

# *Cordyceps militaris* as an alternative source of food, nutrition and medicine

Rohit Rawat <sup>1,\*</sup>, Amita Gupta <sup>2</sup> and Nidhi Tripathi <sup>3</sup>

<sup>1</sup> PhD Scholar, Department of Biochemistry, Mansarovar Global University, Bhopal, India.

<sup>2</sup> Department of Biochemistry, Mansarovar Global University, Bhopal, India.

<sup>3</sup> Department of Biotechnology, Career College, Bhopal, India.

World Journal of Advanced Research and Reviews, 2024, 22(01), 1600–1620

Publication history: Received on 31 January 2024; revised on 09 March 2024; accepted on 11 March 2024

Article DOI: <https://doi.org/10.30574/wjarr.2024.22.1.0767>

---

## Abstract

In 2020 Covid 19 outbreak wreaked havoc on the entire world. Through constant hard days, the pandemic has taught us how important it is to have better immunity in our body to avoid diseases like covid 19. In the present-day scenario, there are a handful of factors like pollution, adulterated food items, chemical fertilizers, and pesticides, etc. which are slowly decreasing our immunity. In such a situation, *Cordyceps militaris* has emerged as a great solution. *Cordyceps militaris* is a medicinal mushroom, its products have been used as medicine in China for centuries, slowly, *Cordyceps militaris* is gaining fame in India and many other countries due to its exceptional immunomodulatory and other medicinal properties. Nutrition and immunity are two of the essential factors behind a healthy life. *Cordyceps militaris* imparts a positive effect on both. It is known for its nutritional and medicinal properties such as anti-aging, anti-inflammatory, antioxidant, anticancer, antiviral, effective in liver disorders, effective sexual disorder, cardiovascular diseases, antimalarial, anti-hyperlipidemia, anti-osteoporotic, anti-arthritic, anti-diabetic anti-fungal, immunomodulatory, etc. Due to the aforesaid exceptional properties, it increases health benefits manifold.

**Keywords:** *Cordyceps militaris*; Mushroom; Nutrition; Health; Medicine

---

## 1. Introduction

Since 1964, the Chinese Pharmacopoeia has legally recognized *Cordyceps militaris* (L.) Link, a traditional Chinese medicine (TCM), as a herbal drug. Nucleotides (cordycepin and adenosine), polysaccharides (galactomannan), cordycepic acid, amino acids, and sterols (ergosterol and beta-sitosterol) are among the many advantageous compounds that cordyceps are rich in (Ontawong, A et al, 2024). Tyrosine and leucine are the most prevalent essential amino acids found in *C. militaris*, a well-known tonic food and staple in traditional Chinese medicine (TCM) (Aung, W.L et al., 2023).

The fruiting body of *C. militaris* was formally declared edible by the People's Republic of China Ministry of Health in 2009 (People's Republic of China Ministry of Health 2009), which encouraged additional study on the fungus. Numerous bioactive compounds, including polycystin, adenosine, cordyceps polysaccharide, amino acids, and ergosterol, are found in *Cordyceps militaris* (Jędrejko et al. 2021). Cordycepin is the most significant of these drugs and the benchmark used to assess the caliber of *C. militaris* (Qin et al. 2019).

The first adenosine analog to be isolated from *C. militaris* is cordycepin, or 3'-deoxyadenosine (Cunningham et al. 1951). Cordycepin possesses properties that make it useful in commerce, medicine, and scientific research (Qin et al. 2019). These properties include antitumor (Khan and Tania 2020; Zheng et al. 2020), antibacterial (Jiang et al. 2019), antifungal (Sugar and Mccaffrey 1998), antiviral (Verma 2020), antioxidation, and immune regulation. Through chemical synthesis, liquid fermentation optimization, fruit body extraction, and genetics, cordycepin yield was recently increased from 380 to 6840 mg/L (Zhang, H. et al. 2023).

---

\* Corresponding author: Rohit Rawat

In comparison to typical plant diets, *C. militaris* also has a higher concentration of vitamins, carotenoids, polysaccharides, and other substances. Given its therapeutic potential, it has been used into complementary medicine regimens to treat neurological, cardiovascular, kidney, and liver conditions as well as malignancies and boost immunity (Wang et al., 2024).

Furthermore, because *C. militaris* includes biologically active substances such polysaccharides, ergosterol, adenosine, and cordycepic acid that are similar to those of *Cordyceps sinensis*, it has been utilized as a model and alternative for the latter. But *C. militaris* also has pentostatin and cordycepin, which are absent from *C. sinensis*. Cordycepin and pentostatin, two of the compounds produced by *C. militaris*, have been shown to have anti-cancer properties (Lou, Lin, et al., 2019; Song et al., 2015; Qin et al., 2019; Hung et al., 2015; Yoon et al., 2018). Ergosterol is the precursor of fat-soluble vitamin D2, which is known to cause cell death and reduce inflammation (Nallathamby et al., 2015; Sun et al., 2019). Its content has been observed to be relatively constant in *C. militaris*. Furthermore, *C. militaris* polysaccharides (CMP) are increasingly gaining attention due to their diverse biological and pharmacological effects, and their concentration can vary from  $7.15 \pm 0.25\%$  to  $14.89 \pm 0.68\%$  in *C. militaris* (Chen et al., 2014; Shi et al., 2020).

## 2. *Cordyceps militaris* as the new health landscape

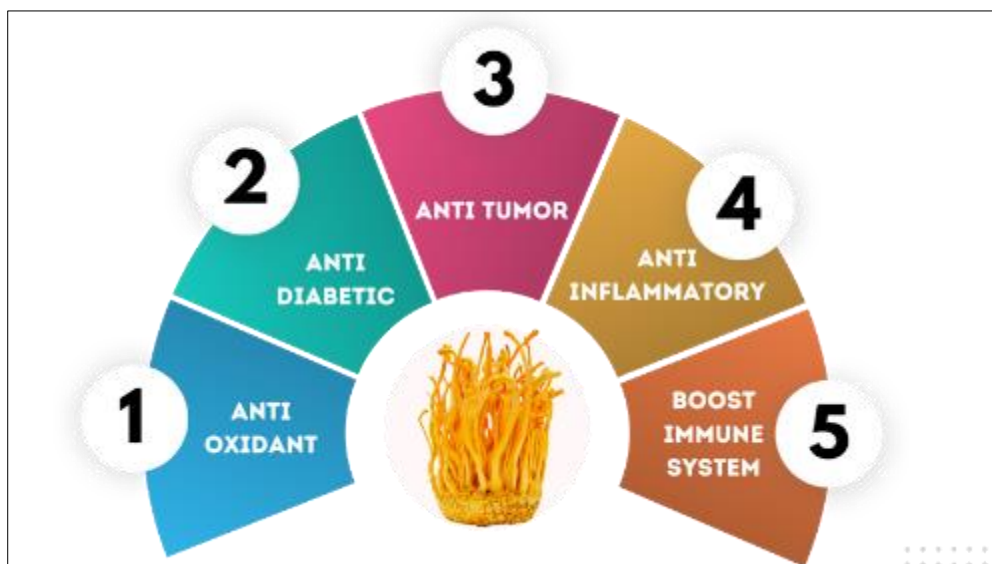
At present, the trend of people is turning towards health benefits through natural products. Edible Mushroom is gaining focus as one of the important natural products for health management. Now a days importance of edible mushroom is increased due to their high nutritional and therapeutic value. *Cordyceps militaris* is a rare mushroom, native to the Himalayas and known for medicinal use in China since centuries. Cordyceps is a combination of two Latin words 'cordy' and 'cep' which literally means mushroom with club like head (Fabroni et.al 2020). Basically, Cordyceps are comes under entomopathogenic mushroom, where extensions of the stroma and fruiting body arise from insect larvae carcasses (Zhou et.al. 2009). *Cordyceps sinensis* is naturally obtained from the forests of Himalayas which is primarily lives on the head of a species of moth called *Hepialus armoricanus*. Mycological data of *C. militaris* is discussed below (Das, S.K et. al., 2010):

**Table 1** Scientific classification of *C. militaris*

Kingdom:	<b>Fungi</b>
Division:	<u>Ascomycota</u>
Class:	<u>Sordariomycetes</u>
Order:	<u>Hypocreales</u>
Family:	<u>Cordycipitaceae</u>
Genus:	<u>Cordyceps</u>
Species:	<b><i>C. militaris</i></b>

*Cordyceps sinensis* has to be cultivated in large scale for medicinal use but studies reported that laboratory cultivation of *Cordyceps sinensis* has not proved to be very effective. In such condition, scientists are getting cultivated *Cordyceps militaris* in the laboratory, as an alternative of *Cordyceps sinensis*. *Cordyceps militaris* belongs to the Ascomycota phylum and is classified under the order hypocreales. Besides *C. militaris* many other species of Cordyceps have been reported in previous studies few examples are *C. tuberculata*, *C. subsessilis*, *C. minuta*, *C. myrmecophila*, *C. Canadensis*, *C. agriota*, *C. gracilis*, *C. ishikariensis*, *C. konnoana*, *C. nigrella*, *C. nutans*, *C. pruinosa*, *C. scarabaeicola*, *C. sphecocephala*, *C. tricentri*, etc. They are also cultivated for their medicinal properties, but research is yet to be done on their phylogenetic evidence and medicinal properties (Shrestha and Sung 2005; Wang et al. 2008; Zhou et al. 2009). About 80 - 95 percent of mushroom products are extracted from fruiting bodies, whereas only 15 percent of the mushroom's products are obtained from its mycelium culture (Lindequist et al. 2005). It has been reported that like *Cordyceps sinensis*, *Cordyceps militaris* also produced cordycepin and adenosine which have medicinal importance in various diseases like cancer etc. Medicinal mushrooms produce many bioactive compounds like proteoglycans, terpenoids, phenolic compounds, steroids, and lectins. In addition to this, it was found in different studies that *C. militaris* is rich in crude fats, proteins, fibre, carbohydrate, cordycepic acid, polysaccharide and a vitamin etc. which enhance its health management quality. All the above-mentioned compounds have therapeutic effect, all of this compound reported as immunomodulator anticarcinogenic, antiviral, antioxidant, and anti-inflammatory agents (Badalyan, 2012; Villares et al., 2012).

Let us discuss some important medicinal properties of *Cordyceps militaris*:



**Figure 1** Benefits of *Cordyceps militaris*

(Image courtesy: HARI Lifesciences)

### 2.1. *Cordyceps militaris* in diabetes management:

Diabetes is the third deadliest disease in the world due to the large number of patients and the high complexity of treatment. Diabetes mellitus is a chronic metabolic disorder involving the endocrine system because of defect in insulin secretion. Due to which the level of glucose in the blood may increase and a condition of hyperglycemia arises which damages the delicate organs of the body. *Cordyceps militaris* extract is a harmless pharmaceutical agent, presents outstanding antidiabetic and antinephropathic activities and thus has great potential as a new source for diabetes treatment (Dong et.al 2014). Zhang et al. (2006) compared the anti-diabetic effects of crude extract obtained from fruiting bodies and mycelia of many medicinal fungi including *C. militaris*, *C. sinensis*, *Omphalia lapidescens* and *Tricholoma mongolicum*. Dong et al. (2010) worked on the water or alcoholic extract of *Cordyceps militaris* and administered a diabetic Sprague- Dawley rats with the extracts, he concluded that this extract caused significant decrease in blood glucose levels by promoting glucose metabolism and powerfully suppressed total cholesterol and triglycerides concentration. *C. militaris* has been reported to demonstrate an antidepressant- like activity, which attenuates the diabetes induced increase in blood glucose concentrations (Ji et al., 2009). Yun et. al (2003) conclude after their studies that Cordycepin from *Cordyceps militaris* may be useful tools in the control of blood glucose level in diabetes and promising new drug as an anti-hyperglycemic agent without defects of immune responses and other side effects.

### 2.2. Anti hyperlipidemia effect of *Cordyceps militaris*:

Hyperlipidemia is a broad term that covers all acquired and genetic disorders that result in an increase in the amount of lipids in the blood. Hyperlipidemia is also called high cholesterol in common language, high cholesterol level in blood may also be a genetic disorder or due to adopting unhealthy lifestyle. Previous studies reported that *Cordyceps militaris* decrease triglyceride level and LDL cholesterol level in the blood. LDL can raise risk of heart disease by leading to the accumulation of cholesterol in the arteries, *C. militaris* lowers the risk of accumulation by increasing metabolic rate. The Impact of *C. militaris* on the Cardiovascular System.

Cordycepin increases vascular responses in smooth muscle cells, making it a possible antiatherosclerotic drug (Won K.-J. et. al., 2009). Cordycepin from *C. militaris* has been proven in mouse studies to reduce triglycerides, total cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) levels in an animal model of hyperlipidemia. Cordycepin showed properties of an AMPK activator and an inhibitor of lipoprotein and hepatic lipase (Gao J. et. al., 2011, Guo P. et. al., 2010). Cordycepin decreased adipogenesis and lipid accumulation in adipocytes during in vitro tests. Cordycepin's biological activity involves suppressing the C/EBP $\beta$ , PPAR $\gamma$ , and mTORC1 pathways while activating AMPK (Takahashi S. et. al., 2012). Cordycepin has hypolipidemic action and the potential to activate AMPK, the  $\gamma$ 1 region, according to in vitro tests (Wu C. et. al., 2014). In vitro and in vivo studies in rodents verified the hypolipidemic

efficacy of the polysaccharide fractions extracted from *C. militaris* (Hu S. et. al., 2019, Wang L. et. al., 2015). Similarly, Huang et al. (2018) found that intracellular (IPCM) and extracellular polysaccharides (EPCM) from *C. militaris* had hypolipidemic properties in mice fed a high fat diet.

An in vitro experiment verified the antiaggregation activity of cordycepin extracted from *C. militaris*. Cordycepin inhibited human platelet aggregation by increasing cGMP and cAMP activity, decreasing calcium ion concentration, and inhibiting TXA2 synthesis (Cho H.-J. et. al., 2006). Cordycepin demonstrated cardioprotective properties in an isolated ischemic rat heart (Park E.-S. et. al., 2014). In an in vivo experiment in mice, the sodium nitrite-induced toxicity and ischemia tests revealed that a percentage of CMN1 polysaccharides extracted from *C. militaris* fruiting bodies avoided hypoxia (Dong Y. et. al., 2015). In vitro investigations shown that *C. militaris* extract supplemented with cordycepin prevented collagen-induced platelet aggregation. The antiaggregation action was achieved by inhibiting fibrinogen attachment to glycoprotein IIb/IIIa, stimulating VASP phosphorylation, inhibiting PI3K/A-kinase phosphorylation, and increasing cAMP concentration (Lee D.-H. et. al., 2015). Further in vitro and in vivo tests confirmed the neuroprotective properties of *C. militaris* (WIB801C) extract with a measured cordycepin concentration. Cordycepin reduced ischemia, cerebral edema, and blood-brain barrier damage in rats. The neuroprotective effect was linked to the anti-inflammatory activity of cordycepin (Hwang S. et. al., 2016). More current studies indicate better antiplatelet activity than anticoagulant activity of *C. militaris* (Choi E. et. al., 2020).

### 2.3. Anti-oxidative property of *Cordyceps militaris*:

Antioxidants are natural substances that protect body tissues from damage. Naturally antioxidants are found in fruits and vegetables but due to improper cooking, the antioxidants are destroyed in the food. High antioxidant food protects the body from many types of diseases like cancer, heart disease etc. Antioxidants protect the body from the bad effects of oxidation by removing free radicals from the body. According to the studies of Dong et.al (2014) extracts from *C. militaris* have valuable antimicrobial, antioxidant, and cytotoxic natural sources and seemed to be relevant in health and medicine as well as in the food industry.

The antioxidant action was verified mostly for polysaccharides found in *C. militaris*. Cordycepin's antioxidant effects have been investigated in only a few research (He Y.T. et. al., 2013). *C. militaris* antioxidant activity may also be impacted by other chemical elements found in fruiting bodies, such as ergothioneine, phenolic compounds, carotenoids, and selenium. Many in vitro tests have shown that the polysaccharide fractions have antioxidant activity for the components WCBP50, CMP, CMP-1, and SeCSP-I (Chen X. et. al., 2013; Jing Y et. al., 2014; Chen R. et. al., 2014). The addition of selenium to the *C. militaris* medium increased the antioxidant activity of the polysaccharide fractions (Hu T. et. al., 2019). Experiments on mice given *C. militaris* containing polysaccharides revealed a rise in the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and GPX, as well as a decrease in the level of malondialdehyde (MDA) (Zhang J. et. al., 2019; Liu J. et. al., 2016). *C. militaris* has a higher antioxidant capacity for preventing lipid peroxidation than *C. sinensis*. The antioxidant activity of *C. militaris* fruiting bodies was found to be related to their polysaccharide and phenolic component composition (Yu H.M. et. al., 2006). Previous research has confirmed the efficacy of the polysaccharides P70-1 and CBP-1 derived from *C. militaris* to remove hydroxyl radicals (Yu R. et. al., 2007, Yu R. et. al., 2009). The polysaccharide was also shown to have antioxidant activity and the ability to bind iron ions (Fe<sup>2+</sup>) were also proven for the polysaccharide designated as CM-hs-CPS2 (Fengyao W. et. al., 2011).

### 2.4. Anti-inflammatory Properties:

Inflammation is a type of biological response that occurs in the body by the entry of any foreign substances such as bacteria, virus and other pathogens. Inflammation may protect the body from infection, but excessive inflammation can damage the heart and lead to cancer. Jo et.al (2010) found that *Cordyceps militaris* extract may prevent inflammation by suppressing LPS-induced inflammatory mediators it may be considered a potential medicinal food for the prevention of inflammatory disease when hot water extract from *C. militaris* fruiting bodies is consumed. Smiderle et. et.al (2014) observed that the isolated  $\beta$ -(1→3)-D-glucan presented antinociceptive and anti-inflammatory activities against formalin-induced nociception and LPS-induced peritonitis in mice. Park et.al (2021) also reported that the *C. militaris* hydrolytic extract helps in the prevention and resolution of inflammation under LPS stress.

Cordycepin has been demonstrated to lower TNF- $\alpha$ , COX-2, iNOS, and NF- $\kappa$ B production in macrophages during LPS-induced inflammation (Kim H.G et. al., 2006). In vitro experiments demonstrated that *C. militaris* inhibits the generation of proinflammatory mediators, such as NO, TNF- $\alpha$ , and IL-6, generated by LPS in murine macrophages. The study (Jo W.S et. al., 2010) did not specify *C. militaris*' category of bioactive chemicals.

In vitro experiments show that cordycepin and ergosterol from *C. militaris* block the release of inflammatory mediators such as NO, TNF- $\alpha$ , and IL-12, leading to antiproliferative action in colon tumour cells (Rao Y.K. et. al., 2010). Cordycepin

(from *C. militaris*) reduces COX-2 and iNOS enzyme activity and lowers levels of inflammatory mediators such as NO, TNF- $\alpha$ , PGE<sub>2</sub>, and IL-1 $\beta$  in mouse microglia. Cordycepin has been proven to suppress the activity of NF- $\kappa$ B and the phosphorylation of MAPKs. These findings supported the neuroprotective effects of cordycepin and *C. militaris* extracts, opening up new avenues for *C. militaris* usage in neurodegenerative disease research and therapy (Jeong J. et. al., 2010).

In scientific investigation, Won and Park (2005) confirmed in vivo the ability of cordycepin present in mycelium *C. militaris* to suppress iNOS activity and lower NO concentration in inflammatory responses. The study also showed analgesic activity. In mouse research, Smiderle et al. (2014) determined that a polysaccharide with a linear structure of  $\beta$ -(1  $\rightarrow$  3)-D-glucan derived from *C. militaris* demonstrated anti-inflammatory and antinociceptive effects. This polysaccharide's biological activity involves inhibiting COX-2, TNF- $\alpha$ , and IL-1 $\beta$  activity. The polysaccharide's anti-inflammatory and antinociceptive action was comparable to those of reference compounds from the nonsteroidal anti-inflammatory medication class (acetylsalicylic acid, indomethacin, diclofenac). Cerebrosides, a new class of chemicals, were identified as a component having anti-inflammatory properties. Inhibiting the expression of COX-2, iNOS, NF- $\kappa$ B, IL-1 $\beta$ , and IL-6 was found to decrease the inflammatory process (Chiu C. et. al. 2016).

## 2.5. Anti-microbial properties

As the use of modern resources is increasing, the immunity of the people is decreasing. Due to the advent of new bacteria, viruses etc. every day, especially after COVID 19 pandemic peoples have started needing health supplements to increase immunity. Research on pathogenic microorganism suggests that *C. militaris* increases immune response and is effective against pathogenic micro-organisms. Jiang et.al (2019) suggested that membrane damage was one of the reasons for cordycepin efficacy against bacteria, they found that the mode of bactericidal action of cordycepin against *E. coli* and *B. subtilis* was of dual mechanism, disrupting bacterial cell membranes and binding to bacterial genomic DNA to interfere in cellular functions, ultimately leading to cell death. Whole world is suffering from COVID 19 from 2019, Scientist observed significant activities of *C. militaris* against COVID 19 virus. Kaymakci and Güler (2020) suggested that *C. militaris* can be used for the treatment of the COVID-19 for dropping inflammation and fibrosis, increasing immune response and antiviral effect. It may be a better option to use anciently known and well-studied agents rather than discovering new ones to find a rapid treatment for COVID-19 in these pandemic times.

## 2.6. Fertility enhancer

Infertility problem is increasing in people as a result of running life of today. Infertility treatment is not only expensive, but it also causes a lot of damage to the woman's body. Cordyceps species have been used for centuries to increase level of progesterone in men and testosterone in women. In this way Cordyceps is very useful in increase the rate of fertility.

## 2.7. Thrombolytic properties

Since 2019, the entire world is battling the COVID 19 pandemic. After having COVID 19, the problem of cardiac arrest has been reported in people. It is believed that the drugs used during the treatment are causing blood clots in the arteries which are causing the cardiac arrest. Xiaolan et.al (2017) reported a fibrinolytic enzyme from *Cordyceps militaris*, this purified enzyme degraded  $\alpha$  chains of fibrinogen first and then  $\beta$  and  $\gamma$  chains and also activated plasminogen into plasmin. It can also act as an anticoagulant and prevent clot creation by degrading fibrinogen. Based on these studies, the purified enzyme has great potential to be developed as a natural agent for prevention and treatment of thrombolytic diseases.

## 2.8. Effect on the locomotor system

Scientific research has shown that *C. militaris* may have potential benefits in the treatment of osteoporosis. An in vitro investigation revealed that *C. militaris* hindered osteoclast development and decreased the expression of genes involved in this process (Choi K.-H. et. al., 2012). Cordycepin has been shown to have anti-inflammatory action in human chondrocytes with osteoarthritis. Cordycepin reduced IL-1 $\beta$ -induced PGE<sub>2</sub> and NO generation, as well as NF- $\kappa$ B expression (Ying X. et. al., 2014). Cordycepin inhibited bone loss in an inflammatory-induced osteoporosis model in rats (Zhang D. et. al., 2014).

In vitro investigations demonstrated that cordycepin and *C. militaris* suppressed osteoclast differentiation. Their biological function involves inhibiting the NF- $\kappa$ B ligand receptor activator (RANKL). Furthermore, CME and cordycepin suppressed the mRNA expression of osteoclastogenesis-related genes (TRAP, Cathepsin K, MMP-9, and NFATc1). Cordycepin dramatically reduced RANKL-induced p38 and NF- $\kappa$ B phosphorylation. Furthermore, in a mouse model of LPS-induced osteoporosis, cordycepin and *C. militaris* reduced bone loss (Kim J. et. al., 2015). Cordycepin, a polyadenylation inhibitor, was found in a rat osteoarthritis model to reduce pain and inflammation in the synovium (Ashraf S. et. al., 2019).

## 2.9. Anti-cancer properties

In Cancer, some of the body's cells grow uncontrollably. They can also spread to other parts of the body. Rapid cell growth becomes lethal and it becomes very difficult to control these cells. Results of Park et.al. (2017) suggested that *C. militaris* is able to inhibit cancer growth through regulation of p85/AKT-dependent or GSK3 $\beta$ -related caspase-3-dependent apoptosis. Yoon et.al (2018) researched that the molecular mechanisms by which cordycepin functions as a singular or combinational anticancer therapeutic agent. They also reported that cordyceps is not only exhibits proapoptotic and anti-proliferative effects in cancer cells, but also inhibits cell metastasis in tumour cells, demonstrating its potential as a therapeutic agent in the larger scope of cancer. According to studies of Robinson et.al (2017) cordycepin is expected to be a potential combinational therapeutic drug for cancer treatment.

## 3. Medicinal significance of bioactive compounds of *Cordyceps militaris*

Based on scientific research findings, it is possible to gather information on bioactive chemicals from the nucleoside and polysaccharide groups found in *C. militaris*. Cordycepin and adenosine, two nucleosides, have been confirmed to be present in *C. militaris*, and their concentration is higher than that of *C. sinensis*. *C. militaris* contains biologically active substances such as  $\gamma$ -aminobutyric acid (GABA) and ergothioneine, glycolipids (cerebrosides), glycoproteins (lectins), D-mannitol (cordycepic acid), xanthophylls (lutein and zeaxanthin), sterols (ergosterol), statins (lovastatin), phenolic compounds (including phenolic acids and flavonoids), vitamins, and biominerals/bioelements (magnesium, potassium, selenium, and sulfur) (Cohen N. et. al., 2014; Chen S.Y. et. al., 2012; Chan J.S.L. et. al., 2015).

Previous research has found that the concentration and distribution of bioactive chemicals in fruiting bodies is not homogeneous. The exterior sections of *C. militaris* fruiting bodies contain the most nucleosides, polysaccharides, carotenoids, and selenium chemical compounds. Table 1 compares the bioactive component composition of *C. militaris* mycelium and fruiting bodies. The ideal drying temperature for *C. militaris* is 60°C. The amount of cordycepin and phenolic compounds decreases with increasing temperature (Wu X.F. et. al., 2019).

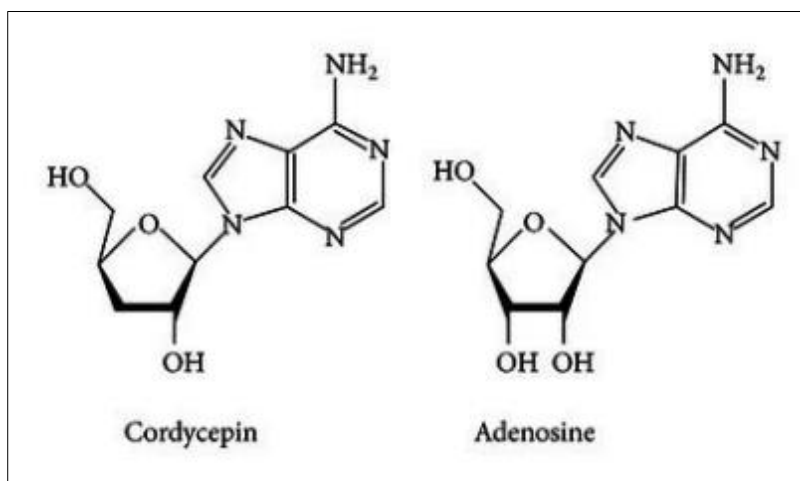
**Table 2** Content of bioactive compounds and nutrients existing in the mycelium and fruiting bodies of *C. militaris*

Bioactive compound	Mycelium	Fruiting bodies	References
Cordycepin	1.82 mg/g	1.10 mg/g	(Chan J.S.L. et. al., 2015)
Cordycepin	1.74 mg/g	5.28 mg/g (Water extract)	(Cohen N. et. al., 2014)
Cordycepin		8.37 mg/g (Ethanol extract)	(Cohen N. et. al., 2014)
D-mannitol	5.2 mg/kg	4.7 mg/kg	(Chan J.S.L. et. al., 2015)
Ergothioneine	130.6 mg/kg	782.3 mg/kg	(Chan J.S.L. et. al., 2015)
Ergothioneine	123.4–785.1 mg/kg	409.8 $\mu$ g/g	(Cohen N. et. al., 2014, Chen S.Y. et. al., 2012)
GABA	68.6–180.1 mg/kg	756.30 $\mu$ g/g	(Cohen N. et. al., 2014, Chen S.Y. et. al., 2012)
Lovastatin	37.7–57.3 mg/kg	2.76 $\mu$ g/g	(Cohen N. et. al., 2014, Chen S.Y. et. al., 2012)
Vitamins			
Vit. A	100 mg/kg	96 mg/kg	(Chan J.S.L. et. al., 2015)
Vit. E (tocopherols)	1.3 mg/kg	3.6 mg/kg	(Chan J.S.L. et. al., 2015)
Vit. B2 (riboflavin)	0.32 mg/kg	0.16 mg/kg	(Chan J.S.L. et. al., 2015)
Vit. B3 (niacin)	15.2 mg/kg	4.9 mg/kg	(Chan J.S.L. et. al., 2015)
Vit. C	Not detected	<2 mg/kg	(Chan J.S.L. et. al., 2015)
Bio elements			
Magnesium	3414 mg/kg	4227 mg/kg	(Chan J.S.L. et. al., 2015)
Sulphur	2558 mg/kg	5088 mg/kg	(Chan J.S.L. et. al., 2015)

Potassium	12,183 mg/kg	15,938 mg/kg	(Chan J.S.L. et. al., 2015)
Selenium	<0.5 mg/kg	0.4 mg/kg	(Chan J.S.L. et. al., 2015)
Iron	9 mg/kg	31 mg/kg	(Chan J.S.L. et. al., 2015)
Calcium	11 mg/kg	797 mg/kg	(Chan J.S.L. et. al., 2015)
Zinc	10 mg/kg	Not detected	(Chan J.S.L. et. al., 2015)
Nutrients			
Protein	39.5%	59.8%	(Chan J.S.L. et. al., 2015)
Protein	Not analyzed	29.7%	(Cohen N. et. al., 2014)
Fat	2.2%	8.8%	(Chan J.S.L. et. al., 2015)
Fat	Not analyzed	2.9%	(Cohen N. et. al., 2014)
Carbohydrate	39.6%	29.1%	(Chan J.S.L. et. al., 2015)
Carbohydrate	Not analyzed	54.3%	(Cohen N. et. al., 2014)

### 3.1. Nucleosides

Cordycepin (3'-deoxyadenosine) is a water-insoluble chemical molecule that is structurally similar to the nucleoside adenosine (Figure 2).



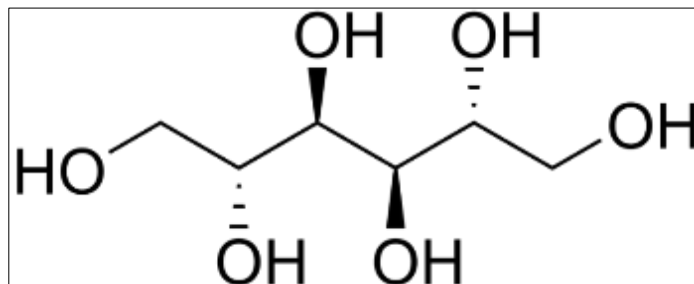
**Figure 2** Structure of cordycepin and adenosine

(<https://alchetron.com/cdn/cordycepin-2b08a399-0078-4138-8515-8fe0103547b-resize-750.jpg>)

Cordycepin was discovered from *C. militaris* in 1950. Based on previous in vitro and in vivo research, this chemical has been shown to have the following properties: immunostimulating, anti-inflammatory, antiviral, anticancer, ergogenic, hypolipidemic, hypoglycemia, and steroidogenesis and spermatogenesis regulation. Cordycepin's antioxidant activity has only been established in a few research. Scientific research have explained the antioxidant effect of polysaccharide fractions found in *C. militaris* fruiting bodies by studying the molecular mechanisms of their activity. Cordycepin's immunostimulatory action is due to its ability to generate cellular and humoral immunological responses, as established in mouse experiments. The research demonstrated a rise in the levels of interleukins IL-4, IL-10, and IL-12, as well as Th1 and Th2 cytokines, and a decrease in concentration of IL-2 and transforming growth factor- $\beta$  (TGF- $\beta$ ) and an increase in the level of T lymphocytes (CD4 and CD8). Cordycepin's mode of action includes augmenting "produced" energy in the form of adenosine-5'-triphosphate (ATP). Cordycepin can also enhance nitric oxide (NO) levels (Tuli H.S. et. al., 2014; Qin P. et. al., 2019).

### 3.2. Carbohydrates

D-Mannitol, a polyhydric alcohol, is one of *C. militaris* most essential metabolic metabolites. D-Mannitol from *C. militaris* is also known as cordycepic acid. *C. militaris* uses it as a carbohydrate reserve as well as a transporter of other chemicals for osmoregulation and metabolic pathway control. D-mannitol has osmotic activity, therefore it can be utilised in clinical practice as a diuretic and anti-edematous agent (Cohen N. et. al., 2011; Shawkat H. et. al., 2012).



**Figure 3** Structure of D-mannitol

([https://cdn2.bigcommerce.com/server300/ad7b7/products/351/images/20029/D\\_Mannitol\\_1\\_kg\\_09637.1426137088.1280.1280.png?c=2](https://cdn2.bigcommerce.com/server300/ad7b7/products/351/images/20029/D_Mannitol_1_kg_09637.1426137088.1280.1280.png?c=2))

In addition to D-mannitol, *C. militaris* has saccharides with more complicated structures called polysaccharides. Depending on where polysaccharide production occurs in *C. militaris* hyphae, they can be secondary intracellular (IPS) or extracellular (EPS) metabolites. Polysaccharides extracted from the *C. militaris* mycelium exhibit a distinct chemical structure. The chemical structure of polysaccharides is determined by the type of monosaccharides used, their linear sequence, spatial configuration, glycosidic bond location, and the degree of chain branching (cross-linking) (Zhang J. et. al., 2019).

Significant changes have been identified in the chemical structure, as well as the qualitative and quantitative content, of monosaccharides derived from the proportion of polysaccharides present in *C. militaris* growing in the natural environment and cultivated in the laboratory. Mannose, glucose, and galactose are the most important monosaccharides found in saccharide polymers. In further scientific studies on *C. militaris* polysaccharides, the following monosaccharides were discovered: arabinose, rhamnose, and xylose (Zhang J. et. al., 2019). In the CPSN Fr II polysaccharide produced from *C. militaris* culture broth, the proportion concentration of monosaccharides is as follows: mannose (65.12%), galactose (28.72%), and glucose (6.12%) (Lee J.S. et. al., 2010). The WCBP50 polysaccharide comprises  $\alpha$ -D-glucose,  $\alpha$ -D-mannose, and  $\alpha$ -D-arabinose units joined by an  $\alpha$ -glycosidic linkage (Chen X. et. al., 2013).

CMN1 is a 37.8 kDa polysaccharide derived from *C. militaris* mycelium. It is made up of D-galactose, D-mannose, L-arabinose, and L-rhamnose subunits linked by glycosidic bonds (1  $\rightarrow$  2 and 1  $\rightarrow$  3). The side substituents branch at locations (1  $\rightarrow$  4) and (1  $\rightarrow$  6) (Dong Y., et. al., 2015). The CMP-1 polysaccharide has a molecular weight of 4.4 kDa and is composed of the following combined units: (1  $\rightarrow$  4)  $\alpha$ -D-glucose, (1  $\rightarrow$  6)  $\beta$ -D-glucose, and (1  $\rightarrow$  4)  $\beta$ -D-glucose, with the side branches containing (1  $\rightarrow$  3)  $\alpha$ -L-rhamnose (Jing Y. et. al., 2014). The novel structure CMPB90-1 isolated from *C. militaris* was discovered to be constituted of  $\alpha$ -D-glucose linked by (1  $\rightarrow$  6) and (1  $\rightarrow$  3) side branches containing (1  $\rightarrow$  4)  $\beta$ -D-mannose (Bi S. et. al., 2018).

To summarise, the discrepancies in the obtained results for the chemical structure of polysaccharides are attributed to the source of *C. militaris*, cultivation methods and conditions, and extraction technique. The biological activity of *C. militaris* polysaccharides is influenced by their molecular weight, spatial conformation, glycosidic bond type, and degree of branching (cross-linking) (Zhang J. et. al., 2019).

In vitro and/or in vivo studies revealed that the polysaccharides found in *C. militaris* have immunostimulatory, anticancer, anti-inflammatory, antioxidant, hypoglycemic, hypolipidemic, and hepatoprotective properties. Polysaccharide fractions isolated from *C. militaris* have immunostimulatory activity, stimulating macrophages to produce NO, IL-1 $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ , T and B lymphocytes, and natural killer (NK) cells, as well as increased phagocytosis (Zhang J. et. al., 2019). The investigations demonstrated that polysaccharides have anticancer action by inhibiting proliferation and inducing apoptosis in tumour cells. Inhibiting carcinogenesis involved inhibiting cyclin-dependent kinase and arresting the tumour cell cycle in the G0/G1 and G2/M phases (Zhang J. et. al., 2019).

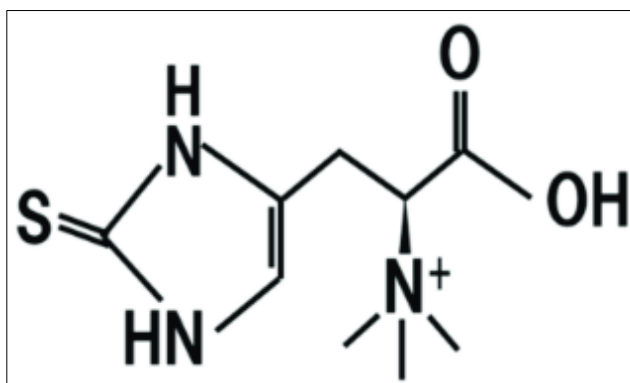


### 3.3. Amino Acids

*C. militaris* fruiting bodies contain 57.39 mg of amino acids per gramme dry weight. In addition to protein amino acids, the fruiting bodies of *C. militaris* also contain non-protein amino acids such GABA and ergothioneine (Chan J.S.L et. al., 2015). GABA is a non-protein amino acid that the human body synthesises from glutamic acid. GABA is an inhibitory neurotransmitter in the central nervous system that influences the cerebellum, hippocampus, hypothalamus, striatum, and spinal cord. GABA inhibits the function of GABAergic receptor subtypes A, B, and C. It governs sleep, memory, and learning, as well as emotional processes like anxiety and stress. GABA also exhibits myorelaxant and anticonvulsant properties (Boonstra E. et. al., 2015).

Previous scientific study has revealed variations in the pharmacokinetic and pharmacodynamic characteristics of GABA following oral ingestion in humans. Some research suggest that GABA has low bioavailability after oral administration. Other difficulties with GABA comprises of difficulty reaching the blood-brain barrier and a short biological half-life (Hepsomali P. et. al., 2020). Some scientific articles support the bioavailability and efficacy of oral GABA supplementation in humans (Li J. et. al., 2015; Yamatsu A. et. al., 2016). Studies on *C. militaris* mycelium and fruiting bodies found GABA concentrations of 68.6-180.1 mg/kg and 756.30 µg/g dry weight (Cohen N. et. al., 2014; Chen S.Y. et. al., 2012).

Ergothioneine (2-thiol-L-histidine-betaine) is a water-soluble sulphur analogue of the amino acid L-histidine that has an attached fragment of the betaine molecule (Figure 4). Ergothioneine is a non-protein amino acid generated by bacteria, plants, and fungus, but mammals do not synthesise it, hence it must be obtained by diet (Muszyńska B. et. al., 2017). Various kinds of fungi are an excellent source of ergothioneine, with concentrations ranging from 0.2 mg/g to 2.6 mg/g dry weight. *Agaricus bisporus* has around 0.55 mg of ergothioneine per gramme dry weight. Ergothioneine concentrations have been confirmed in the following species: *Lentinula edodes* (shiitake): 1.98 mg/g dry weight; *Pleurotus osteratus* (oyster): 2.59 mg/g dry weight; and *Grifola frondosa* (maitake): 1.13 mg/g dry weight (Muszyńska B. et. al., 2017; Dubost N.J. et. al., 2007; Weigand-Heller A.J. et. al., 2012). The concentration of ergothioneine in *C. militaris* fruiting bodies was found to be 782.3 mg/kg dry weight, whereas in mycelium of *C. militaris* it achieves range 130.6 mg/kg dry weight (Chan J.S.L. et. al., 2015).



**Figure 4** Structure of ergothioneine

(<https://www.researchgate.net/publication/350360422/figure/download/fig6/AS:1016527008587781@1619370333511/Chemical-structure-of-ergothioneine.png>)

The human body is unable to produce ergothioneine. This substance's unique transporter, carnitine/organic cation transporter 1 (OCTN1), has been identified, and large levels of ergothioneine have been found in several tissues and cells, including erythrocytes, the spleen, the liver, and the eyes. Ergothioneine's antioxidant, cytoprotective, and radioprotective effects have been proven in vitro and in vivo on animal models (Borodina I. et. al., 2020). Ergothioneine supplementation (at doses of 5 mg/day and 25 mg/day) was observed to correspond with a small reduction in oxidative stress indicators in healthy volunteers aged 21 to 35 years. Ergothioneine's antioxidant action may be particularly essential in settings that predispose to the formation of oxygen free radicals, such as diseases with inflammatory processes or physical activity (Cheah I.K. et. al., 2017).

### 3.4. Carotenoids

Carotenoids, particularly xanthophyll derivatives, have been found in the fruiting bodies of a variety of fungal species, including *C. militaris*. Carotenoids are responsible for the bright yellow-orange colour of *C. militaris* fruiting bodies. *C.*

*militaris* fruiting bodies contain several xanthophylls, including  $\beta$ -carotene, lycopene, lutein, and zeaxanthin (Dong J.Z. et al., 2019; Muszyńska B. et al., 2016). Lutein and zeaxanthin are also found in the human eye's macula, a cluster of cones responsible for colour vision throughout the day (Bovier E.R. et al., 2015). In addition to studies on the protective effects of lutein and zeaxanthin on eye structures, previous scientific reports have shown that carotenoid pigment supplementation improves cognitive functions, lowers cortisol levels and stress symptoms in both young and adult people, and induces antioxidant effects (Bovier E.R. et al., 2015; Renzi-Hammond L. et al., 2017; Stringham N.T. et al., 2018).

A diet rich in carotenoids, such as tomato juice (high concentration of lycopene) and carrot juice (high concentration of  $\beta$ -carotene), has been shown to improve immune function in healthy males who previously had a low level of carotenoids in their diet (Watzl B. et al., 2003). There are differences in the impact of  $\beta$ -carotene on human health. Some reviews suggest that  $\beta$ -carotene supplementation can help prevent cancer (Gul K et al., 2015), while others suggest that it may increase the risk of certain types of cancer, such as lung or stomach cancer. Supplementing with high dosages of  $\beta$ -carotene (20-30 mg/day) was linked to an increased risk of lung or stomach cancer (Druesne-Pecollo N. et al., 2010). Lycopene supplementation has been shown to improve the vascular endothelial functioning in patients with cardiovascular disease (CVD). However, there was no substantial effect on endothelial function in healthy participants (Gajendragadkar P.R. et al., 2014). The association between lycopene supply and metabolic syndrome prevention has been confirmed (Senkus K.E. et al., 2019). Lycopene has been shown in in vitro and in vivo investigations to decrease prostate cancer cell progression and induce apoptosis. Lycopene is an auxiliary medication that complements basic chemotherapy and hormone therapy in prostate cancer patients (Mirahmadi M. et al. 2020).

*C. militaris* fruiting body extract was tested for  $\beta$ -carotene and lycopene concentrations. The concentrations of  $\beta$ -carotene and lycopene were 0.328 mg/g and 0.277 mg/g, respectively (Joshi M. et al., 2019). Choi et al. (2020) reported that in the aqueous extract of *C. militaris*, the concentration of  $\beta$ -carotene was found to be 24.51  $\mu$ g/g, whereas lycopene was 3.42  $\mu$ g/g. In example, the concentration of  $\beta$ -carotene in *A. bisporus* (Turkey) is 0.04 mg/g, whereas in *Pleurotus ostreatus* (India) is 0.03 mg/g (Muszyńska B. et al., 2016). *Tricholoma acerbum* contains 75.48  $\mu$ g/g of  $\beta$ -carotene and 39.65  $\mu$ g/g of lycopene, according to research (Barros L. et al., 2008).

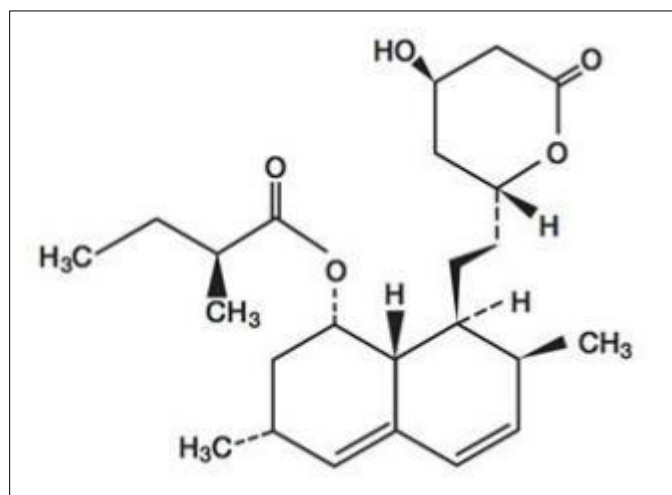
Cordyxanthins, a unique class of carotenoids, have been identified in *C. militaris* fruiting bodies. Cordyxanthin I-IV is the numerical designation for four cordyxanthins found in *C. militaris* fruiting bodies. The concentrations of cordyxanthin I, cordyxanthin II, cordyxanthin III, and cordyxanthin IV were 0.289 mg/g, 0.235 mg/g, 0.401 mg/g, and 0.175 mg/g. Cordyxanthins are more water-soluble than lutein, zeaxanthin,  $\beta$ -carotene, and lycopene due to variations in chemical structure, including fewer lipophilic methyl groups. Cordyxanthins are more water-soluble than lutein, zeaxanthin,  $\beta$ -carotene, and lycopene due to their chemical structure, which includes less lipophilic methyl groups and more hydroxyl substituents. Cortixanthin II stands out among the marked cordyxanthins because, unlike most carotenoids, it consists of one six-membered carbon ring and one five-membered carbon structure (Dong J.Z. et al., 2013).

### 3.5. Statins

*C. militaris* fruiting bodies contain lovastatin, a statin, which is extensively used as a cholesterol-lowering medication (Cohen N. et al., 2014; Chen S.Y. et al., 2012). Lovastatin is a naturally occurring substance that selectively inhibits the production of endogenous cholesterol. It was first discovered from *Aspergillus terreus* in 1978 and released as a pharmaceutical product by Merck in 1987. Lovastatin consists of a six-part lactone ring with a hydroxyl group and a partly hydrogenated naphthalene with a hydroxyl substituent esterified with a 2-methylbutyric acid residue (Figure 5).

Lovastatin is a precursor that, during enzymatic processes, is transformed from a lactone to a hydroxy acid, therefore competitively inhibiting 3-hydroxymethylglutaryl-coenzyme A. As a result, the conversion of HMG-CoA to mevalonate, a critical step in cholesterol production, is prevented. Statin drugs also have pleiotropic effects, such as protecting the vascular endothelium. Lovastatin is an approved medicine at a dose of 20 mg and is intended for the main treatment of hypercholesterolemia in patients as well as the prevention of coronary atherosclerosis in patients with coronary artery disease (Oesterle A. et al., 2017; Tobert J.A. 1998).

The concentration of lovastatin in *C. militaris* mycelium ranges between 37.7 mg/kg and 57.3 mg/kg dry weight. In this regard, *C. militaris* has a lower lovastatin concentration than *C. sinensis*, which is 1365.3 mg/kg (Chen S.Y. et al., 2012). In comparison, *C. militaris* fruiting bodies contain 2.76  $\mu$ g/g of lovastatin. The fruiting bodies of *Hericium erinaceus* (14.38  $\mu$ g/g) and *Ganoderma lucidum* (11.54  $\mu$ g/g) contain the highest concentrations of lovastatin (Cohen N. et al., 2014).



**Figure 5** Structure of lovastatin

(<https://medlibrary.org/lib/images-rx/lovastatin-36/lovastatin-01.jpg>)

### 3.6. Phenolic Compounds

Flavonoids and phenolic acids are two key types of phenolic chemicals found in *C. militaris*. Their potential is linked to a strong antioxidant impact and the capacity to preserve vital components including proteins, enzymes, lipids, and nucleic acids from oxidative damage. Phenolic acids, such as vanillic and caffeic acids, display the strongest antioxidant effects. In vitro and in vivo investigations have shown that p-Hydroxybenzoic, gallic, and protocatechuic acids present in edible mushrooms have antioxidant activity as well as antibacterial, antifungal, antiviral, and anti-inflammatory properties (Muszyńska B et. al., 2023). The concentrations of phenolic acids in *C. militaris* fruiting bodies were also determined. The concentrations of p-hydroxybenzoic acid and cinnamic acid were determined to be 0.02 mg/100 g dry weight and 0.11 mg/100 g dry weight, respectively (Reis F.S. et. al., 2013). The content of flavonoids in *C. militaris* fruiting bodies extract was determined to be 1.56 mg/g (Joshi M. et. al., 2019). The flavonoid concentration was estimated using the rutin equivalent (RE) method. The flavonoids concentration in fruiting bodies and mycelium was determined to be 5.54 mg RE/g and 2.26 mg RE/g, respectively (Huang S.J. et. al., 2015). *C. militaris* aqueous extract contained 275.52 mg/g of flavonoids and 19.79 mg/g of polyphenols (Choi E. et. al., 2020). The extract contains more flavonoids than the fresh fruiting bodies of *C. militaris*. According to Awang M.A. et. al., the total content of flavonoids was 6.6 mg RE/100 g and 4.5 mg RE/100 g respectively in the extract and fresh fruiting bodies of *C. militaris* (Awang M.A. et. al., 2021).

### 3.7. Other Bioactive Compounds

Lectins, which can be found in *C. militaris* fruiting bodies due to their chemical structure, are protein molecules with associated saccharide fragments (glycoproteins). Lectins have been shown to exhibit mitogenic action. These bind to sugar residues on cell surfaces, initiating the process of cell clumping (agglutination) (Singh R.S. et. al., 2010; Hassan M. et. al., 2015). This species also contains beauveriolides, which have a complicated chemical structure and are known as cyclodepsipeptides. Beauveriolides showed anti-atherosclerotic action and reduced  $\beta$ -amyloid levels (Chen B. et. al., 2020). Militarinones are a relatively unknown class of chemical substances classed as alkaloids. These are pyridine derivatives or tetramic acids (pyrrolidine-2,4-dione), which have been proven to have antibacterial and cytotoxic properties (Chen B. et. al. 2020).

Pentostatin, isolated from the fruiting bodies of the identified species is an analogue of the purine base hypoxanthine. It has inhibitory effect against the enzyme adenine deaminase. It also exhibits anticancer and immunosuppressive action. Pentostatin has been approved as a chemotherapeutic agent for the treatment of cancer in oncology and haematology hospital departments (Chen B. et. al., 2020; Tsimberidou A. et. al., 2004). Cordymin is a substance identified in *C. militaris* fruiting bodies that is classed as an antibacterial peptide (Wong J.H. et. al., 2011).

The fruiting bodies of *C. militaris* contain both water-soluble vitamins (vitamin B2, vitamin B3, and vitamin C) and fat-soluble vitamins (vitamin A and vitamin E) (Chan J.S.L. et. al., 2015). Vitamins B2 (riboflavin) and B3 (niacin) help to alleviate tiredness and exhaustion while also regulating energy metabolism. Vitamin C protects cells from oxidative

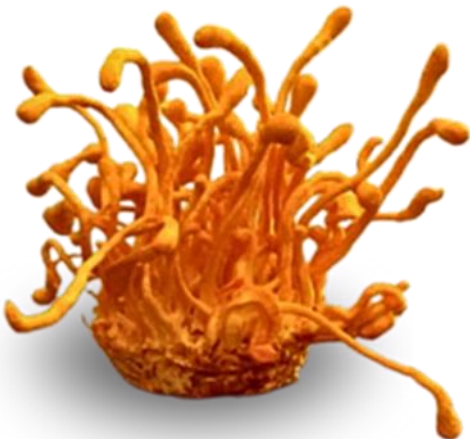

stress, helps to maintain immune system function, promotes collagen production, and increases iron absorption from the gastrointestinal tract. Vitamin A contributes to cell specialisation and the maintenance of proper vision. Vitamin E protects cells from oxidative damage (Commission Regulation (EU), 2012).

Magnesium, potassium, selenium, and sulphur have been found in the fruiting bodies of *C. militaris*. *C. militaris* contains a high concentration of several bioelements, making it an alternate source of these minerals in the human diet. The mineral composition of *C. militaris* is summarised in table 1. Biomineral concentrations such as boron, manganese, copper, and iron are generally negligible, ranging from 5 to 31 mg/kg dry weight (Cohen N. et. al., 2014).

Selenium is found in organic form in the fruiting bodies of *C. militaris*, coupled to amino acids or proteins. Selenium is chelated using the amino acids L-methionine (selenomethionine) and L-cysteine (selenocysteine). It reacts with proteins to produce methylselenocysteine. The addition of selenium (sodium selenate) to *C. militaris* medium enhances the content of active chemicals in fruiting bodies, including nucleosides, polysaccharides, amino acids, and organic selenium (Dong J.Z. et. al., 2012; Dong J.Z et. al., 2012). Enriching the *C. militaris* substrate with organic or inorganic selenium (sodium selenate (IV) or sodium selenate (VI)) enhances the levels of cordycepin and adenosine in fruiting bodies (Hu T. et. al., 2019). Selenium-fortified polysaccharide was produced from *C. militaris* mycelium (SeCSP-I). An in vitro investigation revealed SeCSP-I's antioxidant activity (Zhu Z.Y. et. al., 2016).

#### 4. *Cordyceps militaris* as alternative source of food supplement

Nutrition is the pivot of any person to lead a successful and healthy life. It is said that a healthy mind resides in a healthy body, but the daily running has only taken the pleasure of sitting and eating comfortably from life. The excessive use of pesticides and fertilizers in agriculture and vegetable production has taken away their nutrients from the food items. Lack of nutrients, lack of exercise and obesity has given rise to which later causes fatal diseases like diabetes and cancer. In such a situation, a person has to depend on food supplements for nutrients. Excessive use of synthetic supplements is also not right and they can have side effects. In such a situation, *Cordyceps militaris* has emerged as a natural and safe food supplement. Due to huge requirement of *Cordyceps militaris*, it is necessary to cultivate mycelium biomass organically in controlled and sterilized environment (image 1 and 2), this type of cultivation have been proposed by many research groups (LU et.al 2019).

	
<p><b>Figure 6</b> Mature fruiting bodies of <i>Cordyceps militaris</i></p>	<p><b>Figure 7</b> Dried <i>Cordyceps militaris</i> (Image courtesy: HARI Lifesciences)</p>

Researchers working on the nutritional aspects of *Cordyceps militaris* in cultivation laboratories with the use of right extract techniques and ensure the purest form of bioactive compound in order to make pharmaceutical and nutraceutical grade *C. militaris*. Various studies on *C. militaris* described that amount of bioactive components like proteins, fats, essential amino acids, volatile oils, carotenoids, phenolic compounds, minerals (Fe, Ca, Mg, Ni, Sr, Na, Ti, Pi, Se, Mn, Zn, Al, Si, K, Cr etc.), flavonoids, vitamins (B1, B2, B12, E and K) as well as various types carbohydrates like monosaccharides, oligosaccharides, polysaccharides, sterols, nucleosides, etc. (Elkhateeb et.al, 2019; Yang et.al, 2009, Hur 2008 Zhu et.al, 1998). At present, the food industry does not only make food based on taste, but it is a revolutionary time in which more attention is given to nutrition along with taste. Many restaurants have started making organic, tasty

and healthy recipes using *C. militaris*. Some recipes are so easy that anybody can easily make them at home and enjoy the taste as well as nutrition, some of them are Cordyceps salad, Cordyceps broth, Cordyceps with linguine, Cordyceps soup, Cordyceps pasta, Cordyceps Butter Biscuits, Cordyceps biryani, Cordyceps powder and wheat flour chapati, Cordyceps milk shake, Cordyceps ice cream, Cordyceps candies, Cordyceps chocolate, Cordyceps dalia, Cordyceps smoothies etc.

---

## 5. Different food supplements of *Cordyceps militaris*

Cordyceps extract containing products and supplements have gained peoples interest in recent times due to its innumerable health benefits. Studies Showed that *C. militaris* is a safe nutritional Supplement. Popular products of *C.militaris* available in markets are:

### 5.1. Cordyceps Hot Water Extract

Cordyceps hot water extracts are the best way for people taking workout supplements or breathing exercises. It is easy to go already water extracted cordyceps concentrate, which can be directly put into your tea, coffee, juices and shakes.

### 5.2. Cordyceps Mycelium Powder

Cordyceps mycelium powder comprises of mycelium which is the support, immune and natural intelligence system of mushrooms. It is a rich and powerful source of nutrition. Freeze drying ensures optimized health-supporting power. The powder is Packed in sealed carton lined with plastic seal or sealed double plastic bags. It is recommended to Put it in a Cold and dry place. Shelf Life of cordyceps powder is 3 years if sealed and store away from direct sun light. Different companies sell cordyceps powder like; Naturalin, Rooted, Real Mushrooms, cordyceps etc.

It has been researched that *Cordyceps militaris* may alleviate severity of murine Acute lung injury through miRNAs-mediated CXCR2 inhibition (Sheng Liu, et. al., 2015). Cordyceps extract also nourishes the lungs and kidney, and tonifies the essence and the vital energy. Cordyceps polysaccharide is the most ample content and the most vital biological active substances in the body of Cordyceps. It can be used for:

- Strengthen body & enhanced Immunity; anti-aging;
- Improve sexual performance;
- Treat neurasthenia, improve sleep;
- Protect the liver;

### 5.3. Cordyceps Tea

Cordyceps tea is an excellent way of getting these immunomodulatory substances which can be taken daily as morning and evening tea.

### 5.4. Cordyceps Dried Fruiting Body

A good quality dried cordyceps fruiting body helps to enhance immune system, maintain energy levels, manage cholesterol and glucose levels. It can be taken directly in soups and salads. Orange chrome colonies formed fruiting bodies more readily, as compared to those of lighter colour. Cordycepin production generally reduced in orange chrome to apricot orange and white colonies. There was, however, no relationship between cordycepin production and colony colour in the slow growing strains. Cordyceps farmer claims that fruiting bodies of their extract Boost Immunity by increasing immune response by red blood cells and improving function of white blood cells, Boost Energy level by increasing oxygen efficiency in the body, Improves testosterone secretion so it used as natural muscle building supplement with no side effects, Enhancement of VO2 max due to high oxygen efficiency of body which improves stamina, very useful for athletes and sportsperson, Enhance immunity, power, stamina, detox whole body with regular use. Mushroom Essence is another brand which sells mushroom dried fruiting bodies.

### 5.5. Cordyceps Capsules

Cordyceps capsules are mostly water-soluble polysaccharide (total glucan including beta-glucans) apart from other specific compounds like triterpenes in pure forms.

## 5.6. Cordycep Tincture

A tincture is on the top ways of taking all mushroom and herbal medicines. Tincture utilizes a double extraction process to extract both water-soluble polysaccharides and alcohol soluble antioxidants for wholesome benefits. PowerFunGuy, rooted, nuvedo, amazing organics are some of the brands who sell cordyceps tincture.

## 6. Conclusion

Mushrooms are popular valuable foods in all over the world due to their amazing nutritional properties. *C. militaris* is also a type of mushrooms having extraordinary health benefits like antiviral, antibacterial, immune system enhancer, cholesterol lowering agents etc. Additionally, they are important sources of bioactive compounds like cordycepin and adenosine. *C. militaris* because of its outstanding nutraceutical and medicinal properties has huge demand as health care product. Many in-vitro and in-vivo studies suggested its diverse biological activities and its medicinal potential. Even if we put aside the therapeutic value of the mushroom, it is still a very good nutritious mushroom. It is complete nutritional supplement having all the essential amino acids, fibers, sterols, carbohydrates, vitamins (E, K, B1, B2 and B12) and minerals (magnesium, maganase, iron, copper, potassium, calcium and zinc) Unlike *C. sinensis* which need a caterpillar for their growth, *C. militaris* cultivated in laboratories in organic substrate like brown rice medium due to this property, this mushroom can also be eaten by vegetarians and vegans. *C. militaris* contain excellent amount of adenosine which enhances the production of adenosine triphosphate (ATP) and in this manner it fights against fatigue. Cordycepin might improve immunity and have activity against cancer cells, having antimicrobial activities and also reported as anti-depressant. As *C. militaris* has numerous health benefits; it can be recommendations as nutraceuticals or food supplement for better health and life in this era of COVID 19 pandemic.

## Compliance with ethical standards

### Disclosure of conflict of interest

No conflict of interest to be disclosed.

## References

- [1] Ashraf S., Radhi M., Gowler P., Burston J.J., Gandhi R.D., Thorn G.J., Piccinini A.M., Walsh D.A., Chapman V., de Moor C.H. (2019). The Polyadenylation Inhibitor Cordycepin Reduces Pain, Inflammation and Joint Pathology in Rodent Models of Osteoarthritis. *Sci. Rep.* 9:4696. doi: 10.1038/s41598-019-41140-1.
- [2] Aung, W.L.; Kyaw, M. (2023), Identification and Determination of Secondary Metabolites and Amino Acids in *Cordyceps*. *Partn. Univers. Int. Innov. J.* 1, 251–258.
- [3] Awang M.A., Daud N.N.N.N.M., Ismail N.I.M., Cheng P.G., Ismail M.F., Ramaiya S.D. (2021). Antioxidant and Cytotoxicity Activity of *Cordyceps militaris* Extracts against Human Colorectal Cancer Cell Line. *J App Pharm Sci.* 11:105–109.
- [4] Badalyan, S. (2012). Medicinal Aspects of edible ectomycorrhizal mushrooms. Springer, Verlag, Germany 34: 317-334.
- [5] Barros L., Venturini B.A., Baptista P., Estevinho L.M., Ferreira I.C.F.R. (2008). Chemical Composition and Biological Properties of Portuguese Wild Mushrooms: A Comprehensive Study. *J. Agric. Food Chem.* 56:3856–3862. doi: 10.1021/jf8003114.
- [6] Bi S., Jing Y., Zhou Q., Hu X., Zhu J., Guo Z., Song L., Yu R. (2018). Structural Elucidation and Immunostimulatory Activity of a New Polysaccharide from *Cordyceps militaris*. *Food Funct.* 9:279–293. doi: 10.1039/C7FO01147D.
- [7] Boonstra E., de Kleijn R., Colzato L.S., Alkemade A., Forstmann B.U., Nieuwenhuis S. (2015). Neurotransmitters as Food Supplements: The Effects of GABA on Brain and Behavior. *Front. Psychol.* 6:1520. doi: 10.3389/fpsyg.2015.01520.
- [8] Borodina I., Kenny L.C., McCarthy C.M., Paramasivan K., Pretorius E., Roberts T.J., van der Hoek S.A., Kell D.B. (2020). The Biology of Ergothioneine, an Antioxidant Nutraceutical. *Nutr.* 33:190–217. doi: 10.1017/S0954422419000301.

- [9] Bovier E.R., Hammond B.R. (2015). A Randomized Placebo-Controlled Study on the Effects of Lutein and Zeaxanthin on Visual Processing Speed in Young Healthy Subjects. *Arch. Biochem. Biophys.* 572:54–57. doi: 10.1016/j.abb.2014.11.012.
- [10] Chan J.S.L., Barseghyan G.S., Asatiani M.D., Wasser S.P. (2015). Chemical Composition and Medicinal Value of Fruiting Bodies and Submerged Cultured Mycelia of Caterpillar Medicinal Fungus *Cordyceps militaris* CBS-132098 (Ascomycetes) *Int. J. Med. Mushrooms.* 17:649–659. doi: 10.1615/IntJMedMushrooms.v17.i7.50.
- [11] Cheah I.K., Tang R.M.Y., Yew T.S.Z., Lim K.H.C., Halliwell B. (2017). Administration of Pure Ergothioneine to Healthy Human Subjects: Uptake, Metabolism, and Effects on Biomarkers of Oxidative Damage and Inflammation. *Antioxid. Redox Signal.* 26:193–206. doi: 10.1089/ars.2016.6778.
- [12] Chen B., Sun Y., Luo F., Wang C. (2020). Bioactive Metabolites and Potential Mycotoxins Produced by *Cordyceps* Fungi: A Review of Safety. *Toxins.* 12:410. doi: 10.3390/toxins12060410.
- [13] Chen R., Jin C., Li H., Liu Z., Lu J., Li S., Yang S. (2014). Ultrahigh Pressure Extraction of Polysaccharides from *Cordyceps militaris* and Evaluation of Antioxidant Activity. *Sep. Purif. Technol.* 134:90–99. doi: 10.1016/j.seppur.2014.07.017.
- [14] Chen S.Y., Ho K.J., Hsieh Y.J., Wang L.T., Mau J.L. (2012). Contents of Lovastatin,  $\gamma$ -Aminobutyric Acid and Ergothioneine in Mushroom Fruiting Bodies and Mycelia. *LWT.* 47:274–278. doi: 10.1016/j.lwt.2012.01.019.
- [15] Chen X., Wu G., Huang Z. (2013). Structural Analysis and Antioxidant Activities of Polysaccharides from Cultured *Cordyceps militaris*. *Int. J. Biol. Macromol.* 58:18–22. doi: 10.1016/j.ijbiomac.2013.03.041.
- [16] Chiu C.-P., Liu S.-C., Tang C.-H., Chan Y., El-Shazly M., Lee C.-L., Du Y.-C., Wu T.-Y., Chang F.-R., Wu Y.-C. (2016). Anti-Inflammatory Cerebrosides from Cultivated *Cordyceps militaris*. *J. Agric. Food Chem.* 64:1540–1548. doi: 10.1021/acs.jafc.5b05931.
- [17] Cho H.-J., Cho J.Y., Rhee M.H., Park H.-J. (2007). Cordycepin (3'-Deoxyadenosine) Inhibits Human Platelet Aggregation in a Cyclic AMP-and Cyclic GMP-Dependent Manner. *Eur. J. Pharmacol.* 558:43–51. doi: 10.1016/j.ejphar.2006.11.073.
- [18] Choi E., Oh J., Sung G.-H. (2020). Antithrombotic and Antiplatelet Effects of *Cordyceps militaris*. *Mycobiology.* 48:228–232. doi: 10.1080/12298093.2020.1763115.
- [19] Choi E.-J., Park B., Lee J., Kim J. (2020). Anti-Atopic Dermatitis Properties of *Cordyceps militaris* on TNF $\alpha$ /IFN $\gamma$ -Stimulated HaCaT Cells and Experimentally Induced Atopic Dermatitis in Mice. *Phys. Act. Nutr.* 24:7. doi: 10.20463/pan.2020.0022.
- [20] Choi K.-H., Yoo J.-E., Hwang G.-S., Yoo D.-Y. (2012). Effects of *Cordyceps militaris* (CM) on Osteoclastogenesis and Gene Expression. *Obstet. Gynecol. Sci.* 25:16–26.
- [21] Cohen N., Cohen J., Asatiani M.D., Varshney V.K., Yu H.-T., Yang Y.-C., Li Y.-H., Mau J.-L., Wasser S.P. (2014). Chemical Composition and Nutritional and Medicinal Value of Fruit Bodies and Submerged Cultured Mycelia of Culinary-Medicinal Higher Basidiomycetes Mushrooms. *Int. J. Med. Mushrooms.* 16:273–291. doi: 10.1615/IntJMedMushr.v16.i3.80.
- [22] Commission Regulation (EU) No 432/2012 Commission Regulation (EU) No 432/2012 of 16 May 2012 Establishing a List of Permitted Health Claims Made on Foods, Other than Those Referring to the Reduction of Diseases Risk and to Children's Development and Health. *OJEU.* 2012;136:1–40.
- [23] Cunningham KG, Manson W, Spring FS, Hutchinson SA (1951) Cordycepin, a metabolic product from cultures of *Cordyceps militaris* (Linn.) link. Part I. isolation and characterization. *J Chem Soc* 2:2299–2300. <https://doi.org/10.1039/JR9510002299>
- [24] Das, S.K.; Masuda, M.; Sakurai, A.; Sakakibara, M. (2010). Medicinal uses of the mushroom *Cordyceps militaris*: Current state and prospects. *Fitoterapia*, 81, 961–968.
- [25] Dong Cai-Hong, Tao Yang, Tiantian Lian. (2014). A comparative study of the antimicrobial, antioxidant, and cytotoxic activities of methanol extracts from fruit bodies and fermented mycelia of caterpillar medicinal mushroom *Cordyceps militaris* (Ascomycetes). *Int J Med Mushrooms.* 2014;16(5):485-95.
- [26] Dong J.Z., Ding J., Yu P.Z., Lei C., Zheng X.J., Wang Y. (2013). Composition and Distribution of the Main Active Components in Selenium-Enriched Fruit Bodies of *Cordyceps militaris* Link. *Food Chem.* 137:164–167. doi: 10.1016/j.foodchem.2012.10.021.

- [27] Dong J.Z., Lei C., Ai X.R., Wang Y. (2012). Selenium Enrichment on *Cordyceps militaris* Link and Analysis on Its Main Active Components. *Appl. Biochem.* 166 doi: 10.1007/s12010-011-9506-6. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [28] Dong J.Z., Wang S.H., Ai X.R., Yao L., Sun Z.W., Lei C., Wang Y., Wang Q. (2013). Composition and Characterization of Cordyxanthins from *Cordyceps militaris* Fruit Bodies. *J. Funct. Foods.* 5:1450–1455. doi: 10.1016/j.jff.2013.06.002.
- [29] Dong Y., Hu S., Liu C., Meng Q., Song J., Lu J., Chen G. Y., Gao C., Liu Y., Wang D., et al. (2015). Purification of Polysaccharides from *Cordyceps militaris* and Their Anti-Hypoxic Effect. *Mol. Med. Rep.* 11:1312–1317. doi: 10.3892/mmr.2014.2786.
- [30] Dong Yuan, Tianjiao Jing, Qingfan Meng, Chungang Liu, Shuang Hu, Yihang Ma, Yan Liu Jiahui Lu, Yingkun Cheng. (2014). *Cordyceps militaris* Extract in Diet Streptozotocin-Induced Diabetic Sprague-Dawley Rats. BioMed Research International
- [31] Dong, C.H., T. Yang, and T. Lian (2010). A comparative study of the antimicrobial, antioxidant, and cytotoxic activities of methanol extracts from fruit bodies and fermented mycelia of caterpillar mushroom *Cordyceps militaris* (Ascomycetes). *International Journal of Medicinal Mushrooms*, vol. 16, no. 5, pp. 485–495. *Mycobiology*. 38(1): 46– 51
- [32] Druesne-Pecollo N., Latino-Martel P., Norat T., Barrandon E., Bertrais S., Galan P., Hercberg S. (2010). Beta-carotene Supplementation and Cancer Risk: A Systematic Review and Metaanalysis of Randomized Controlled Trials. *Int. J. Cancer Res.* 127:172–184. doi: 10.1002/ijc.25008. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [33] Dubost N.J., Ou B., Beelman R.B. (2007). Quantification of Polyphenols and Ergothioneine in Cultivated Mushrooms and Correlation to Total Antioxidant Capacity. *Food Chem.* 105:727–735. doi: 10.1016/j.foodchem.2007.01.030. [[CrossRef](#)] [[Google Scholar](#)]
- [34] Fabroni S, Marszałek K and Todaro A. (2020). Cordycepin for Health and Wellbeing: A Potent Bioactive Metabolite of an Entomopathogenic Medicinal Fungus *Cordyceps* with Its Nutraceutical and Therapeutic Potential. 25(12): 2735.
- [35] Fengyao W., Hui Y., Xiaoning M., Junqing J., Guozheng Z., Xijie G., Zhongzheng G. (2011). Structural Characterization and Antioxidant Activity of Purified Polysaccharide from Cultured *Cordyceps militaris*. *Afr. J. Microbiol. Res.* 5:2743–2751. doi: 10.5897/AJMR11.548. [[CrossRef](#)] [[Google Scholar](#)]
- [36] Gajendragadkar P.R., Hubsch A., Mäki-Petäjä K.M., Serg M., Wilkinson I.B., Cheriyan J. (2014). Effects of Oral Lycopene Supplementation on Vascular Function in Patients with Cardiovascular Disease and Healthy Volunteers: A Randomised Controlled Trial. *PLoS ONE.* 9:e99070. doi: 10.1371/journal.pone.0099070. [[PMC free article](#)] [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [37] Gao J., Lian Z.-Q., Zhu P., Zhu H.-B. (2011). Lipid-Lowering Effect of Cordycepin (3'-Deoxyadenosine) from *Cordyceps militaris* on Hyperlipidemic Hamsters and Rats. *Acta Pharm. Sin.* 46:669–676.
- [38] Gul K., Tak A., Singh A.K., Singh P., Yousuf B., Wani A.A. (2015). Chemistry, Encapsulation, and Health Benefits of  $\beta$ -Carotene-A Review. *Cogent Food Agric.* 1:1018696. doi: 10.1080/23311932.2015.1018696.
- [39] Guo P., Kai Q., Gao J., Lian Z., Wu C., Wu C., Zhu H. (2010). Cordycepin Prevents Hyperlipidemia in Hamsters Fed a High-Fat Diet via Activation of AMP-Activated Protein Kinase. *J. Pharmacol. Sci.* 113:395–403. doi: 10.1254/jphs.10041FP.
- [40] Hassan M., Rouf R., Tiralongo E., May T., Tiralongo J. (2015). Mushroom Lectins: Specificity, Structure and Bioactivity Relevant to Human Disease. *Int. J. Mol. Sci.* 16:7802–7838. doi: 10.3390/ijms16047802.
- [41] He Y.T., Zhang X.L., Xie Y.M., Xu Y.X., Li J.R. (2013). Extraction and Antioxidant Property *in Vitro* of Cordycepin in Artificially Cultivated *Cordyceps militaris*. *Adv. Mater. Res.* 750–752:1593–1596. doi: 10.4028/www.scientific.net/AMR.750-752.1593.
- [42] Hepsomali P., Groeger J.A., Nishihira J., Scholey A. (2020). Effects of Oral Gamma-Aminobutyric Acid (GABA) Administration on Stress and Sleep in Humans: A Systematic Review. *Front. Neurosci.* 14:923. doi: 10.3389/fnins.2020.00923.
- [43] Hu S., Wang J., Li F., Hou P., Yin J., Yang Z., Yang X., Li T., Xia B., Zhou G. (2019). Structural Characterisation and Cholesterol Efflux Improving Capacity of the Novel Polysaccharides from *Cordyceps militaris*. *Int. J. Biol. Macromol.* 131:264–272. doi: 10.1016/j.ijbiomac.2019.03.078. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]



- [44] Hu T., Liang Y., Zhao G., Wu W., Li H., Guo Y. (2019). Selenium Biofortification and Antioxidant Activity in *Cordyceps militaris* Supplied with Selenate, Selenite, or Selenomethionine. *Biol. Trace Elem. Res.* 187:553–561. doi: 10.1007/s12011-018-1386-y. [PubMed] [CrossRef] [Google Scholar]
- [45] Huang S.J., Lin C.P., Mau J.L., Li Y.S., Tsai S.Y. (2015). Effect of UV-B irradiation on physiologically active substance content and antioxidant properties of the medicinal caterpillar fungus *Cordyceps militaris* (Ascomycetes) *Int J. Med. Mushrooms.* 17:241–253. doi: 10.1615/IntJMedMushrooms.v17.i3.40.
- [46] Huang Z., Zhang M., Zhang S., Wang Y., Jiang X. (2018). Structural Characterization of Polysaccharides from *Cordyceps militaris* and Their Hypolipidemic Effects in High Fat Diet Fed Mice. *RSC Adv.* 8:41012–41022. doi: 10.1039/C8RA09068H.
- [47] Hwang S., Cho G.-S., Ryu S., Kim H.J., Song H.Y., Yune T.Y., Ju C., Kim W.-K. (2016). Post-Ischemic Treatment of WIB801C, Standardized *Cordyceps* Extract, Reduces Cerebral Ischemic Injury via Inhibition of Inflammatory Cell Migration. *J. Ethnopharmacol.* 186:169–180. doi: 10.1016/j.jep.2016.03.052.
- [48] Jędrejko KJ, Lazur J, Muszyńska B (2021) *Cordyceps militaris*: an overview of its chemical constituents in relation to biological activity. *Foods* 10:2634. <https://doi.org/10.3390/foods10112634>
- [49] Jeong J.-W., Jin C.-Y., Kim G.-Y., Lee J.-D., Park C., Kim G.-D., Kim W.-J., Jung W.-K., Seo S.K., Choi I.-W. (2010). Anti-Inflammatory Effects of Cordycepin via Suppression of Inflammatory Mediators in BV2 Microglial Cells. *Int. Immunopharmacol.* 10:1580–1586. doi: 10.1016/j.intimp.2010.09.011.
- [50] Ji D. B, Ye J, Li C. L, Wang Y. H, Zhao J, Cai S. Q. (2009). Antiaging effect of *Cordyceps sinensis* extract. *PhytotherRes.* 23:116–22.
- [51] Jiang Q, Lou Z, Wang H, Chen C (2019) Antimicrobial effect and proposed action mechanism of cordycepin against *Escherichia coli* and *Bacillus subtilis*. *J Microbiol* 57:288–297. <https://doi.org/10.1007/s12275-019-8113-z>
- [52] Jiang, Qi Zaixiang Lou, Hongxin Wang and Chen Chen. (2019). Antimicrobial effect and proposed action mechanism of cordycepin against *Escherichia coli* and *Bacillus subtilis*.
- [53] Jing Y., Cui X., Chen Z., Huang L., Song L., Liu T., Lv W., Yu R. Elucidation and Biological Activities of a New Polysaccharide from Cultured *Cordyceps militaris*. *Carbohydr. Polym.* 102:288–296. doi: 10.1016/j.carbpol.11.061.
- [54] Jo W.S., Choi Y.J., Mm H.J., Lee J.Y., Nam B.H., Lee J.D., Lee S.W., Seo S.Y., Jeong M.H. (2010). The Anti-Inflammatory Effects of Water Extract from *Cordyceps militaris* in Murine Macrophage. *Mycobiology.* 38:46–51. doi: 10.4489/MYCO.2010.38.1.046. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [55] Joshi M., Sagar A., Kanwar S.S., Singh S. (2019). Anticancer, Antibacterial and Antioxidant Activities of *Cordyceps militaris*. *Indian J. Exp. Biol.* 57:15–20.
- [56] Kaymakci MA, Güler EM. (2020). Promising Potential Pharmaceuticals from the Genus *Cordyceps* for COVID-19 Treatment: A Review Study. *Bezmialem Science.* 8(Supplement 3):140-4.
- [57] Khan MA, Tania M (2020) Cordycepin in anticancer research: Molecular mechanism of therapeutic effects. *Curr Med Chem* 27:983–996. <https://doi.org/10.2174/0929867325666181001105749>
- [58] Kim H.G., Shrestha B., Lim S.Y., Yoon D.H., Chang W.C., Shin D.-J., Han S.K., Park S.M., Park J.H., Park H. il. (2006). Cordycepin Inhibits Lipopolysaccharide-Induced Inflammation by the Suppression of NF-KB through Akt and P38 Inhibition in RAW 264.7 Macrophage Cells. *Eur. J. Pharmacol.* 545:192–199. doi: 10.1016/j.ejphar.2006.06.047.
- [59] Kim J., Lee H., Kang K.S., Chun K.-H., Hwang G.S. (2015). *Cordyceps militaris* Mushroom and Cordycepin Inhibit RANKL-Induced Osteoclast Differentiation. *J. Med. Food.* 18:446–452. doi: 10.1089/jmf.2014.3215. [PubMed] [CrossRef] [Google Scholar]
- [60] Lee D.-H., Kim H.-H., Lim D.H., Kim J.-L., Park H.-J. (2015). Effect of Cordycepin-Enriched WIB801C from *Cordyceps militaris* Suppressing Fibrinogen Binding to Glycoprotein IIB/IIIa. *Biomol. Ther.* 23:60. doi: 10.4062/biomolther.2014.086. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [61] Lee J.S., Kwon J.S., Won D.P., Lee K.E., Shin W.C., Hong E.K. (2010). Study on Macrophage Activation and Structural Characteristics of Purified Polysaccharide from the Liquid Culture Broth of *Cordyceps militaris*. *Carbohydr. Polym.* 82:982–988. doi: 10.1016/j.carbpol.2010.06.025. [CrossRef] [Google Scholar]

- [62] Li J., Zhang Z., Liu X., Wang Y., Mao F., Mao J., Lu X., Jiang D., Wan Y., Lv J.-Y., et al. (2015). Study of GABA in Healthy Volunteers: Pharmacokinetics and Pharmacodynamics. *Front. Pharmacol.* 6:260. doi: 10.3389/fphar.2015.00260. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [63] Lindequist U, Niedermeyer THJ, Julich WD. (2005). The pharmacological potential of mushrooms. *Evid Based Complement Alternat Med.* 2:285–299.
- [64] Liu J., Feng C., Li X., Chang M., Meng J., Xu L. (2016). Immunomodulatory and Antioxidative Activity of *Cordyceps militaris* Polysaccharides in Mice. *Int. J. Biol. Macromol.* 2016;86:594–598. doi: 10.1016/j.ijbiomac.02.009. [PubMed] [CrossRef] [Google Scholar]
- [65] Mao XB, Eksriwong T, Chauvatcharin S, Zhong JJ. (2005). Optimization of carbon source and carbon/nitrogen ratio for cordycepin production by submerged cultivation of medicinal mushroom *Cordyceps militaris* (2005) *Process Biochem.* 40(5):1667–1672.
- [66] Ministry of Health of the People's Republic of China (2009) The Ministry of Health on approval of *C. militaris* as new resources food announcement (Ministry of Health of the People's Republic of China, 2009 No. 3), 2009–3–16. (in Chinese)
- [67] Mirahmadi M., Azimi-Hashemi S., Saburi E., Kamali H., Pishbin M., Hadizadeh F. (2020). Potential Inhibitory Effect of Lycopene on Prostate Cancer. *Biomed. Pharmacother.* 129:110459. doi: 10.1016/j.biopha.2020.110459. [PubMed] [CrossRef] [Google Scholar]
- [68] Muszyńska B., Kała K., Rojowski J., Grzywacz A., Opoka W. (2017). Composition and Biological Properties of *Agaricus bisporus* Fruiting Bodies- a Review. *Polish J. Food Nutr. Sci.* 67:173–181. doi: 10.1515/pjfn-2016-0032. [CrossRef] [Google Scholar]
- [69] Muszyńska B., Mastej M., Sułkowska-Ziaja K. (2016). Biological Function of Carotenoids and Their Occurrence in the Fruiting Bodies of Mushrooms. *MIR.* 107:113–122.
- [70] Muszyńska B., Sułkowska-Ziaja K., Ekiert H. (2013). Phenolic Acids in Selected Edible Basidiomycota Species: *Armillaria mellea*, *Boletus badius*, *Boletus edulis*, *Cantharellus cibarius*, *Lactarius deliciosus* and *Pleurotus ostreatus*. *Acta Sci. Pol. Hortorum Cultus.* 12:107–116.
- [71] Oesterle A., Laufs U., Liao J.K. (2017). Pleiotropic Effects of Statins on the Cardiovascular System. *Circ. Res.* 120:229–243. doi: 10.1161/CIRCRESAHA.116.308537.
- [72] Olatunji OJ, Feng Y, Olatunji OO, Tang J, Ouyang Z, Su Z (2016) Cordycepin protects PC12 cells against 6-hydroxydopamine induced neurotoxicity via its antioxidant properties. *Biomed Pharmacother* 81:7–14. <https://doi.org/10.1016/j.biopha.2016.03.009>
- [73] Ontawong, A., Pengnet, S., Thim-Uam, A. et al. A randomized controlled clinical trial examining the effects of *Cordyceps militaris* beverage on the immune response in healthy adults. *Sci Rep* 14, 7994 (2024). <https://doi.org/10.1038/s41598-024-58742-z>
- [74] Park E.-S., Kang D.-H., Yang M.-K., Kang J.C., Jang Y.C., Park J.S., Kim S.-K., Shin H.-S. (2014). Cordycepin, 3'-Deoxyadenosine, Prevents Rat Hearts from Ischemia/Reperfusion Injury via Activation of Akt/GSK-3 $\beta$ /P70S6K Signaling Pathway and HO-1 Expression. *Cardiovasc. Toxicol.* 14:1–9. doi: 10.1007/s12012-013-9232-0. [PubMed] [CrossRef] [Google Scholar]
- [75] Park Yoon jin, Seoyoon Choi, Boyong Kim and Seung Gwan Lee. (2021). Article Effects of *Cordyceps militaris* Extracts on Macrophage as Immune Conductors. *Applied Sciences*: 11, 2206.
- [76] Qin P, Li X, Yang H, Wang ZY, Lu D (2019) Therapeutic potential and biological applications of cordycepin and metabolic mechanisms in cordycepin-producing fungi. *Molecules* 24:2231.
- [77] Qin Peng, Hui Yang, XiangKai Li and DengXue Lu. (2019). Therapeutic Potential and Biological Applications of Cordycepin and Metabolic Mechanisms in CordycepinProducing Fungi. *Molecules*, 24(12).
- [78] Rao Y.K., Fang S.-H., Wu W.-S., Tzeng Y.-M. (2010). Constituents Isolated from *Cordyceps militaris* Suppress Enhanced Inflammatory Mediator's Production and Human Cancer Cell Proliferation. *J. Ethnopharmacol.* 131:363–367. doi: 10.1016/j.jep.2010.07.020.
- [79] Reis F.S., Barros L., Calheta R.C., Ćirić A., van Griensven L.J.L.D., Soković M., Ferreira I.C.F.R. (2013). The Methanolic Extract of *Cordyceps militaris* (L.) Link Fruiting Body Shows Antioxidant, Antibacterial, Antifungal and Antihuman Tumor Cell Lines Properties. *Food Chem. Toxicol.* 62:91–98. doi: 10.1016/j.fct.2013.08.033.

- [80] Renzi-Hammond L, Bovier E., Fletcher L., Miller L., Mewborn C., Lindbergh C., Baxter J., Hammond B. (2017). Effects of a Lutein and Zeaxanthin Intervention on Cognitive Function: A Randomized, Double-Masked, Placebo-Controlled Trial of Younger Healthy Adults. *Nutrients*. 9:1246. doi: 10.3390/nu9111246.
- [81] Robinson D.R., Wu Y.-M., Lonigro R.J., Vats P., Cobain E., Everett J., Cao X., Rabban E., Kumar-Sinha C., Raymond V. (2017). Integrative clinical genomics of metastatic cancer. *Nature*. ;548:297.
- [82] Senkus K.E., Tan L., Crowe-White K.M. (2019). Lycopene and Metabolic Syndrome: A Systematic Review of the Literature. *Adv. Nutr.* 10:19–29. doi: 10.1093/advances/nmy069.
- [83] Shawkat H., Westwood M.-M., Mortimer A. (2012). Mannitol: A Review of Its Clinical Uses. *BJA Edu.* 12:82–85. doi: 10.1093/bjaceaccp/mkr063. [[CrossRef](#)] [[Google Scholar](#)]
- [84] Sheng Liu, Jian Tang, Lei Huang, Qirong Xu, Xiang Ling, Jichun Liu; (2015-07-24). *Cordyceps militaris* Alleviates Severity of Murine Acute Lung Injury Through miRNAs-Mediated CXCR2 Inhibition. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology*
- [85] Shrestha B, Sung JM. (2005). Notes on Cordyceps species collected from the central region of Nepal. *Mycobiology*. 33:235–239.
- [86] Singh R.S., Bhari R., Kaur H.P. (2010). Mushroom Lectins: Current Status and Future Perspectives. *Crit. Rev. Biotechnol.* 30:99–126. doi: 10.3109/07388550903365048. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [87] Smiderle F.R., Baggio C.H., Borato D.G., Santana-Filho A.P., Sasaki G.L., Iacomini M., van Griensven L.J.L.D. (2014). Anti-Inflammatory Properties of the Medicinal Mushroom *Cordyceps militaris* Might Be Related to Its Linear (1→3)-β-D-Glucan. *PLoS ONE*. 9:e110266. doi: 10.1371/journal.pone.0110266. [[PMC free article](#)] [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [88] Stringham N.T., Holmes P.V., Stringham J.M. (2018). Supplementation with Macular Carotenoids Reduces Psychological Stress, Serum Cortisol, and Sub-Optimal Symptoms of Physical and Emotional Health in Young Adults. *Nutr. Neurosci.* 21:286–296. doi: 10.1080/1028415X.2017.1286445. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [89] Takahashi S., Tamai M., Nakajima S., Kato H., Johno H., Nakamura T., Kitamura M. (2012). Blockade of Adipocyte Differentiation by Cordycepin. *Br. J. Pharmacol.* 167:561–575. doi: 10.1111/j.1476-5381.2012.02005.x. [[PMC free article](#)] [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [90] Tobert J.A. (1988). Efficacy and Long-Term Adverse Effect Pattern of Lovastatin. *Am. J. Cardiol.* 62:J28–J34. doi: 10.1016/0002-9149(88)90004-5. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [91] Tsai Yung-Jen, Lie-Chwen Lin, and Tung-Hu Tsai. (2010). Pharmacokinetics of Adenosine and Cordycepin, a Bioactive Constituent of *Cordyceps sinensis* in Rat. *J. Agric. Food Chem.* 2010, 58, 8, 4638–4643.
- [92] Tsimberidou A., Giles F., Duvic M., Fayad L., Kurzrock MD R. (2004). Phase II Study of Pentostatin in Advanced T-cell Lymphoid Malignancies: Update of an MD Anderson Cancer Center Series. *Cancer*. 100:342–349. doi: 10.1002/cncr.11899. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [93] Tuli H.S., Sandhu S.S., Sharma A.K. (2014). Pharmacological and Therapeutic Potential of *Cordyceps* with Special Reference to Cordycepin. *3 Biotech.* 4:1–12. doi: 10.1007/s13205-013-0121-9. [[PMC free article](#)] [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [94] Verma AK (2020) Cordycepin: a bioactive metabolite of *Cordyceps militaris* and polyadenylation inhibitor with therapeutic potential against COVID-19. *J Biomol Struct Dyn* 40:3745–3752.
- [95] Villares, A., Lafuente, A.G., Guillamón, E. and Ramos, A. 2012. Identification and quantification of ergosterol and phenolic compounds occurring in Tuber spp. truffles. *Journal of Food Composition and Analysis* 261(2): 177-182
- [96] Wang L, Zhang WM, Hu B, Chen YQ, Qu LH. (2008). Genetic variation of *Cordyceps militaris* and its allies based on phylogenetic analysis of rDNA ITS sequence data. *Fungal Divers.* 31:147–156
- [97] Wang L., Xu N., Zhang J., Zhao H., Lin L., Jia S., Jia L. (2015). Antihyperlipidemic and Hepatoprotective Activities of Residue Polysaccharide from *Cordyceps militaris* SU-12. *Carbohydr. Polym.* 131:355–362. doi: 10.1016/j.carbpol.2015.06.016. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]
- [98] Wang X, Xi D, Mo J, Wang K, Luo Y, Erbin X, Huang R, Luo SR, Wei J, Ren ZH, Pang H, Yang RR (2020) Cordycepin exhibits a suppressive effect on T cells through inhibiting TCR signaling cascade in CFA-induced inflammation mice model. *Immunopharmacol Immunotoxicol* 42:119–127. <https://doi.org/10.1080/08923973.2020.1728310>

- [99] Wang, Lihong, Ganghua Li, Xueqin Tian, Yitong Shang, Huanhuan Yan, Lihua Yao, and Zhihong Hu. 2024. "Research Progress in Understanding the Molecular Biology of *Cordyceps militaris*" *Fermentation* 10, no. 3: 167. <https://doi.org/10.3390/fermentation10030167>
- [100] Watzl B., Bub A., Briviba K., Rechkemmer G. (2003). Supplementation of a Low-Carotenoid Diet with Tomato or Carrot Juice Modulates Immune Functions in Healthy Men. *Ann. Nutr. Metab.* 47:255–261. doi: 10.1159/000072397. [PubMed] [CrossRef] [Google Scholar]
- [101] Weigand-Heller A.J., Kris-Etherton P.M., Beelman R.B. (2012). The Bioavailability of Ergothioneine from Mushrooms (*Agaricus bisporus*) and the Acute Effects on Antioxidant Capacity and Biomarkers of Inflammation. *Prev. Med.* 54:S75–S78. doi: 10.1016/j.ypmed.2011.12.028. [PubMed] [CrossRef] [Google Scholar]
- [102] Won K.-J., Lee S.-C., Lee C.-K., Lee H.M., Lee S.H., Fang Z., Choi O.B., Jin M., Kim J., Park T. (2009). Cordycepin Attenuates Neointimal Formation by Inhibiting Reactive Oxygen Species-Mediated Responses in Vascular Smooth Muscle Cells in Rats. *J. Pharmacol. Sci.* 109:403–412. doi: 10.1254/jphs.08308FP.
- [103] Won S.-Y., Park E.-H. (2005). Anti-Inflammatory and Related Pharmacological Activities of Cultured Mycelia and Fruiting Bodies of *Cordyceps militaris*. *J. Ethnopharmacol.* 96:555–561. doi: 10.1016/j.jep.2004.10.009.
- [104] Wong J.H., Ng T.B., Wang H., Sze S.C.W., Zhang K.Y., Li Q., Lu X. (2011). Cordymin, an Antifungal Peptide from the Medicinal Fungus *Cordyceps militaris*. *Phytomed.* 18:387–392. doi: 10.1016/j.phymed.2010.07.010.
- [105] Wu C., Guo Y., Su Y., Zhang X., Luan H., Zhang X., Zhu H., He H., Wang X., Sun G. (2014). Cordycepin Activates AMP-activated Protein Kinase (AMPK) via Interaction with the  $\Gamma 1$  Subunit. *J. Cell. Mol. Med.* 18:293–304. doi: 10.1111/jcmm.12187. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [106] Wu X.F., Zhang M., Li Z. (2019). Influence of Infrared Drying on the Drying Kinetics, Bioactive Compounds and Flavor of *Cordyceps militaris*. *LWT.* 111:790–798. doi: 10.1016/j.lwt.2019.05.108. [CrossRef] [Google Scholar]
- [107] Xiaolan Liu, Narasimha kumar, Kopparapu Yao, Li Yongping Deng, and Xiqun Zheng. (2017). Biochemical characterization of a novel fibrinolytic enzyme from *Cordyceps militaris*: 94, 793-801.
- [108] Yamatsu A., Yamashita Y., Pandharipande T., Maru I., Kim M. (2016). Effect of Oral  $\gamma$ -Aminobutyric Acid (GABA) Administration on Sleep and Its Absorption in Humans. *Food Sci. Biotechnol.* 25:547–551. doi: 10.1007/s10068-016-0076-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [109] Yang, T. Yaguchi, C.-R. Lim, Y. Ishizawa, T. Nakano, and T. Nishizaki, (2010). Tuning of apoptosis-mediator gene transcription in HepG2 human hepatoma cells through an adenosine signal. *Cancer Letters*:291. 225–229
- [110] Yang, T. Yaguchi, H. Yamamoto, and T. Nishizaki. (2007). Intracellularly transported adenosine induces apoptosis in HuH-7 human hepatoma cells by downregulating c-FLIP expression causing caspase-3/-8 activation. *Biochemical Pharmacology*, vol. 73, no. 10, pp. 1665–1675.
- [111] Ying X., Peng L., Chen H., Shen Y., Yu K., (2014). Cheng S. Cordycepin Prevented IL- $\beta$ -Induced Expression of Inflammatory Mediators in Human Osteoarthritis Chondrocytes. *Int. Ort.* 38:1519–1526. doi: 10.1007/s00264-013-2219-4. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- [112] Yong Tianqiao , Shaodan Chen , Yizhen Xie , Diling Chen , Jiyan Su , . Ou Shuai, Chunwei Jiao and Dan Zuo. (2018). Cordycepin, a Characteristic Bioactive Constituent in *Cordyceps militaris*, Ameliorates Hyperuricemia through URAT1 in Hyperuricemic Mice. *Front Microbiol*: 25, 9:58.
- [113] Yoon So Young, 1 Soo Jung Park, 2 and Yoon Jung Park. (2018). The Anticancer Properties of Cordycepin and Their Underlying Mechanisms *Int J Mol Sci.* 19(10):3027
- [114] Yu H.M., Wang B.-S., Huang S.C., Duh P.-D. (2006). Comparison of Protective Effects between Cultured *Cordyceps militaris* and Natural *Cordyceps sinensis* against Oxidative Damage. *J. Agric. Food Chem.* 54:3132–3138. doi: 10.1021/jf053111w. [PubMed] [CrossRef] [Google Scholar]
- [115] Yu R., Yang W., Song L., Yan C., Zhang Z., Zhao Y. (2007). Structural Characterization and Antioxidant Activity of a Polysaccharide from the Fruiting Bodies of Cultured *Cordyceps militaris*. *Carbohydr. Polym.* 70:430–436. doi: 10.1016/j.carbpol.2007.05.005.
- [116] Yu R., Yin Y., Yang W., Ma W., Yang L., Chen X., Zhang Z., Ye B., Song L. (2009). Structural Elucidation and Biological Activity of a Novel Polysaccharide by Alkaline Extraction from Cultured *Cordyceps militaris*. *Carbohydr. Polym.* 75:166–171. doi: 10.1016/j.carbpol.2008.07.023.
- [117] Yun Y, Han S, Lee S, Ko S, Lee C, Ha N, Kim K. (2003). Anti-diabetic effects of CCCA, CMES, and cordycepin from *Cordyceps militaris* and the immune responses in streptozotocin- induced diabetic mice. *Nat Prod Sci.* 9:291–298

- [118] Zhang D., Wang Z., Qi W., Lei W., Zhao G. (2014). Cordycepin (3'-Deoxyadenosine) down-Regulates the Proinflammatory Cytokines in Inflammation-Induced Osteoporosis Model. *Inflammation*. 37:1044–1049. doi: 10.1007/s10753-014-9827-z.
- [119] Zhang J., Wen C., Duan Y., Zhang H., Ma H. (2019). Advance in *Cordyceps militaris* (Linn) Link Polysaccharides: Isolation, Structure, and Bioactivities: A Review. *Int. J. Biol. Macromol.* 2019;132:906–914. doi: 10.1016/j.ijbiomac.04.020.
- [120] Zhang L, Chen SZ, Liu SS. (2006) Prosecutable function of *Cordyceps sinensis* extracts for hepatic mitochondrial oxidative injuries in diabetic mice. *Chin J Clin Rehabil*;10:132–4.
- [121] Zhang, H., Yang, J., Luo, S. *et al.* (2023). A novel complementary pathway of cordycepin biosynthesis in *Cordyceps militaris*. *Int Microbiol.* <https://doi.org/10.1007/s10123-023-00448-9>
- [122] Zheng Q, Sun J, Li W, Li S, Zhang K (2020) Cordycepin induces apoptosis in human tongue cancer cells in vitro and has antitumor effects in vivo. *Arch Oral Biol* 118:104846. <https://doi.org/10.1016/j.archoralbio.2020.104846>
- [123] Zhou X., Gong Z., Su Y., Lin J., Tang K. (2009). *Cordyceps* fungi: Natural products, pharmacological functions and developmental products. *J. Pharm. Pharmacol.* ;61:279– 291. doi: 10.1211/jpp.61.03.0002.