Review article

A review on unravelling the medicinal properties of magical mushrooms: *Cordyceps militaris*

Payal Mago[1], Simran Kaur[2], Isha Srivastava[2], Rekha Mehrotra[2], Kohinoor Kaur[2], Richa Sharma[2], Aarti Yadav[2]

[2]Department of Microbiology, [1]Shaheed Rajguru College of Applied Sciences for Women, University of Delhi, Vasundhara Enclave, Delhi, 110096, India

(Received: June 2023 Revised: September 2023 Accepted: September 2023)

Corresponding author: **Aarti Yadav.** Email: aartiyadav003@gmail.com

ABSTRACT

Nowadays, the public and the scientific communities are choosing and looking for natural remedies as an alternative to the elaborate chemically synthesised drugs. As a result, due to its immunostimulatory potential, Cordyceps genus has grabbed attention from the scientific community in recent years. Various *in vivo* and *in vitro* investigations on the endo-parasitic fungi have shown its tremendous pharmaceutical potential owing to the various bioactive constituents. Pre-clinical studies have revealed its activities like anti-cancer, anti-diabetic, antioxidant, vasorelaxation, antihyperlipidemic, anticholesterolemic, hypotensive, anti-aging, anti-fatigue, kidney protection and aphrodisiac. Moreover, Cordyceps species are also related with stimulation of the immune system- stimulating inflammatory response mediated *via* mitogen activated protein (MAP) kinase pathway, stimulation of phagocytosis, and cytokine production such as interleukins (IL)-10, IL-12, and tumour necrosis factor alpha (TNF) etc. In the present review, we discuss the various bioactive compounds of the fungi such as nucleosides, alkaloids, flavonoids and their therapeutic potential. We also highlight its culturing methods and its current status in the global market.

Keywords: Mushrooms; mushroom cultivation; Cordyceps mushroom; medicinal mushrooms; fungi.

INTRODUCTION

Medicinal mushrooms have always been a significant part of human civilization. They are a rich source of antioxidants and it is believed that about two-third fatalities due to cancer could be prohibited if we modify our diet with mushrooms (1,2). Cordyceps mushrooms have an ancient legacy of usage as an organic ingredient in traditional Asian medicine. The name Cordyceps comes from Latin words, first being the *cord* meaning club and second being the *ceps* meaning the head. One of the largest genera in the Clavicipitaceae family, 'Cordyceps' is a member of the group Ascomycota because it produces spores internally, in a sac-like structure, known as ascus (3). With over 750 species, they exhibit wide diversity in terms of morphology and acclimatisation on various hosts (4,5). Their medicinal usage is attributed to their adaptogenic and stimulating effects, as well as the potential to ease fatigue and enhance the efficacy of the immune system in humans (6,7).

Within its genus, *Cordyceps sinensis* is the most studied species followed by *Cordyceps militaris*. *C. sinensis* has been used as an ingredient in foods and medicines since ancient times and is therefore better known among consumers. Since it is difficult to isolate *C. sinensis* from culture media, several alternative sources have been sought. Further, the increasing demand for this species, and the high cost due to limited natural resources, have bound researchers to look for better alternatives. *C. militaris*, a similar species that can be grown and obtained in vitro, has emerged as the solution to this problem (8).

The medicinal fungus *Cordyceps militaris* is commonly used as a crude medicament in Asia and is prominent in conventional Chinese medicine and potential food supplement (6). Several medicinal benefits of *C. militaris* have been demonstrated, activities against tumour, microbes, virus, protozoan, and has antioxidant, anti-inflammatory, blood glucose management, hypolipidemic, neuroprotective, and immuno-protective effects. Cordycepin, a constituent of *C. militaris*, can be used as a therapeutic agent to prevent chronic inflammatory response (6,9). Owing to its tremendous clinical value, it is also referred to as "Himalayan Gold" or "Himalayan Viagra".

This article reviews the intricacies of Cordyceps as a medicinal mushroom, highlighting important aspects like culturing of Cordyceps, pharmacologically important compounds and their mode of action, along with global market potential and future prospects.

Culturing of *Cordyceps* species

In Korea, China, Japan and other east Asian countries, Cordyceps species are regarded as medicinal mushrooms (10). There are interesting stories about their collection in the mycological literature of these countries (11). The literature reported more than 1200 entomopathogenic fungi. Cordyceps make up the largest part of it, containing about 500 different species. The Cordyceps species that are being cultivated owing to their pharmaceutical and medicinal properties are *C.sinensis, C.militaris, C ophioglossoides, C. cicadicola, C. liangshanesis, C. sobolifera*. A particular set of conditions are required for the growth of Cordyceps that hinders its large-scale collection. Since Cordyceps has been so

widely used over the previous five years, it is now much less common in the wild (12,13). To manage the situation, artificial cultivation methods such as submerged or surface are being considered and attempted.

With the aim of cultivating Cordyceps species under artificial conditions, their nutritional requirements and cultural properties have been studied for many years (14). Ascospores are generally used to prepare cultures of Cordyceps species. There are variations in the growth rates of different species, for instance, *O. pentatomae*, *M. yongmunensis*, *C. bassiana*, *C.militates*, *C.pruinosa*, *C.scaraebaeicola*, *C.bifusispora*, and *Shimizuomyces paradoxa* have higher growth rates, while *O. gracilis*, *O.heteropoda*, and *C. nakazawai* grow slowly (15,16). *C. ramosopulvinata*, *C. rosea*, *C. ochraceostromata*, *C. martialis*, *O. sphecocephala*, *O. vakushimensis*, and *O. longissima*, on the other hand, have very low growth rates.

The products of medicinal mushrooms are majorly extracted from their fruiting bodies (about 80-85%) whereas a small portion is taken from the mycelium culture (nearly 15%; 17). A major challenge that is presented in the collection is the small blade-like structure of the fruiting body of Cordyceps. In order to meet the tremendous requirement of the bio metabolites of medicinal mushrooms, alternatives like cultivation of mycelium biomass artificially have been proposed (18). Although mycelium is capable of growing on a medium containing nutrients, for industrial large scale cultivation and fermentation, various cereal grains and insect larvae (residue of silkworm) have been used previously. From both of them, it is possible to obtain the fungus' fruiting body, which has medicinal characteristics that are nearly identical.

Types of fermentation techniques available

There are two types of fermentation techniques that are associated with mycelial cultivation i.e., biomass of the Cordyceps include- Submerged and Surface. The first step in surface fermentation is the formation of microbial biomass on the top of the solid or liquid substrate. Due to the high cost, labor requirements, and inconvenience of this process, it is rarely used at industrial level.

On the other hand, as the name suggests, submerged fermentation involves the cultivation of microorganisms aerobically in a liquid medium that involves proper agitation in order to obtain homogenised growth of the culture and mixing of the media nutrients. However, this technique is disadvantageous as it involves loss of extracellular constituents from the broth, especially post-harvest of mycelium. For the purpose of production of secondary metabolites on a large scale, it is crucial to improve the culture media composition and downstream processing technologies. Repeated batch culture technique yields the highest cell and bio-metabolite productivity., which involves eliminating the spent medium at the final stage of the procedure and further replenishing the medium (19).

The nutritional requirements for *C. militaris* growth

Insects

The pupal and larval stages of various insects have been used as a substrate for the laboratory growth and stroma generation of the *C. militaris*. The insects that have been used are- *Antheraea pernyi*, *Tenebrio molitor*, *Bombyx mori*, *Heliothis virescens*, *Spodoptera frugiperda*, *Philosamia cynthia*, *Clanis bilineata*, *Spodoptera litura*, *Mamestra brassicae*, *H. zea*, *Ostrinia nubilalis*, *Andraca bipunctata* (20).

Natural organic substrates

Since it is difficult to handle insects and there are increased chances of contamination, other alternative sources have been documented (21). However, a mixture of rice and silkworm pupae are routinely used as a substrate for cultivation of the *C. militaris* due to its efficiency. While finding the appropriate media composition for the cultivation of stroma, some important conclusions were made- In order to ensure efficient differentiation of the fruiting body, the nitrogen levels should be lower in the media (22). A mixture of brown rice, malt and soybean are a superior choice for media than a chemically defined one and Agar media cannot be used for the cultivation (23).

Media components

It has been reported that certain plant hormones can enhance the stroma production such as colchicine. Certain mineral salts can also do the task of enhancing the cultivation such as Mg^{2+}, K+ and Ca^{2+} (26).

Table 1: The optimum conditions for culturing of *Cordyceps* species

Parameters	**Optimal Range**
Temperature	20–25°C
pH	6.0-8.0
Light intensity	500–1,000 lx with a 12-h light/dark cycle
Air exchange and Humidity	A hydrophobic fluorophore membrane is used to cover the culture bottles as it ensures high air exchange and a high humidity of 70-90% is optimal

The optimal environmental parameters for successful cultivation of Cordyceps species are given in Table 1 (19).

Pharmacologically important compounds

A lot of biologically active compounds, particularly its extract, have been identified from Cordyceps such as Adenosine, Cordycepin, cordycepic acid, vitamins, enzymes, exo-polysaccharides, etc. Among these,

Cordycepin (3′-deoxyadenosine) which is isolated from *C. militaris*, has been studied most widely as it is the major active constituent of the fungus exhibiting a broad-spectrum biological activity (24). The major bioactive pharmaceutical compounds that have been isolated from Cordyceps have been summarized below.

Table 2: Summary of major bioactive pharmaceutical compounds from Cordyceps (25-29).

S. No.	Bioactive substances	Function
1	Cordycepin	Natural defence against inflammatory injury for many diseases including asthma, hepatitis, atherosclerosis, acute lung injury (ALI), rheumatoid arthritis, and Parkinson's disease (PD).
2	Cordycepic acid	The pharmacological benefits of cordycepic acid is to suppress and treat liver fibrosis by alleviating the inflammatory reaction that is induced by lipopolysaccharides, and fibrogenic response of cultured hematopoietic stem cells (HSCs) induced by TGF (Transforming Growth Factor)-1.
3	Adenosine	Modulation of neurotransmitter release, synaptic plasticity and neuroprotection in oxidative stress events
4	Hypoxanthine	Naturally occurring purine derivative.
5	Ergosterol and ergosteryl esters	Regulates permeability and fluidity
6	Protease	Protein peptide linkages are hydrolyzed, resulting in shorter polypeptides and amino acids.
7	N-acetylgalactosamine	Amino sugar, an important component of the fungal cell wall.
8	Chitinase	Degrade chitin, plays a central role in plant-fungi interactions
10	Acid deoxyribonuclease	Degrades DNA via hydrolysis of its phosphodiester backbone
11	Macrolides ($C_{10}H_{14}O_4$)	Class of drugs used to manage and treat various bacterial infections.
12	Superoxide dismutase	Important antioxidant defense against oxidative stress in the body
13	Bioxanthracenes	Antimalarial activity and cytotoxicity.
14	Cicadapeptins and myriocin	Antifungal antibiotics
15	Dipicolinic acid	Has a role in the heat resistance of bacterial endospores.
17	Cordyheptapeptide	Cytotoxicity against multiple cancer cell lines
18	Lectin	Proteins responsible for cell-cell interactions, signalling pathways
19	Naphthoquinone	Possess cytotoxic, antibacterial, antiviral, antifungal, insecticidal, antipyretic and anti-inflammatory activities.
20	Cordymin	It is an antifungal peptide that can inhibit growth of some fungal species such as *Candida albicans* and *Rhizoctonia solani*. It has also reportedly shown antiproliferative activity against breast cancer cells.

Mechanisms of action for the metabolites obtained from Cordyceps

Cordycepin

As stated previously, the major pharmaceutical component of Cordyceps spp. is Cordycepin.

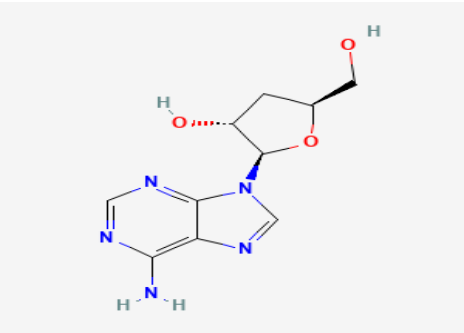

Fig. 1: Structure of Cordycepin (Adapted from PubChem) (30)

As shown in Figs.1 and 2, due to the structural similarities, cordycepin behaves similarly to adenosine, a nucleoside analogue, and can be utilised as a possible alternative for the treatment of chronic diseases such as cancer. Cordycepin has also been shown to regulate a number of body signalling pathways involved in apoptosis, cell proliferation, angiogenesis, metastasis and inflammation.

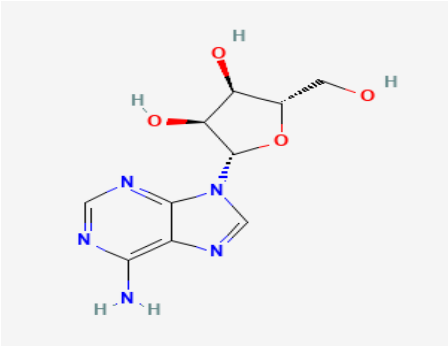

Fig. 2: Structure of adenosine (Adapted from PubChem) (31)

Inhibition of purine biosynthesis pathway

DNA synthesis is known to occur by salvage or *de novo* pathways. Cordycepin is known to be

metabolized to 5′ monophosphate, diphosphate, and triphosphates intracellularly. These components suppress the enzymes involved in de-novo purine biosynthesis, as shown in the figure. (32).

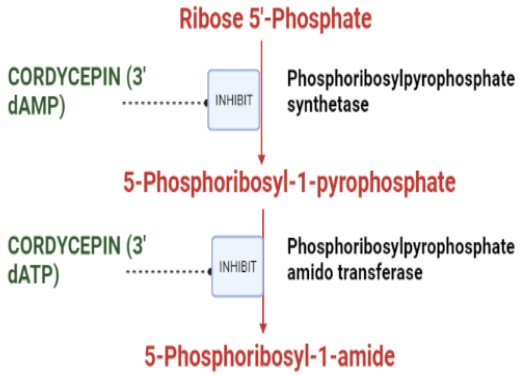

Fig.3: Enzymes involved in purine biosynthesis pathway

Cordycepin provokes RNA chain termination

Adenosine is a nitrogenous base that is required for various biological pathways in cells, including DNA and/or RNA synthesis. The absence of a 3′ hydroxyl group in the structure of cordycepin, in contrast to adenosine, is the key difference between the two compounds. During transcription (RNA synthesis), some enzymes of the purine biosynthetic pathway, including phosphoribosyl pyrophosphate synthase (PRS) and phosphoribosyl pyrophosphate amido transferase, fail to distinguish between adenosine and cordycepin. As a result, 3′-deoxyadenosine or cordycepin is incorporated instead of a normal nucleoside. This prevents further addition of the nitrogenous bases (A, U, C, and G) in the future, prematurely terminating the process of transcription. (33).

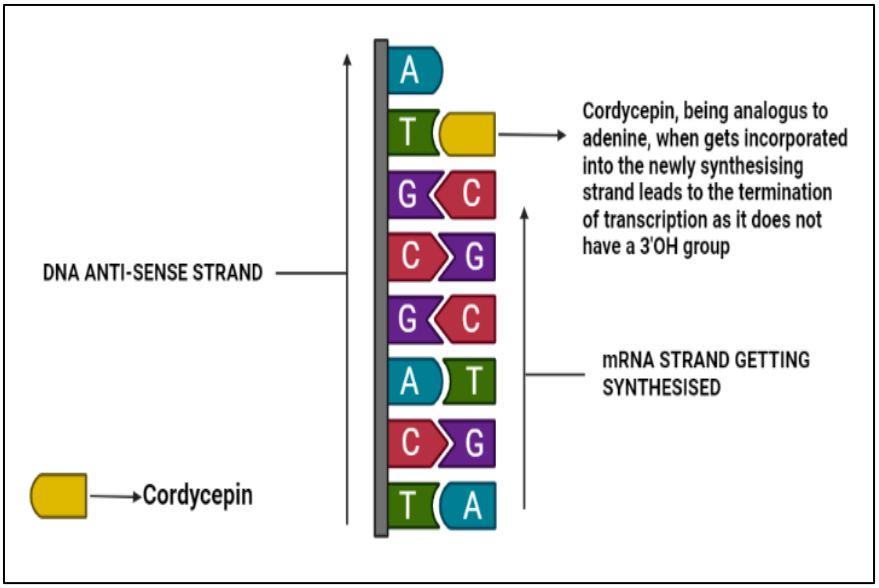

Fig. 4: Mechanism of RNA chain termination by Cordycepin

Cordycepin interferes in mammalian target of rapamycin (mTOR) pathway

It has been demonstrated that cordycepin reduces the mRNA's poly-A tail, thereby affecting its stability in the cytoplasm. At higher doses, cordycepin reduces focal adhesion and impairs cell adhesion. If the cordycepin dose is further increased, the mTOR signalling cascade may be deactivated. The term mTOR is derived from the active ingredient rapamycin, which inhibits the activity of mTOR. mTOR is a 298 kDa serine/threonine protein kinase that belongs to the phosphatidylinositol 3-kinase (PIKK) family.

The mTOR pathway is crucial for regulating protein synthesis. On the other hand, mTOR is influenced by a number of cellular signals, including hormones, growth factors, the cellular energy levels of the cells and its nutritional environment (34).

Fig. 5 shows the steps:

I. i. Binding of growth factors to cellular receptors activates phosphatidylinositol 3-kinase (PI3K)p and converts phosphatidylinositol bisphosphate (PIP-2) to phosphatidylinositol triphosphate (PIP-3).

ii. PIP3 initiates a cascade activating the phosphor-inositide-dependent protein kinase 1 (PDK1). PDK1 then activates AK tribe (AKT) kinase 1 by phosphorylating it, which is then further getting activated by the mTORC2 complex.

iii. The mTORC1 complex is now stimulated by the active AKT1 kinase which causes phosphorylation of 4 Eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) and rendered inactive, turning on the process of protein synthesis. Studies demonstrated AMPK activity being stimulated by cordycepin, thus suppressing the mTORC1/2 complex. Further leading to inability of mTORC2 to fully activate AKT 1 kinase, that inhibits mTOR cascade and prevents cellular proliferation and growth (35).

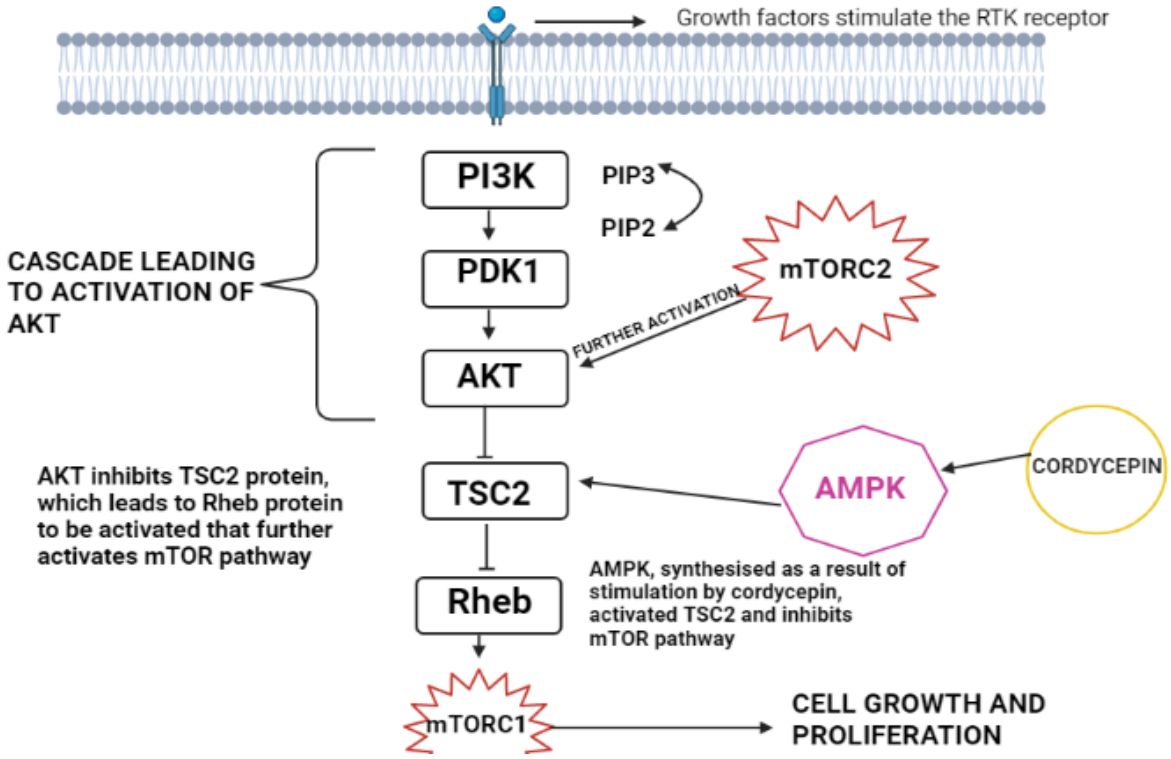

Fig. 5: Mechanism of Cordycepin interference with mTOR signal transduction

Adenosine

A primary nucleoside in Cordyceps spp. is adenosine which is crucial to the organism's metabolic processes. Adenosine functions in cells for energy transfer and signal transduction. It has a variety of cytoprotective effects that can cure chronic heart failure, reduce inflammation, and heal seizures (36). Moreover, adenosine is also known to inhibit cell proliferation through a variety of intrinsic and extrinsic signalling mechanisms. It activates caspases- protease enzymes that have an important role in programmed cell death. This nucleoside also plays a crucial role in inflammation and immunity, and the adenosine A2A is also involved in treating depression, locomotion, and anxiety (37). This endogenous nucleoside may help protect and repair dermal tissue, especially in skin cells by acting at one or more of its receptors.

Polysaccharides

Extracellular and intracellular polysaccharides, composed mainly of mannose, rhamnose, galactose and glucose make up most of the polysaccharides found in Cordyceps. The percentage of polysaccharides in cordyceps can range from 3 to 8 % of the total weight (38). Experimental evidence has proven that fungal polysaccharides exhibit an array of biological-activities, including antioxidant effects, anti-tumour, anti-influenza effect, hypoglycaemic, hypocholesterolaemia, and immunopotentiation (39). Additional studies have demonstrated that the pharmacological effects of polysaccharides are associated with their characteristics. For instance, the antitumor activity of polysaccharides is influenced by their large molecular weight (40).

Global market potential for Cordyceps species

Since the 1990s, the markets for nutraceuticals, i.e., food or dietary supplements have significantly gained popularity due to their positive health effects. Nutraceutical products exhibit both nutritional and pharmaceutical effects. These products have shown potential in the treatment of a wide range of chronic lifestyle diseases (hypertension, cancer, arthritis, cardiovascular disease, and many others). Moreover, they also contribute in as well as in delaying the process of aging, hence, eventually enhancing the quality of life (41).

Consumer health awareness, weight management, and net calorie intake, in countries such as India, China and the United States have already backed many nutraceutical applications, producing a significant impact on the industry's growth. The global nutraceutical market might reach USD 722.49 billion by 2027, according to data provided online by the Grand View research team, and is predicted to grow at a CAGR of 8.3% over the forecast period. Amway, Abbott, PepsiCo Inc., General Mills Inc., Nestle S.A., Danone S.A., The Archer Daniels Midland Company, Glanbia Nutritional, and Herbalife International of America are among the leading firms participating in nutraceutical research and development. The global cordycepin market, on the other hand, is expected to exceed $1 billion by 2026. With an estimated 47 percent of the worldwide nutraceutical industry, When it comes to the production or extraction of cordycepin from *C. sinensis* and *C. militaris*, Asia Pacific—particularly China—is regarded as the world leader (42).

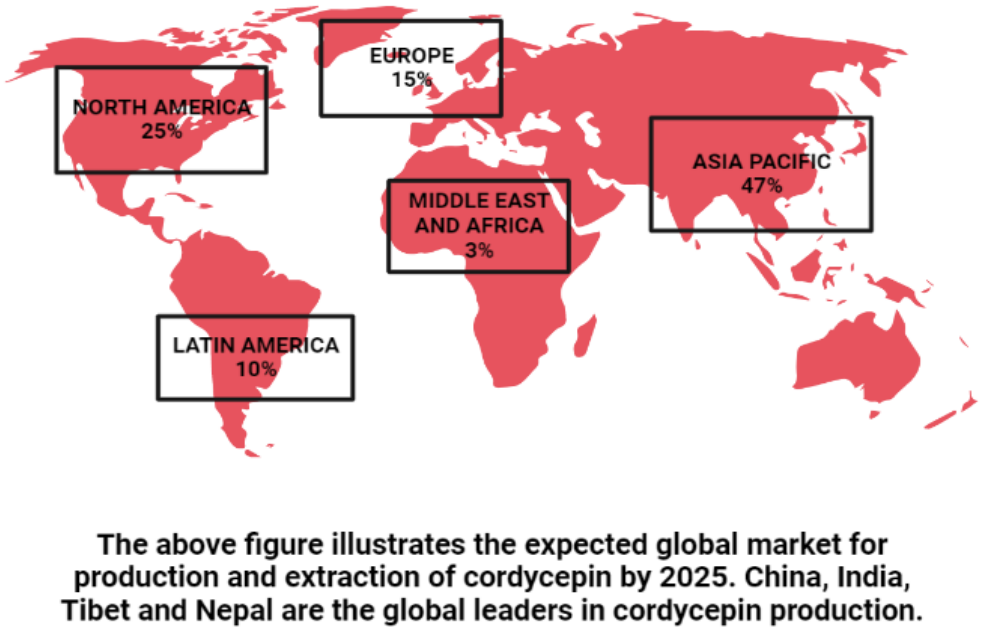

Fig. 6: Global market potential of Cordycepin

Cordyceps for industrially important products

Some of the nutraceuticals that can be produced from Cordyceps and are available in the global market are highlighted in Table 3.

Table 3: Nutraceutical products derived from Cordyceps spp (42)

Name of the Product	Benefit provided	Manufactured by
Dragon Herbs	Improves the major stimulus for basic life processes.	Iherb Holdings LLC, USA
Mycoformulas Endurance™	Improved circulation, efficient cellular exchange of energy, and better stamina.	Myco Formulas, USA
Mushroom Plus	Helps to boost the immune system, enhances energy levels and improves cognitive abilities.	Link Nutrition Ltd., UK
Nutricafe-organic	Provides enhanced endurance to the body, and acts as an antioxidant.	Aloha Medicinals USA
OM™ Maitake	Supports in the maintenance of a healthy weight and blood sugar level	Yukiguni Maitake CO., LTD, Japan
CaféCeps® Packets	Various health-enhancing properties,	Madre Labs LLC, France
Host defense mushrooms	Energy booster	Host Defense, USA
Bhutan Cordyceps Tea	Immune system strengthening, antioxidant, anti-aging, and anti-cancer properties, boosts the digestive and renal systems.	Bhutan Natural, Singapore
MycoNutri Cordyceps organic	Immune system support	The Really Healthy, UK
MRM Cordyceps CS-4 strain	Strengthens the natural metabolism of the body.	All Star Health, USA
Collagen C ReLift capsules	For fewer wrinkles and better complexion	Zein Pharma, Germany

CONCLUSION

Nature provides us with the raw materials for natural medicines. Majority of pharmaceuticals originate from botanical ingredients. People tend to choose organic/ natural medication for a variety of reasons, primarily to avoid the possibility of an adverse reaction that might be associated with chemically produced drugs. Contrastingly, organic remedies like medicinal mushrooms may treat, or to a larger extent manage several fatal conditions with fewer side effects.

However, *Cordyceps* has a few drawbacks as a therapeutic fungus, including inadequate information, a lack of in-depth research and knowledge, and disregard for it. It was initially only accessible to a small group of people, but with time, things have improved. It is important that individual producers should prioritize research on Cordyceps, but so should other industries like those involved in manufacture of functional foods, pharmaceuticals, and others.

It is necessary to conduct further research and analysis on drug efficacy, adverse effects, biosafety, and

biosecurity. Edible mushroom-based medicines have the potential to be transformed by the use of bio-originated precursors, such as secondary metabolites, in conjunction with chemistry and biotechnology. As a result, the study of green pharmacogenetics and pharmacology will be greatly influenced by cordycepin, peptides, polysaccharides, and other active compounds obtained from *Cordyceps*.

ACKNOWLEDGEMENT

The authors would like to thank the institution-Shaheed Rajguru College of Applied Sciences for Women, University of Delhi for providing required facilities to carry out a comprehensive review.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Pathak RK, Singh D, Gupta KK, Maurya S. Anti-proliferative effect of Oyster mushroom, Pleurotus from Florida (misnomer) P. florida (Agaricomycetes) against HeLa and SIHA cervical cancer cells: Mushroom-boon for cancer therapies. Biomedicine. 2019;39(3):491-496.
2. Zaidman, B. Z., Yassin, M., Mahajna, J., Wasser, S. P. Medicinal mushroom modulators of molecular targets as cancer therapeutics. Appl. Microbiol. Biotechnol. 2005; 67(4): 453-468.
3. Wang, L., Zhang, W. M., Hu, B. A., Chen, Y. Q., Qu, L. H. Genetic variation of *Cordyceps militaris* and its allies based on phylogenetic analysis of rDNA ITS sequence data. Fungal Divers. 2008; 31:147-155.
4. Kim, H. G., Song, H., Yoon, D. H., Song, B. W., Park, S. M., Sung, G. H., *et al., Cordyceps pruinosa* extracts induce apoptosis of HeLa cells by a caspase dependent pathway. J. Ethnopharmacol. 2010; 128(2):342-351.
5. Sung, G. H., Shrestha, B., Han, S. K., Sung, J. M. Cultural characteristics of *Ophiocordyceps heteropoda* collected from Korea. Mycobiology. 2011;39(1): 1-6.
6. Das, S. K., Masuda, M., Sakurai, A., Sakakibara, M. Medicinal uses of the mushroom *Cordyceps militaris*: Current state and prospects. Fitoterapia. 2010; 81(8): 961-968.
7. Holliday, J. Cordyceps: A highly coveted medicinal mushroom. Medicinal Plants and Fungi: Recent Advances in Research and Development. Springer. 2017; pp: 59-91.
8. Wang, J., Kan, L., Nie, S., Chen, H., Cui, S.W., Phillips, A.O., *et al.,* Comparison of chemical composition, bioactive components and antioxidant activity of natural and cultured *Cordyceps sinensis*. LWT-Food Sci Technol. 2015; 63: 2-7.
9. Olatunji, O. J., Tang, J., Tola, A., Auberon, F., Oluwaniyi, O., Ouyang, Z. The genus *Cordyceps*: An extensive review of its traditional uses, phytochemistry and pharmacology. Fitoterapia. 2018; 129:293-316.
10. Sung, G. H., Shrestha, B., Han, S. K., Kim, S. Y., Sung, J. M. Growth and cultural characteristics of *Cordyceps cardinalis* collected from Korea. Mycobiology. 2010; 38(4): 274-281.
11. Paterson, R. R. Cordyceps: a traditional Chinese medicine and another fungal therapeutic biofactory?. Phytochem, 2008; 69(7):1469-1495.
12. Negi, C. S., Koranga, P. R., Ghinga, H. S. Yartsa Gumba (*Cordyceps sinensis*): A call for its sustainable exploitation. Int. J. Sustain. Dev. 2006; 13(3):165-172.
13. Winkler, D. Yartsa Gunbu (*Cordyceps sinensis*) and the fungal commodification of Tibet's rural economy. Econ. Bot. 2008; 62(3):291-305.
14. Sasaki, F., Miyamoto, T., Tamai, Y., Yajima, T. Optimum temperature and pH for mycelial growth of *Cordyceps mutans* Pat. (Ascomycetes). Int. J. Med. Mushrooms. 2005; 7(1):301-304
15. Lee, J. O., Shrestha, B., Sung, G. H., Han, S. K., Kim, T. W., Sung, J. M. Cultural characteristics and fruiting body production in *Cordyceps bassiana*. Mycobiology. 2010; 38(2):118-121.
16. Sung, G. H., Shrestha, B., Park, K. B., Sung, J. M. Cultural characteristics of *Shimizuomyces paradoxus* collected from Korea. Mycobiology. 2010; 38(3):189-194.
17. Lindequist, U., Niedermeyer, T. H., Jülich, W. D. The pharmacological potential of mushrooms. Evid. Based Complementary Altern. Med. 2005; 2(3):285-299.
18. Masuda, M., Urabe, E., Sakurai, A., Sakakibara, M. Production of cordycepin by surface culture using the medicinal mushroom *Cordyceps militaris*. Enzyme Microb. 2006; 39(4):641-646.
19. Shrestha, B., Zhang, W., Zhang, Y. The medicinal fungus *Cordyceps militaris*: research and development. Mycol Progress. 2012; 11: 599-614.
20. Lin, Q.Y., Song, B., Li, T.H. Studies on *Cordyceps militaris* infecting pupae of Tenebrio molitor. Mycosystema. 2005;24: 24:322–326
21. Lin, Q.Y., Zhong, Y.J., Li, T.H. Recent research advances in Cordyceps biology. Acta Edulis Fungi. 2006; 13(2): 93-98.
22. Gao, X.H., Wu, W., Qian, G.C. Study on influences of abiotic factors on fruitbody differentiation of *Cordyceps militaris.* Acta Agric Shanghai. 2000;16:93-98.
23. Yahagi, N., Yahagi, R., Takano, F. Growth of ascoscarps from cultured *Cordyceps militaris* and *Cordyceps formicarum Kobayasi* in an agar medium. Nippon Kingakukai Kaiho. 2004;45:15-19.
24. Phull, A. R., Ahmed, M., Park, H. J. *Cordyceps militaris* as a bio functional food source: Pharmacological potential, anti-inflammatory actions and related molecular mechanisms. Microorganisms. 2022;10(2): 405.
25. Cunningham, K. G., Manson, W., Spring, F. S., Hutchinson, S. A. Cordycepin, a metabolic product isolated from cultures of *Cordyceps militaris*. Nature, 1950; 166(4231): 949-949.
26. Chatterjee, R., Srinivasan, K. S., Maiti, P. C. *Cordyceps sinesis* (Berkeley) Saccardo: structure of cordycepic acid. J Am Pharm Assoc. 1957;46(2):114-118.
27. Watanabe, N., Hattori, M., Yokoyama, E., Isomura, S., Ujita, M., Hara, A. Entomogenous fungi that produce 2,6-pyridine dicarboxylic acid (dipicolinic acid). J. Biosci. Bioeng. 2006; 102(4):365-368.
28. Ng, T. B., Wang, H. X. Pharmacological actions of Cordyceps, a prized folk medicine. J Pharm Pharmacol. 2005; 57(12):1509-1519.
29. Lee, K. H., Min, T. J. Purification and characterization of a chitinase in culture media of *Cordyceps militaris.* Korean J. Mycol. 2003; 31(3):168-174.
30. National Center for Biotechnology Information. PubChem Compound Summary for CID 6303, Cordycepin.
31. National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 60961, Adenosine.
32. Chen, L. S., Stellrecht, C. M., Gandhi, V. RNA-directed agent, cordycepin, induces cell death in multiple myeloma cells. Br J Haematol. 2008; 140(6): 682-391.
33. Tuli, H.S., Sharma, A.K., Sandhu, S. S., Kashyap D. Cordycepin: A Cordyceps Metabolite with promising therapeutic potential. Life Sci. 2013; 93(23): 863-869.
34. Hawley, S.A., Ross, F.A., Russell, F.M., Atrih, A., Lamont, D.J., Hardie, D.G. Mechanism of Activation of AMPK by Cordycepin. Cell Chem. Biol. 2020; 27(2):214-222.
35. Tuli, H. S., Sandhu, S. S., Sharma, A. K. Pharmacological and therapeutic potential of Cordyceps with special reference to Cordycepin. 3 Biotech. 2014; 4(1): 1-12.
36. Liu, Y., Wang, J., Wang, W., Zhang, H., Zhang, X., Han, C. The chemical constituents and pharmacological actions of *Cordyceps sinensis*. Evid. Based Complementary Altern. Med. 2015; 575063.

37. Coelho, J. E., Alves, P., Canas, P. M., Valadas, J. S., Shmidt, T., Batalha, V. L., *et al.*, Overexpression of adenosine A2A receptors in rats: Effects on depression, locomotion, and anxiety. Front Psychiatry. 2014; 5: 67-67.
38. Li, S. P., Li, P., Dong, T. T., Tsim, K. W. Anti-oxidation activity of different types of natural *Cordyceps sinensis* and cultured Cordyceps mycelia. Phytomedicine. 2008; 8(3):207-212.
39. Ohta, Y., Lee, J. B., Hayashi, K., Fujita, A., Park, D. K., Hayashi, T. *In vivo* anti-influenza virus activity of an immunomodulatory acidic polysaccharide isolated from *Cordyceps militaris* grown on germinated soybeans. J. Agric. Food Chem. 2007; 55(25):10194-10199.
40. Zhou, X., Gong, Z., Su, Y., Lin, J., Tang, K. Cordyceps fungi: natural products, pharmacological functions and developmental products. J. Pharm. Pharmacol. 2009; 61(3): 279-291.
41. Devi, A., Chennakesavulu, S., Suresh, C., Reddy, A. B. M. Nutraceuticals and their role in human health and disease. Functional Food and Human Health. 2018; 375-403.
42. Ashraf, S. A., Elkhalifa, A., Siddiqui, A. J., Patel, M., Awadelkareem, A. M., Snoussi, M., *et al.*, Cordycepin for health and wellbeing: A Potent bioactive metabolite of an entomopathogenic medicinal fungus Cordyceps with its nutraceutical and therapeutic potential. Molecules (Basel, Switzerland). 2020; 25(12):2735-2735.