



## Cultivation of *Cordyceps* spp. as an economic boom in Shimla, Himachal Pradesh: A review

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### Abstract

The extensive research in cultivation of the prodigious mushroom species, that is, *Cordyceps*, has developed a mammoth in the scientific world because of the various properties possessed by this fungus species. *Cordyceps* spp. consist of mushrooms that have been classified into the group of *Ascomycota* and has been used in Asia widely since centuries due to its medicinal properties mainly by stimulating the immune system and reducing fatigue in humans. *Cordyceps militaris* has been accredited to possess a number of medicinal properties, some of which are anti-tumor, anti-inflammatory, anti-fungal, anti-bacterial, anti-viral, hypoglycemic, anti-malarial, neuroprotective, hypopolipidemic, immunoprotective, antioxidant and prosexual. Some other medicinal properties of *Cordyceps* spp mentioned are anti-cancer, anti-angiogenic, apoptosis induction, anti-proliferative, antimetastatic, anti-fibrotic, steroidogenesis, anti-hypertensive, anti-arteriosclerosis, antidiabetic, antithrombotic, anti-asthmatic, anti-aging and spermatogenic. This review focuses on studies spotlighting the research and development that has been conducted with respect to the two species of *Cordyceps*, i.e., *C. sinensis* and *C. militaris*, their biological composition, cultivation and production, traditional uses, phytochemistry and pharmacology, their role in serving as a potential champion in booming the Indian economy via meeting their increased demand around the globe.

**Keywords:** *Cordyceps* spp, economic, hypoglycemic

### Introduction

In recent years, the engrossment in the *Cordyceps* genus has escalated due to the humungous qualities that this fungus possesses. *Cordyceps* spp. consist of mushrooms that have been classified into the group of *Ascomycota* and has been used in Asia widely since centuries due to its medicinal properties mainly by stimulating the immune system and reducing fatigue in humans (Das *et al.*, 2021) <sup>[18]</sup>. The word *Cordyceps* has been originated from "kordyle", a Greek term meaning "club", and "ceps", the Latin term, which means "head". In order to survive and multiply, *Cordyceps* spp. evade the immune system of their hosts, i.e., arthropods, insects or other fungi (Olatunji *et al.*, 2018) <sup>[4]</sup>. For centuries, people in Tibet, China, India and Nepal have taken this species of mushrooms to help their bodies adapt to harsh high-altitude circumstances like low temperature range, high pressure of air, and reduced levels of oxygen in the environment. *Cordyceps* spp. is used in medicine of China traditionally to cure a variety of human diseases, including respiratory and cardiovascular diseases, kidney and liver abnormalities, malignancies, diabetes, parasite infections, and sexual dysfunctions. Massive research has been conducted in approximately 750 species of *Cordyceps*, with *Cordyceps sinensis* leading the charts. But due to the numerous complications involved with this spp., a great area of interest for research has been developed in *Cordyceps militaris* (Masuda *et al.*, 2010; Holiday 2017) <sup>[1]</sup>. *Cordyceps militaris* has been accredited to possess a number of medicinal qualities, some of which are anti-tumor, anti-inflammatory, anti-fungal, anti-bacterial, anti-viral, hypoglycemic, anti-malarial, neuroprotective, hypopolipidemic, immunoprotective, antioxidant and prosexual (Olatunji *et al.*, 2018; Zhang *et al.*, 2019; Das *et al.*, 2021) <sup>[4, 18]</sup>. Some other medicinal properties of *Cordyceps* spp mentioned are anti-cancer, anti-angiogenic, apoptosis induction, anti-proliferative, antimetastatic, anti-fibrotic, steroidogenesis, anti-hypertensive, antidiabetic, anti-arteriosclerosis, antithrombotic, anti-asthmatic, anti-aging and spermatogenic (Liu Y *et al.*, 2015) <sup>[23]</sup>. As an entomopathogenic fungus, the prevalence of *Cordyceps* spp. in the natural environment is a distinctive characteristic of the species. These species are only found in the Himalayas at altitudes of 2000 metres above sea level, where they are endemic (Jedrejko *et al.*, 2021). *Cordyceps sinensis* is parasitic in nature which feeds on the larvae of *Lepidoptera* and *Thitarodes* species of moths. The larvae live 15 cm beneath the ground, and are invaded by *C. sinensis*, that eventually consumes the complete inside of the larvae before the production of the fruiting bodies on the shells that can be seen above the soil surface. In months of May and June, indigenous people gather *C. sinensis* larvae, keep it for drying, then after pulverising it, an extract is produced along with hot water, that can be ingested (Holiday 2017) <sup>[61]</sup>. The long steps of symbiosis in between the larva and the fungus, between autumn and spring takes a lot of time and the process of harvesting of this mushroom species results in a highly priced amount due to its limited resources, growth pattern, its rare

occurrence and life cycle in the environment. Availability of this species in wildlife has become unsatisfactory to cope with the required growth for materials for the manufacture of functional foods, nutraceuticals and nutritional supplements, particularly in the United States, Europe and Asia (Cheong *et al.*, 2018) [5].

Due to the difficulties faced in manufacturing *C.sinensis* from culture media, high demand and price of this fungus has led to the research in alternative spp. The quantitative and qualitative makeup of biologically active chemicals from *C. militaris* cultivated in labs is identical to substances in fruit body of *C. sinensis*, *C. militaris* is a viable alternative to *C. sinensis* (Jedrejko *et al.*, 2021). “Fungalicious delights” in Shimla, Himachal Pradesh has taken the initiative of *in vitro* cultivation of *C.sinensis* and *C.militaris* for economic purposes. This review focuses on studies spotlighting the research and development that has been conducted with respect to the two species of this fungus, i.e., *C.sinensis* and *C.militaris*, their biological composition, cultivation and production, traditional uses, phytochemistry and pharmacology, their role in serving as a potential champion in booming the Indian economy via meeting their increased demand around the globe.

### Taxonomy

The genus *Cordyceps*, as per its cylinder-shaped asci, thick ascus apices, ascospores as filiform, that disengage into part-spores has been classified in the family, *Clavicipitaceae* and consists of over 400 species (Mains, 1959). The development of external to totally submerged perithecia over the stipitate, mostly capitate and club shaped stromata, as well as the biology with respect to the disease of insects and the species of fungus *Elaphomyces*, distinguishes *Cordyceps* from rest of the genera of the family ((Sung *et al.*, 2007) [7, 11]. The genus *Cordyceps* was distinguished in three subgenera (*C. subg. Neocordyceps*, *C. subg. Ophiocordyceps*, and *C. subg. Cordyceps*), as per the layout of perithecia, ascospores and asci and part-spore form (Kobayasi 1941, 1982) [8, 9]. *Cordyceps* was divided into three sub-genera by Kobayasi, which are *Ophiocordyceps*, *Eucordyceps*, and *Neocordyceps*. The formation of submerged or superficial perithecia formed almost perpendicular to exterior of the ascospores and stroma which disengage to form part-spores at reaching maturity were characteristics of the subgenera of this fungus species *Cordyceps* of the type *C. militaris*. The development of all ascospores that do not disengage into part-spores, the lack of asci conspicuous spherical caps at the apical site characterised the subgenera of this mushroom species, *Ophiocordyceps*. Other subgenera of this fungus species, *Neocordyceps* has perithecia submerged at angles that are oblique in nature in the region of the clava of ascospores and stroma and that disengage to form part spores at reaching maturity (Stensrud *et al.*, 2005) [10]. The *Cordycipitaceae* family is named after the *Cordyceps* species *C. militaris*, and it contains all *Cordyceps* species with a fleshy and strongly coloured stromata (Sung *et al.*, 2007) [7, 11].

**Table 1:** The taxonomical classification of *Cordyceps* is given in the table below:

Kingdom	Fungi
Phylum	<i>Ascomycota</i>
Class	<i>Ascomycetes</i>
Order	<i>Hypocreales</i>
Family	<i>Clavicipitaceae</i>
Genus	<i>Cordyceps</i>
Species	<i>Cordyceps sinensis</i> , <i>C. militaris</i>
Synonyms	<i>Isaria</i> , <i>Buevaria</i> , <i>Metarhizium</i>
Anomorphs	<i>Cephalosporium donqchongxiacao</i> , <i>Chrysosporium sinense</i> , <i>Cephalosporium sinensis</i> , <i>Mortierella hepiali</i> , <i>Hirsutella sinensis</i> , <i>Paecilomyces hepiali</i> , <i>Scytalidium sp.</i> , <i>Scytalidium hepiali</i> , <i>Tolypocladium sinensis</i>
Names in India	Keera Jari
Names in Japan	Totsu kasu, Tochukasu
Names in China	Dongchongxiacao [chongcao], Hia tsao tong tchong
Names in English countries	<i>Cordyceps</i> mushroom, Caterpillar Fungus

### Characteristics and Distribution

The genus *Cordyceps* consists of more than 700 recognised species, among which 20 species parasitise *Elaphomyces* genus, while the rest species parasitise on arthropods belonging to the classes, *Isoptera*, *Hymenoptera*, *Arachnida*, *Hemiptera*, *Coleoptera* and *Lepidoptera* (Pal and Mishra, 2018). This fungus species has various properties, such as pharmacological capabilities, which have attracted the practitioners of traditional medicine in China right from the 1990s, with *C. sinensis* being examined the most and used. The distribution and abundance of this species is primarily determined by dispersion of their hosts; nonetheless, they can grow at altitudes of 3,500–4,200 meters of elevation. This mushroom species has been discovered on Asia, Europe, North America, China, Nepal, Vietnam, Japan, Korea and Thailand. The higher altitudes of the subalpine regions of India namely, Garhwal Himalaya and Kumaun Himalaya consist of this species. (Maity, 2013; Chakraborty *et al.*, 2014) [13, 22, 14].

The *Cordyceps* mushroom, a unique pharmacological mushroom, disperses via rain, insects and air, rain, and during whole life cycle of the insects, which is divided into three different phases that are; firstly infection,

secondly parasite stage and lastly saprophyte stage (Pal and Misra, 2018) <sup>[12, 15]</sup>. This species of fungus first causes infection and then germinates inside the host in the larval stage via its ascospores which are emitted to the atmosphere from ripe fruit bodies over the early autumn and summer. In certain situations, infection is caused through consuming eatables that have been infected with the mycelia of *Cordyceps* spp. The stage of the parasite begins post infestation and then this fungus species feeds on the host's gut. During the winter, the fungal cells move all through the body and grow quickly, eating all of the larva's inner organs but leaving the exoskeleton undamaged. The fungal cell then transforms to a whitish structure within the body of the larva which is known as endosclerotium (Tuli *et al.*, 2013; Baral *et al.*, 2015) <sup>[16, 17, 19]</sup> Environmental circumstances are harsh during this procedure, and the mushroom must withstand snow and low temperatures. When the temperature outside rises in the springtime, the endosclerotium starts to grow and ejects through the host's oral cavity, maturing in the summertime, creating the fruit body, and while in the saprophytic phase it disposes ascospores. The gathering of this mushroom species takes place throughout this season (Das *et al.*, 2021) <sup>[18]</sup>.

Villagers have historically been the principal hunters of these species, collecting them during grazing season (Baral *et al.*, 2015) <sup>[19]</sup>. Principal catchers remain in highlands for months to look after their pets that are Yaks, and harvest mushrooms and other therapeutic plants (Panda, 2010). The people involved in medicine making locally also go to the locations to pick mushrooms, dry substance and save it for later use. Because of the therapeutic value of *Cordyceps* spp., its business has expanded, resulting in over-harvesting and a dearth of exotic species. As a result, a number of researchers have been finding ways to decipher the production along with the multiplication of this fungus since the 1970s. For many decades, this mushroom species of *Cordyceps* have been linked with medicinal characteristics and curative behaviours, they have thus been proved a boom to the medicines made traditionally to serve as a cure and therapy for many health-related issues of human body. (Das *et al.*, 2021) <sup>[18]</sup>.

### **Ethnopharmacological uses of *Cordyceps* spp.**

*Cordyceps* has been used in a traditional way medicinally for centuries in China to serve as a natural medicament for curing a variety of ailments, including respiratory ailments, liver or kidney difficulties, cancer, hyperglycaemia and tumour complications. Furthermore, this fungus species is also used to enhance energy levels and endurance, as well as aerobic capacity and cell - mediated immunity. The most common species used were *C. sinensis* and *C. militaris* (L.) Fr., which were formally designated as drugs in the Chinese Pharmacopoeia in 1964 (Shashidhar *et al.*, 2013) <sup>[21]</sup>. The prescription and application of *C. sinensis* in some places, including China, Bhutan, Tibet, India and Nepal are depending on expertise along with abilities possessed by local folk therapists using a testing process (Maity, 2013) <sup>[13, 22]</sup>. Some communities, for example, mixing the mushroom in alcohol hot water or milk, alcohol and drinking it like a stimulant of increasing the sexual potential, also like a dawn medicine (Panda and Swain, 2011) <sup>[20]</sup>. This fungus's activity when combined with other bioactive compounds has also been documented. Some folk healers, for example, recommend combining *Cordyceps* spp. with *Taxus* leaves and roots act as a cancer cure.

Moreover, the Chinese populace has regarded *C. sinensis* as nutritious food, owing to the presence of nutrient content like vitamins (B2, B12, K, and B1), carbohydrates and vital amino acids. Astonishingly, this fungus type is a nutritional supplement that meets US Food and Drug Administration (FDA) requirements, making this mushroom popular in a number of nations (Wu *et al.*, 2015). *Cordyceps* spp. has been used as a cure for exhaustion and tiredness, ailing altitude sickness and providing an energy boost to the individual. Folk's soreness lessens as they get older. TCM experts also advocate taking *C. sinensis* on a frequent basis to avoid illnesses, common cold, and flues because of its potential to reduce congestion and phlegm, asthma, and respiratory illnesses (Lo *et al.*, 2013) <sup>[24]</sup>. Because of such factors, this mushroom has been used to treat lung degeneration, in patients with severe respiratory diseases. All of these traits are linked to *C. sinensis*' potential to enhance the lung, according to TCM beliefs (Chiu *et al.*, 2016) <sup>[25]</sup>. Advantages of this species has been discovered in athletes as per increase in ATP levels of cells, that generate power in the tissue of the muscle, resulting in an increase in energy.

*C. militaris* (L.) Fr. Possesses qualities as a stamina booster, erotic source, and bronchial problem therapy are similar to those of *C. sinensis*. This species has also been linked to hypoglycemic, antibacterial, anti-inflammatory, anticancer, antioxidant, antifungal, and immunoprotective effects. As a result, it is considered a good affordable replacement for *C. sinensis* ranking second among the most sold species (Chou *et al.*, 2014) <sup>[26]</sup>. This fungus has traditionally been consumed like a herbal ailment, also its widespread distribution goes all the way back to the year 2000. It is used as a nutritional supplement in multiple nations due to its various medical benefits. Since its renown grew in tandem with scientific proof, it has become a highly desirable product. Wild *C. sinensis* can cost up to Rs.50,00,000 per kilogramme, making it one of the most expensive mushrooms on the planet.

### **Phytochemistry**

*Cordyceps* spp. consists of numerous compounds that are chemical in nature and have their respective derivatives as secondary metabolites. Cordycepin, a nucleoside analogue of adenosine, also known as 3'-deoxyadenosine, was discovered in *C. militaris* in 1950. Antitumor, immunomodulatory, antibacterial, and anti-diabetic properties are among the biological functions of the molecule (Jiapeng *et al.*, 2014) <sup>[27]</sup>. It is a chemical signature for fungus in this mushroom genus and is indeed among the active principal constituents of *C. militaris*

and *C. sinensis*, according to previous research. Cordycepin's antioxidant properties has only been established in a few research. The antioxidant properties of polysaccharide fragments found in *C. militaris* fruiting bodies has been described in research activities using the processes of biological processes of polysaccharide fragments. Experiments on mice revealed that cordycepin's immunomodulating action is due to its ability to trigger cell-mediated immune responses. The researchers discovered a rise in the concentrations of the interleukins IL-10, IL-12, and IL-4, also of the cytokines Th2 and Th1, reduction in the concentrations of TGF- and IL-2, a rise in the amount of T cells; CD8 and CD4. Complementing "produced" energy as molecules of adenosine-5'-triphosphate (ATP) is among cordycepin's modes of action. The concentration of Nitrous Oxide can also be increased with the Cordycepin's help (Tuli *et al.*, 2014; Qin *et al.*, 2019) [28, 29].

The nitrogenous compounds and proteins found in this species of fungus consist of proteins, essential amino acids, polyamines and peptides. Cyclo-[Leu-Pro], cyclo-[Gly-Pro], cyclo-[Ala-Pro], cyclo-[Thr--Leu], and cyclo-[Val-Leu] are just a few of the unusual cyclic dipeptides found in *Cordyceps* spp. The polyamines like spermidine, 1,3-diamino propane, putrescine, spermine and cadaverine were found in higher amounts. Other nitrogenous compounds have been discovered, such as putrescine (Mizuno, 1999; Mishra and Upadhyay, 2011) [31, 30]. This fungus species is high in nucleotides and its derived compounds. Nucleosides are the main component in *C. sinensis* that contributes to medicinal applications (Li *et al.*, 2001) [32]. *C. sinensis* has produced nucleosides like adenosine, inosine, cytosine, cytidine, uridine, guanine, thymidine, guanosine and hypoxanthine. Guanosine has the highest concentration ratio of the nucleotide constituents compared to the other constituents (Shaoping *et al.*, 2001) [33].

Various forms of polysaccharide compounds found in the *Cordyceps* spp. *Cordyceps* spp. fruiting bodies contain polysaccharides ranging between 3 to 8 percent (Li *et al.*, 2001) [32]. The polysaccharides produced from this mushroom are recognised to be important medicinally and could be used among the key ingredients in medication formulations. These polysaccharides have immunoprotective, antioxidant and anti-influenza properties, and can totally manage sugar levels in blood (Kiho *et al.*, 1993) [35]. They also have antitumor and antimetastatic properties (Nakamura *et al.*, 1999) [36], as well as immunoprotective, antioxidant properties and anti-influenza. Polysaccharides from this species are physically varied macromolecules that are bioactive with a wide range of properties that are physiochemical in nature. These polysaccharides can be found both inside and outside the cell. It has been demonstrated that molecules with a molecular weight larger than 16,000 exhibit anticancer effects (Zhou *et al.*, 2009) [37, 51, 52].

The polysaccharides produced via this consumable, therapeutic fungus have been proven to have anticancer and immunomodulatory effects, initially described in 1969 through the fruiting body of *Lentinusedodes*. As a result, over the last 30 years, a vast variety of consumable and therapeutic polysaccharides, including this fungus species, have been thoroughly researched. Aside from that, a slew of new anticancer and immuno-boosting polysaccharides have been created and marketed (Wasser, 2002; Xiao *et al.*, 2002, 2003) [38, 39, 40]. *C. sinensis*, *C. Cicadae*, *C. ophioglossioides*, *C. kyushuensis* and *C. militaris* 5 are some of the significant *Cordyceps* spp. from which polysaccharides mixed with other chemotherapeutic medications demonstrated synergy and higher resistance to body (Xiao *et al.*, 2002; Yang *et al.*, 2005; Zhang W *et al.*, 2005; Chen *et al.*, 2006) [38, 41, 42, 43]. This genus has sterols as ergosterol, which is a significant portion of vitamin D2's medicinal potential. Ergosterol, ergosterol peroxide, ergosterol-3, daucosterol, campesterol and 3-sitosterol are just a few of the sterol-type chemicals discovered in *Cordyceps* spp (Zhou *et al.*, 2009) [37, 51, 52].

The chemical structure of the compounds present in the *Cordyceps* spp. is given in the figure below:

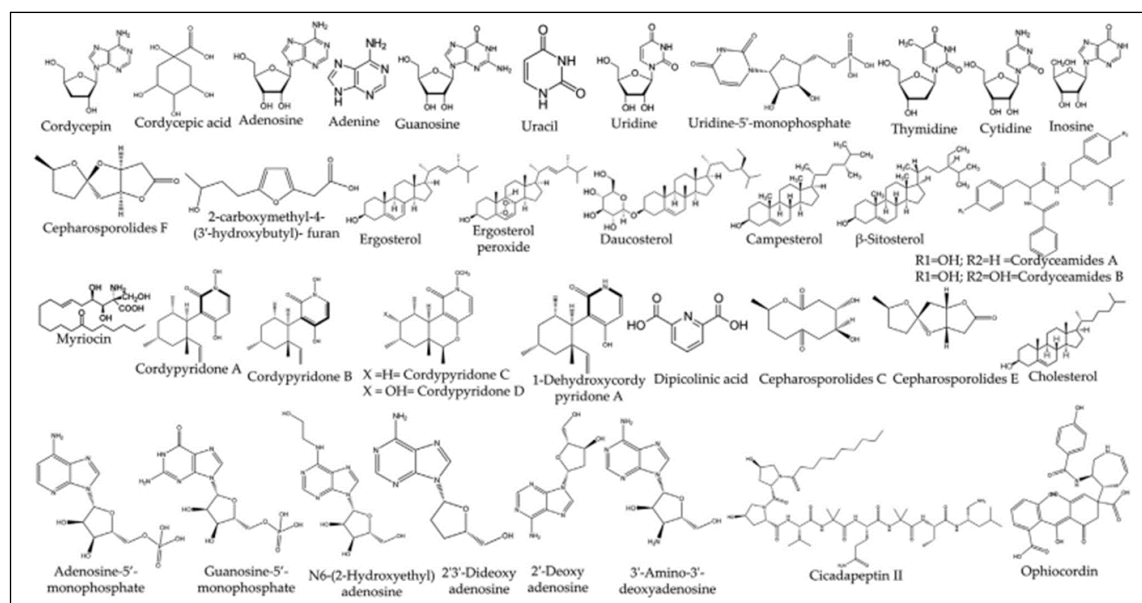


Fig 1

### Pharmacological Potential OF *Cordyceps* spp.

The anti-inflammatory potential of this genus has been researched upon and proven via the clinical trials conducted by scientists over the past decades. In the carrageenin-induced edoema, cultivated mycelia of *C. militaris* (L.) Fr. has an extract that shows substantial inflammatory preventive activity and reduces the induced impression of nitric oxide synthase in the macrophages. This function validates iNOS' anti-inflammatory impact, as no production by iNOS increases in diseases that are inflammatory and thus causes harm to the cells (Won and Park, 2005). No generation was inhibited in lipopolysaccharide (LPS)-induced macrophages by the fraction of *C. militaris* (L.) Fr. that was butanolic in nature, with cordycepin being main chemical. Cordycepin was discovered to decrease the phosphorylation of some proteins and translocation were likewise inhibited in such macrophages. As a result, it was suggested that cordycepin could be used to treat inflammation-related illnesses (Kim *et al.*, 2006). The cell mediated immunity can also be strengthened by *C. sinensis* (Liu *et al.*, 2007) [46]. Immunomodulators are chemicals or molecules that provide help in the regulation of the immune system. Numerous chemicals found in this fungus species that have immunoregulatory properties. A few of these are covered farther down. Lectin receptors like CLR and TLR show active *Cordyceps* spp. during the onset of regulation of immune system and decreases response in antigen-presenting cells. The ingredients that are active not only change the expression of the lectin receptors in APCs, but also control signalling between the cells. (Das *et al.*, 2021) [18].

This genus also possesses anti-viral properties. Intranasal treatment of a polysaccharide acidic in nature was derived from a *C. militaris* (L.) Fr. extract and when it was cultured via a medium of soybeans that were germinated, a reduced virus in the bronchoalveolar lavage fluid tethered and the lungs of mice that were infested with influenza A virus, resulted in a survival rate higher in nature. IFN- and TNF- levels were likewise elevated by APS. In murine macrophage cells; RAW 264.7, it elevated no generation and stimulated protein expression. The elevation of cytokine mRNA expression, like IL-10, TNF-, IL-1 and IL-6, revealed positive curative effects on virus infestation of influenza A via altering macrophage immunomodulating activity (Ohta *et al.*, 2007) [47]. *Cordyceps* spp. also contains chemical compounds that have anti-tumour effects. Due to different bioactive chemicals present, such as polysaccharides, sterols, and adenosine, many genera of this fungus species have established to possess the ability of inhibiting the tumour growth (Yoshida *et al.*, 1989; Bok *et al.*, 1999; Li and Wang, 2008; Zhou *et al.*, 2009) [37, 51, 52]. The ergosterol that is glycosylated which is found in the extract methanolic in nature of *C. sinensis*, has been found to be a potent antiproliferative agent in a variety of tumour cell lines (Bok *et al.*, 1999) [49]. Furthermore, the extract of water of *C. sinensis* speeds up phagocytosis that is cell-mediated which helps metastasis to be prevented (Nakamura *et al.*, 1999) [36]. Because this mushroom species may be artificially produced, a comparison investigation found that the farmed mushroom has more powerful anticancer activity against lines of cancer like HepG2, MCF-7, HL-60 B16 than natural *Cordyceps* spp (Zhang Q *et al.*, 2005).

Intraperitoneal treatment of polysaccharides derived via mycelia that has been farmed of *C. sinensis* that is CS-F30 lowers glucose levels of plasma to normal. Thus, *Cordyceps* spp. also displays hypoglycemic activity. CS-F30 accelerates glucose metabolism by potentiating hexokinase, glucose-6-phosphate dehydrogenase and glucokinase activities, which led to its anti-diabetic action (Kiho *et al.*, 1996) [54]. CordyMax™ Cs-4, a commercial fermentation product derived from a patented strain of mycelia of *C. sinensis* that is naturally found, is said to prove beneficial in decreasing basic glucose present in the blood and insulin levels in the plasma. This also enhances glucose metabolic activity by enhancing sensitivity of insulin and improving tolerance to glucose orally. When diabetic rats were induced with STZ and nicotinamide, it was found that this mushroom species exhibits lower glycaemic effects, as seen by decreased weight loss, hyperglycemia and polydipsia (Lo *et al.*, 2004) [55]. In diabetes mellitus-II mouse model, *C. sinensis* had one extract that has been shown enhancement of cell survival. (Kan *et al.*, 2012) [56].

The kidney is the principal organ in the body that filters and eliminates waste through urine secretion. One of the many uses for the parts of *C. sinensis*, its usefulness in regulating some kidney imbalances, such as the lowering of proteinuria and hematuria with an obvious tissue recovery as proven by historic investigation can be seen (Ding *et al.*, 2011) [57]. The species of *Cordyceps*, since a long period of time, has been in the use as a medication to help persons suffering from weakness and exhaustion due to high altitude. The *Cordyceps* spp. fungus first came to prominence in the year 1993, wherein certain sports champions of the world disclosed segment of their winning approach, which included a *Cordyceps* spp.-based diet (Kashyap *et al.*, 2016) [58]. This functions along raising ATPs of the cells, which increases biological energy and allows for more better oxygen usage (Geng *et al.*, 2017) [59]. Surprisingly, the athletes use the species of *Cordyceps* to combat weariness and lethargy, resulting in increased energy and endurance (Zhu *et al.*, 1998) [60]. Thus, this mushroom also possesses anti-fatigue properties.

### Cultivation and Harvesting

*Cordyceps* cultivation currently is done using two main approaches. Liquid culture or fermentation is a method of introducing the organism into a sterilised liquid medium that has been created to give all of the essential nutrient content for the fast growth of the mycelium. It is primarily utilised in China. The collection of mycelium is done when it is filtered out of the medium that is liquid and drying for further processing and use after it has grown in the liquid medium. The extracellular chemicals that the fungus in its growth phase released are typically eliminated along with the broth that is spent in the procedure. Even though many of the active elements

are extracellular and only detected in modest amounts in the mycelium, this implies a significant loss of bioactive chemicals (Holiday *et al.* 2004) <sup>[61]</sup>. The solid/substrate approach is the second method of cultivation. Plastic bags or glass jars filled with a sterilised media are used for the cultivation of mycelium, which is nearly typically cereal grains, in this growing system. Although many various types of grains have been utilised, the most common ones are wheat, rice, and rye. The mycelium is gathered along with the leftover grain after a time of growth. While this is a simple to learn and low-cost growth method, the downside is that the content of the grain is frequently higher as compared to the content of the mycelium. The extracellular chemicals are extracted simultaneously with the mycelium and substrate, which is a benefit of this approach (Singh *et al.*, 2021) <sup>[18, 62]</sup>. “Fungalicious delights” in Shimla, Himachal Pradesh has also taken the initiative of *in vitro* cultivation of *C.militaris* and *C.sinensis* for economic purposes. It is established by Mr.Nikhil Chauhan and Mr.Vishal Thakur, both belonging to a non-scientific background, with their determined zeal to explore this wonderful fungus’s photochemical and economical limits.

### Major Cultivation Centers Currently in India

1. Omcar india training center, Gwalior, M.P.
2. The Directorate of Mushroom Research-ICAR, Solan, Himachal Pradesh
3. Khan Mushroom Farm & Training Centre, Una, Himachal Pradesh
4. Best Cordycepsmilitaris culture & Training in India, Anupshahar, Uttar Pradesh
5. Dr. Harisingh Gour Vishwavidhayalaya, Sagar, M.P. (Grown for research work)

There have also been some successful examples of the artificial cultivation of this mushroom documented. Despite the many challenges that lie ahead in artificially cultivating Chinese *cordyceps*, considerable advances have been made in the field, including massive artificial culture success (Dong 2016). Yichang Shanchengshuidu Cordyceps Co., LTD in Yidu county, Hubei province, built a Chinese cordyceps development and production base (Li *et al.* 2016), with an annual yield of 15 tonnes in 2017. Some institutes, such as teams from Sichuan Agricultural University under Prof. Zuji Zhou, Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences under Prof. Darong Yang and Guangdong Institute of Applied Biological Resources under Prof. Richou Han, had finally finished the life cycle of *O. sinensis*’s life cycle in its host from anamorph to teleomorph (Qin *et al.*, 2018) <sup>[65]</sup>.

### Progress in Industrial and Commercial Potential

Despite the fact that there are over 400 *Cordyceps* species, 36 were intentionally cultured as a part of development of fruit bodies (Wang 1995; Sung 1996; Li *et al.* 2006) <sup>[66, 67, 68]</sup>. Commercially only *C. militaris* developed among the species that have been artificially produced; development commercially has centred on *C. militaris* due to its superior pharmacological property and quick manufacturing duration. The growth of *Cordyceps militaris* has been done in both liquid and solid media to extract inducing fruit body and mycelia. Even though circumstances for subsurface development of inoculum of *C. militaris* have been improved, *C. militaris* fruiting-body's production on a greater scale still relies on medium that is solid in nature such as substrates that are artificial or arthropods. The cultivation exhibited on arthropods is expensive, so *C. militaris* fruiting bodies are generally grown on media that is artificial with rice as the major segment. In China, the substrates utilised for cultivation in industries of *C. militaris* were examined recently. Spawn media, pre-culture spawn and stock culture are among them (Li *et al.* 2006) <sup>[68]</sup>.

There are two main applications for *Cordyceps militaris* cultures. To begin with, the fruiting bodies can be eaten immediately. *C. militaris* can be added in a variety of dishes, including hot pot, stewed duck, stewed chicken, tea and soup. In Taiwan, China, Hong Kong and Guangdong, *C. militaris* used in soup is quite famous. Second, the mycelia and fruit body of *C. militaris* could be employed as healthy supplements and medications. *C. militaris* is found in a variety of Chinese medical products, including capsules, vinegars, wines, yoghurt, oral liquids, capsules, wines, vinegars, teas, soy sauce and yoghurt (Wang and Yang 2006) <sup>[70]</sup>. *C. militaris* cultures are also utilised to make medications for lung and kidney function management, chronic bronchitis, sleep control and anti-aging (Dai *et al.* 2007). *C. militaris* health items, more than 30 in number and medications in the market exhibit their availability (Huang *et al.* 2010).

### Safety, Toxicology and Regulatory Status

Among the chemicals with cytotoxic properties found in *C. militaris* are beauveriolides and militarinones. Cordycepin and pentostatin were gastrotoxic in nature. The lungs and neurological system are also affected by pentostatin (Chen *et al.*, 2020) <sup>[73]</sup>. In murine cells, 18-kDa nonglycosylated protein (CMP) that causes apoptosis that is dependent on mitochondria was found. In an elevated temperature or alkaline environment, CMP is fragile and degrades. To disable CMP for further processing of *C. militaris* for dietary supplements, medications and food, thermal treatment of *C. militaris* is required (Bai *et al.*, 2018) <sup>[74]</sup>. Heavy metals like lead, mercury, arsenic and cadmium are toxicologically dangerous to humans. Lead concentrations in the fruit body of wild-growing *C. militaris* did not surpass 0.2 mg/kg dry weight, while mercury concentrations did not cross the limits of 0.5 mg/kg dry weight, according to a quantitative analysis. Arsenic and cadmium levels were considered to be comparatively high, at 0.4 mg/kg and 0.2 mg/kg dry weight, respectively (Cohen *et al.*, 2014; Uzun *et al.*, 2009) <sup>[76, 75]</sup>.

The toxic effects of *Cordyceps* spp. highlight that metabolites that are secondary in nature of hydrocarbons that are polycyclic and aromatic, predominantly produced by *C. sinensis* react with a compound in common bags called polypropylene, that results in harmful byproducts for *C. sinensis* and rapid advancement. The organism is unavoidably harmed by these polypropylene/PAH by-products. *C. sinensis* should always be cultivated in metal or glass vessels to lengthen the organism's development time. Living culture consists of PAH chemicals, but on drying the culture they are lost due to their volatility. While most species of fungus strains could not be cultivated in common bags, to make this possible, new strains that produce less PAH are being developed (Holliday *et al.*, 2004) <sup>[77]</sup>. The regulatory status of *Cordyceps*, is as an unrecognised substance in many countries around the world, having only recently come under the attention of modern science. Many governments do not prescribe medication to acquire or use *Cordyceps*, with the exception of import/export tariffs and limitations, which vary by nation (many of which prohibit the importing of any such item). A doctor's prescription is required in a few nations, like Austria, Portugal and Romania. (Bhandari *et al.*, 2010) <sup>[78]</sup>.

### Conclusion and Future Prospectives

*Cordyceps* is a unique fungus that has a rich history as a medicinal plant with a number of therapeutic purposes and is utilised in a variety of nations. *Cordyceps* is reported to be the world's most costly herb today, with a kilogramme costing more than \$10,000 on the international market. The problems associated with the future prospects of this mushroom include the degeneration of isolates in its cultivation. Cultivation of *C. militaris* is plagued with isolate degeneration. Less rate of growth, density of the mycelia, fruit body yield and pigmentation as well as alterations in shape and size of fruit body, are all signs of degeneration. Reduced synthesis of desirable chemicals from fermented cultures can potentially indicate degeneration. Apart from this, stimulation of immunological functions and the reduction of weariness are two ways to improve human endurance that are provided by this mushroom. To conclude, edible fungus, such as *C. militaris*, include a number of bioactive chemicals that qualify them as a food that is functional in nature. Incorporating the extract of *C. militaris* into one's diet might have a variety of benefits related to health; also, intake of many mushroom species that can have their cultivation on domestic wastes will uplift mushroom industry in many parts of world's stable economy. Simultaneously, numerous chemicals that are bioactive in nature complicate drug development using mushroom extracts. A single component, on the other hand, might possess less curative or healing impact and might not interact with rest of the components found in fruit body of the fungus in a synergistic manner. Cordycepin has the best therapeutic potential of all the bioactive compounds described in the studies. Cordycepin may have antiviral activity against SARS-CoV-2 in COVID-19, according to recent research publications. Since a product that is natural like *Cordyceps* possesses a strong history of use, it does seem reasonable to assume that there is some reality to the legends. In the modern period, our issue is to scientifically resolve the various claims and disagreements. Because of the substance's high cost and rarity, *Cordyceps* has posed a greater barrier than most natural herbals. *Cordyceps* still has a lot of secrets up its sleeve. More research into this and other medicinal mushroom species is required. For a comprehensive scenario involving *Cordyceps* conservation, understanding and scientific understanding are required.

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