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The effectiveness and efficacy of *Ophiocordyceps sinensis* supplementation: A systematic review of randomized clinical trials on healthy humans

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Abstract
To critically assess the current evidence from randomized clinical trials performed on healthy human subjects for or against the effectiveness or efficacy of *O. sinensis*. Randomized studies testing the efficacy and effectiveness of *O. sinensis* against a placebo, conducted with healthy human subjects were included in this systematic review following The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). Searches of PubMed, Library of Congress, JISC Library, Clinical Trials.gov, mRCT, Google Scholar, Embase, Web of Science, CINAHL, Medline, and Cochrane were conducted. Of the 4,308 potentially relevant articles, 29 full-text articles were reviewed, 7 of which were randomized trials conducted with healthx`y human subjects. All studies were classified as low risk with a total of 286 participants. Of the included studies, 5 noted significant pre/post intergroup differences. 5 results supported the utilization of *O. sinensis* as a powerful dietary supplement. The effect of supplementation with *O. sinensis* on aerobic performance could have implications in various athletic events. Insufficient reporting of the details of the *O. sinensis* preparation utilized is a common issue within included studies. Despite great efforts, there is a possibility not all relevant data was obtained.

Keywords: *Ophiocordyceps sinensis*, *Cordyceps sinensis*, randomized clinical trials, dong Chong Xia Cao

1. Introduction
Ophiocordyceps sinensis, also known as the Chinese caterpillar fungus or “Dong Chong Xia Cao”, meaning summer plant and winter worm, belongs to the fungal family *Ophiocordycipitaceae* [1]. This fungus, formerly known as *Cordyceps sinensis*, is an entomopathogenic fungus endemic to the alpine regions of the Tibetan Plateau [2]. It parasitizes ghost moth larvae and other insects, producing fruiting bodies which are collected and used in medicinal tonics [2].

O. sinensis has been used in traditional Chinese and Tibetan medicine for centuries for its perceived health benefits. The use of *O. sinensis* as a medicinal agent can be traced back to at least the 15th century in Tibetan medicine [3]. The fungus gained recognition in the Western world in the 19th century, with several Western botanists and naturalists documenting its use in traditional medicine in Tibet and the Himalayan region [3]. *O. sinensis* supplementation was brought to the forefront of the sports world in 1993, during the Chinese National Games in Beijing. This competition featured several female Chinese athletes breaking world records by wide margins in multiple long-distance events [4]. The rapid improvement in the performance of the Chinese women’s track team led to speculation of illegal drug use [4]. According to their coach, the factors that led to their improved performance was intense, high-altitude training and a tonic prepared from a "caterpillar fungus" [4].

The main active ingredient in *O. sinensis* is cordycepin, which is a type of adenosine analogue that has been shown to have anti-inflammatory and immunomodulatory properties in rodent-based laboratory studies [5, 6] as well as anti-tumor properties *in vitro* studies [7]. Human clinical trials have demonstrated the effectiveness of *O. sinensis* treating conditions such as infertility, night sweats, asthma, arrhythmias, and heart, respiratory, renal, and liver diseases [8]. Other studies have shown the effectiveness of the fungus to improve athletic performance and respiratory system function [9, 11]. However, there are several clinical trials that reveal contrary findings [12, 13]. Overall, more high-quality clinical studies are needed to determine the potential health benefits and risks of *O. sinensis*.

The purpose of this review is to critically evaluate the available randomized clinical trials on the effects of *O. sinensis* on healthy human subjects.

This review will provide a comprehensive analysis of the available evidence, with a focus on the methodology, standardization and quality control, results, and limitations of the studies. The findings of this systematic review will provide valuable insight into the potential health benefits of *O. sinensis* and help guide future research in this area. The review will also highlight the importance of conducting well-designed, randomized clinical trials to establish the safety and efficacy of *O. sinensis* as a therapeutic agent.

2. Methods

2.1 Search strategy

The following electronic databases were searched in February of 2023: PubMed, Library of Congress, JISC Library, ClinicalTrials.gov, mRCT, Google Scholar, Embase, Web of Science, CINAHL, Medline, and Cochrane (via the OVID interface for the first three databases, and EBSCO interface for the last three databases). The titles and abstracts were searched for the following terms: *Ophiocordyceps sinensis*, *Cordyceps sinensis*, *Sphaeria sinensis*, jinshuiba capsule, Bai ling capsule, corbin capsule, and Chinese winter worm. The search parameters excluded articles with the words 'rats' or 'mice' in the title and required the phrase 'clinical trial' to be present anywhere in the text. No language or date restrictions were imposed. A manual search was carried out through scoping searches of major electronic databases. The references list of retrieved articles were manually searched for potentially relevant studies. Experts in the field of herbal medicine as well as clinical researchers of dietary supplementation were contacted to identify any unpublished material.

2.2 Inclusion and exclusion criteria

Only randomized clinical trials testing the efficacy and effectiveness of preparations of *O. sinensis* as the only treatment against a control (placebo, active control, or no treatment) in healthy human subjects were included. Trials that examined *O. sinensis* in any sort of blend or mixture with another active ingredient were excluded. After the removal of duplicates using EndNote 20 software [14], the titles and abstracts of found studies were screened. The entire text of studies that appeared to meet inclusion criteria based on their titles and abstracts were independently screened by two reviewers. Any disagreements between reviewers were settled by the third reviewer. A study was included if at least two reviewers agreed that it met all inclusion criteria.

2.3 Data retrieval

All citations were combined using EndNote 20 [14]. The data such as the details of study design, quality of the study, participants, intervention, outcomes, and adverse events were extracted and discussed by reviewers using predefined criteria.

2.4 Quality review and analysis

Each included study was assessed independently by two reviewers using the Cochrane risk-of-bias tool for randomized trials [15], the CONSORT statement extension for Chinese herbal medicine [16] and the Jadad Scale (table 2) [17]. Key data from each selected study was summarized in a table (Table 1). Analysis of the main outcomes between groups was presented. Any disagreements between the two reviewers were settled by a third reviewer.

3. Results

The database and manual searches identified 4,308 potentially relevant articles. Removal of duplicates and initial screenings of titles and abstracts yielded 29 relevant references. The full text of all 29 references was retrieved and reviewed. 22 papers were excluded for the following reasons: 13 as they were not on healthy human subjects [18-30], 5 were not randomized clinical studies [1, 31-34], 4 duplicate papers were excluded. 7 randomized clinical studies met the inclusion criteria and were included in the review [9-13, 35-36]. A flow chart of the selection process is depicted in figure 1.

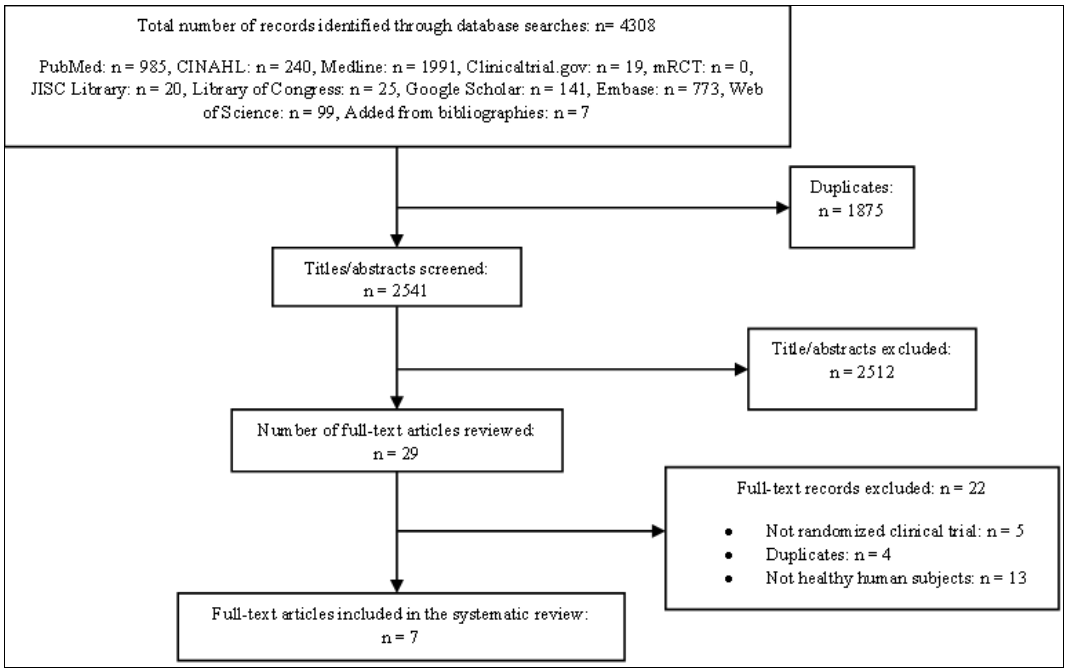

Fig 1: Flow chart depicting the selection process for inclusion

Fig Caption 1: Figure 1 depicts the step-by-step selection process for inclusion in the systematic review. The database search yielded 4308 results, through the removal of duplicates, review of titles and abstracts, followed by full-text reviews, it was determined that 7 articles were to be included in the review.

Table 1: Randomized controlled trials of *Ophiocordyceps sinenis*

First Author (Reference Type, year)	Study Design	Sample Size (Treatment/ Control), (Age Range)	Treatment	Control	Duration	Main Outcome Measures and Assessment Schedule	Between-Group Analysis	Adverse Events/Dropouts
Chen S. (Article, 2010) [10]	Double blind; placebo-controlled; 2 parallel groups	20 healthy individuals (10/10), (50-75)	333 mg *O. sinensis* capsules; 3 times per day	Placebo	12 weeks	(1) VO_2 max (2) metabolic threshold (3) work rate at metabolic threshold (4) ventilatory threshold (5) work rate at ventilatory threshold; Baseline, 12 weeks	There were no significant changes VO_2 max, work rate at metabolic threshold, and work rate at ventilatory threshold. Metabolic threshold and ventilatory threshold improved significantly in the treatment group compared to the control group.	None; 5
Hsu C. (Article, 2011) [13]	Double blind; placebo-controlled; 2 parallel groups	16 healthy male volunteers (8/8), (19-25)	400 mg of *O. sinensis* capsules; 6 times per day	Placebo (maltodextrin)	8 weeks	(1) Muscle strength measurements: 1 repetition maximum in bench press, leg press, and seated rowing (2) body composition (3) blood biochemical measurements: blood urea nitrogen, creatine, aspartate transaminase, alanine transaminase, and testosterone; baseline and 8 weeks.	There were no significant changes in muscle strength, body composition, and blood biochemistry.	None; None
Nicodemus J. (Free Communication, 2001) [36]	Double blind; placebo-controlled; 2 parallel groups	30 endurance trained male athletes (15/15, 27-35)	4.5 g of *O. sinensis*; daily	Placebo	6 weeks	(1) VO_2 (2) VCO_2 (3) ventilatory threshold (4) heart rate during maximal and submaximal exercise (5) Blood Lactate; baseline, 6 weeks.	There were no significant differences between groups in VO_2, VCO_2, heart rate, and blood lactate during maximal exercise. The treatment group had significant decrease at all time points in respiratory exchange ratio and at minute 30 in blood lactate during the submaximal exercise.	None; None
Parcell A. (Article, 2004) [12]	Double blind; placebo-controlled; 2 parallel groups	22 endurance trained male athletes (10/22), (20-30)	3.15 g of *O. sinensis*; 3 times per day	Placebo (maltodextrose)	7 weeks (5 weeks supplementation)	(1) Endurance time trial (2) VO_2 max (3) Ventilatory threshold; baseline, 5 weeks	There was no significant difference between groups in VO_2 max, ventilation threshold, and in the endurance time trial.	None; None
Savioli D. (Article, 2022) [11]	Double blind; placebo-controlled; 2 parallel groups	30 endurance trained athletes (amateur marathon runners) (15/15), (24-54)	667 mg of *O. sinensis*; 3 times per day	Placebo (maltodextrin)	12 weeks	(1) Aerobic performance: VO_2 max, L1, and L2 (2) 5 km time trail; baseline, 8 weeks, 12 weeks	There was no significant difference between groups for the aerobic performance at 8 weeks. Changes and differences for the 5k time trial were insignificant at 8 and 12 weeks. There was a significant improvement in aerobic performance for the treatment group at 12 weeks.	None; 8
Xiao Y. (Article, 2004) [9]	Double blind; placebo-controlled; 2 parallel groups	37 healthy elderly subjects (18/19), (58-78)	3g of *O. sinensis*; daily	Placebo	6 weeks	(1) Maximum work rate (2) VO_2 max (3) metabolic equivalents (4) VE max (5) Anaerobic threshold; baseline, 6 weeks	There were no significant changes in the maximum work rate. There were significant increases in VO_2 max, metabolic equivalents, and VE max in the treatment group compared to the control group.	3; 7
Zhu J. (Conference Poster, 2004) [35]	Double blind; placebo-controlled; 2 parallel groups	131 healthy middle aged to elderly volunteers (61/70), (40-70)	3g of *O. sinensis*; daily	Placebo	12 weeks	(1) VO_2 max (2) respiratory exchange ratio (3) 1 mile time trial (4) work output; baseline, 6 weeks, 12 weeks	The treatment group experienced a significant increase in exercise work output, anaerobic threshold, and VO_2 max, and a significant decrease in body weight, diastolic blood pressure, time to VO_2 max, respiratory exchange ratio, and the duration of the 1-mile time trial compared to the control group.	None; None

Fig. Table 1: Table 1 is a summary of key data presented in each study that was included in this review.

Table 2: Methodological quality of trials

First Author (Reference Type, year)	Was the allocation sequence random?	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Domain 1: Risk-of-bias judgement	Were participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Were there deviations from the intended intervention that arose because of the trial context?	Were these deviations likely to have affected the outcome?	Were these deviations from intended intervention balanced between groups?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	Domain 2: Risk-of-bias judgement	Items met from the Checklist of Items for Reporting Trials of Chinese Herbal Medicine Formulas from CONSORT Extension for Chinese Herbal Medicine Formulas 2017(n=25)	Jadad Scale Rating
Chen S. (Article, 2010) [10]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	18	5
Hsu C. (Article, 2011) [13]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	22	3
Nicodemus J. (Free Communication, 2001) [36]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	8	3
Parcell A. (Article, 2004) [12]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	20	2
Savioli D. (Article, 2022) [11]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	25	5
Xiao Y. (Article, 2004) [9]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	21	3
Zhu J. (Conference Poster, 2004) [35]	Yes	Yes	No	Low risk	No	No	N/A	N/A	N/A	Yes	N/A	Low risk	13	3

Fig.Table 2: Table 2 is an assessment of the methodological quality of studies included in this review. Methodological quality was evaluated utilizing the Cochrane risk-of-bias tool [15], CONSORT Extension for Chinese Herbal Medicine [16], and the Jadad Scale [17].

The main characteristics of all included studies are presented in table 1. The studies were published between 2001 and 2022 in English. There were four countries represented in the selected studies: Brazil [11], USA [10, 12, 35, 36], Taiwan [13], and China [9]. There was a total of 286 participants with ages ranging from 19 [10] to 78 [35] between all 7 studies with sample sizes ranging from 16 [13] to 131 [35]. 3 studies were conducted using endurance trained athletes [11, 12, 36] 2 studies utilized an apparently healthy population [10,36], and 2 studies utilized elderly subjects [9, 13]. Two studies were conducted using only male subjects [12, 13], while 5 used male and female subjects [9-11, 35, 36]. 6 studies submitted their participants to an endurance test [9-12, 35, 36], while 1 explored strength performance [13]. All 7 studies utilized a placebo control with only three identifying the substance used in the placebo: maltodextrin [11, 13]/ malt dextrose [12].

3.1 Aerobic performance

Out of the 7 included studies, 6 yielded results pertaining to aerobic exercise performance [9-12, 35, 36]. In all 6 studies, participants were tasked with performing an endurance stress test such as cycling, running, and walking. These stress tests were done at baseline and after multiple weeks of supplementation with *O. sinensis* or placebo.

Three studies found that there was no significant increase in VO_2 max in the treatment group compared to the placebo [10, 12, 36]. Three studies found an increase in VO_2 max associated with *O. sinensis* supplementation [9, 11, 35]. Two studies found improvements in the anaerobic/metabolic threshold of the treatment groups [10, 35]. One study found no significant difference in ventilation threshold between the treatment and control groups [12], another found the improvements in the treatment group ventilation threshold to be significant [10]. Two studies measured subject performance in an endurance related time trial, with one finding improvements in the treatment group [35] and the other finding none [12].

3.2 Muscular performance

One of the included studies assessed the effect of *O. sinensis* supplementation on muscular performance [13]. This study found improvement in one repetition maximum bench press, leg press, and seated rowing in the treatment group, but these results were not significantly different from the improvements seen in the control group. This study also found that there was no significant difference between body composition changes between the control and treatment groups.

3.3 Physiological biomarkers

Three of the included studies assessed the impact of *O. sinensis* on biologically derived indicators [13, 35, 36]. One study found significant decreases in heart rate and diastolic blood pressure in the treatment group [35]. Another found the change in heart rate observed in the treatment group to be insignificant [36]. One study documented the blood biochemistry of subjects [13]. This study demonstrated there was no significant change or difference in creatine concentration, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, and plasma testosterone between the control and treatment groups after supplementation.

3.4 Adverse events

One study reported adverse events [9]. In the placebo group, one subject experienced vomiting while two others were suspected of developing myocardial ischemia during the end-of-trial exercise tests.

4. Discussion

There was a total of 7 randomized clinical trials of *O. sinensis* that met the inclusion criteria of this review were identified [9-13, 35, 36]. By following PRISMA [37], the Cochrane risk-of-bias tool [15] was applied to the data (Table 2). All trials were determined to have a low risk of bias based upon this tool. Studies are considered to be of good methodological quality if they receive 3 or more points on the Jadad scale (Table 2) [17]. and there were 6 studies that met this threshold [9-11, 13, 35, 36]. One study [11] met the maximum score of 25 points on the Checklist of Items for Reporting Trials of Chinese Herbal Medicine Formulas from CONSORT Extension for Chinese Herbal Medicine Formulas (Table 2) [16]. There were 4 studies that scored above 20 [9, 11-13], while 2 scored between 10 and 20 [10, 35], and 1 trial scored less than 10 [36]. This evaluation highlights the need to conduct high quality, low bias clinical trials.

The results demonstrate supplementation with *O. sinensis* may have a positive impact on aerobic exercise performance, specifically on VO_2 max and anaerobic/metabolic threshold, as seen in some of the included studies [9-11, 35]. However, results are not consistent across all studies. There are some that show no significant differences between the treatment and placebo groups [11, 12, 36]. There is limited information on the impact of *O. sinensis* on muscular performance, with only one study assessing its effect and finding no significant difference between the treatment and control groups [13]. A much larger sample size of high-quality studies is needed to form a reliable verdict.

Out of the two trials that did not report any significant improvement in the treatment group compared to the control group, only one measured aerobic athletic performance [12]. Improvements to aerobic athletic performance is the reason *O. sinensis* is regarded as a powerful dietary supplement. More high-quality studies examining aerobic performance with *O. sinensis* are needed to validate or refute the claim that has popularized the use of the fungus.

There were 3 studies that described their method of preparation or the manufacturer of *O. sinensis* used in the study [9, 10, 13]. There are multiple methods to prepare this dietary supplement derived from the fruiting bodies produced by this specific fungus [8]. Insufficient reporting of the details of the preparation of *O. sinensis* utilized is a common issue. Future researchers should adequately collect and report such information according to the CONSORT Extension for Chinese Herbal Medicine Formulas. Future comparable studies could utilize supplement derived from a standardized preparation method. There were also 3 studies that identified the specific compound used in the placebo capsules in their study. Future studies should clearly identify the substance used as placebo [11-13].

The current data suggests that *O. sinensis* is a safe dietary supplement. Out of all the trials on a total of 286 participants, there were only 3 cases of adverse events, all taking place in the placebo group. Other studies confirm this observation [32].

Our review has multiple limitations. Even though we went to great lengths to ensure we retrieved all relevant studies, we cannot be sure that we were successful. Publication bias is another concern for this study as only 1 source of data did not originate from a scientific journal. This study focused on clinical trials using healthy human subjects while many of the clinical utilization of *O. sinensis* in individuals with some form of disease or ailment. Studies have also shown that *O. sinensis* can successfully treat side-effects of organs transplants [18, 24], male infertility [19], cancer [23], kidney

disease [21], high cholesterol [20], and lingering symptoms of COVID-19 [22]. These studies are pertinent to the health benefits of *O. sinensis* and should be evaluated in future reviews.

5. Conclusion

O. sinensis may have beneficial effects on aerobic physical performance and several physiological biomarkers. However, there is a lack of quality studies assessing this claim on healthy human subjects. The potential benefits of *O. sinensis* on muscular performance lack supporting evidence. There are no apparent side-effects of *O. sinensis* supplementation for healthy individuals. More research is needed on this herbal supplement.

5.1 Registration and protocol

This review is not registered, and the protocol is not available.

5.2 Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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