -age, sex, any underlying disease, a history of medication related to nephrotoxicity, dosage form, dosage regimen and duration of the consumption of a product containing *C. militaris*, and eGFR of all cases were collected. A product containing *C. militaris* was identified by patients' self-report and a product label.

A causality of an association between AKI and *C. militaris* was evaluated by the modified Naranjo algorithm [20]. The score of the modified Naranjo algorithm and interpretation are shown in Table 1. An eGFR in this report was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21].

## Results

Records of 20 patients taking *C. militaris* were derived from this retrospective study. Six patients were excluded as their eGFR was declined less than 25%, compared to eGFR at baseline. Three patients were excluded due to the use of both *C. militaris*

and NSAIDs. A total of eleven cases of kidney function deterioration related to *C. militaris* were summarized in Figure 1 and Table 2. The mean (SD) age of patients was 67 (11) years and 73% were female. Their underlying diseases were non-communicable diseases (NCDs), e.g. diabetes, hypertension, dyslipidemia, cardiovascular diseases, gout and/or chronic kidney disease. Five patients had chronic kidney disease (CKD) stage 3 to 5. Five patients did not have a baseline eGFR. They were diagnosed AKI by physicians because their eGFR levels were improved after they ceased usage of *C. militaris* (Table 3).

Seven patients took legal dietary supplements containing an extract or powder of *C. militaris* at a recommended dose on a product label. The main ingredient of these products was either *C. militaris* or cordycepin. Two patients drank cordyceps tea and two consumed cordyceps coffee. Only 36% of the patients knew the exact dose of cordycepin extract (range 350-700 mg/day) and the remaining patients could not remember the brand name of their product.

Median duration of dietary supplements containing *C. militaris* consumption was 3 months before they developed AKI (Table 3). The mean (SD) of a declined eGFR level in the patients (N=6) was 16.67 (7.37) ml/min/1.73m<sup>2</sup>. The kidney function of seven patients was improved within 1-3 months after stopping taking cordyceps products.

One inpatient who was admitted to hospital due to AKI related to using an extract of *C. militaris* had been treated by normal saline together with stopping taking cordyceps products, and then his eGFR substantially improved from 17 to 46 ml/min/1.73m<sup>2</sup> within four days. The kidney functions of three patients with CKD stage 4 and 5 were not improved although they stopped taking a cordyceps product. One of these patients developed end-stage kidney disease and received peritoneal dialysis.

All patients self-reported not taking any pain killers or other herbal products related to nephrotoxicity, and most of them received the same medications and dosage regimen during cordyceps consumption. They did not have any conditions causing a rapid decline in eGFR, e.g. proteinuria. To assess the causality between cordyceps and AKI, the modified Naranjo algorithm was used and it found scores of 6-8 (probable), see Table 3.

## Discussion

Eleven patients had AKI related to *C. militaris* and most of them were elderly and female. This adverse event of *C. militaris* related to AKI was unexpected as several clinical trials have reported that *C. sinensis* may decrease proteinuria and improve kidney function in patients with kidney disease and has been an old traditional Chinese medicine [1]. One randomized controlled trial of *C. militaris* in which 98 patients with both CKD and proteinuria received 100 mg/day for 3 weeks, reported a decrease in proteinuria and improved eGFR [22]. It should be emphasized that the main effect of cordyceps is more likely to be a decrease in proteinuria linked to the improvement of kidney function rather than directly affecting kidney function. Sun T, et al. (2019) reported anti-inflammation effects of cordycepin extracted from *C. militaris* related to improved kidney function, and proposed the possible mechanism of anti-inflammatory effects via toll-like receptor 4 (TLR4), nuclear factor kappa light chain enhancer of activated B cells (NF-κB), COX2, IL-1β and TNF-α inhibition [22].

The effect of COX2-inhibition against the kidney function is well established in that it causes vasoconstriction and decreases blood flow in kidneys which leads to AKI [10, 23]. People who currently take a COX2-inhibitor have a high risk of hospitalization for AKI, compared to non-users (adjusted odd ratio 2.73, 95% confidence interval 2.28–3.28) [24]. Thirty-six percent of our patients took a higher amount of *C. militaris* (350–700 mg/day) than Sun's study and 73% took cordyceps longer than Sun's study (at least 3 months vs 1 month). We propose that the high dose and long duration of cordyceps use is more likely to increase the potency of COX2-inhibition and risk of AKI.

Previous literature regarding *in vitro* and *in vivo* studies indicates that *C. militaris* possibly induces nephrotoxicity via pre-renal AKI and direct toxicity at kidney tubule [3, 5]. There is a lack of scientific evidence reporting that *C. sinensis* causes nephrotoxicity. In addition, *C. sinensis* contains a lower amount of cordycepin than *C. militaris* and does not have an anti-inflammatory effect via COX-2 inhibition [3, 4, 8]. That may be the reason that *C. sinensis* is less likely to cause nephrotoxicity.

Our findings are the first to report convincingly that *C. militaris* with enriched cordycepin, is associated with AKI. The benefit of our report is to inform people and patients with kidney insufficiency that they should be aware of taking dietary products containing *C. militaris* and that it is very different from *C. sinensis*.

Kidney insufficiency is a risk factor of this adverse effect. The nephrotoxicity of *C. militaris* seems to be widespread and serious in Thailand as we found a high number of patients with NCDs suffered from AKI linked to *C. militaris*, particularly in primary care clinics (Table 2). Three patients had serious adverse effects; one patient developed end-stage kidney disease; one patient was admitted to hospital due to AKI; and one patient received short-term hemodialysis. The aim of this report is to urgently warn consumers, health care providers and the Thai FDA about serious adverse effects of dietary supplements containing *C. militaris*.

More than 400 products containing a high amount of *C. militaris* as a main ingredient are available in Thailand. The high number of such products, their advertising on television, radio and social media, and easy accessibility are likely to encourage a high number of Thai consumers to take them. The cases of AKI associated with *C. militaris* increased six-fold in 2020, compared with 2019 (Table 2). Elderly people and patients with renal insufficiency should avoid using products containing a high amount of *C. militaris* or cordycepin or at least taking them for a long duration.

The relationship of cordyceps to AKI has been identified by several Thai nephrologists, the organizations of consumer protection, e.g. the Foundation for Consumers (Thailand), the Thai Rural Doctor Foundation, and the Thai Drug Watch, and this information has been provided on their websites and social media during 2020–2021. A high number of consumers have responded to this warning and have shared their experience that some of their parents and relatives have suffered from AKI related to *C. militaris*.

Thai people are less likely to report their health problems associated with herbal products to the Thai FDA as they did not know that their health problems were linked to the products. The spontaneous reporting system of adverse events from health products in Thailand is less likely to detect the kidney adverse event related to *C. militaris*. We suggest that the Health Product Vigilance Center (HPVC) of Thai FDA should provide intensive surveillance on AKI related to cordyceps and a proper method should be established to prevent the adverse event from dietary supplements, e.g. a warning label or a product recall. Only the *C. sinensis* ingredient should be used or the amount of cordyceps contained in dietary supplements should be reduced in order to prevent adverse effects.

Limitations of this report are that the data came from interviewing patients so there may have been a recall bias regarding the details of *C. militaris* consumption, with some patients unable to remember an exact brand name of cordyceps products. Dosage is also very important to clinical studies, and not always easily ascertained in case reports. Also, people with kidney insufficiency may progress over time to various stages of kidney decline. Older age is another risk factor related AKI [25]. This report provides a signal of the association of AKI with *C. militaris*, but cannot establish the exact cause and effect. The findings of this study should be carefully interpreted and further prospective cohort studies are needed to confirm the findings of this report.

## Conclusions

Eleven cases of AKI related to *C. militaris* were found in central Thailand. One person developed end-stage kidney disease and received peritoneal dialysis. Elderly and patients with kidney insufficiency should avoid using dietary supplements containing *C. militaris* or cordycepin extract. Health care providers should be aware of this issue, the Thai FDA should intensively investigate and deal with this problem, and the media should broadcast this potential problem to the public.

## Abbreviations

AK  
Acute Kidney Injury

ALT  
Alanine aminotransferase  
AST  
Aspartate aminotransferase  
CAT  
Catalase  
CKD  
Chronic Kidney Disease  
CKD-EPI  
Chronic Kidney Disease Epidemiology Collaboration  
COX  
Cyclooxygenase  
eGFR  
estimated glomerular filtration rate  
FDA  
Food and Drug Administration  
GPx  
Glutathione Peroxidase  
HPVC  
Health Product Vigilance Center  
IL  
Interleukin  
NCDs  
Non-Communicable Diseases  
NSAIDs  
Non-Steroidal Anti-Inflammatory Drugs  
NF- $\kappa$ B  
Nuclear factor kappa light chain enhancer of activated B cells  
SD  
Standard Deviation  
SOD  
Superoxide Dismutase  
TNF  
Tumor Necrosis Factor  
TLR4  
Toll-Like Receptor 4

## **Declarations**

### **Ethics approval and consent to participate**

The study was approved by the Institutional Review Board for Research in Human Subjects in Srinakharinwirot University (SWUEC/E-045/2564) and Sena hospital (AY 0032.202.2/001), Thailand. The Institutional Review Board for Research in Human Subjects in Srinakharinwirot University and the Institutional Review Board for Research in Human Subjects in Sena hospital provided a waiver of written informed consent for the present study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### **Consent for publication**

N/A

### **Availability of data and materials**

N/A

### **Conflict of Interest**

The authors declare that they have no competing interests.

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### **Authors' contributions**

Siribha Changsirikulchai and MT conceived the study, performed the statistical analysis, coordination of the study and drafted the manuscript. Supatyada Chaiyarak, SS, UL and WA participated in the coordination of the study, data collection and analyses. All authors reviewed the manuscript and have read and approved the final manuscript.

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## Tables

**Table 1** The modified Naranjo algorithm

Question	Yes	No	Do not know
1. Is there any notification about the adverse event on the label or package insert of HDS?	+1	0	0
2. Did the adverse event appear after the suspected HDS intake?	+2	-1	0
3. Did the adverse event improve when the suspected HDS was discontinued?	+2	0	0
4. Did the adverse event reappear when the HDS was retaken?	+3	-1	0
5. Are there any alternative causes (other than the suspected HDS) that could on their own have caused the event?	-1	+2	0
6. Was the event more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
7. Did the consumer have a similar event to the same or a similar HDS in any previous exposure?	+1	0	0
8. Was the adverse event confirmed by any objective evidence?	+2	0	0

The total score > 9: highly probable; 5-8 scores: probable; 3-4 scores: highly possible; 1-2 score(s): possible; < 0: unlikely

HDS = Herbal and dietary supplement

**Table 2** The distribution of AKI cases-related to *C. militaris*

Year	Number of case report	Accumulate number
2018	1	1
2019	1	2
2020	6	8
2021	3	11

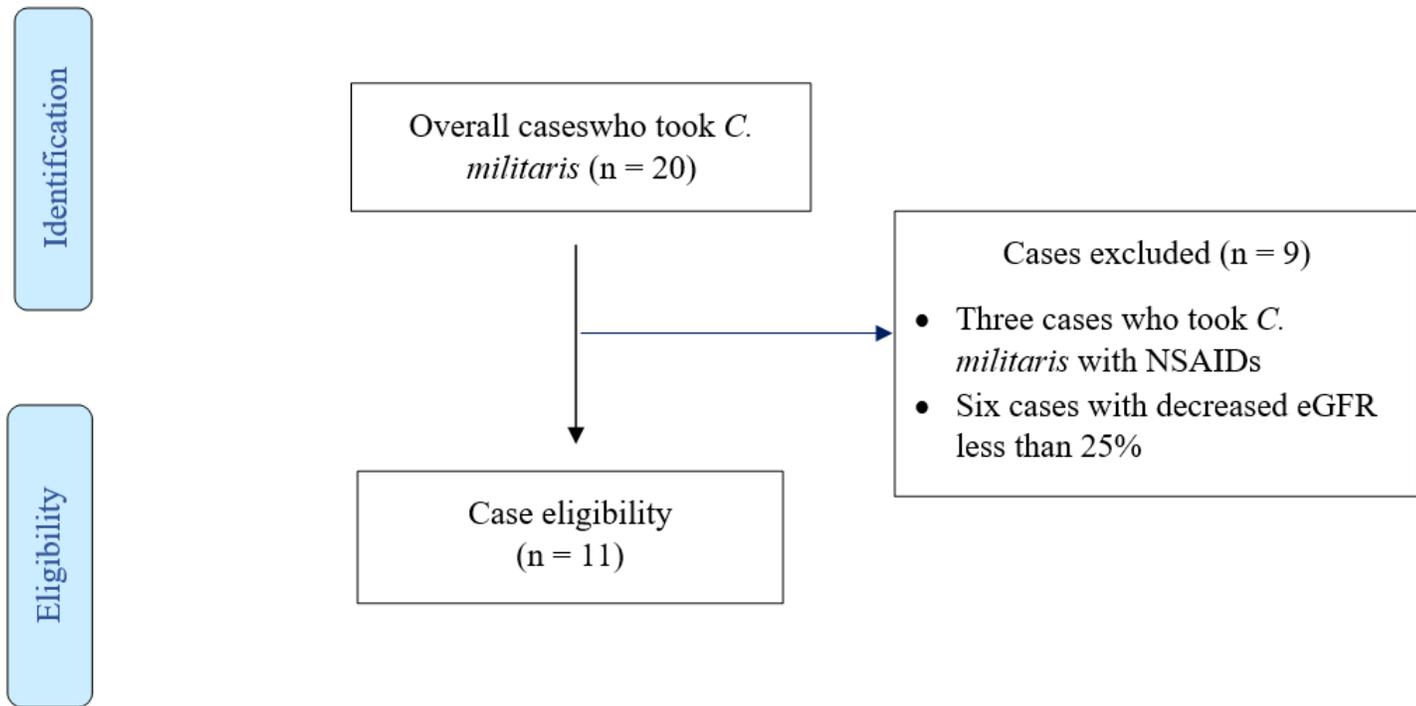
**Table 3** Case report series of patients suffering from acute kidney injury related to *C. militaris*

No.	Year	Dosage form	Dosage regimen	Duration of use (month)	eGFR baseline (ml/min/1.73m <sup>2</sup> )	eGFR after taking a suspected product (ml/min/1.73m <sup>2</sup> )	eGFR after stopped use of a suspected product	Causality score
1	2018	Tea	One cup per day	6	14	3	Received peritoneal dialysis	6
2	2019	Capsule	One capsule per day (350 mg/capsule)	14	26	14	19	8
3	2020	Capsule	One capsule per day	0.7	unknown	17	46	8
4	2020	Capsule	One capsule per day (350 mg/capsule)	1	unknown	58	72	8
5	2020	Coffee	Two cups per day (300 mg/cup)	3	unknown	40	68	8
6	2020	Capsule	Two capsule per day	6	75	51	69	8
7	2020	Capsule	One capsule per day	3	24	12	12	6
8	2020	Capsule	Two capsule per day (350 mg/capsule)	1	unknown	40	67	8
9	2021	Coffee	One cup per day	3	35	7	After received hemodialysis for a week, kidney function improved and had CKD stage 4	8
10	2021	Capsule	One capsule per day	3	50	37	Unknown	6
11	2021	Tea	One cup per day	3	unknown	30	42	8

Abbreviation: AKI = Acute kidney injury, eGFR = estimated glomerular filtration rate, M = Male, F = Female, CKD = chronic kidney disease

The total score of the causality between *C. militaris* and AKI > 9 = highly probable; 5 to 8 scores = probable; 3 to 4 scores = highly possible; 1 to 2 score(s) = possible; < 0 = unlike

## Figures



**Figure 1**

Flow chart of inclusion process