**Exploring the World of *Cordyceps*: Ecology, Cultivation, Biotechnology, and Future Horizons**

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**Abstract**

The world of Cordyceps, a fascinating genus of fungi, has become a subject of intense exploration across various scientific disciplines. This manuscript presents a comprehensive overview of Cordyceps, delving into its ecology, cultivation, biotechnological applications, and future prospects. Ecologically, Cordyceps have intrigued researchers with their intricate life cycles and intriguing interactions with insect hosts. Their unique ability to manipulate host behavior and propagate within their bodies underscores their evolutionary adaptations, with potential implications for pest control and biodiversity conservation. Advancements in cultivation techniques have enabled the mass production of Cordyceps, alleviating pressure on wild populations and stimulating interest in their commercial exploitation. This newfound cultivation potential has opened doors for their use in the nutraceutical and pharmaceutical industries, as they serve as a source of bioactive compounds and medicinal properties. The biotechnological applications of Cordyceps hold tremendous promise in medicine and agriculture. Their production of bioactive compounds, such as cordycepin and polysaccharides, has shown therapeutic potential for various ailments. Additionally, their role in bioremediation and agriculture showcases their versatility in addressing modern challenges. Integrating traditional knowledge with modern scientific approaches will yield comprehensive insights into their ecological roles and potential benefits. the exploration of the world of Cordyceps offers a captivating journey that unites ecology, cultivation, biotechnology, and future prospects. By leveraging scientific curiosity, technological advancements, and environmental responsibility, we can tap into the vast potential of Cordyceps for the betterment of humanity and our planet. This manuscript serves as a stepping stone to uncover the enigmatic secrets of Cordyceps and embrace the boundless opportunities they present.



**Figure 1. Graphical abstract**

**Keywords:** Cordyceps**, caterpillar fungus, *Cordyceps sinensis* and *Cordyceps militaris*, Mycology**

1. **INTRODUCTION**

 Mushrooms stand as prominent macro fungi, boasting spore-bearing structures known as fruiting bodies. They manifest either as saprophytes on the soil's surface or as parasites on their host organisms. Displaying a remarkable nutritional profile akin to various vegetables, mushrooms often act as a meat substitute [6-10]. Beyond their culinary significance, their saprophytic nature contributes significantly to ecological recycling, transforming agricultural residues, culinary remnants, and decaying matter into profoundly nourishing sustenance [11-15]. Moreover, mushrooms emerge as abundant reservoirs of diverse compounds like terpenes, phenolic substances, fatty acids, glucans, polysaccharides, and proteins. These compounds underscore the extensive array of biological activities witnessed across several mushroom species, encompassing anticancer, antiviral, antitumor, antidiabetic, antidepressant, antioxidant, immunomodulatory, anti-inflammatory, neuroprotective, hepatoprotective, nephroprotective, osteoprotective, hypotensive, antiallergic, and antimicrobial properties [16-20]. While research has traditionally concentrated on specific species, particularly those entrenched within Asian cultures [21-25], recent attention has pivoted towards elucidating mushrooms' chemical composition. This exploration seeks to unveil biotechnological possibilities, encompassing potential medical and pharmaceutical applications of these magnanimous macrofungi [26-32]. Among such mushrooms Cordyceps mushrooms are amongst those parasitic fungi that include over 400 different species. They grow all over the world in countries like China, Japan, India, the United States, Australia, Peru, Bolivia, and many more. Among these remarkable mushrooms, Cordyceps species emerge as intriguing parasitic fungi, with over 400 distinct members. Spanning the globe in locales such as China, Japan, India, the United States, Australia, Peru, Bolivia, and more, Cordyceps derive their name from Latin roots: "cord" denoting 'club,' and "ceps" alluding to 'head.' The fruiting bodies of Cordyceps fungi often erupt from the craniums of both larval and adult stages of diverse insect species. These entomophagous fungi fall within the Ascomycota phylum, Ophiocordycipitaceae family, and Hypocreales order. They exhibit the ability to parasitize insects across various developmental stages, from larvae to adults.

 The genus Cordyceps bears a prestigious history, having been harnessed for over two millennia in traditional Chinese medicine for treating infectious ailments. References to Cordyceps can be traced back to ancient texts such as "Ben-Cao-Cong-Xin" (New Compilation of Materia Medica), which dates back 1757 years AD, and "Ben Cao Gang Mu Shi Yi" penned by Xueming Zhao in 1765 AD. Notably, the Cordyceps genus harbors some of the most cherished and revered medicinal fungi. Despite their global distribution, a considerable number of Cordyceps species hail from Asian regions. Although "Cordyceps" commonly refers to two primary species, Cordyceps sinensis and Cordyceps militaris, the genus encompasses a staggering 400 mushroom species. The former, Cordyceps sinensis, hosts a broad range of hosts, encompassing Lepidopteran larvae, various Thitarodes caterpillars, and its predominant host, the Himalayan bat moth Hepialus armoricanus. A kin species, C. militaris, also known as the orange caterpillar fungus, boasts comparable chemical composition and medicinal attributes to C. sinensis. [34].

1. **WILD *CORDYCEPS SINENSIS* – THE CATERPILLAR FUNGUS**

Certainly, the Cordyceps genus is prominently represented by Cordyceps sinensis, which has been formally reclassified as Ophiocordyceps sinensis. This species exhibits a remarkable parasitic relationship with the caterpillar of the Hepialus moth. Cordyceps sinensis predominantly thrives at elevated altitudes in regions such as Tibet and the Chinese provinces of Sichuan, Yunnan, Qinghai, and Gansu. Although it can also be located in other areas including India, Nepal, and Bhutan, its abundance is notably lower in these regions. The name "Yarsagumba" or "yartsa gunbu" is associated with this species in Tibet, while in China, it is referred to as "Dōnɡ Chónɡ Xià Cǎo," which translates to "summer grass, winter worm." This nomenclature highlights the unique seasonal pattern of its life cycle

1. **HISTORY OF YARTSA GUNBU**

The mushroom mentioned has an extensive history of collection in the Tibetan plateau, spanning several centuries. Interestingly, it has recently emerged as a significant economic driver in that region. Yartsa Gunbu, as it is known, takes root on caterpillars within the Himalayan shrub lands. This unique fungus infects the caterpillars during the autumn months, gradually consuming their bodies over the winter. As spring arrives, Yartsa Gunbu produces a fruiting body that matures throughout the summer and releases spores in late summer. Notably, caterpillars in the area undergo molting, shedding their skin, making them particularly vulnerable to infection during the late summer. To collect this valuable fungus, harvesters typically venture out in the months of May and June.

The economic impact of Yartsa Gunbu on rural Tibetan families is substantial, contributing to nearly 40% of their income. This mushroom's significance is not a recent discovery; it was documented in medicinal texts dating back to approximately 1450 in Tibet. Likewise, within the realm of Traditional Chinese Medicine, it made its literary debut in 1694. Although the Cordyceps genus itself was classified by Carl Linnaeus in 1753, the introduction of Yartsa Gunbu to Western audiences is a relatively recent development, taking place around the early 2000s. This underscores the mushroom's growing recognition and relevance beyond its traditional context.(33)

1. **HISTORY OF CORDYCEPS MILITARIS HISTORY**

The naming journey of *Cordyceps militaris* has been marked by changes from its initial classification in 1753 until it eventually received its current nomenclature in 1818 in Paris. While Cordyceps is distributed across Europe and the United States, it tends to be more prevalent to the east of the Rocky Mountains in the U.S. This parasitic mushroom follows a lifestyle of consuming insect larvae and pupae, with a primary preference for those of moths and butterflies.

Interestingly, the cultivation of *Cordyceps militaris* has a longer history in Asia compared to the United States. The cultivation efforts gained momentum in Asia during the early 2000s, particularly following a surge that commenced in the late 1990s. A significant turning point in the United States was in the late 2015 period when individuals such as William Padilla-Brown, a technical advisor for the project, and Ryan Gates, achieved success in growing fruiting bodies. They identified a specific combination of substrate and strain that led to fruiting body production. Subsequently, numerous trials involving various strains and substrates have been carried out to identify a commercially viable combination. Since the early months of 2016, a growing number of farms and cultivators in the U.S. have taken a keen interest in the cultivation of *Cordyceps militaris.* (34)

1. ***CORDYCEPS* ECOLOGY**

Cordyceps species exhibit a dietary preference for insect larvae and sometimes even mature insects. Their host range spans various insect groups, encompassing crickets, cockroaches, bees, centipedes, black beetles, ants, and more. While numerous Cordyceps species possess medicinal potential, only a select few are actively cultivated, with the most recognized being Cordyceps sinensis and Cordyceps militaris. It's important to note that Cordyceps fungi are not limited exclusively to insects; they can also thrive on other arthropods and even the fungi Elaphomyces Nees.

Within the order Hypocreales, there is a broad representation of Cordyceps species, totaling 912 known members, classified under the families Cordycipitaceae, Ophiocordycipitaceae, and partial Clavicipitaceae [35]. It's worth highlighting that the term "Cordyceps" specifically pertains to macrofungi. These macrofungi were formerly categorized under the previous genus Cordyceps Fr. within the Clavicipitaceae family and Clavicipitales order.

Given their unique blend of edible and medicinal attributes, Cordyceps species enjoy immense popularity in China, particularly within a robust domestic market. In the Chinese context, the term "Cordyceps" often specifically refers to "Dongchong Xiacao," which translates to "worm in winter, herb in summer." This refers specifically to Ophiocordyceps sinensis, the most esteemed and expensive type, exclusively sourced from the Tibetan Plateau. It's notable that other Cordyceps species available in the market might be labeled as "fake Dongchong Xiacao." Some of these alternatives might not align with the traditional usage and consumption of the genuine species .

1. **ECOLOGICAL ROLES OF FUNGI**

Fungi within ecosystems generally perform three distinct ecological roles: parasitic, mycorrhizal, and saprophytic.

**Saprophytic Fungi:** These organisms play a crucial role in decomposing dead matter. They are responsible for breaking down materials such as wood, leaves, manure, and corpses. Saprophytic fungi are essential for the cycle of nutrient flow on Earth, connecting the processes of death and life. Cultivating saprophytic fungi, such as mushrooms, is relatively straightforward since they can be provided with dead material and favorable conditions for growth. Substrates like logs, sawdust, and wheat bran are easily manageable, making it simpler to create the required conditions for mushroom cultivation. Notably, Cordyceps militaris is a versatile fungus that can exhibit both saprophytic and parasitic behaviors, allowing for the cultivation of mushroom fruiting bodies even in the absence of a living host.

**Mycorrhizal Fungi:** These fungi establish symbiotic relationships with plant roots. The term "myco" refers to fungi, and "rhizal" pertains to roots, essentially indicating a fungal-root association. Mycorrhizal fungi are present on over 90% of plant species. Trees in particular often have fungal partners attached to their root systems. Mycorrhizal fungi play diverse roles in aiding plant health, facilitating nutrient access, and enabling communication between individual plants. Intriguingly, these fungi form intricate networks that connect plants of the same and different species. Nutrients flow through these networks, bridging healthy and unhealthy trees, as well as young and mature trees. This mycorrhizal communication system even conveys information about potential stressors like pest invasions. At the individual plant level, mycorrhizal fungi effectively extend the plant's root system, allowing access to nutrients like phosphorus and pockets of water that would otherwise remain inaccessible due to their smaller filament size. In return for these nutrients and water, plants offer the fungi sugars produced through photosynthesis.

**Parasitic Fungi:** This category includes fungi that attack and parasitize living organisms. Parasitic fungi sometimes contribute to the negative reputation associated with the entire fungal kingdom due to their perceived adverse effects on human systems. These parasites significantly impact crop yield in agricultural systems. Practices like monoculture and the cultivation of weak plants create environments conducive to fungal diseases. During wet periods, these diseases can rapidly spread, affecting entire regions over a single growing season. Many of these parasitic fungi do not produce mushrooms; instead, they exist primarily in the mycelial and spore stages of their life cycle. Some employ asexual reproduction, generating genetically identical spores for dispersal. While most parasitic fungi attack plants or trees, Cordyceps stands out as a parasite of insects. Cordyceps targets living insect larvae or pupae, consuming them and eventually fruiting from the deceased insect's body. Certain Cordyceps species are even capable of adopting a saprophytic lifestyle, enabling human cultivation of fruiting bodies without the presence of insects.

1. **CORDYCEPS GROWTH AND CULTIVATION**

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 [38], presenting the need increased cultivation of Cordyceps in vitro using an artifi cial medium. The percentage of species that been successfully cultivated in artifi cial media to the total identifi ed Cordyceps species is very low. Examples of some medicinally important Cordyceps species such as Cordyceps sinensis, artifi cial 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 fi rst 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 fi lled 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 [39]. On the other hand, Arora, et al. [40], succeeded in using submerged conditions for culturing Cordyceps sinensis at pH 6 and temperature 15ºC.The growth of C. sinensis on sabouraud’s dextrose with yeast extract broth medium was also investigated using diff erent carbon sources, nitrogen sources, and additives (vitamins and minerals) [41]. 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 [42]. Moreover, using folic acid signifi cantly 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 artifi cial 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 differrant factors such as growth media, temperature, pH, and some environmental factors, but after trying diff erent media, potato dextrose agar was proven to be the best medium using a pH range of 8.5-9.5 at 20- 25°C [43]. Complete artifi cial 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 [44].

 Cultivation of C. militaris mycelium using artifi cial media has lately been developed specially for the purpose

 of Cordycepin production using diff erent 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 [45]. 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

 [46]. 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

 [47].

**6. Biotechnological applications of *Cordyceps***

*Cordyceps* is a genus of fungi that has been used for centuries in traditional medicine, particularly in East Asian countries. *Cordyceps* is not only edible, but also valuable source of various bioactive metabolites that offer numerous medicinal advantages. In recent years, there has been growing interest in the biotechnological applications of *Cordyceps* due to its potential health benefits and medicinal properties. Here are some of the key biotechnological applications of *Cordyceps*:

1. **Medicinal Properties:** Cordyceps is known for its various medicinal properties, including antioxidant, immunomodulatory, anti-inflammatory, and anticancer activities. Biotechnological research is focused on understanding the mechanisms behind these properties and developing pharmaceutical products based on Cordyceps extracts or bioactive compounds. Cordyceps species are known for their diverse medicinal properties, including antioxidant, immunomodulatory, anti-inflammatory, antimicrobial, and anticancer activities. They have been used to treat various ailments and promote overall well-being (Lo et al., 2019; Patel et al., 2021).
2. Immunomodulatory Activity:

Cordyceps has been shown to enhance the immune response by stimulating the production and activity of immune cells. Biotechnological studies are exploring the development of immunomodulatory products from Cordyceps that can be used to boost the immune system and prevent or manage various diseases. Immunomodulation:

Cordyceps extracts have been shown to modulate the immune system by enhancing the activity of immune cells, promoting the production of cytokines, and improving overall immune function. They have potential applications in immunotherapy and as adjuvants in vaccine development (Patel et al., 2021; Zhu et al., 2019).

 Cordyceps exhibits immunomodulatory effects, meaning it can modulate the immune system by enhancing immune function or regulating an overactive immune response. It has been shown to stimulate the production of immune cells, such as natural killer (NK) cells, T cells, and B cells, and promote the release of immune-modulating cytokines (Borchers et al., 2012; Lo et al., 2017). This immunomodulatory activity is believed to contribute to the potential therapeutic effects of Cordyceps in supporting the immune system.

1. Antioxidant Properties:

Cordyceps is rich in antioxidants, which are compounds that help protect the body against oxidative stress caused by free radicals. Free radicals are highly reactive molecules that can damage cells and contribute to various diseases and aging. The antioxidants in Cordyceps, such as cordycepin and polysaccharides, help neutralize free radicals and reduce oxidative damage, thereby promoting overall health and well-being (Patel et al., 2012; Phan et al., 2018).

1. Anti-inflammatory Effects:

 Chronic inflammation is associated with many diseases, including cardiovascular diseases, neurodegenerative disorders, and autoimmune conditions. Cordyceps has been found to possess anti-inflammatory properties by inhibiting the production of pro-inflammatory cytokines and reducing the activity of inflammatory enzymes (Phan et al., 2018; Wang et al., 2018). These anti-inflammatory effects may contribute to the potential therapeutic benefits of Cordyceps in managing inflammation-related conditions.

1. Adaptogenic Properties:

 Cordyceps is classified as an adaptogen, a substance that helps the body adapt to stress and maintain balance (homeostasis). It is believed to support the body's resilience and enhance its ability to cope with physical, mental, and environmental stressors. Cordyceps may help improve energy levels, reduce fatigue, and support overall vitality and stamina (Koh et al., 2003; Li et al., 2017).

1. Potential Anticancer Activity:

Studies have suggested that Cordyceps may possess anticancer properties by inhibiting the growth of cancer cells, promoting apoptosis (programmed cell death) in cancer cells, and suppressing tumor angiogenesis (the formation of new blood vessels to support tumor growth) (Ma et al., 2019; Wang et al., 2020). However, further research is needed to fully understand the mechanisms and potential clinical applications of Cordyceps in cancer treatment.

1. **Anti-Microbial Activity:** Cordyceps extracts have demonstrated antimicrobial activity against various pathogenic bacteria, fungi, and viruses. This has potential applications in developing natural antimicrobial agents or supplements to combat drug-resistant infections.

Antibacterial Activity:

Several studies have reported the antibacterial effects of Cordyceps species against a range of bacterial strains. For example, a study found that Cordyceps militaris exhibited antibacterial activity against Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa (Zhao et al., 2012). Another study demonstrated that Cordyceps sinensis extracts inhibited the growth of Methicillin-resistant Staphylococcus aureus (MRSA) (Zhong et al., 2015). These findings suggest the potential of Cordyceps as a natural antibacterial agent.

Antifungal Activity:

Cordyceps species have also shown antifungal activity against various fungal pathogens. A study found that Cordyceps sinensis exhibited antifungal effects against Candida albicans, a common fungal pathogen causing infections in humans (Wu et al., 2007). Another study reported that Cordyceps militaris extracts displayed antifungal activity against dermatophytes, which are fungi causing skin infections (Yang et al., 2013). These findings suggest the potential of Cordyceps in managing fungal infections.

Antiviral Activity:

Cordyceps species have been investigated for their antiviral properties. Research has shown that Cordyceps extracts possess antiviral activity against various viruses, including influenza viruses, herpes simplex virus, and hepatitis B virus (Chen et al., 2014; Liu et al., 2015; Yue et al., 2017). These studies suggest that Cordyceps may have the potential to inhibit viral replication and provide antiviral effects.

Antiparasitic Activity:

Cordyceps species have also demonstrated activity against parasites. In a study, Cordyceps militaris extracts exhibited antiparasitic effects against Plasmodium falciparum, the parasite responsible for malaria (Li et al., 2018). Another study showed that Cordyceps extracts inhibited the growth of Leishmania donovani, a parasite causing leishmaniasis (Ghosh et al., 2012). These findings suggest the potential of Cordyceps in the management of parasitic infections.

1. **Anti-Aging and Anti-Oxidant Effects**: Cordyceps contains bioactive compounds that possess anti-aging and antioxidant properties. These compounds help neutralize free radicals in the body, reduce oxidative stress, and protect against age-related diseases. Biotechnological research aims to identify and isolate these compounds for use in anti-aging and skincare products. Protecting against damage of cells by free radicals is

one of the biological activities exerted by Cordyceps species extracts. This activity is corresponding to polysaccharide fraction. C. sinensis has potent antioxidant and anti-ageing properties. Many studies elucidated the antioxidant eff ect of extracts obtained from C. militaris. The fruiting bodies extract

of C. militaris had a potent DPPH· radical scavenging activity, whereas the fermented extract of mycelia had stronger total antioxidant activity, and reducing ability [63].

1. **Therapeutic effects and Health Benefits:** Species of Cordyceps are widely researched due to the endless list of medicinal biological activities exerted by their extracted compounds as shown by some examples in

table 1, with various medical and nutritional values. The main uses of Cordyceps have been known in oriental old medicine for curing respiratory diseases such as asthma and bronchial cases, as well as for providing body with energy and for boosting sexual power. Modern research now confirms the efficiency of Cordyceps in many other fields. One of the breakthroughs of modern research has been the discovery of cordycepin, which has a strong antimicrobial activity against almost all species of bacteria exhibiting resistance to frequently used antibiotics. Cordyceps showed strong activity against tuberculosis, leprosy and human leukaemia, as shown in many clinical trials in Asia and elsewhere. Cordyceps was shown to be potent in increasing the maximum amount of oxygen and to improve respiratory function. There are a number of components like

deoxynucleosides produced by Cordyceps sinensis, such as the compounds 2’, 3’ deoxyadenosine which is marketed under the trade name "Didanosine" in the USA as a medication for treatment of AIDS. Similarly, Quinic acid derived from Cordycepin (3’ deoxyadenosine) present in Cordyceps is found to have antiviral and antibacterial property [49]. Numerous studies have verified the benefits of C. *sinensis* in treating disturbances in heart rhythm as cardiac arrhythmia and chronic heart failure.

Table 1: Common therapeutic effects of different *Cordyceps* sp. (Elkhateeb *et al*., 2022)

|  |  |  |
| --- | --- | --- |
| Therapeutic effects | Cordyceps spp. | Major bioactive compounds |
| Antitumor | C. sinensis | CordycepinCordyglucansMonosaccharide saponinsEPSF |
|  | C. militaris | cordycepin and mannitol |
| Anti-diabetic effects | C. sinensisC. militaris | CordyminCordycepin, adenosine |
| Anti-infl ammatory | C. sinensisC. militaris | CordycepinAdenosineβ-(13)-D-glucan |
| Anti-oxidant activity | C. sinensis | Exopolysaccharide fraction,EPSFCPS-1CME-1 |
|  | C. militaris | Polysaccharide (PSC) |
| Antimicrobial activity | C. sinensisC. militaris | CordycepinErgosterolMannitol, trehalose,Polyunsaturated fattyacids, δ-tocopherol andp-Hydroxybenzoic acid |
| Anti-infl uenza | C. militaris | Polysaccharide (PSC) |
| Anticonvulsant activity | C. sinensis | Adenosine |

1. **Anticancer Activities of Cordyceps:**

Various biologically active compounds exerting an anticancer activity were extracted from Cordyceps.

Cordycepin has an antitumor activity in B16 melanoma cells. Cordycepin induced apoptosis in Mouse Leydig tumor cell in vitro. Also, it inhibits cell proliferation and further apoptosis of human colorectal carcinoma using SW480 and SW620 in vitro. In gallbladder cancer cell, cordycepin causes loss of cancer cell viability and apoptosis via inhibiting the mammalian target of rapamycin complex 1 [50]. C. militaris was found to inhibit U937 cells grown in a dose dependent manner and also in the treatment of human leukaemia. Cordyceps has shown promising activities in inhibiting the growth of cancer cells [51] and in some cases could reduce tumor size. Clinical trials on cancer patients have been conducted in many Asian countries, showing promising results in reducing tumor size, improving tolerance for chemotherapy and/or radiation and in stimulating the immune system which hence enhances the effi ciency of chemotherapy. Ethanolic extract of C. militaris showed a potent antitumor eff ect in RMA cell-derived tumors at a xenograft mouse model [52]. Moreover, some Cordyceps species have anti-leukaemia activities and ameliorate suppressive eff ects of chemotherapy on bone marrow function as a model for cancer treatment [53].

1. **Hypoglycemic and Hypocholesterolemic Effect**

Cordyceps are found to regulate and also lower the blood sugar levels by improving metabolism of glucose and conserving hepatic glycogen [3]. Furthermore, Cordyceps can increase secretion of glucokinase and hexokinase which are glucose regulating enzymes secreted by the liver [54]. Polysaccharides are the key player in showing the hypoglycaemic activity of Cordyceps. For example, the polysaccharide (CS-F30) obtained from C. sinensis culture mycelium exerted a potent hypoglycaemic activity when intraperitoneal administrated in genetically diabetic mice. In addition, dramatic reduction in plasma glucose level was

reported after intravenous administration of CS-F30 in normal and streptozocin-induced diabetic mice. A diff erent polysaccharide, (CS-F10), was extracted and identifi ed from a hot-water extract of C. sinensis cultured mycelia and composed of galactose, glucose and mannose in a molar ratio of 43:33:24, could successfully lower the level of plasma glucose in normal, adrenaline-induced hyperglycaemic and diabetic mice. Hypercholesterolemia is an indicator for high risk of cardiovascular attack. Many studies have reported

the role of C. sinensis in lowering the total cholesterol level and the level of triglycerides (Geng 1985). It also helps in increasing the ratio of the good cholesterol [High Density Lipoprotein (HDL cholesterol)] to bad cholesterol [Low Density Lipoprotein (LDL cholesterol)]. A hot-water extract of the mycelia of C. sinensis has been proven to decrease serum total cholesterol concentration in tested mice, by reducing LDL and very-low-density lipoprotein, and elevating the concentration of the good cholesterol (HDL cholesterol) [55].

1. **Bioremediation:** Cordyceps has shown the ability to degrade or detoxify pollutants in the environment, making it a potential candidate for bioremediation of contaminated soils or water bodies. Biotechnological research is exploring the use of Cordyceps to clean up pollutants and mitigate environmental damage.

Cordyceps fungi have been studied for their potential role in bioremediation, particularly in the degradation and removal of various pollutants from the environment. Here are some studies that highlight the role of Cordyceps in bioremediation:

* **Degradation of Organic Pollutants:**

Cordyceps species have shown potential in the degradation of organic pollutants. For example, a study demonstrated that Cordyceps militaris was able to degrade polycyclic aromatic hydrocarbons (PAHs), a group of organic pollutants commonly found in contaminated soil and water (Wu et al., 2011). The study found that Cordyceps militaris effectively degraded various PAH compounds and suggested its potential use in bioremediation strategies.

**Heavy Metal Remediation:**

Cordyceps fungi have also shown promise in the removal of heavy metals from contaminated environments. In a study, Cordyceps militaris was found to have the ability to bioaccumulate and remove lead (Pb) and cadmium (Cd) from contaminated soils (Wu et al., 2013). The study demonstrated that Cordyceps militaris effectively reduced the concentration of these heavy metals in soil, indicating its potential as a bioremediation agent for heavy metal-contaminated sites.

**Mycoremediation of Pesticides:**

Cordyceps species have shown potential in the degradation of pesticides. A study investigated the mycoremediation ability of Cordyceps sp. in the degradation of the pesticide chlorpyrifos in contaminated soil (Wu et al., 2014). The results indicated that Cordyceps sp. significantly enhanced the degradation of chlorpyrifos, suggesting its potential use in pesticide-contaminated soil remediation.

**Biodegradation of Synthetic Dyes:**

Cordyceps fungi have also demonstrated their capability in the degradation of synthetic dyes, which are common pollutants in wastewater. A study investigated the biodegradation of a textile dye, Reactive Black 5, by Cordyceps sp. (Kavitha et al., 2016). The study found that Cordyceps sp. effectively degraded the dye, indicating its potential application in the treatment of dye-containing wastewater.

Overall, the biotechnological applications of Cordyceps are diverse and promising. Ongoing research and development in this area have the potential to revolutionize the medicinal mushroom industry and improve human health and well-being.

1. **Global Market, Future Trends and Challenges**

The Cordyceps industry is strong and growing. Various products were commercialized for compounds originated from Cordyceps species. Some major Cordyceps based companies are listed in table 2, and examples for some cosmetics containing Cordyceps sinensis and Cordyceps militaris extracts and their benefi cial functions are mentioned in table 3.

Table 2: List of major Cordyceps based companies.

|  |  |
| --- | --- |
| Cordyceps Company | Country of origin |
| ALOHA MEDICINALS | USA https://www.alohamedicinals.com |
| DOCTORS BEST | USA https://www.drbvitamins.com |
| HOSTDEFENSEMUSHROOMS | USA https://hostdefense.com |
| PARADISE | USA https://paradiseherbs.com |
| SOLARAY | USA https://www.naturalhealthyconcepts.com |

Table 3: Cosmetic products containing *Cordyceps sinensis* and *Cordyceps militaris* extract and their functions.

|  |  |  |
| --- | --- | --- |
| Product name | Function | References |
| CORDYCEPS (MUSHROOM EXTRACT) | Improved lungs and kidney function |  |
| CORDYCEP | Support healthy immune and vascular systems |  |
| ULTRA CORDYCEPS PLUS | Support lung health and liver function |  |
| HOST DEFENSE CORDYCEPS | Promotes healthy kidney function and Augments oxygen uptake |  |
| PERFECT CORDYCEPS | Boost the Immune System and Improve Sexual Function |  |

The decline in wild-harvest, compounded by ever increasing global demand is leading to record prices and global attention [65]. Global production of just O. sinensis is estimated to be in the region of 85 to 185 tons, with further tonnage provided by other Cordyceps species. The harvesting and sale of non-cultivated Cordyceps can have a signifi cant impact on household incomes in the regions in which it is collected. For example, a survey in 2004 of rural Tibet revealed that 40% of annual household cash income and 8.5% of GDP was generated by sales of O. sinensis [66]. This sizable contribution to the Tibetan economy is refl ected in the fact that global prices have risen dramatically at an average rate of 21.2% per annum, infl ationadjusted, between 1997 and 2004. This high value product is an economic boon to rural areas but this comes at a cost.

For example, confl icts over collecting-grounds may be common, causing diffi culties for local governing bodies and occasionally resulting in violence, such as the death of seven farmers in 2009. A dramatic rise in harvesting intensity has also been implicated in a possible collapse of this species in some areas, such as rural china where a few thousand kgs were collected 2001, representing a decrease of over 70%. Further, associated conservational issues with high intensity collection in these sensitive grassland ecosystems on fl ora and fauna can be signifi cant [67]. Indeed, the flora that is being impacted may itself be important for O. sinensis survival, further contributing to a decline [68]. Clearly continued wild-harvesting of Cordyceps at the current rate may not be sustainable and this is where the burgeoning cultivation industry may be able to contribute. Cultivation of currently exploited as well as new species, is an emerging trend in the Cordyceps industry, with new isolates frequently being reported. However, despite the recent successes in cultivation, there remains many challenges including (1) how to reduce the rearing cost of the ghost moth; (2) how to prevent contaminating microbes during the cultivation cycle; (3) how to streamline the cultivation process [69]. Cordyceps cultivation remains an area of intense activity and developments are expected that may aid the economic and reliable cultivation of these

species. The intense global interest and value assigned to Cordyceps has led to a large range of commercial products derived from these fungi all over the world as shown in fi gures 1-3. In parallel, there has emerged an issue with counterfeit and contaminated products [70]. Although this is not an issue confi ned to Cordyceps products, increased quality control and authentication methods are needed and these are being developed using, for example, nucleosides, ergosterol, mannitol and polysaccharides markers. Despite the challenges in cultivation, harvesting and downstream products, top quality Cordyceps trade for around 100,000 USD/kg [65] a clear sign that the industry is strong and here to stay.

**Conclusion**

In conclusion, delving into the world of Cordyceps has unveiled a wealth of knowledge and possibilities in the fields of ecology, cultivation, biotechnology, and beyond. This manuscript has shed light on the captivating aspects of this unique genus of fungi and its immense potential for various applications. Ecologically, Cordyceps have exhibited fascinating life cycles and interactions with their insect hosts. Their ability to manipulate host behavior and propagate within their bodies showcases a remarkable adaptation that continues to intrigue researchers and nature enthusiasts alike. Understanding the intricate ecological relationships between Cordyceps and their hosts not only contributes to the broader field of mycology but also has implications for pest control and biodiversity conservation. On the front of cultivation, advancements in technology and research have paved the way for mass production of Cordyceps. The breakthroughs in artificial cultivation methods have not only alleviated pressure on wild populations but have also opened doors for their commercial exploitation in the nutraceutical and pharmaceutical industries. The potential of Cordyceps as a valuable source of bioactive compounds and medicinal properties is now more tangible than ever. Biotechnological applications of Cordyceps have provided exciting prospects for medicine and agriculture. The production of bioactive compounds and functional metabolites, such as cordycepin and polysaccharides, holds promise for various therapeutic purposes. Additionally, their potential use in bioremediation and agriculture shows the versatility of this fungus in addressing modern-day challenges. As we conclude this manuscript, let us remain committed to unraveling the mysteries of Cordyceps and preserving the delicate balance between scientific progress and ecological harmony. By doing so, we can truly unlock the secrets of these enigmatic fungi and embrace the boundless opportunities they offer.

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