Cordyceps militaris (L.) Link: Chemical Bioactive Compounds and Pharmacological Activities

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Abstract: *Cordyceps militaris (L.) Link* is an important medicinal mushroom used in traditional medicine for treatment of many diseases and improving human health. *C. militaris* are now widely used in many modern pharmaceutical dosages. It contains many bioactive compounds such as cordycepin, adenosine, sterols, polysaccharides, etc. These compounds provided many beneficial biological activities such as anticancer, antiproliferative, pro-sexual, antioxidant, antibacterial, antifungal, antiviral, immunomodulatory, antiinflammatory and others for *C. militaris*. The present review highlights the chemical bioactive compounds and pharmacological activities of this medicinal mushroom *C. militaris*.

Keywords: *Cordyceps militaris*, cordycepin, bioactive compound, pharmacological activity, traditional medicine.

INTRODUCTION

There are various *Cordyceps* strains which have different cordycepin level, a most important compound in *Cordyceps* strains. One of the *Cordyceps* strains widely commercial and using in medicinal is *Cordyceps militaris (L.) Link* (Figure **1**). It has been used in traditional medicine consisted of dried fungus, is belonging to the genus *Cordyceps*, growing on the caterpillar. It is a parasite that grows on insects, or insect larvae. *C. militaris* contains various types of bioactive compounds including cordycepin, polysaccharides, ergosterol, mannitol, etc. It exhibits the tonic properties and many others important pharmacology. *C. militaris* is now used for multiple medicinal aims such as memory failure, antifatigue, motor function improving effects, diabetes, sexual impotence, anemia, illness, etc [1]. But there are still other clinical applications to discovery. There is a growing interested using of this material in medicinal functions nowadays. In this study, we summarize the chemical components and pharmacological activity of this precious material to give a detail view for using in medicine.

Chemical Bioactive Compounds

Many compounds of *C. militaris* have been isolated and elucidated the structures. Cordycepin (3'-deoxyadenosine), adenosine, ergosterol, polysaccharides. homocitrullyl aminoadenosine, 3'-amino-3'-deoxyadenosine and cordycepic acid, etc. have been discovered theirs presence in *C. militaris*. Table **1** summarized known bioactive compounds of *C. militaris*.

Figure 1: *Cordyceps militaris (L.) Link*.

Cordycepin

Cordycepin, 3′-deoxyadenosine (9-(3-deoxy-β-D-ribofuranosyl) adenine), a nucleoside analogue, has molecular formula $C_{10}H_{13}N_5O_3$, molecular weight 251.24, melting point 228°C–231°C (Figure **2**). Cordycepin is a main active compound of *C. militaris* [2]. It has been used as a valuable chemical marker for quality control of *Cordyceps* strains [3]. Cordycepin has been shown to exert potential therapeutic for the treatment of cancer and other diseases. Cordycepin has many intracellular targets such as nucleic acid,

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Table 1: Known Bioactive Compounds of *C. militaris*

Name	Molecular formula	Pharmacological activity
Cordycepin	$C_{10}H_{13}N_5O_3$	Anticancer, immunomodulatory, anti-inflammatory; antioxidant
Cordycepin triphosphate,	$C_{10}H_{16}N_5O_{12}P_3$	
Adenosine	$C_{10}H_{13}N_5O_4$	Antioxidant; anti-virus; antitumor
2'-deoxyadenosine	$C_{10}H_{13}N_5O_3$	
2'3'-dideoxyadenosine	$C_{10}H_{13}N_5O_2$	
Dimethylguanosine	$C_{12}H_{17}N_5O_5$	
3'-amino-3'-deoxyadenosine	$C_{10}H_{14}N_6O_3$	
6,7,2′,4′,5′-pentamethoxyflavone	$C_{20}H_{20}O_7$	
Ergosterol	$C_{28}H_{44}O$	Antibacterial, antifungal, antiviral, immunomodulatory
Ergosterol peroxide	$C_{28}H_{44}O_3$	
3- sitosterol	$C_{29}H_{50}O$	
Daucosterol	$C_{35}H_{60}O_6$	
Campeasterol	$C_{28}H_{48}O$	
Fatty acids (lauric acid, myristic acid, pentadecanoic acid, palmitoleic acid, palmitic acid, linoleic acid, oleic acid, stearic acid, docosanoic acid and lignoceric acid)		Reduce the blood lipids and preventing the cardiovascular disease.
Polysaccharides (mannose, galactose, glucose ; glucogalactomannan; CPS-2, CPS-3, CPS-4 and CPS-5		Antitumor, anti-influenza virus, hypoglycemic, antioxidant, anti-inflammatory, immunomodulator, hypocholesterolemic
Proteins (lysine; methionine; amino acids of glutamic acid and aspartic acid; tyrosine)		Antifungal and anticancer activities; nutrient and effective ingredients.

apoptosis and cell cycle. The structure of cordycepin is similar to the adenosine, a cellular nucleoside. Therefore it can act as a nucleoside analogue. The main mechanism of cordycepin is to inhibit purine biosynthesis pathway. Cordycepin also induces RNA or DNA chain termination and interacts with receptors for mTOR which has an important role in the regulation of protein synthesis. Cordycepin is converted into 5'mono-, di- and tri-phosphates and can inhibit the activity of ribose-phosphate, pyrophosphokinase and 5-phosphoribosyl-1-pyrophosphate amidotransferase enzyme which play important role in biosynthesis of purines [4]. Cordycepic acid is also a principal bioactive compound of *C. militaris*. The structure was identified first as 1,3,4,5-tetrahydroxycyclohexane-1-carboxylic acid. Later, this compound was crystallized and identified as d-mannitol. It is used in the anti-aging nutritional supplement and also for pro-sexual [5].

Adenosine

Adenosine (molecular formula $C_{10}H_{13}N_5O_4$) (Figure **3**) has an important role in many biochemical processes in the cell. It is also the main nucleoside in *C. militaris*. Many other adenosine analogues such as 2'-deoxyadenosine, 2'3'-dideoxyadenosine, cordycepin

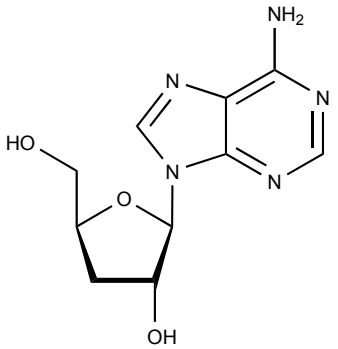

Figure 2: Chemical structure of cordycepin.

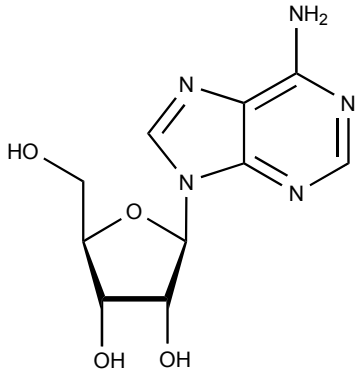

Figure 3: Chemical structure of adenosine.

triphosphate, and 3'-amino-3'-deoxyadenosine also were found in *C. militaris*. Jiang *et al*., have isolated 6,7,2′,4′,5′-pentamethoxyflavone (molecular formula $C_{20}H_{20}O_7$) and dimethylguanosine (molecular formula $C_{12}H_{17}N_5O_5$) from fruiting bodies of *C. militaris* by using the macroporous adsorption resin and HPLC method. They also showed the antioxidant and HIV-1 protease inhibiting activities of these compounds. These compound may counteract the oxidative stress process and be suggested as drug for the treatment of AIDS [6].

Polysaccharides

C. militaris contains large amount of polysaccharides, may be in the range of 3–8% of the total weight. Polysaccharides attribute for *C. militaris* various biological activities such as antitumor, anti-influenza virus, immunopotentiation, hypoglycemic, hypocholesterolemic, and antioxidant effects. Some polysaccharides such as mannose, galactose, and glucose have been reported present in *C. militaris*. Furthermore, other authors have isolated some different polysaccharides. Fhernanda *et al*., have isolated glucogalactomannan from 5% KOH solution *OF* dried *C. militaris* fruiting bodies [7]. Wang *et al.,* have proposed a method hydrothermal refluxing extraction to extract both cordycepin and polysaccharides in *C. militaris*. This method provided the highest yield of cordycepin and polysaccharide extraction. The extraction was run three times with the raw material-water ratio at 1/10 and each time of 90 minutes [8]. In addition, Rongmin Yua *et al*., also have isolated four polysaccharides named as CPS-2, CPS-3, CPS-4 and CPS-5 from the water extract of cultured *C. militaris* by using ethanol precipitation, deproteination and gel-filtration chromatography methods [9].

Sterols

C. militaris contain many sterol-type compounds such as ergosterol (Figure **4**), δ-3ergosterol, ergosterol peroxide, 3- sitosterol, daucosterol, campeasterol. They are an important precursor to vitamin D2 [10]. Li

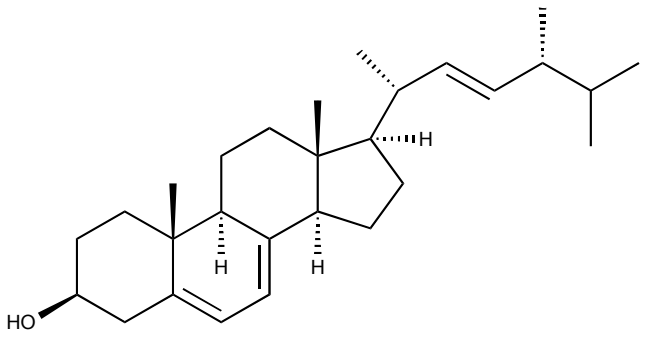

Figure 4: Chemical structure of ergosterol.

et al., have developed a method for the simultaneous determination of ergosterol, nucleosides and their bases from natural and cultured *Cordyceps* strains by using pressurized liquid extraction and high-performance liquid chromatography [11].

Fatty Acids

Cordyceps strains can contain the level of the unsaturated fatty acid up to 57.84% and the saturated fatty acid up to 42.16% [12]. The fatty acids present in *Cordyceps* strains such as lauric acid, myristic acid, pentadecanoic acid, palmitoleic acid, palmitic acid, linoleic acid, oleic acid, stearic acid, docosanoic acid and lignoceric acid have been identified and quantified [13]. Kwan-Won *et al.,* have shown a large quantity of essential fatty acids, including linolenic acid (31.9%) and linoleic acid (12.3%), and unsaturated fatty acid of oleic acid (33.8%) in the freeze-dried stromata of *C. militaris* [14]. The fatty acids can reduce the blood lipids and are helpful in preventing the cardiovascular disease.

Proteins

C. militaris also have high amount of crude protein, up to 11.5% in the freeze-dried stromata. Kwan showed *C. militaris* has a high ratio of the essential amino acids, such as lysine (101.2 mg/g), methionine (62.7 mg/g), and acidic amino acids of glutamic acid (57.5 mg/g) and aspartic acid (43.9 mg/g), a low of tyrosine content (4.7 mg/g) [14].

Pharmacological Activity

Many studies have shown that the extracts of *C. militaris* have various pharmacological actions, including anticancer, antitumor, antileukemic, antiproliferative, pro-sexual, antioxidant, antibacterial, antifungal, antiprotozoal, antiviral, immunomodulatory, antiinflammatory and so on. Therefore, *C. militaris* may be one of the most important medicinal material used in future for human's health [4].

Anticancer/Antitumor/Antileukemic/ Antiproliferative

C. militaris is a traditional medicine for patients suffering from cancer in Asia. Bizarro *et al.,* have studied the anti-cancer activity and mechanism of methanolic extract of *C. militaris* fruiting body using the non-small cell lung cancer cell line (NCI-H460). They have shown that the extract inhibited cellular proliferation, induced cell cycle arrest at G0/G1 and increased apoptosis. The *C. militaris* extract enhanced the expression of the levels of p53 and p21 proteins,

also increased the p-H2A.X and 53BP1 levels, together with an increase in the number of 53BP1 foci/cell, and showed a DNA damage of cancer cell [15]. Moreover, Lin *et al.,* has shown *C. militaris* were cultured *Radix astragali* as the medium had a better anti-tumor activity than that culturing in synthetic medium. *C. militaris* showed to inhibit the growth of four tumor cells *in vitro* including human gastric cancer AGS cells with IC_{50} of 465 μg/mL, human breast cancer MCF-7 cells with IC_{50} of 37 μg/mL, human hepatocellular carcinoma Hep G2 cells with IC_{50} of 25 μg/mL, and murine colorectal adenocarcinoma CT26 cells with IC_{50} of 20 μg/mL. *In vivo*, tumor volume and tumor weight were reduced in CT26 cells-induced tumor BALC/c mice by the *C. militaris* treatment [16]. Jie *et al.,* reported that *C. militaris* may inhibit the growth of the tumor, prolong the survival period of mice implanted with S180, inhibit the growth and metastasis of Lewis pneumonic cancer in the implanted mice [17]. In addition, Park C *et al.,* have reported the strong antileukemic of aqueous extract of *C. militaris* in human leukemia U937 cells. They found that aqueous extract of *C. militaris* suppressed cell growth of U937 cells in a dose-dependent manner. The cells were changed morphological, formation of DNA fragmentation and induced the apoptosis. The anti-apoptotic Bcl-2 expression was down-regulated and caspase-3 was activated in U937 cells treated with *C. militaris*. Moreover, *C. militaris* inhibited the cyclooxygenase-2 and prostaglandin E2. This explained that *C. militaris* be effected in human leukemia treatment [18]. The methanolic *C. militaris* extract can inhibit the proliferation of different cell lines such as MCF-7 (breast with IC_{50} value of 90.11 μg/mL), NCI-H460 (non-small lung with IC_{50} value of 47.79 μg/mL), HCT-15 (colon with IC_{50} value of 72.57 μg/mL) and HeLa (cervical human carcinoma, with IC_{50} value of 66.32 μg/mL [19]. The polysaccharide (CMP-1) which was isolated by Yongshuai Jing which has an average molecular weight of 4.3 kDa, also significantly stimulated the mouse splenocyte proliferation. Furthermore, CMP-1 also inhibited the proliferation of HT-29 (IC_{50} 137.66 μg/mL), HeLa (IC_{50} 162.59 μg/mL), HepG2 (IC_{50} 176.29 μg/mL) and K562 (IC_{50} 364.01 μg/mL) cells line [20].

Antioxidant

The methanolic *C. militaris* extract showed strong antioxidant activity. Filipa *et al*., reported that the methanolic extract of *C. militaris* has EC_{50} value for lipid peroxidation inhibition of 1.05 mg/ml; EC_{50} value of 12.17 mg/ml by DPPH radical-scavenging assay and total phenol content by Folin–Ciocalteu assay was equivalent to 15.04 mg gallic acid/g extract. The antioxidant activity of *C. militaris* may be due to the presence of some compound such as d-tocopherol or p-hydroxybenzoic acid which provides its antioxidant activity [19]. Other authors showed that a water-soluble polysaccharide, P70-1, was isolated from the fruiting bodies of cultured *C. militaris*. This polysaccharide has a backbone of (1→6)-linked β-d-mannopyranosyl residues. P70-1 possesses hydroxyl radical-scavenging activity with an IC_{50} value of 0.548 mg/ml, showed high antioxidant activity [21]. Additionally, the polysaccharide CMP-1 also exhibited strong antioxidant activity. This compound demonstrated free radical-scavenging effects, ferrous ions-chelating ability and reducing power [20].

Immunomodulatory/Anti-Inflammatory

C. militaris has been shown to possess immunomodulatory activity *in vitro* and *in vivo*. *C. militaris* extract may induce the production of proinflammatory cytokines IL-1β, IL-6, TNF-α, and PGE2, nuclear transcription factor, NF-κB, and the expression of co-stimulatory molecules such as ICAM-1, B7-1 and B7-2 in macrophages [22]. *C. militaris* extract also augmented the production of NO and induced the protein levels of iNOS, COX-2 [22]. Ohta *et al*., isolated a new polysaccharide (named APS) from *C. militaris* extract, which showed to increase the expression of TNF-α and IFN-γ levels in mice. This polysaccharide increased nitric oxide (NO) production and iNOS mRNA and protein expressions in RAW 264.7 murine macrophage cells. Also mRNA expression of cytokines including IL-6, IL-10, IL-1β and TNF-α was increased. These data demonstrated the immunomodulatory of macrophages of APS [23]. Additionally, Jong Seok Lee showed the immuno-stimulating of polysaccharides isolated from fruiting body of *C. militaris* in macrophages. They demonstrated that *C. militaris* can increase the expression of NO, ROS, TNF-α and phagocytic uptake in mouse peritoneal macrophages and RAW264.7 macrophages. Macrophages were activated by *C. militaris* may be via NF-κB and MAPKs pathways. Moreover, they showed that *C. militaris* inhibited *in vivo* growth of melanoma in mouse [24]. *C. militaris* also exhibited the anti-inflammatory effects on a murine model of acute colitis. *C. militaris* extract significantly decreased the DSS-induced DAI scores including body weight loss, diarrhea, gross bleeding. In addition, *C. militaris* extract also suppressed iNOS and TNF-α mRNA expression in colon tissue of DSS-induced colitis and in LPS-stimulated RAW264.7 cells. These authors suggested *C. militaris* may be a promising drug

for prevention and treatment of inflammatory bowel diseases by its down-regulating production and expression of inflammatory mediators ability [25]. In another study, BALB/c mice were induced asthma by intraperitoneal and intranasal ovalbumin. Mice were administered *C. militaris* significantly reduced airway inflammation less effectively than prednisolone or montelukast [26]. Moreover, So-Young Won *et al*., have studied the anti-inflammatory of the 70% ethanolic extracts of cultured mycelia and fruiting bodies of *C. militaris*. Both extracts exhibited strong topical antiinflammatory activity in the croton oil-induced ear edema in mice. Additionally, cultured mycelia extract can inhibit the acute anti-inflammatory in carrageenin-induced edema mice model. The cultured mycelia extract of *C. militaris* inhibited the NO production and iNOS expression in RAW 264.7 cells stimulated by lipopolysaccharide in a dose-dependent manner [27].

Antibacterial/ Antifungal/ Antiprotozoal/Antiviral

The methanolic extract of *C. militaris* showed strong antibacterial activity against *Bacillus cereus* (MIC- 0.015 mg/ml; MBC- 0.03 mg/ml) and *Pseudomonas aeruginosa* (MIC- 0.015 mg/ml; MBC- 0.03 mg/ml). *Salmonella typhimurium* showed to be resistant with antibacterial effect of the extract (MIC- 3.00 mg/ml; MBC- 6.25 mg/ml). Antibacterial of *C. militaris* was stronger than streptomycine and ampicilline against *Bacillus cereus* and *Pseudomonas aeruginosa* [19].

A cytotoxic antifungal protease protein was isolated from the dried fruiting bodies of *Cordyceps militaris* using anion-exchange chromatography. This protein called *C. militaris* protein (CMP), has shown to inhibit the serine protease. It exerts strong antifungal effect against the growth of the fungus *Fusarium oxysporum*. Furthermore, it showed cytotoxicity against human breast and bladder cancer cells [28]. Cordymin, an antifungal peptide, was purified from the medicinal mushroom *C. militaris*. Cordymin exerts antifungal activity against several fungal species including *B. maydis*, *M. arachidicola* and *R. solani*. It is noted that the antifungal potency of cordymin is higher than that of many antifungal proteins. Cordymin also reduced the proliferation of MCF-7 breast cancer cells. Moreover, cordymin inhibits the activity of HIV-reverse transcriptase IC_{50} of 55 μM. The mechanism of inhibition probably involves protein–protein interaction [29]. Filipa *et al*., also have shown the strong antifungal of the methanolic extract of *C. militaris* fruiting body on *Aspergillus fumigatus, Aspergillus ochraceus, Aspergillus versicolor, Aspergillus niger* about (MIC- 0.04 mg/ml); on *Penicillium funiculosum*, *Penicillium ochrochloron* and *Trichoderma viride* (MFC- 0.17 mg/ml). The antifungal activity of *C. militaris* extract was stronger than two drugs used as bifonazole and ketoconazole [19]. Trigg *et al*., have shown the strong inhibition growth effects of cordycepin on cultures of the erythrocytic stages of *Plasmodium knowlesi* incubated *in vitro*. At very low concentrations (10 μM), cordycepin inhibited the growth *in vitro* of the parasite after incubating for 4 hours. The mechanism may be related to partially prevent by adenosine synthesized and no effect on the host red cell [30].

Hwan Hee Lee showed anti-influenza effects of Cordyceps extract using a DBA/2 mouse model. Mice were pretreated with *Cordyceps* extract then intranasally infected with 2009 pandemic influenza H1N1 virus. The DBA/2 mouse was highly susceptible to H1N1 virus infection. They showed that Cordyceps extract provided strong an antiinfluenza effect on mice. The mice were treated with extract shown stable body weight and reduced mortality. The antiviral activity of *C. militaris* extract on influenza infection may be mediated by increasing of IL-12 expression and production of NK cells [31]. Other authors have shown that an acidic polysaccharide isolated from the extract of *C. militaris* can inhibit the influenza A virus titers. This acidic polysaccharide was intranasally administered, and is reduced virus titers of mice infected with influenza A virus in the bronchoalveolar lavage fluid and the lung and also enhanced survival rate [23].

Pro-Sexual

Traditional medicine has used Cordyceps species for improving the sexual function. Wen-Hung Lin *et al.,* have shown the spermatogenic effect of *C. militaris*. These authors administered the diet supplemented with *C. militaris* mycelium to subfertile boars for 2 months. The sperm production was increased significantly in boars fed with diet contained *C. militaris* extract in both quality of fertile sperm and the quantity of semen volume and total sperm number. They also detected the cordycepin in plasma in boars supplemented with *C. militaris*. More interesting, an amount of motile sperm cells and sperm morphology were also enhanced significantly [32].

Anti-Fatigue

The tonic effect of *C. militaris* has been reported in traditional medicine. Jung *et al*., investigated the tonic effect of *C. militaris* on the forced swimming capacity and the change of biochemical parameters in mice.

They showed that the mice were fed with *C. militaris* extract had the swimming times to exhaustion longer. These mice also have lower the plasma triglyceride levels [33].

Anti-Diabetic

C. militaris extract also have an antidiabetic effect. Soo Bong Choi *et al.,* have shown the effect of *C. militaris* extract on the insulin secretion and insulin resistance. These authors reported that the extract reduced the fasting serum glucose levels, improved insulin resistance by enhancing glucose utilization in skeletal muscles and increased the insulin secretion in 90% pancreatectomized male Sprague Dawley rats [34].

CONCLUSION

As we have summarized in this review, *C. militaris* has many beneficial pharmacological activities for human health such as anticancer, antitumor, immunomodulatory, antioxidant, anti-pathogenic activities, etc. The bioactive compounds responsible for these pharmacological activities have been identified. They are cordycepin, adenosine, polysaccharides, sterols and other more. It is now very needed to elucidate the chemical structures of the remaining bioactive compounds principles and discovery other pharmacology activity of *C. militaris.*

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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