



Received: 02-10-2023
Accepted: 12-11-2023

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

A Review: *Cordyceps* with its Nutraceutical and Therapeutic Potential

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Abstract

Many mushroom genera are famous for their promising therapeutic capabilities. One of the mushrooms genera attracting attention is *Cordyceps* which has long been used in Asian countries for maintaining long and healthy life. Numerous studies on different metabolic activities of *Cordyceps* have been performed both *in vitro* and *in vivo*. Numerous studies on different metabolic activities of

Cordyceps have been performed both *in vitro* and *in vivo*. However, it is debatable whether *Cordyceps* is a food supplement for health maintenance or a therapeutic "drug" carrying medicinal properties. The *Cordyceps* industry has developed greatly and offers thousands of products, commonly available in a global marketplace.

Keywords: *Cordyceps*, Fungi, Traditional Medicine

Introduction

Cordyceps is a type of fungus that grows on the larva of caterpillars. It has been used for centuries in traditional Chinese medicine (TCM) to improve fatigue, cough, sexual desire, kidney function, and weakness after a severe illness^[1].

The name *Cordyceps* comes from the Latin words **Cord** which means 'club', and **Ceps** referring to 'head'^[2]. The fruiting bodies of these fungi often erupts from the head of the larva and adult stages of many different species of insect. *Cordyceps* are entomophagous fungi from the phylum Ascomycota, family Ophiocordycipitaceae, order Hypocreales, and they are known to parasitize many orders of insects at different life stages from larva to adult stages. Numerous species within the genus have a golden reputation due to their long safe history of use in traditional medicines. Used for over 2000 years in China for treating infectious diseases, *Cordyceps* are also described in the ancient books of Ben-Cao-Cong-Xin (New Compilation of Materia Medica) which is as old as 1757 years AD, and 'Ben Cao Gang Mu Shi Yi' written by Xueming Zhao in 1765 AD, *Cordyceps* is also known as 'Dong Chong Xia Cao', which means 'Worm in winter and grass in summer' in China^[3, 4, 5].

The *Cordyceps* genus contains some of the most highly prized and revered of all medicinal fungi. In spite of having a global distribution, the majority species of *Cordyceps* have been described from Asia. Grasslands, providing habitat for Thitarodes ghost moths and thus for *Cordyceps sinensis*, are a particularly important habitat and consists predominantly of sedges (*Kobresia* sp.), covering up to 80-90% of the subalpine grasslands^[6].

Cordyceps is considered as one of the largest genus containing approximately 500 species. Several species of *Cordyceps* have been cultivated for their therapeutic properties such as *Cordyceps sinensis*, *Cordyceps sobolifera*, *Cordyceps cicadicola*, *Cordyceps liangshanensis*, *Cordyceps ophioglossoides* and *Cordyceps militaris*^[7].

The most famous and widely used species of *Cordyceps* is *C. sinensis* were known as Dongchongxiacao (winter-worm summer-grass) in Chinese, is one of the most famous traditional Chinese medicines and medicinal mushrooms. The fungus attacks the larva of some species of insects (Fam. Hepialidae), and converts each larva to a sclerotium, from which the fruiting body grows *C. militaris* or as commonly known, the orange caterpillar fungus has a similar chemical composition and medicinal biological activities as *C. sinensis*^[8]. Fig (1).

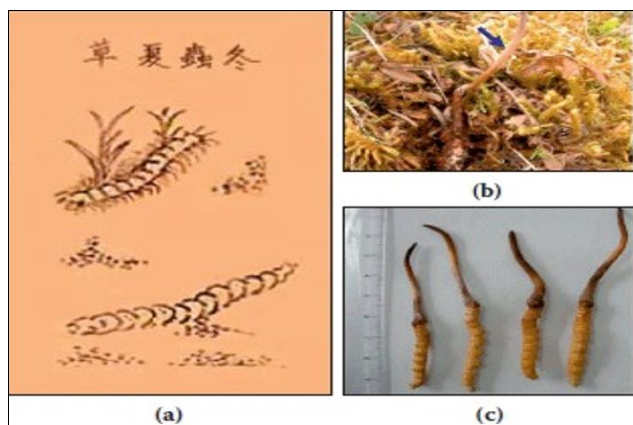


Fig 1: Illustrated (a) *Cordyceps sinensis*, (b) *C. sinensis* found in the soil (arrowhead indicates *C. sinensis*) and (c) collected as raw materials

Cordyceps Ecology

Generally, *Cordyceps* species feed on insect larvae and sometimes they also parasitize on mature insects. *Cordyceps* grow on all groups of insect-crickets, cockroaches, bees, centipedes, black beetles, and ants, to name a few. Although there are several species known to have medicinal value, only a few are cultivated and the most popular and well known are *Cordyceps sinensis* and *Cordyceps militaris*. However, *Cordyceps*, are not limited to insects and may grow on other arthropods as well as the fungi *Elaphomyces* Nees. This group belongs to the order Hypocreales, which includes 912 known species that are assigned to the families Cordycipitaceae and Ophiocordycipitaceae and partial Clavicipitaceae^[9]. *Cordyceps* only refers to the macrofungi, *Cordyceps* is very popular in China, where a huge domestic market exists.

Cordyceps Natural Products

Cordyceps have a wide range of various compounds, some are characterized as nutritional compounds, since they possess all of the important amino acids, vitamins such as K and E, besides the water-soluble B vitamins (B1, B2, and B12). In addition, they contain many sugars, including mono-, di-, and oligosaccharides, and many complex polysaccharides, proteins, sterols, nucleosides, and trace elements (Na, K, Ca, Mg, Al, Fe, Cu, V, Pi, Se, Ni, Sr, Si, Ti, Cr, Ga, Zn, and Zr)^[10, 11].

Cultivation and Growing of Cordyceps

The natural fruiting bodies of *Cordyceps* are very rare and costly to collect. Moreover, natural populations of key *Cordyceps* species are decreasing rapidly due to over collection^[12], presenting the need increased cultivation of *Cordyceps in vitro* using an artificial medium. The percentage of species that been successfully cultivated in artificial media to the total identified *Cordyceps* species is very low. Examples of some medicinally important *Cordyceps* species such as *Cordyceps sinensis*, artificial *O. sinensis*, *Cordyceps militaris*, and artificial *Cordyceps militaris*. Strain CS-4 (*Paecilomyces hepiali* Chen.) was isolated as early as 1982 as one of the first commercially used strains of *Cordyceps*. After a lot of clinical trials, the chemical composition, biological activity and toxicity of this strain became well known. The first large scale fruiting techniques used for growing *Cordyceps* reduced the natural growing cycle from 5 to 2 years, this technique included

breeding the host larvae, *Thitarodes* (*Hepialus*), then placing about 100 larvae into shoe cartonsized plastic containers covered with lids, which are filled with grassland soil comprising tubers and roots originated from their natural foods, as well as other roots from cultivation. The *C. sinensis* spores are inoculated after two years and about 10% of the larvae are actually taken over by *Cordyceps* and grow stromata^[13]. On the other hand, Arora, *et al.*^[14], succeeded in using submerged conditions for culturing *Cordyceps sinensis* at pH 6 and temperature 15° C. The growth of *C. sinensis* on sabouraud's dextrose with yeast extract broth medium was also investigated using different carbon sources, nitrogen sources, and additives (vitamins and minerals)^[15]. The greatest number of conidia were obtained under the physical stress of freeze-shock. Sucrose was the best carbon source for *C. sinensis* growth while Beef extract and yeast extract were the best nitrogen sources^[16]. Moreover, using folic acid significantly increased the yield, and adding calcium chloride and zinc chloride as micro and macronutrients, respectively increased the total yield significantly. One of the remarkably important artificial techniques for *C. sinensis* culturing was using sterile rice media at 9-13° C for 40-60 days followed by lowering temperature to 4° C for inducing stroma production and at 13° C for 40 days for the process of developing the fruiting bodies. It should be mentioned that the *Cordyceps* mycelium growth depends on different factors such as growth media, temperature, pH, and some environmental factors, but after trying different media, potato dextrose agar was proven to be the best medium using a pH range of 8.5-9.5 at 20- 25° C^[17]. Complete artificial cultivation is achieved by inoculating reared larvae with cultured strains and the infected larvae were monitored and fed indoors for one or two years. After that, *C. sinensis* could be collected. On the contrary, in seminatural cultivation, the natural habitats was used to allow infected larvae to grow freely for 3-5 years, then *C. sinensis* could be collected from the released areas. *Cordyceps militaris* cultivation is much easier than *C. sinensis* in both solid and broth media using numerous carbon and nitrogen sources, since *C. militaris* can complete its whole life cycle when cultivated in-vitro^[18]. Cultivation of *C. militaris* mycelium using artificial media has lately been developed specially for the purpose of Cordycepin production using different methods such as surface culture and submerged culture. Generally, *C. militaris* Stromata production requires 35-70 days. Nevertheless, culturing duration is critically affected by various conditions such as medium amount, volume and shape of the container used in culturing process. The growth of *C. militaris* stroma cultivation *in vitro* started with using insects to grow stromata of *C. militaris* followed by laboratory trials using various organic substrates. Cereals such as rice have been commonly used with some organic substrates for commercial production of *C. militaris* stromata^[19]. Other successful substrates include cottonseed coats, wheat grains, bean powder, corn grain, corn cobs, millet, and sorghum. The optimum organic substrate currently used is a mixture of rice and silkworm pupae. Additionally, studies have reported malt, brown rice, and soybean as superior nutritional sources for *C. militaris* in comparison with chemical media. *C. militaris* cultivation requires a relatively low level of nitrogen, which may explain lower yields when using insects in comparison with higher yields achieved when cereals were used in the culture. Plant hormones such

as colchicines, 2, 4-D, citric acid triamine can promote *C. militaris* stroma production [20]. Additionally, potassium, calcium, and magnesium salts at a concentration of 0.1 g/l can increase the yield of fruiting bodies. Mycelia production for the purpose of biologically active compounds production is also possible and has been conducted in submerged culture. *C. militaris* cultivation has been further advanced, resulting in a high yield of stromata production and high content of Cordycepin. Furthermore, the fruiting bodies production has been investigated using multi-ascospore isolates and their progeny strains for three successive generations and it was found that F1 progeny strains produced a higher number of fruiting bodies [21]. Also using different media [22].

Cordyceps Improve Athletic Performance

Cordyceps supplements are popular among athletes. The fungus is believed to benefit athletic performance by improving blood flow, increasing oxygen utilization, and functioning as an antioxidant. One study examined the effects of a mushroom blend containing *Cordyceps militaris* on high-intensity exercise after one and three weeks [23].

Cordyceps Benefit Heart Health

Cordyceps may benefit heart health by improving blood lipid (fat) levels and treating arrhythmia (irregular heartbeat). High levels of fats in the blood, also known as hyperlipidemia, is a key risk factor for heart disease [24].

A 2020 review of studies found that Cordycepin, the main bioactive compound in *Cordyceps*, can reduce the accumulation of low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides in animals [25].

A 2022 review of nineteen trials that included 1,805 patients found *Cordyceps* effective at adjusting the heart rate to a normal level in patients with arrhythmia [26].

Cordyceps Help Manage Diabetes

Diabetes is a health condition that occurs when your blood sugar is too high. It is the eighth leading cause of death in the U.S. [27] Animal studies have shown that *Cordyceps militaris* extract may help decrease blood sugar levels by improving glucose metabolism, or how efficiently the body processes sugar from foods we eat. It may also help protect against nerve damage caused by diabetes [28].

Cordyceps Reduce Inflammation

Inflammation is a normal response to injury or infection and a necessary part of the healing process. But chronic inflammation that lasts for months or years can lead to several chronic health conditions, including:

- Heart disease
- Autoimmune diseases like rheumatoid arthritis
- Irritable bowel disease
- Diabetes
- Depression
- Certain types of cancer
- Asthma
- Neurodegenerative diseases like Parkinson's disease

In fact, chronic diseases related to inflammation account for more than half of deaths worldwide [29].

A 2020 review of studies found cordycepin regulates specific pathways involved in inflammation, suggesting its potential to protect against chronic inflammatory diseases.

Cordycepin may also help boost immunity and prevent the replication of viral RNA, thereby protecting against viral infections [30].

Cordyceps Anti-Aging Properties

Oxidative stress-the imbalance between free radicals and antioxidants in the body-plays a significant role in aging and the development of age-related diseases, including dementia, arthritis, and cancer [31].

Several compounds in *Cordyceps*, including cordycepin and polysaccharides, are thought to have potent antioxidant properties [32].

Antioxidants interact with and neutralize free radicals, protecting the body from oxidative stress [33].

Cordyceps Anti-Tumor Effects

While human studies are needed, emerging evidence suggests that compounds in cordyceps may help treat cancer.

According to one 2022 review of studies, the fungus may directly act on tumor cells to kill them or prevent the growth or spread of cancer cells to other parts of the body. *Cordyceps* may also help improve the body's immune response against cancer [34].

In particular, test-tube studies have shown that cordyceps has anti-tumor effects on leukemia and cancer cells of the colon, lung, liver, bladder, breast, and prostate [35].

Cordyceps for Enhance Activity Sexual and Reproductive Function

Testosterone is necessary for normal sperm development. It activates genes in Sertoli cells, which promote differentiation of spermatogonia. *Cordyceps* has traditionally been used for the enhancement of sexual function in human beings. Evidence shows that *C. sinensis* and *C. militaris* can improve reproductive activity and restore impaired reproductive function, A protein in *C. sinensis* contributed to the observed hypotensive and vasorelaxant properties by improving the production of NO [36]; this protein might help the penis trap blood for erection, thereby improving sexual function [37].

Cordyceps Improving Kidney and Liver Functions

The results of some clinical trials revealed that the administration of *C. sinensis* could significantly improve kidney function and overall immunity of patients suffering from chronic renal failure. Moreover, treating patients with gentamicin induced kidney damage helped in recovering 89% of normal kidney function in a relatively short time. The mechanism of kidney enhancing activity of *Cordyceps* is owing to its capability to elevate 17- ketosteroid and 17-hydroxycorticosteroid levels in the body, protect sodium pump activity of tubular cells, accelerate tubular cells regeneration, and reduce calcium content in certain tissues. *Cordyceps* is universally involved as co- treatment of chronic hepatitis B and C. Extract mixture of *Cordyceps* in combination with other medicinal mushrooms in addition to the antiviral drug, lamivudine, was used for treating hepatitis B [38]. On the other hand, daily consume of *Cordyceps* improved liver functions in patients suffering from post-hepatic cirrhosis.

Cordyceps Protect Organs and Glands

Cordyceps sinensis also has obvious effects on other organ

systems. For example, in the central nervous system, *C. sinensis* has cooling, anticonvulsant and sedative activities. For the respiratory, *C. sinensis* has a strong relaxant activity on the bronchi, considerably, and also plays a key role in contraction of trachea caused by histamine, it as well has an antitussive, expectorant and anti-asthmatic effect and prevents pulmonary emphysema. Concerning endocrine system, *C. sinensis* increases secretion of adrenaline, has effects as a male hormone; Polysaccharides extracted from *Cordyceps* can increase corticosterone level in plasma. *Cordyceps* is used in traditional medicine for decades to improve men fertility. A study has proven the positive effect of using *C. militaris* mycelium on sperm motility, morphology, productivity, and enhancement of sexual activity, *Cordyceps* extracts contain adenosine, deoxyadenosine, related adenosine type nucleotides, and nucleosides which help in stabilizing heartbeat and correcting heart arrhythmias. Such compounds have an effect on coronary and cerebral circulation. *Cordyceps* is known to be used in treatment of chronic hepatitis B and C. Moreover, consuming *Cordyceps* resulted in improving liver function tests in patients suffering from post-hepatic cirrhosis^[39].

***Cordyceps* Reduction of Fatigue**

Cordyceps has been used from centuries as a remedy for weakness and fatigue by residents living in the high mountains of Tibet to give them energy which is achieved by increasing cellular ATP^[40]. Nowadays, *Cordyceps* is used by athletes to fight fatigue and weakness and to increase endurance and improve energy levels. Additionally, clinical trials involving elderly patients with chronic fatigue, results indicated that treatment with *C. sinensis* resulted in improvement of fatigue and dizziness, increasing cold intolerance, and amnesia^[41].

***Cordyceps* Side Effects and Safe**

Cordyceps is generally safe in recommended dosage and no major side effects were reported^[42].

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