EXPLORING THE WORLD OF *CORDYCEPS*: ECOLOGY, CULTIVATION, BIOTECHNOLOGY, AND FUTURE HORIZONS

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

Authors

Madhavi Tiwari
Department of Applied Sciences
Shri Rawatpura Sarkar University
SRU
Raipur, Chhattisgarh, India.

Aashish Saraf
MATS School of Sciences
MATS University
Raipur, Chhattisgarh, India.

Tuneer Khelkar
Department of Botany
Government Kaktiya P.G. College
Jagdalpur, Chhattisgarh, India.

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

I. 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 [1]. Beyond their culinary significance, their saprophytic nature contributes significantly to ecological recycling, transforming agricultural residues, culinary remnants, and decaying matter into profoundly nourishing sustenance [2]. 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 [3]. While research has traditionally concentrated on specific species, particularly those entrenched within Asian cultures [4], 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 [5]. 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. [6].

II. 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 "Dōng Chóng 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[7].

2. **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* [8].

III. *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 [9]. 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.

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

1. **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.

2. **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.

3. **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.

IV. CORDYCEPS GROWTH AND CULTIVATION

Cultivating Cordyceps fungi, given their rarity and the rapid decline of natural populations due to overharvesting [10], has become increasingly important. This necessitates in vitro cultivation using artificial mediums. It's important to note that only a small percentage of Cordyceps species have been successfully cultivated in artificial media. Notable examples include Cordyceps sinensis and its artificial counterpart, O. sinensis, as well as Cordyceps militaris and its artificial equivalent, Cordyceps militaris.

One commercially significant strain of Cordyceps, CS-4 (Paecilomyces hepiali Chen.), was isolated as early as 1982. This strain was among the first to be used for commercial cultivation of Cordyceps. Extensive clinical trials have led to a comprehensive understanding of its chemical composition, biological activities, and toxicity. Innovative techniques have been developed to facilitate large-scale fruiting and reduce the natural growing cycle from five to two years. These techniques involve breeding the host larvae, Thitarodes (Hepialus), and placing around 100 larvae into shoe carton-sized plastic containers covered with lids. These containers are filled with grassland soil comprising tubers and roots from their natural foods, along with other roots from cultivation. After two years, C. sinensis spores are inoculated, and approximately 10% of the larvae are colonized by Cordyceps, ultimately giving rise to stromata [10].

In another approach, Arora *et al*. [11] successfully cultured Cordyceps sinensis under submerged conditions at a pH of 6 and a temperature of 15ºC. The study explored the growth of C. sinensis using different carbon sources, nitrogen sources, and additives such as vitamins and minerals [12]. Notably, the highest number of conidia was obtained when the fungi were subjected to the physical stress of freeze-shock. Sucrose was found to be the most suitable carbon source for *C. sinensis* growth, while beef extract and yeast extract were identified as optimal nitrogen sources [13]. Furthermore, the addition of folic acid significantly increased the yield, and the incorporation of calcium chloride and zinc chloride as micro and macronutrients, respectively, led to a substantial increase in the total yield [11]. These findings highlight the importance of optimizing growth conditions and nutrient supplementation in *Cordyceps* cultivation.

Cultivating Cordyceps sinensis using artificial techniques has yielded remarkable results. One significant method involves using sterile rice media at temperatures between 9-13°C for 40-60 days. Subsequently, the temperature is lowered to 4°C to induce stroma production and then raised again to 13°C for 40 days to facilitate the development of fruiting bodies. It's worth noting that Cordyceps mycelium growth is influenced by various factors, including growth media, temperature, pH, and environmental conditions. After experimenting with different media types, it was determined that potato dextrose agar with a pH range of 8.5-9.5 at temperatures between 20-25°C is the most effective medium [14]. Achieving complete artificial cultivation involves inoculating reared larvae with cultured strains, closely monitoring the infected larvae, and providing indoor care for one or two years. Following this period, Cordyceps sinensis can be collected. In contrast, semi-natural cultivation utilizes natural habitats, allowing infected larvae to grow freely for 3-5 years before collecting C. sinensis from the release sites.

Cultivating Cordyceps militaris is notably simpler than C. sinensis, both in solid and broth media, and can be done using various carbon and nitrogen sources. C. militaris can complete its entire life cycle when cultivated in vitro [15]. Mycelium cultivation of C. militaris for Cordycepin production has gained attention and employs methods such as surface culture and submerged culture. Generally, the production of C. militaris stromata takes 35-70 days. However, the duration of cultivation is significantly influenced by factors like the quantity of medium used, as well as the volume and shape of the container employed.

The evolution of C. militaris stroma cultivation in vitro began with the use of insects to grow C. militaris stromata, followed by laboratory experiments using various organic substrates. Common substrates include cereals like rice, cottonseed coats, wheat grains, bean powder, corn grain, corn cobs, millet, and sorghum. The currently favored organic substrate is a mixture of rice and silkworm pupae. Additionally, studies have identified malt, brown rice, and soybean as superior nutritional sources for C. militaris compared to chemical media. *C. militaris* cultivation requires a relatively low level of nitrogen, which may explain why using insects results in lower yields compared to using cereals in the culture. The application of plant hormones such as colchicines, 2,4-D, and citric acid triamine has been found to promote *C. militaris* stroma production [8]. Moreover, the inclusion of potassium, calcium, and magnesium salts at a concentration of 0.1 g/l can increase fruiting body yields. It's also possible to produce mycelia for the purpose of extracting biologically active compounds, and this has been successfully conducted in submerged culture. Advancements in C. militaris cultivation have led to high yields of stromata production and an increased content of Cordycepin. Furthermore, research has explored fruiting body production using multi-ascospore isolates and their progeny strains for three successive generations. It was observed that F1 progeny strains produced a higher number of fruiting bodies [15].

V. 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 (16).

   - **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 [16].

     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 [5]. This immunomodulatory activity is believed to contribute to the potential therapeutic effects of Cordyceps in supporting the immune system.

   - **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 [16].

   - **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 [8]. These anti-inflammatory effects may contribute to the potential therapeutic benefits of Cordyceps in managing inflammation-related conditions.

- **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 [4].

- **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) [7]. However, further research is needed to fully understand the mechanisms and potential clinical applications of Cordyceps in cancer treatment.

2. **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 [4]. Another study demonstrated that Cordyceps sinensis extracts inhibited the growth of Methicillin-resistant Staphylococcus aureus (MRSA) [7]. 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 [9]. Another study reported that Cordyceps militaris extracts displayed antifungal activity against dermatophytes, which fungi are causing skin infections [12]. 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 [8]. 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 [5]. Another study showed that Cordyceps extracts inhibited the growth of Leishmania donovani, a parasite causing leishmaniasis [6]. These findings suggest the potential of Cordyceps in the management of parasitic infections.

3. **Anti-Aging and Anti-Oxidant Effects:** Cordyceps is rich in bioactive compounds known for their anti-aging and antioxidant properties. These compounds play a vital role in combating free radicals within the body, reducing oxidative stress, and safeguarding against age-related illnesses. Biotechnological research is actively focused on identifying and isolating these bioactive compounds for potential use in anti-aging and skincare products.

   One of the key biological activities exhibited by *Cordyceps* species extracts is their ability to protect cells from damage caused by free radicals. This protective activity is often attributed to the presence of polysaccharide fractions. *Cordyceps sinensis*, for instance, is renowned for its potent antioxidant and anti-aging properties. Numerous studies have substantiated the antioxidant effects of extracts derived from *Cordyceps militaris*. The extract from the fruiting bodies of *C. militaris* has demonstrated strong DPPH• radical scavenging activity. Meanwhile, the fermented extract of *C. militaris* mycelia has exhibited even more robust total antioxidant activity and reducing ability [6]. These findings underscore the potential of Cordyceps-derived compounds in the field of anti-aging and antioxidant research.

4. **Therapeutic effects and Health Benefits:** Cordyceps species have become a subject of extensive research due to the wide array of medicinal and biological activities exhibited by their extracted compounds, as exemplified in Table 1. These compounds offer a range of medical and nutritional benefits. While Cordyceps has a long history of use in traditional Oriental medicine for addressing respiratory conditions like asthma and bronchial issues, as well as for enhancing energy levels and sexual vitality, modern research has unveiled a multitude of other applications.

   One of the significant breakthroughs in contemporary research has been the discovery of cordycepin, a compound with potent antimicrobial activity against nearly all bacterial species, including those resistant to commonly used antibiotics. Cordyceps has demonstrated remarkable effectiveness against conditions like tuberculosis, leprosy, and human leukemia in various clinical trials conducted in Asia and other regions. Cordyceps has also proven effective in increasing maximum oxygen intake and enhancing respiratory function. Notably, Cordyceps sinensis produces several deoxynucleosides, such as 2',3'-deoxyadenosine, which is marketed as "Didanosine" in the USA for AIDS treatment. Additionally, quinic acid derived from Cordycepin (3'-deoxyadenosine), found in Cordyceps, and possesses antiviral and antibacterial properties [9].

   Numerous studies have provided evidence of the benefits of C. sinensis in treating cardiac disturbances, including heart rhythm irregularities such as cardiac arrhythmia and chronic heart failure. This extensive body of research underscores the multifaceted therapeutic potential of Cordyceps and its various applications in modern medicine [9].

Table 1: Common Therapeutic Effects of Different *Cordyceps* sp. [5]

Therapeutic effects	Cordyceps spp.	Major Bioactive Compounds
Antitumor	C. sinensis	Cordycepin Cordyglucans Monosaccharide saponins EPSF
	C. militaris	cordycepin and mannitol
Anti-diabetic effects	C. sinensis C. militaris	Cordymin Cordycepin, adenosine
Anti-infl ammatory	C. sinensis C. militaris	Cordycepin Adenosine
Anti-oxidant activity	C. sinensis	Exopolysaccharide fraction, EPSF CPS-1 CME-1
	C. militaris	Polysaccharide (PSC)
Antimicrobial activity	C. sinensis C. militaris	Cordycepin Ergosterol Mannitol, trehalose, Polyunsaturated fatty acids, δ-tocopherol and p-Hydroxybenzoic acid
Anti-infl uenza	C. militaris	Polysaccharide (PSC)
Anticonvulsant activity	C. sinensis	Adenosine

5. **Anticancer Activities of Cordyceps:** Cordyceps is a rich source of biologically active compounds with notable anticancer properties. Several of these compounds have demonstrated their effectiveness in combating various types of cancer cells:

   - **Cordycepin:** Cordycepin has exhibited antitumor activity, particularly against B16 melanoma cells. It induces apoptosis (programmed cell death) in Mouse Leydig tumor cells in vitro. Cordycepin also inhibits cell proliferation and promotes apoptosis in human colorectal carcinoma cells (SW480 and SW620) in vitro. In gallbladder cancer cells, cordycepin leads to a reduction in cancer cell viability and induces apoptosis by inhibiting the mammalian target of rapamycin complex 1 (mTORC1) [17].

   - **Cordyceps militaris:** This species of Cordyceps has been found to inhibit U937 cells in a dose-dependent manner and has shown promise in the treatment of human leukemia. Cordyceps has demonstrated its ability to inhibit the growth of cancer cells, and in some instances, it has been associated with a reduction in tumor size. Clinical trials conducted in various Asian countries have shown promising results, including the reduction of tumor size, enhanced tolerance for chemotherapy and radiation therapy, and stimulation of the immune system, which subsequently improves the efficiency of chemotherapy. The ethanolic extract of C. militaris has shown a potent antitumor effect in xenograft mouse models derived from RMA cells [5]. Additionally, some Cordyceps species exhibit anti-leukemia activities and ameliorate the suppressive effects of chemotherapy on bone marrow function, serving as a model for cancer treatment [3].

6. **Hypoglycemic and Hypocholesterolemic Effect:** Cordyceps has been found to play a significant role in regulating and lowering blood sugar levels by enhancing glucose metabolism and conserving hepatic glycogen [3]. One of the mechanisms through which Cordyceps achieves this is by increasing the secretion of glucokinase and hexokinase, enzymes responsible for regulating glucose in the liver [4]. Polysaccharides are instrumental in mediating Cordyceps' hypoglycemic activity. For instance, the polysaccharide CS-F30, derived from C. sinensis culture mycelium, has demonstrated potent hypoglycemic activity when administered intraperitoneally in genetically diabetic mice. Intravenous administration of CS-F30 has also led to a dramatic reduction in plasma glucose levels in both normal and streptozocin-induced diabetic mice. Another polysaccharide, CS-F10, extracted from a hot-water extract of C. sinensis cultured mycelia, composed of galactose, glucose, and mannose in specific proportions, has successfully lowered plasma glucose levels in normal, adrenaline-induced hyperglycemic, and diabetic mice [3].

   Furthermore, Cordyceps has been investigated for its role in managing hypercholesterolemia, a condition associated with a high risk of cardiovascular disease. Studies have reported that C. sinensis can lower total cholesterol levels and reduce triglycerides. Additionally, it has been shown to increase the ratio of high-density lipoprotein (HDL cholesterol), often referred to as "good" cholesterol, to low-density lipoprotein (LDL cholesterol), known as "bad" cholesterol. A hot-water extract of C. sinensis mycelia has been found to decrease serum total cholesterol concentrations in tested mice by reducing LDL and very-low-density lipoprotein (VLDL) levels, while simultaneously elevating HDL cholesterol concentrations [5]. These findings suggest the potential of Cordyceps in managing blood sugar levels and improving cardiovascular health.

7. **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 [11]. 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 [11]. 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 [11]. 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. [18]. 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.

8. Global Market, Future Trends and Challenges: The increasing global demand for Cordyceps, combined with a decline in wild harvesting, has led to record-high prices and global attention [19]. The global production of Ophiocordyceps sinensis alone is estimated to range from 85 to 185 tons, with additional tonnage contributed by other Cordyceps species. Harvesting and selling non-cultivated Cordyceps can significantly impact household incomes in the regions where it is collected. For example, in rural Tibet, sales of O. sinensis accounted for 40% of annual household cash income and 8.5% of GDP in 2004 [20]. This economic contribution has resulted in a substantial increase in global prices, averaging an annual inflation-adjusted rate of 21.2% between 1997 and 2004. However, these economic benefits come with associated challenges.

Challenges in the Cordyceps industry include conflicts over collecting grounds, which can lead to difficulties for local governing bodies and even violence. The intensive harvesting of Cordyceps has been implicated in possible population declines in certain areas, such as rural China, where collections have decreased by over 70% since 2001. High-intensity collection can also impact the delicate grassland ecosystems and their flora and fauna. Some of these impacted flora may be vital for the survival of *O. sinensis*, further contributing to its decline [19]. Given these challenges, continued wild harvesting at current rates may not be sustainable.

To address these issues, the cultivation of Cordyceps species has emerged as a growing trend in the industry. Cultivation offers the potential to reduce pressure on wild populations and ensure a more sustainable supply. However, there are still challenges to overcome in cultivation, including reducing the rearing cost of the ghost moth (the host of Cordyceps), preventing microbial contamination during the cultivation process, and streamlining the overall cultivation process [20]. Despite these challenges, Cordyceps cultivation is an active area of research, and ongoing developments are expected to improve the economic and reliable cultivation of these valuable fungi.

The surging global interest and value assigned to Cordyceps have resulted in a wide range of commercial products derived from these fungi worldwide, However, there is also a growing issue of counterfeit and contaminated products in the market. To address this concern, increased quality control and authentication methods are being developed, often utilizing markers such as nucleosides, ergosterol, mannitol, and polysaccharides. Despite these challenges, top-quality Cordyceps can command prices of around 100,000 USD per kilogram, indicating the industry's strength and sustainability [19].

VI. 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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