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REVIEW ARTICLE

Cordyceps More Than Edible Mushroom-A Rich Source of Diverse Bioactive Metabolites with Huge Medicinal Benefits

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ABSTRACT

Many mushroom genera are famous for their promising therapeutic capabilities. One of the mushrooms genera attracting attention is *Cordyceps* which has long been used in Asian countries for maintaining long and healthy life. Numerous studies on different metabolic activities of *Cordyceps* have been performed both *in vitro* and *in vivo*. Numerous studies on different metabolic activities of *Cordyceps* have been performed both *in vitro* and *in vivo*. However, it is debatable whether *Cordyceps* is a food supplement for health maintenance or a therapeutic "drug" carrying medicinal properties. The *Cordyceps* industry has developed greatly and offers thousands of products, commonly available in a global marketplace. This review describes the importance and the current status of the world *Cordyceps* cultivation, a range of products and industry practices along with suggestions for facilitating further research.

INTRODUCTION

Mushrooms are macrofungi that have spore-bearing structures (fruiting bodies) and can be seen on soil surface as saprophytes, or growing as a parasite over their host. Mushrooms exist in two fungal phyla Basidiomycota and Ascomycota, and over 14,000 species are identified [1-5]. Mushrooms have well known nutritional value that can be compared to that of many vegetables, and act as substitute for meat [6-10]. Also, the saprophytic nature of mushrooms has contributed in the recycling capabilities of mushrooms which allow them to convert agro-wastes, food remains, and dead bodies to highly nutritious food [11-15]. On the other hand, mushrooms are rich sources of different compounds such as terpenes, phenolic compounds, fatty acids, α- and β-glucans, polysaccharides, proteins. Such compounds are responsible for the biological activities reported for many mushroom species including having anticancer, antiviral, antitumor, antidiabetic, antidepressive, antioxidant, immunomodulatory, anti-inflammatory, neuroprotective, hepatoprotective, nephroprotective, osteoprotective, hypotensive, antiallergic, antimicrobial, antihyperlipidemic, and hypocholesterolemic activity [16-20]. Previously, majority of studies have focused on certain species, especially those traditionally used among Asian culture [21-25]. However, there is a recent attention for the exploring mushrooms chemical composition in order to investigate the potential medical and pharmaceutical uses of these generous rich macrofungi [26-32].

The name *Cordyceps* comes from the Latin words cord which means 'club', and ceps, referring to 'head'. The fruiting bodies of these fungi often erupts from the head of the larva and adult stages of many different species of insect. *Cordyceps* are

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entomophagous fungi from the phylum Ascomycota, family Ophiocordycipitaceae, order Hypocreales, and they are known to parasitize many orders of insects at different life stages from larva to adult stages. Numerous species within the genus have a golden reputation due to their long safe history of use in traditional medicines. Used for over 2000 years in China for treating infectious diseases, *Cordyceps* are also described in the ancient books of Ben-Cao-Cong-Xin (New Compilation of Materia Medica) which is as old as 1757 years AD, and 'Ben Cao Gang Mu Shi Yi' written by Xueming Zhao in 1765 AD. The *Cordyceps* genus contains some of the most highly prized and revered of all medicinal fungi. In spite of having a global distribution, the majority species of *Cordyceps* have been described from Asia. Grasslands, providing habitat for Thitarodes ghost moths and thus for *Cordyceps sinensis*, are a particularly important habitat and consists predominantly of sedges (*Kobresia* sp.), covering up to 80-90% of the subalpine grasslands [33]. The most famous and widely used species of *Cordyceps* is *C. sinensis* (Berk.) Sacc (syn. *Ophiocordyceps sinensis* (Berk.) Sung, Sung, and Hywel-Jones & Spatafora.), and was also described as *Sphaeria sinensis*, then later renamed by Saccardo in 1878 as *Cordyceps sinensis*. Nowadays, the preferred scientific name is *Cordyceps sinensis* (Berk.) Sacc. The host range of this species is wide, including different species of Lepidopteran larvae, numerous species of Thitarodes caterpillars, and its most common host, the Himalayan bat moth *Hepialus armoricanus*. A similar species, *C. militaris* or as commonly known, the orange caterpillar fungus has a similar chemical composition and medicinal biological activities as *C. sinensis* [34].

Cordyceps Ecology

Generally, *Cordyceps* species feed on insect larvae and sometimes they also parasite on mature insects. *Cordyceps* grow on all groups of insect-crickets, cockroaches, bees, centipedes, black beetles, and ants, to name a few. Although there are several species known to have medical value, only a few are cultivated and the most popular and well known are *Cordyceps sinensis* and *Cordyceps militaris*. However, *Cordyceps*, are not limited to insects and may grow on other arthropods as well as the fungi *Elaphomyces* Nees. This group belongs to the order Hypocreales, which includes 912 known species that are assigned to the families Cordycipitaceae and Ophiocordycipitaceae and partial Clavicipitaceae [35]. *Cordyceps* only refers to the macrofungi, and these macrofungi were previously placed in the old genus *Cordyceps* Fr. (Clavicipitaceae, Clavicipitales). Due to their special edible and medicinal values, *Cordyceps* is very popular in China, where a huge domestic market exists. By most Chinese people's standards, *Cordyceps* only refers to 'Dongchong Xiacao (worm in winter, herb in summer; *O. sinensis*, which is the most expensive type and only produced from the Tibetan Plateau; other *Cordyceps* species in the marketplace are termed 'fake Dongchong Xiacao', some of which may not be consumed in this way.

Cordyceps Natural Products

Cordyceps have a wide range of various compounds, some are characterized as nutritional compounds, since they possess all of the important amino acids, vitamins such as K and E, besides the water-soluble B vitamins (B1, B2, and B12). In addition, they contain many sugars, including mono-, di-, and oligosaccharides, and many complex polysaccharides, proteins, sterols, nucleosides, and trace elements (Na, K, Ca, Mg, Al, Fe, Cu, V, Pi, Se, Ni, Sr, Si, Ti, Cr, Ga, Zn, and Zr) [9,15]. *Cordyceps* contains abundance of polysaccharides, which represents in the range of 3–8% of the overall weight, and commonly originated from the fruiting bodies. *Cordyceps* polysaccharide, is one of the main bioactive components along with nucleotides (including adenosine, uridine and guanosine). Investigations show that guanosine is the nucleotide in greatest abundance in both natural and cultivated *Cordyceps* [15]. *Cordyceps sinensis* is the most expensive and the most extensively studied *Cordyceps* species. *C. sinensis* contains crude fats, proteins, fiber, carbohydrate, cordycepin (30-deoxyadenosine), cordycepic acid (D-mannitol), polysaccharide and a series of vitamins. The therapeutic applications of *Cordyceps* are focusing mostly on the major effects of increasing utilization of oxygen and production of ATP, besides stabilizing sugar metabolism in blood. Such activities may be attributed to compounds as cordycepin, cordycepic acid and numerous vitamins, polysaccharides and trace elements. Although all the medically active compounds of *C. sinensis* are still unknown, at least two chemical compounds, cordycepin and cordycepic acid, have been purified and identified as medically important active compounds. It is now believed that cordycepic acid is, in fact, D-mannitol, and that cordycepin is 30-deoxyadenosine (30-dA), a purine alkaloid. Of all *Cordyceps* species, *Cordyceps militaris* has been most successfully cultivated and most intensively studied. Most *Cordyceps* products in the marketplace are developed from the fruiting bodies of cultivated *C. militaris*. According to chemical analysis, *C.* **militaris** contains cordycepin, Adenosine, Polysaccharide, Mannitol, Trehalose, Polyunsaturated fatty acids, δ-tocopherol, p-Hydroxybenzoic acid and β-(1→3)-D-glucan [36,37].

Cultivation and Growing of *Cordyceps*

The natural fruiting bodies of *Cordyceps* are very rare and costly to collect. Moreover, natural populations of key *Cordyceps* species are decreasing rapidly due to over collection [38], presenting the need increased cultivation of *Cordyceps in vitro* using an artificial medium. The percentage of species that been successfully cultivated in artificial media to the total identified *Cordyceps* species is very low. Examples of some medicinally important *Cordyceps* species such as *Cordyceps sinensis*, artificial *O. sinensis*, **Cordyceps militaris,** and artificial **Cordyceps militaris.** Strain CS-4 (*Paecilomyces hepiali* Chen.) was isolated as early as 1982 as one of the first commercially used strains of *Cordyceps*. After a lot of

clinical trials, the chemical composition, biological activity and toxicity of this strain became well known. The first large scale fruiting techniques used for growing *Cordyceps* reduced the natural growing cycle from 5 to 2 years, this technique included breeding the host larvae, Thitarodes (Hepialus), then placing about 100 larvae into shoe carton-sized plastic containers covered with lids, which are filled with grassland soil comprising tubers and roots originated from their natural foods, as well as other roots from cultivation. The *C. sinensis* spores are inoculated after two years and about 10% of the larvae are actually taken over by *Cordyceps* and grow stromata [39]. On the other hand, Arora, et al. [40], succeeded in using submerged conditions for culturing *Cordyceps sinensis* at pH 6 and temperature 15°C. The growth of *C. sinensis* on sabouraud's dextrose with yeast extract broth medium was also investigated using different carbon sources, nitrogen sources, and additives (vitamins and minerals) [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 significantly increased the yield, and adding calcium chloride and zinc chloride as micro and macronutrients, respectively increased the total yield significantly.

One of the remarkably important artificial techniques for *C. sinensis* culturing was using sterile rice media at 9-13°C for 40-60 days followed by lowering temperature to 4°C for inducing stroma production and at 13°C for 40 days for the process of developing the fruiting bodies. It should be mentioned that the *Cordyceps* mycelium growth depends on different factors such as growth media, temperature, pH, and some environmental factors, but after trying different media, potato dextrose agar was proven to be the best medium using a pH range of 8.5-9.5 at 20- 25°C [43]. Complete artificial cultivation is achieved by inoculating reared larvae with cultured strains and the infected larvae were monitored and fed indoors for one or two years. After that, *C. sinensis* could be collected. On the contrary, in semi-natural 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 artificial media has lately been developed specially for the purpose of Cordycepin production using different methods such as surface culture and submerged culture. Generally, *C. militaris* Stromata production requires 35-70 days. Nevertheless, culturing duration is critically affected by various conditions such as medium amount, volume and shape of the container used in culturing process. The growth of *C. militaris* stroma cultivation *in vitro* started with using insects to grow stromata of *C. militaris* followed by laboratory trials using various organic substrates. Cereals such as rice have been commonly used with some organic substrates for commercial production of *C. militaris* stromata [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]. Also using different media [48].

Important Uses of Cordyceps 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

Table 1: Common therapeutic effects of different *Cordyceps* sp.

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-inflammatory	*C. sinensis* *C.* **militaris**	Cordycepin Adenosine β-(1→3)-D-glucan
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-influenza	*C.* **militaris**	Polysaccharide (PSC)
Anticonvulsant activity	*C. sinensis*	Adenosine

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.

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 efficiency of chemotherapy. Ethanolic extract of *C. militaris* showed a potent antitumor effect in RMA cell-derived tumors at a xenograft mouse model [52]. Moreover, some *Cordyceps* species have anti-leukaemia activities and ameliorate suppressive effects of chemotherapy on bone marrow function as a model for cancer treatment [53].

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 different polysaccharide, (CS-F10), was extracted and identified 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].

Improving Kidney and Liver Functions

The results of some clinical trials revealed that the administration of *C. sinensis* could significantly improve kidney function and overall immunity of patients suffering from chronic renal failure. Moreover treating patients with gentamicin induced kidney damage helped in recovering 89% of normal kidney function in a relatively short time. The mechanism of kidney enhancing activity of *Cordyceps* is owing to its capability to elevate 17- ketosteroid and 17-hydroxycorticosteroid levels in the body, protect sodium pump activity of tubular cells, accelerate tubular cells regeneration, and reduce calcium content in certain tissues. *Cordyceps* is universally involved as co- treatment of chronic hepatitis B and C. Extract mixture of *Cordyceps* in combination with other medicinal mushrooms in addition to the antiviral drug, lamivudine, was used for treating hepatitis B [56]. On the other hand, daily consume of *Cordyceps* improved liver functions in patients suffering from post-hepatic cirrhosis.

Reduction of Fatigue

Cordyceps has been used from centuries as a remedy for weakness and fatigue by residents living in the high mountains of Tibet to give them energy which is achieved by increasing cellular ATP [57]. Nowadays, *Cordyceps* is used by athletes to fight fatigue and weakness and to increase endurance and improve energy levels. Additionally, clinical trials involving elderly patients with chronic fatigue,

results indicated that treatment with *C. sinensis* resulted in improvement of fatigue and dizziness, increasing cold intolerance, and amnesia [58].

Protect Organs and Glands

Cordyceps sinensis also has obvious effects on other organ systems. For example, in the central nervous system, *C. sinensis* has cooling, anticonvulsant and sedative activities. For the respiratory, *C. sinensis* has a strong relaxant activity on the bronchi, considerably, and also plays a key role in contraction of trachea caused by histamine, it as well has an antitussive, expectorant and anti-asthmatic effect and prevents pulmonary emphysema. Concerning endocrine system, *C. sinensis* increases secretion of adrenaline, has effects as a male hormone; Polysaccharides extracted from *Cordyceps* can increase corticosterone level in plasma. *Cordyceps* is used in traditional medicine for decades to improve men fertility. A study has proven the positive effect of using *C. militaris* mycelium on sperm motility, morphology, productivity, and enhancement of sexual activity, *Cordyceps* extracts contain adenosine, deoxyadenosine, related adenosine type nucleotides, and nucleosides which help in stabilizing heartbeat and correcting heart arrhythmias. Such compounds have an effect on coronary and cerebral circulation. *Cordyceps* is known to be used in treatment of chronic hepatitis B and C. Moreover, consuming *Cordyceps* resulted in improving liver function tests in patients suffering from post-hepatic cirrhosis [3].

Cordyceps has Anti-Inflammatory Health Benefit

Generally, cordycepin is the metabolite responsible for the anti-inflammatory activity of many *Cordyceps* species. Ethanolic extracts of cultured mycelia and fruiting bodies of *C. militaris* exhibited an anti-inflammatory effect on chorioallantoic membrane angiogenesis of chick embryo, similarly in the croton oil-induced ear edema in mice. On the other hand, an alkaline extract of *C. militaris*, showed a potent anti-inflammatory effect against formalin-induced nociception and LPS-induced peritonitis in mice, due to containing a potent anti-inflammatory compound (linear b-(1R3)-D-glucan) [37]. The strain CBG-CS-2 (Paecilomyces hepiali of the Cordyceps spp.), can be used for its modulatory effects on macrophages inflammatory system as an anti-inflammatory supplement [59]. A butanol fraction from *C. bassiana* exhibited an anti-inflammation activity in LPS-stimulated RAW 264.7 macrophages [60,61]. Adenosine is another compound existing in *Cordyceps* species with a wide spectrum of activities related to preventing tissue damage as anti-inflammatory properties. It's worth noting that the content and number of adenosines existing in cultured *C. sinensis* is higher than that in the natural one. The methanolic fraction of *C. militaris* fruiting bodies exerted an anti-inflammatory activity resulting from the presence of cordycerebroside A, soyacerebroside I, and glucocerebroside which prevented accumulation of the pro-inflammatory iNOS protein and decreased the expression of the COX-2 protein in LPS-stimulated RAW264.7 macrophages [62].

Cordyceps Antioxidant and Anti-ageing Activities

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 effect 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].

Cordyceps Side Effects and Safe

Cordyceps is generally safe in recommended dosage and no major side effects were reported [64].

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 beneficial functions are mentioned in table 3. 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*

Table 2: List of major *Cordyceps* based companies.

Cordyceps Company	Country of the origin
ALOHA MEDICINALS	USA https://www.alohamedicinals.com
DOCTORS BEST	USA https://www.drbvitamins.com
HOSTDEFENSE MUSHROOMS	USA https://hostdefense.com
PERFECTSUPPLEMENTS	USA https://www.perfectsupplements.com
PARADISE	USA https://paradiseherbs.com
SOLARAY	USA https://www.naturalhealthyconcepts.com
OREGONSWILDHARVEST	USA https://www.oregonswildharvest.com
REALHERBS	USA http://www.irealherbs.com
MUSHROOMSCIENCE	USA https://mushroomscience.com
HERBSENS	CHINA https://www.herbsens.com
TEREZIA	CZECH https://www.terezia.eu
ZEINPHARMA	Germany https://www.zeinpharma.com
THE REALLY HEALTHY	UK https://www.healthy.co.uk

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	https://organika.com
CORDYCEP	Support healthy immune and vascular systems	https://moonjuice.com
ULTRA CORDYCEPS PLUS	Support lung health and liver function	https://www.drbvitamins.com
HOST DEFENSE CORDYCEPS	Promotes healthy kidney function and Augments oxygen uptake	https://hostdefense.com
PERFECT CORDYCEPS	Boost the Immune System and Improve Sexual Function	http://www.perfect-supplements.com
PARADISE HERBS TIBETAN CORDYCEPS	Support physical activity, performance, stamina and resistance	https://paradiseherbs.com
SOLARAY CORDYCEPS	Protect against throat infections and promotes healthy cholesterol levels	https://www.naturalhealthyconcepts.com
OREGON'S WILD HARVEST CORDYCEPS	Cardiovascular, respiratory and immune support	https://www.oregonswildharvest.com
CORDYCEPS	Boosts energy and immunity and supports cardiovascular health	http://www.irealherbs.com
CORDYCEPS CS-4	Provide the immune health benefits	https://mushroomscience.com

can have a significant 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 reflected in the fact that global prices have risen dramatically at an average rate of 21.2% per annum, inflation adjusted, between 1997 and 2004. This high value product is an economic boon to rural areas but this comes at a cost. For example, conflicts over collecting-grounds may be common, causing difficulties 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 flora and fauna can be significant [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 figures 1-3. In parallel, there has emerged an issue with counterfeit and contaminated products [70]. Although this

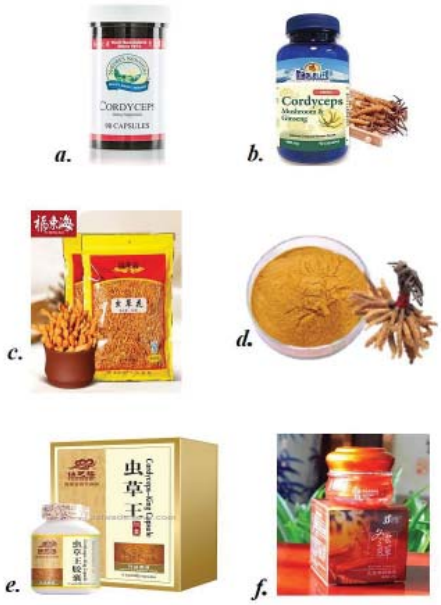

Figure 1 Cordyceps products made in China.
a) Cordyceps sinensis powder capsule (https://www.naturessunshine.com).
b) Cordyceps sinensis powder capsule (https://www.alibaba.com).
c) Cordyceps militaris Soup (https://www.aliexpress.com).
d) Cordyceps Mycelia Extract Powder as food supplements (https://www.alibaba.com).
e) Cordyceps-King Capsule (https://www.ecvv.com).
f) Cordyceps sinensis cream (https://www.aliexpress.com).

is not an issue confined 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.

Conflicts of Interest

The authors declare no conflict of interest.

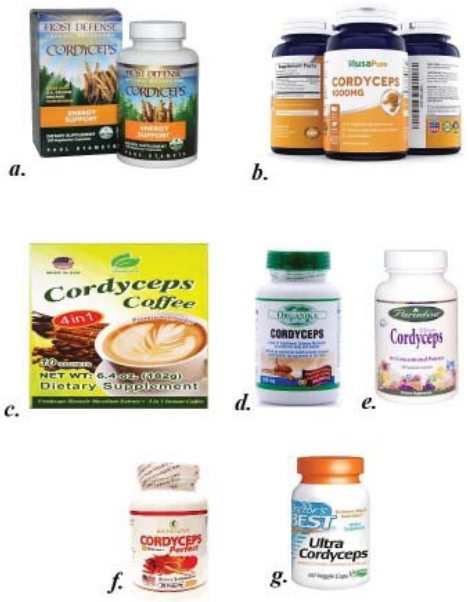

Figure 2 Cordyceps products made in the USA.
a) *Cordyceps* sinensis powder capsules (https://hostdefense.com).
b) Fruiting body extract of Cordyceps sinensis (https://www.nusapure.com).
c) *Cordyceps* sinensis powder sachets with coffee (https://www.iherb.com).
d) *Cordyceps* sinensis anti stress capsules (https://organika.com).
e) *Cordyceps* powder capsules (https://www.paradiseherbs.com).
f) *Cordyceps* sinensis powder capsules (https://usahealthyinc.com).
g) *Cordyceps* powder capsules (https://www.drbvitamins.com).

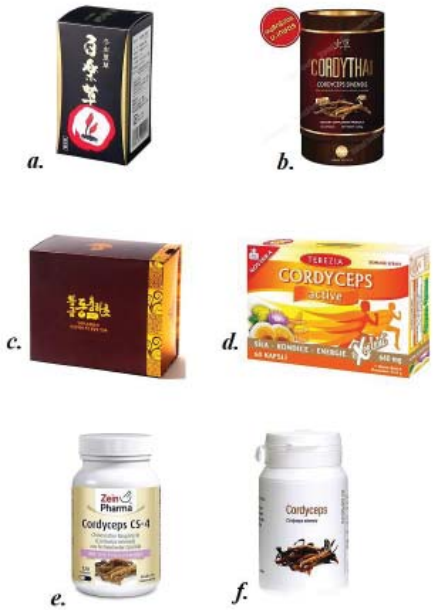

Figure 3 *Cordyceps* products made in different Asia and Europe countries.
a) *Cordyceps* sinensis supplement capsules made in Japan (https://cordyceps.tokyo).
b) *Cordyceps* sinensis supplement capsules made in Thai (https://www.amazon.com).
c) *Cordyceps* Tea sachets made in South Korea (https://www.alibaba.com).
d) *Cordyceps* powder capsules are made in Czech (https://www.terezia.eu).
e) *Cordyceps* sinensis capsules are made in Germany (https://www.zeinpharma.com).
f) *Cordyceps* sinensis capsules are made in the UK. (https://www.healthy.co.uk).

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