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Caterpillar Fungus (Cordyceps): An Entomopathogenic Fungus with Emerging Nutraceutical and Medicinal Importance

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Abstract: Cordyceps, especially *Cordyceps sinensis* and *Cordyceps militaris*, is a very interesting fungus that belongs to the entomopathogenic fungi group and has been gaining limelight in the past few years because of its varied bioactive compounds and medicinal properties. Cordyceps has been traditionally used in Asian medicinal practices for many years and is currently in demand worldwide for its nutritional and pharmaceutical uses. This review aims to comprehensively discuss the taxonomy, biological, bioactive compounds, pharmacological properties, cultivation, and medicinal importance of Cordyceps species. It will give special focus on cordycepin, polysaccharides, and other metabolites that are mainly responsible for the immunomodulatory, anti-inflammatory, antioxidant, and anti-tumor effects of these species. However, despite the medicinal properties, there are many issues associated with its sustainability, standardization, and validation, and this review will highlight the future research aspects of Cordyceps that are required to fully tap its medicinal and commercial potential.

Keywords: *Cordyceps sinensis, Cordyceps militaris, Entomopathogenic fungi, Medicinal Properties.*

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I. INTRODUCTION

Entomopathogenic fungi are an exceptionally specialized ecological guild of fungi that infect and kill insects and other arthropods, and of these, the genus *Cordyceps* is perhaps one of the most intriguing and useful ones overall (Hughes et al., 2011; Sung et al., 2007). The caterpillar fungus, *Cordyceps sinensis* or *Ophiocordyceps sinensis*, has been employed in Traditional Chinese Medicine for over 2,000 years to enhance vitality, respiratory health, and longevity (Zhou et al., 2009; Holliday & Cleaver, 2008; Zhu et al., 1998). The commercial name “Dong Chong Xia Cao,” meaning “Winter Worm, Summer Grass,” reflects the unique seasonal transformation of the fungus from an insect parasite to a grass-like fruiting body (Winkler, 2008; Shrestha & Sung, 2005). The above name refers to an exceptionally interesting biological life cycle of this fungus, in which it infects and kills caterpillar larvae in the winter and develops into a fruiting body in the summer.

The increased demand for natural products and functional foods globally has made Cordyceps a luxury nutraceutical product. The price of *Cordyceps sinensis* has been reported to exceed the price of gold, making *Cordyceps sinensis* one of the costliest biological materials in the world (Winkler, 2008). The price has triggered comprehensive research on the bioactive substances, pharmacological properties, and methods for culturing the organism. Modern scientific research has confirmed traditional applications and discovered new uses of Cordyceps for immunomodulatory, anti-cancer, cardiovascular protective, and metabolic regulatory effects (Paterson, 2008).

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This review will work towards offering a holistic discussion on the Cordyceps species of fungi, in terms of their taxonomy, biological aspects, chemical composition, medicinal uses, technologies used in growing them, and importance. It is the aim of this paper to present a consolidation of the existing literature on these fascinating organisms for the purpose of providing direction for further research.

II. TAXONOMY AND DISTRIBUTION

➢ *Taxonomic*

Cordyceps species belong to the Cordycipitaceae family, which is sub-classified under the Ascomycota, with Hypocreales being the active order. Recent phylogenetic research has contributed greatly to taxonomic changes, thereby renaming *Cordyceps sinensis* to *Ophiocordyceps sinensis* (Quandt et al., 2014; Sung et al., 2007). Currently, more than 400 species of Cordyceps have been described, with *Cordyceps sinensis* and *Cordyceps militaris* receiving the greatest scientific attention due to their medicinal importance (Paterson, 2008; Shrestha & Sung, 2005).

Cordyceps sinensis is a highly specialized parasitic fungus that primarily infects the larvae of ghost moths (*Thitarodes/Hepialus* spp.) inhabiting alpine meadow ecosystems. In contrast, *Cordyceps militaris* exhibits comparatively broader host adaptability and commonly parasitizes lepidopteran larvae and pupae under a range of ecological conditions (Sung et al., 2007; Shrestha & Sung, 2005). The taxonomic classification of the genus Cordyceps has been complicated by the presence of distinct anamorphic (asexual) and teleomorphic (sexual) stages in many species, which historically led to separate naming of different life stages (Quandt et al., 2014; Sung et al., 2007). Moreover, most Cordyceps species possess both sexual (teleomorphic) and asexual (anamorphic) forms, often associated with genera such as Beauveria, Metarhizium, Hirsutella, and Isaria, further contributing to taxonomic ambiguity prior to the adoption of molecular phylogenetic approaches (Sung et al., 2007; Hywel-Jones, 2002).

➢ *Geographic Distribution*

Cordyceps sinensis has a limited geographical range, mainly found in high-altitude areas such as the Tibetan Plateau and other members of the Himalayan Range, including China, Nepal, Bhutan, and India, between 3,000 and 5,000 meters above sea level (Winkler, 2008). Its limited habitat range is a result of a unique combination of environmental factors such as cooler temperatures, higher levels of UV ray exposure, and regional availability of suitable hosts. The main sources of wild *Cordyceps sinensis* are the Tibetan Autonomous Region and the province of Qinghai in China, and they are a vital source of revenue for the population (Shrestha & Sung, 2005).

Conversely, *Cordyceps militaris* has a cosmopolitan pattern in both temperate and tropical areas around the globe. This attribute makes it easy for it to occur naturally and to be cultured artificially due to its capacity to parasitize various host organisms and to withstand various climatic conditions. Some Cordyceps species show a certain level of geographic restriction depending on their host organisms and climatic preferences (Sung et al., 2007).

III. BIOLOGY AND LIFE CYCLE

➢ *Invasion and Parasitem*

The life cycle of the Cordyceps fungus exemplifies an intriguing form of fungal parasitism. Infection of the host insect occurs as a result of contact between ascospores or conidia of the fungus and susceptible insects (Shrestha & Sung, 2005). After successful invasion of the insect, the fungus grows inside its hemocoel, resulting in the production of hyphal bodies or yeast cells that grow inside the insect's tissues while feeding on its nutrients. Ultimately, this results in the death of the insect due to depletion of nutrients, damage, or even mycotoxin production (Paterson, 2008).

One of the striking features of Cordyceps infections is host manipulation. In this case, hosts are compelled by their Cordyceps infections to move towards areas that help in Cordyceps growth and subsequent spore production prior to host death (Sung et al., 2007). In this case, once the host dies, it is mummified by the fungus without its structure being compromised, and is used as a source for future Cordyceps fruiting bodies.

➢ *Fruiting Body*

Under favorable environmental conditions, usually after the winter dormancy period and the subsequent rise in spring temperatures, the fungus develops a club-shaped fruiting structure (stroma), which protrudes from the insect corpse (Winkler, 2008). The stroma reaches lengths of 4-15 cm and has perithecia embedded on its surface that harbor asci filled with ascospores. The development of the fruiting bodies is carefully timed according to the favorable environmental factors for spore shed and the acquisition of new host insect individuals (Shrestha & Sung, 2005).

The whole life cycle, ranging from infection to the maturation of the fruiting bodies, takes about a year in *Cordyceps sinensis*. However, this depends on the prevailing environmental conditions as well as the species involved. The whole process makes it difficult to cultivate the species in large quantities. This makes the wild ones rare and thus highly priced (Paterson, 2008).

IV. BIOACTIVE COMPOUNDS

➢ *Cordy*

Cordycepin (3′-deoxyadenosine) is one of the most extensively studied bioactive compounds of Cordyceps, occurring in higher concentrations in *Cordyceps militaris* than in *Cordyceps sinensis* (Tuli et al., 2014; Nakamura et al., 1999). Cordycepin exhibits anticancer activity by inhibiting mRNA polyadenylation, inducing cell cycle arrest, and activating apoptosis-related signaling pathways such as AMPK–mTOR and mitochondrial caspase cascades (Jin et al., 2018; Nakamura et al., 1999). The mechanism of anti-cancer effect in cordycepin includes multiple pathways.

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Cordycepin inhibits the polyadenylation of mRNA, which affects protein synthesis in cancer cells, and also affects the cell cycle at G2/M phase (Tuli et al., 2014). In addition, cordycepin has a preferential cytotoxic effect on cancer cells and has relatively lower toxicity on non-cancer cells.

➢ *Polysaccharides*

Cordyceps polysaccharides are complex heteropolysaccharides composed mainly of glucose, mannose, and galactose, with molecular weights ranging from several thousand to over one million daltons (Li et al., 2006; Wasser, 2002). These polysaccharides function as biological response modifiers and enhance both innate and adaptive immune responses through macrophage activation, NK cell stimulation, and cytokine production (Chen et al., 2013; Wu et al., 2007). The β-glucans have pronounced immunostimulant properties, which include activation of complement and toll-like receptors on immune cells (Paterson, 2008).

Studies have shown that Cordyceps polysaccharides have immunoenhancing effects on both innate and acquired immunity. They produce immune cell proliferation, the production of antibodies, and modulation of T Helper cells for Th1 cells, which play major roles in tumor and viral immunity (Li et al., 2006). The complexity of the structures of these polysaccharides makes them have complex activities.

➢ *Nucleosides*

Aside from cordycepin, Cordyceps has a number of nucleosides such as adenosine, uridine, guanosine, and their analogs (Li et al., 2006). Adenosine has a high content and is responsible for the cardiovascular activities of Cordyceps due to its vasodilatory, anti-arrhythmic properties, as well as its cardioprotective action.

➢ *Sterols and Fatty Acids*

Ergosterol and ergosterol peroxide are known to be the main sterols in Cordyceps. Ergosterol peroxide has been shown to have anti-inflammatory and anti-tumor properties (Li et al., 2006). The fungus has been found to have unsaturated fatty acids like linoleic acid and oleic acid.

➢ *Other Bioactive Compounds*

Cordyceps also yields other metabolites: cordycepic acids (D-mannitol), peptides, proteins, amino acids, vitamins, and trace elements (Paterson, 2008). Cordycepic acid was considered the major compound that yielded multiple medicinal properties. Later studies identified that cordycepic acid is D-mannitol. Although not very pharmacologically active compared to early estimations, D-mannitol has shown activity on osmotic action and potential positive impacts on cellular defense. The peptide and protein components, including cordymin, have various biological functions that include antimicrobial and antioxidant properties (Li et al., 2006).

V. PHARMACOLOGICAL PROPERTIES

➢ *Immunomodulatory Effects*

Cordyceps exhibits biphasic immunomodulatory activity, stimulating immune responses under immunosuppressed conditions while suppressing excessive inflammation in autoimmune and hypersensitivity states (Ramesh et al., 2020; Paterson, 2008). Various studies have revealed the immunomodulatory properties of Cordyceps extracts, such as increasing the phagocytic ability of macrophages by 50-100%, increasing natural killer cell cytotoxicity, and inducing lymphocyte proliferation. These properties are mainly attributed to the activation of pattern recognition receptors and cytokine cascade stimulation by the polysaccharides and proteins in Cordyceps (Li et al., 2006)

In immunocompromised animals, Cordyceps supplementation has been shown to improve indices of immunity, such as white blood cell count, antibody, and delayed hypersensitivity (Tuli et al., 2014). On the other hand, in autoimmune and inflammatory diseases, Cordyceps has been shown to possess immunosuppressive functions, inhibiting pro-inflammatory cytokines and T cell functions.

➢ *Anti-Cancer Activity*

Preclinical studies have demonstrated significant tumor growth inhibition (40–70%) in animal models following Cordyceps administration, accompanied by enhanced immune surveillance and reduced metastasis (Tuli et al., 2014; Wu et al., 2007). Various mechanisms are involved in these properties, including cytotoxicity, apoptosis induction, cell cycle arrest, anti-angiogenic properties, and immunopotentiating activities against tumors. Cordycepin acts specifically by inducing apoptosis via activation of the mitochondrial pathway; this involves cytochrome C release and caspase activation, and DNA fragmentation (Paterson, 2008).

Animal studies have revealed the inhibitory rate of 40-70% for the growth of tumors upon administration of Cordyceps, along with lower metastatic potential and higher survival rate (Tuli et al., 2014). Immunomodulation is a contributing factor relating to the anti-tumor property due to the increase in immune surveillance and recognition of the tumor cells.

➢ *Cardiovascular Protection*

Cordyceps species have demonstrated significant cardiovascular protective effects, including anti-arrhythmic, vasodilatory, hypotensive, and lipid-lowering activities. These effects are largely attributed to bioactive constituents such as adenosine, cordycepin, and polysaccharides, which modulate vascular tone, improve myocardial energy metabolism, and reduce oxidative stress (Paterson, 2008; Li et al., 2006). Experimental studies have shown that Cordyceps supplementation reduces myocardial ischemic injury, decreases infarct size, and improves cardiac function by enhancing antioxidant defenses and suppressing inflammatory responses (Zhou et al., 2009). Additionally, Cordyceps has been reported to favorably regulate serum

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lipid profiles by reducing total cholesterol, triglycerides, and low-density lipoprotein cholesterol, thereby contributing to overall cardiovascular health (Tuli et al., 2014).

➢ *Hepatoprotective and Renoprotective Effects*

It has strong protective effects against liver and renal injuries caused by various toxic substances (Li et al., 2006). In studies using chemical hepatotoxicity, administration of Cordyceps has led to fewer elevations of liver enzymes, decreased oxidative markers of damage, and maintained cell architecture of the liver (Paterson, 2008). These effects occur through increased expression of antioxidant enzymes, anti-inflammatory responses, and improvement of detoxifying functions of the liver. In respect of renal protection, Cordyceps has proved particularly effective for the management of chronic renal disease. There is evidence that renal function has been improved and the disease course slowed by the reduction of proteinuria (Tuli et al., 2014). This action is considered due to anti-inflammatory effects and protection from oxidative stress.

➢ *Anti-Diabetic and Metabolic Effects*

Cordyceps supplementation has been shown to improve insulin sensitivity, reduce hyperglycemia, and regulate lipid metabolism in diabetic models through antioxidant and anti-inflammatory mechanisms (Zhao et al., 2014; Zhang et al., 2012; Li et al., 2006). The mechanisms involved include the up-regulation of insulin receptors, increased glucose transport, and improved functions of the pancreatic β-cells. Furthermore, Cordyceps has been shown to possess protective effects on diabetes-induced complications, including nephropathy, neuropathy, and retinopathy, due to its anti-oxidative and anti-inflammatory properties (Paterson, 2008).

➢ *Anti-Aging and Antioxidant Activities*

Traditionally, Cordyceps has been used as an anti-aging drug, which has found support in contemporary studies proving it to have improved antioxidant enzyme activity, lowered lipid peroxide levels, and protection against oxidative stress-related cellular injury (Tuli et al., 2014). In animal studies, supplementation with Cordyceps has been found to enhance cognitive and athletic ability and sexual potency and lower pathological lesions of aging in senior organisms. The polysaccharides and cordycepin and polyphenols found in it help prevent aging due to their free radical-scavenging and antioxidant enzyme-inducing properties (Paterson, 2008).

➢ *Respiratory Benefits*

The conventional use of Cordyceps in respiratory disorders has been proven effective by studies showing its bronchodilator properties, improved respiratory function, and protective action against respiratory injuries (Li et al., 2006). Additionally, Cordyceps has been noted to increase the utilization of oxygen, ATP production, and exercise tolerance; hence its common use among athletes. Clinical trials have proven its efficacy in relieving symptoms of chronic respiratory disorders while improving quality of life in patients undergoing Cordyceps supplementation (Paterson, 2008).

VI. CULTIVATION AND PRODUCTION

➢ *Challenges in Natural Harvesting*

The collection of Wild *Cordyceps sinensis* faces several issues in terms of sustainability. The limited range, slow growth rate, and habitat degradation as a result of its overcollection and climate change make this species prone to both habitat quality and sustained supply concerns (Winkler, 2008). The magnitude of harvest pressure has risen significantly because vast numbers of gatherers scour alpine grassland habitats for a very short period. Moreover, climate change has made habitat conditions for both the fungus and its host plant a point for consideration due to changes in environmental conditions (Shrestha & Sung, 2005).

➢ *Artificial Cultivation Techniques*

The high value and availability of wild *Cordyceps sinensis* have led to intensive research on cultivation technology. But the cultivation of fruiting bodies that include all the active compounds is still technically difficult (Paterson, 2008).

The technology used today includes:

- *Liquid Fermentation*

This process entails the use of the fungal mycelium in a liquid media. The process results in the production of biomass with high polysaccharides and other metabolites in weeks, as opposed to months involved in the production of fruit bodies (Li et al., 2006). Though economically sound, the chemical composition of fermented mycelium may not be similar to that of the fruit bodies.

- *Solid Substrate Cultivation*

The species has been cultivated successfully on a number of materials, such as rice, wheat, and silkworm pupae, yielding a high content of cordycepin in the fruit bodies. The easy cultivability of the species has made it the focus for all Cordyceps preparations currently on the market. The proper control of environmental factors, such as temperature, humidity, light, and CO_2, is highly essential for optimizing yields and bioactive compound productions (Tuli et al., 2014).

- *Host-Based Cultivation*

Efforts at cultivation along with natural hosts such as *Cordyceps sinensis* larvae have had limited success, owing to difficulties in host rearing, infection rates, and development time (Winkler, 2008). Semi-controlled systems have been established by certain farms in China; however, commercial viability is still a challenge.

➢ *Quality Control and Standardization*

Because of the variety of Cordyceps products within the market, there is a great use of quality control. Cordyceps products include wild Cordyceps sinensis, mycelium, fermentation broth, and *Cordyceps militaris* fruit bodies, which have particular chemical compositions (Paterson, 2008). HPLC, Spectroscopy, and Molecular techniques have been used in identifying compounds in Cordyceps. Despite

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this, there is a problem of Cordyceps products being resistant to standardization due to natural variations, preparation techniques, and lack of a universal quality system (Li et al., 2006).

VII. CLINICAL APPLICATIONS AND HUMAN STUDIES

Although numerous preclinical studies support the therapeutic potential of Cordyceps, well-designed randomized controlled trials in humans remain limited, highlighting the need for standardized formulations and larger sample sizes (Tuli et al., 2014; Paterson, 2008). The available clinical trials on Cordyceps include trials related to renal disease, respiratory ailments, immunoenhancement, and athletic performance (Tuli et al., 2014). The trials show that the outcomes are effective and safe, but are limited by small sample size and poor product formulation.

A meta-analysis of trials involving patients with chronic kidney disease found that supplementation with Cordyceps resulted in an improvement in blood creatinine and blood urea nitrogen, in addition to reducing proteinuria (Paterson, 2008). On the other hand, patients with respiratory ailments showed improvement in exercise tolerance and quality of life. Indeed, more extensive studies, such as randomized placebo-controlled trials, are needed.

➢ *Safety and Adverse Effects*

The available literature indicates that Cordyceps supplements have favourable safety profiles and that adverse effects are minimal and rarely documented in various clinical trials (Tuli et al., 2014). Symptoms related to gastrointestinal upset are documented as mild adverse reactions that form the main component of adverse effects documented in trials. Extensive documentation on the long-term use and possible interactions with other medicinal products, though beyond the scope for further investigation and comprehension, remains critical for those that are immunosuppressed, those with autoimmune disorders, and those on immunosuppressive therapies due to its proposed immunomodulatory activities (Paterson, 2008).

VIII. COMMERCIAL SIGNIFICANCE AND MARKET TRENDS

The World market for Cordyceps has grown exponentially due to the rising popularity of Natural Health Products and Traditional Medicine (Winkler, 2008). The price of Wild *Cordyceps sinensis* was extraordinary and cost more than $20,000 per kilogram for the best-quality variety. The financial gain that this species brought to the local economies of harvesting areas created a struggle for its conservation. The agriculture market for Cordyceps products triggered affordable alternatives in the market while retaining their healing property (Paterson, 2008).

Market expansion has also seen product diversification, with Cordyceps being incorporated into supplements, functional foods, drinks, and cosmetic products. Quality assurance, authentication, and consumer awareness are some of the most important challenges associated with the development of this market. Increasing validation of traditional uses, along with new uses, place Cordyceps among the most prominent sub-sectors of the natural products industry (Tuli, et al., 2014).

IX. CONCLUSION

The Cordyceps species, specifically *Cordyceps sinensis* and *Cordyceps militaris*, are exemplary biota that integrate traditional medicine and modern pharmacological knowledge and practices. The life cycles, bioactive compounds, and pharmacological attributes of these biotas point to their use as valuable resources for nutritional and pharmaceutical medicine and applications. The validation of traditional medicine claims and the discovery of bioactive properties of these biotas have made natural products research involving Cordyceps biota of prime importance. However, the difficulties associated with sustainable production, cultivation, standardization, and validation continue to be significant but not insurmountable. It is promising that further research incorporating the wisdom of natural traditions and modern scientific approaches will help to reveal the full therapeutic potential hidden in these intriguing organisms. While interest in scientifically supported natural medicine continues to build on a global scale, Cordyceps represents a paradigm that combines the wisdom of the past with the science of the present. It is, however, critical to note that the future of Cordyceps research, development, and use will rely on a well-rounded strategy aimed at ensuring conservation of wild Cordyceps, development of a means of producing Cordyceps in a sustainable way, carrying out sought research on Cordyceps, and ensuring responsible commercialization of Cordyceps. By doing so, these incredible entomopathogenic fungi will continue to contribute to human well-being.

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