

Exploring the multifaceted chemical composition and applications of *Cordyceps militaris*: A comprehensive review

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Abstract

Cordyceps militaris, a medicinal fungus of the phylum Ascomycota, is renowned for its diverse therapeutic applications and traditional use in Asian medicine. Rich in bioactive compounds such as cordycepin, polysaccharides, and ergosterol, it exhibits significant pharmacological properties, including anticancer, immunomodulatory, and adaptogenic effects. Its ability to inhibit tumor growth, combat oxidative stress, enhance immunity, and regulate metabolic health underscores its potential as a powerful medicinal agent. Cultivated *C. militaris* serves as a sustainable and commercially viable alternative to its ecologically constrained counterpart, *Cordyceps sinensis*, demonstrating higher concentrations of therapeutic compounds. Advances in cultivation techniques have enabled a steady supply of *C. militaris*, optimizing its bioactivity and broadening its medicinal applications. Research highlights its contributions to fertility enhancement, cholesterol regulation, anti-inflammatory responses, and neuroprotection. Additional properties such as entomopathogenic and antimicrobial activities further enhance its value, offering eco-friendly solutions for pest and disease control. Compounds like ergothioneine, carotenoids, and selenium-enriched extracts contribute to its antioxidative and cardiovascular benefits. With its broad-spectrum efficacy and sustainable production, *C. militaris* bridges traditional and modern medicine, providing a versatile and effective approach to addressing diverse health challenges, including cancer, diabetes, cardiovascular disorders, and inflammation.

Keywords: Bioactive compounds, anticancer properties, immunomodulation sustainable cultivation, therapeutic applications, entomopathogen

Introduction

Cordyceps militaris, a member of the Ascomycota phylum, has drawn considerable scientific interest due to its noteworthy medicinal properties (figure 1). Historically recognized for its bioactive components, *C. militaris* has been utilized for immune system stimulation, adaptogenic and tonic effects, reduced fatigue, and increased physical endurance in traditional Asian medicine, particularly in China [1]. Cultivating *C. militaris in vitro* presents an achievable alternative to *Cordyceps sinensis*, which has difficulties in natural collection and cultivation. This provides a sustainable source for both commercial applications and research [2].

Research in growing *C. militaris* has increased due to the growing demand for Cordyceps spp. and the difficulties in gathering *C. sinensis* from the wild. Compared to *C. sinensis*, which is difficult to grow *in vitro* because of its particular ecological requirements, *C. militaris* grows well in controlled environments. Because of this, *C. militaris* is a desirable substitute for use in both educational and industrial settings. *C. militaris* may be grown *in vitro*, which guarantees a steady supply and optimizes the number of bioactive compounds it contains, increasing its potential as a medicine [3].

Traditionally, China, Tibet, Nepal, and India have used Cordyceps species including *C. militaris* in their traditional medical practices. Because they could assist people in adapting to the severe conditions of high-altitude environments such as cold temperatures, high air pressure, and low oxygen levels—these mushrooms were especially

prized. Many conditions, including infections, cancer, diabetes, concerns with the liver and kidneys, respiratory and cardiovascular disorders, and sexual dysfunction, have been treated using cordyceps spp. in traditional Chinese medicine. Essentially an entomopathogenic fungus, *C. militaris* parasitizes insect larvae, particularly those belonging to the Lepidoptera species. Throughout its life cycle, the fungus infects host larvae, consuming their internal tissues and eventually developing fruiting bodies that emerge from the larval's remains. The intricacy of its natural harvesting is increased by this special parasitic relationship and the particular ecological conditions necessary for its growth, which are generally found in high-altitude Himalayan locations [4].

Diverse bioactive compounds have been found in *C. militaris*, including glycoproteins, mannitol, ergosterol, polysaccharides, nucleosides (specifically cordycepin), along peptides containing α -aminoisobutyric acid. *C. militaris* has immunomodulatory and anticancer properties due to the presence of polysaccharides, thereby rendering it a useful tool in medicine.

Recent scientific investigations have thoroughly explored the pharmacological characteristics of *C. militaris* in addition to the active chemical components of the plant [5]. Studies have shown that in comparison with naturally occurring *C. sinensis*, *C. militaris* cultivated *in vitro* has a higher content of polysaccharides and cordycepin. This demonstrates that *C. militaris* is a potent replacement for medicinal uses. Numerous medical benefits of *C. militaris* have been demonstrated by research, including the capacity

to inhibit the formation of tumors, lessen inflammation, increase immunity, and enhance metabolic health. Additionally, *C. militaris* has shown promise in neuroprotection and renal protection, broadening the range of potential therapeutic applications [6].



Fig 1: Fully grown *Cordyceps militaris* A. Inside the culture bottle, B. Outside the culture bottle.

As a whole, *C. militaris* is an important advance in the field of medicinal fungus, providing a viable and effective substitute for *Cordyceps sinensis*. It is an important tool for both conventional and modern medicine because of its rich composition of bioactive chemicals and variety of pharmacological effects. In addition to satisfying the increasing demand for this medicinal fungus, the capacity to grow *C. militaris in vitro* enables the optimization of its advantageous characteristics, guaranteeing its continuous relevance and usefulness in therapeutic applications [8].

Chemical composition

1. Nucleosides

Numerous nucleosides, including adenosine, guanosine, cytidine, uridine, adenine, and uracil, are found in *Cordyceps militaris*. Since it can drastically lower the release of neurotransmitters in the central nervous system, adenosine stands out among almost all compounds [9]. One neural modulator of movement, sleep cycles, and seizure susceptibility is adenosine. It is also a neuroprotective and analgesic when administered pharmacologically. Adenosine receptor subtypes that exist in blood arteries have a major impact on peripheral circulation when their receptors are activated [10].

An extensive bioactive metabolite called cordycepin (3'-deoxyadenosine) has been identified in the fermented broth of *C. militaris*. It exhibits a variety of biological actions, such as antiviral, antibacterial, antifungal, anticancer, and immunoregulatory properties [11]. In alloxan-induced diabetic mice, cordycepin has been demonstrated to have antidiabetic effects by lowering blood glucose and glucose tolerance levels. This may be achieved via downregulating diabetes-related genes and suppressing the production of proinflammatory cytokines. Its ability to alleviate cardiovascular illnesses is further enhanced by its anti-hyperlipidemic activity, which is demonstrated by its inhibition of Acetyl CoA carboxylase, reduction of fatty acid production, and activation of AMP kinase. Furthermore, cordycepin's ability to enhance cytokine release and proliferation in peripheral blood mononuclear cells (PBMCs) indicates its immunomodulatory potential [12].

Investigations have shown that the presence of pure bioactive components from *C. militaris* reduces the synthesis of anti-ds-DNA and raises the possibility that

lupus mice would survive. Furthermore, cordycepin has antiosteoporotic effects by restoring bone loss in osteopenic rat models, increasing osteocalcin levels, reducing oxidative stress, and lowering markers of bone resorption. Its potential for treating kidney failure, cancer, breathing disorders, arthritis, and infertility issues is highlighted by its anti-inflammatory, anti-hyperuricemic, antioxidant, and antiparasitic action against malarial parasites in mice [13].

2. Mannitol

Cordyceps militaris is known for producing D-mannitol, also known as cordycepic acid, which is categorized as a polyhydric alcohol (polyol). Since it stores carbohydrates and facilitates the faster transportation of several chemicals both necessary for osmoregulation and the modulation of metabolic pathways D-mannitol is an essential constituent of *C. militaris* [16]. Because of its osmotic properties, d-mannitol is frequently utilized in therapeutic settings as an anti-edematous and diuretic medication. The chemical has the potential to be used in medicine, particularly for the treatment of cerebral edema and other problems affecting osmotic regulation, as demonstrated by its capacity to efficiently lower intracranial pressure and induce diuresis [17].

3. Polysaccharides

Polysaccharides in particular, which have more complex structures, are synthesized by *Cordyceps militaris*. These polysaccharides are categorized as extracellular polysaccharides (EPS) or intracellular polysaccharides (IPS) based on where in the hyphal cells they biosynthesize. Some of the factors influencing the highly variable chemical structure of polysaccharides extracted from the *C. militaris* mycelium are the precise types of monosaccharides that make the constituent polysaccharides, the linear sequence in which these monosaccharides are linked, the three-dimensional spatial configuration of the polysaccharide chains, the specific positions of glycosidic bonds between the monosaccharide units, and the degree of branching or cross-linking within the polysaccharide chains [18].

The observed differences in the chemical structure of polysaccharides from *C. militaris* can be attributed to several factors. These consist of the fungus's location of origin, the cultivation conditions and practices, and the extraction techniques deployed. The molecular weight, spatial conformation, type of glycosidic bond, and degree of branching (cross-linking) of the polysaccharide are all significantly influenced by these parameters. Significant differences have been found in the chemical structure and the qualitative and quantitative content of monosaccharides derived from polysaccharide fractions of *C. militaris* when compared to specimens grown in natural conditions against those cultivated in laboratories [19].

4. Amino Acids

Amino acid composition in *Cordyceps militaris* provides insights into its nutritional and medicinal properties. Analyzing the amino acids helps in understanding the biochemical complexity and potential health benefits of this fungus. The fruiting bodies also include non-proteinogenic amino acids including ergothioneine and GABA in addition to proteinogenic amino acids [20].

Ergothioneine

According to Tuli *et al.* (2014) [22], the mycelium of *Cordyceps militaris* has approximately 130.6 mg/kg dry weight, whereas the fruiting bodies contain 782.3 mg/kg dry weight of the life form. Various measurements indicate that the fruiting bodies contain a concentration of 409.8 µg/g dry weight [23]. Ergothioneine supplementation (at levels of 5 mg/day and 25 mg/day) correlated with a slight decrease in oxidative stress indicators in research including healthy volunteers aged 21-35. Ergothioneine's antioxidant capacity may be important in situations when oxidative stress is likely to occur, such as during physical activity or inflammatory diseases [24].

Carotenoids

Numerous fungus species, including *Cordyceps militaris*, have been shown to contain carotenoids in their fruiting bodies, including derivatives of xanthophyll. The distinctive yellow-orange coloration seen in *C. militaris* fruiting bodies is caused by these carotenoids. *C. militaris* contains four main xanthophylls: lutein, zeaxanthin, lycopene, and β-carotene [25].

The fruiting bodies of *Cordyceps militaris* are known to contain β-carotene and lycopene, both of which are recognized for their potential health benefits. Dietary sources rich in β-carotene, such as carrots, and lycopene, such as tomatoes, have been linked to improved immune function and support for therapies in certain diseases. However, the effects of β-carotene supplementation remain controversial, with studies reporting varying outcomes ranging from potential cancer prevention to increased risks at high doses. Lycopene, on the other hand, has shown promise in enhancing cardiovascular health, mitigating metabolic syndrome, and supporting cancer therapies [26]. *Cordyceps militaris* fruiting bodies have also been found to contain a unique class of carotenoids called cordyxanthins. These carotenoids exhibit greater water solubility compared to conventional ones like lutein, zeaxanthin, β-carotene, and lycopene. This increased solubility is attributed to their distinct chemical structure, characterized by more hydroxyl groups and fewer lipophilic methyl groups. Such properties may enhance their bioavailability and broaden their potential applications in health and nutrition [27].

Statins

The fruiting bodies of *Cordyceps militaris* are a natural source of lovastatin, a widely used statin for lowering cholesterol levels. Originally discovered in *Aspergillus terreus*, lovastatin inhibits cholesterol biosynthesis by targeting HMG-CoA reductase, a key enzyme in the pathway. After enzymatic conversion to its active hydroxy acid form, lovastatin competitively blocks the conversion of HMG-CoA to mevalonate, a critical precursor in cholesterol production. Beyond managing hypercholesterolemia and slowing the progression of coronary atherosclerosis, lovastatin exhibits pleiotropic effects, including protection of the vascular endothelium, further expanding its therapeutic potential. Isolated from *C. militaris* fruiting bodies, pentostatin functions as an adenine deaminase inhibitor and is an analogue of the purine base hypoxanthine. It has been identified as a chemotherapeutic drug used in hematology and oncology for the treatment of cancer and demonstrates anticancer and immunosuppressive properties [28].

Phenolic Compounds

Mushrooms, including *Cordyceps militaris*, are abundant in bioactive compounds such as flavonoids and phenolic acids, recognized for their potent antioxidant properties. Phenolic acids like vanillic and caffeic acids are notable for their strong antioxidative effects, while militarinones, distinct alkaloids found in *C. militaris*, possess cytotoxic and antimicrobial properties due to their unique chemical structures. Additional phenolic compounds, such as p-hydroxybenzoic, gallic, and protocatechuic acids, contribute to antiviral, antibacterial, antifungal, anti-inflammatory, and antioxidative activities [29].

The flavonoid content in *C. militaris* varies significantly depending on its form. Fruiting bodies contain approximately 1.56 mg/g of flavonoids, while mycelium and fruiting bodies show higher levels at 2.26 mg RE/g and 5.54 mg RE/g, respectively. Aqueous extracts of *C. militaris* exhibit notably higher concentrations of flavonoids (275.52 mg/g) and polyphenols (19.79 mg/g) compared to fresh fruiting bodies, highlighting the influence of extraction processes on bioactive compound levels [30].

Vitamins

Moreover, the fruiting bodies of *C. militaris* exhibit water-soluble vitamins B2, B3, and C together with fat-soluble vitamins A and E [34]. Vitamins B2 and B3, riboflavin, and niacin, aid in the metabolism of energy and reduce weariness. Vitamin C enhances iron absorption in addition to boosting collagen formation, immune system support, and cell protection against oxidative stress. Vitamin A is necessary for cell specialization and eyesight, while Vitamin E protects cells from oxidative damage [31].

1. Other Bioactive Compounds

Glycoproteins, or proteins with coupled carbohydrate groups, essentially make up the lectins present in the fruiting bodies of *Cordyceps militaris*. By attaching to sugar residues on cell membranes, these lectins display mitogenic activity by inducing cell agglutination. Beauveriolides are a noteworthy class of cyclodepsipeptides found in *C. militaris* that are distinguished by their complex molecular structure. It has been demonstrated that beauveriolides can lower β-amyloid levels and have antiatherosclerotic qualities [32].

Additionally, *Cordyceps militaris* is a potential dietary supply of magnesium, potassium, selenium, and sulfur due to its notable quantities of these vital bio elements. According to [33], Zhan *et al.* (2019), *C. militaris* contains organic selenium that is linked to amino acids such as L-methionine (as selenomethionine) and L-cysteine (as selenocysteine) to generate methyl-selenocysteine. It has been demonstrated that adding selenium specifically, sodium selenate to the growth medium improves its content of bioactive substances such as amino acids, polysaccharides, nucleosides, and organic selenium.

Applications

1. Anticancer property

Cancer continues to pose a significant global health challenge, necessitating the development of innovative and more effective therapeutic strategies. Cordycepin, a bioactive compound derived from *Cordyceps militaris*, has gained attention in pharmacognosy for its potential in treating various diseases, including cancer, SARS, AIDS, and swine flu. Analytical techniques such as SDS-PAGE

electrophoresis and gel filtration have demonstrated cordycepin's capacity to inhibit the viability of human cancer cells [34]. One key mechanism underlying the anticancer properties of *C. militaris* involves the A3 adenosine receptor (A3 AR), which is highly expressed in cancer and inflammatory cells while remaining minimally expressed in normal cells. Modulation of this receptor plays a critical role in cancer therapy, further supporting the therapeutic potential of cordycepin in managing malignancies [35].

2. Antioxidant property

The diverse range of polysaccharides found in *Cordyceps militaris* plays a significant role in its strong antioxidant properties, which are closely linked to its biological activities. These polysaccharides have been shown to effectively combat free radicals and exhibit additional functions, such as metal ion chelation, enhancing their overall antioxidant potential. Studies have also indicated that cultivation conditions, such as the use of enriched media, can further amplify the bioactive properties of these compounds, underscoring the influence of environmental factors on their efficacy [36]. Animal studies provide additional evidence of the mushroom's antioxidant potential. Mice supplemented with *C. militaris* polysaccharides displayed heightened activity of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX), along with a decrease in malondialdehyde (MDA) levels a key marker of oxidative stress [37].

Polysaccharides in *Cordyceps militaris* are recognized as the primary agents responsible for its potent antioxidant effects: While the antioxidant activity of cordycepin itself remains relatively underexplored, other bioactive components in the fruiting bodies such as ergothioneine, phenolic compounds, carotenoids, and selenium also contribute significantly to its antioxidant properties. Interestingly, *C. militaris* demonstrates a more pronounced ability to inhibit lipid peroxidation when compared to *C. sinensis*, a difference that may be attributed to its higher concentrations of polysaccharides and phenolic compounds. This enhanced antioxidant profile highlights its potential as a superior source of bioactive compounds [38].

Beyond polysaccharides, *C. militaris* is a rich source of secondary metabolites like phenolic compounds, polyketides, terpenes, and steroids. Polyphenols, in particular, are known for their broad biological actions, including free radical scavenging, metal chelation, and inhibition of LDL oxidation. Studies on *C. militaris* fruiting bodies cultivated under optimized conditions have confirmed their antioxidant impact, notably enhancing the activity of catalase, SOD, and GPX, while inhibiting hydroxyl radicals in vivo [39].

3. Immunomodulatory property

Mushrooms, including *C. militaris*, are rich in immunomodulatory proteins such as lectins, ribosome-inactivating proteins, ribonucleases, laccases, and fungal immunomodulatory proteins (FIPs): Among these, FIPs are particularly significant due to their ability to regulate immune cell mitosis, proliferation, differentiation, and maturation, thereby strengthening the immune response. A novel protein identified in *C. militaris*, the *C. militaris* immunomodulatory protein (CMIMP), has demonstrated

potent cytokine-inducing and immunomodulatory activity [40].

A key mechanism underlying the immunomodulatory effects of *C. militaris* and cordycepin involves the activation of the transcription factor NF- κ B. This activation drives macrophages to enhance the production of proinflammatory mediators, highlighting the central role of NF- κ B in regulating the immune response and reinforcing the potential of *C. militaris* as a therapeutic agent for immunomodulation [41].

Fertility enhancer

Infertility is a prevalent issue, prompting a shift towards alternative medical approaches to enhance fertility. Recent trends in healthcare have seen a move from synthetic medications towards traditional herbal remedies. Among these, *Cordyceps militaris*, particularly when cultivated on a drone bee medium, has emerged as a promising candidate for addressing male reproductive health issues linked to low testosterone levels. Research indicates that supplementation with *C. militaris* increases serum levels of cordycepin, which in turn boosts testosterone and estradiol-17 levels, and enhances sperm motility and quality [42].

Additionally, research involving male mice has shown that *C. militaris* supplementation can notably increase serum testosterone levels without affecting body weight, food intake, or water consumption. These findings highlight the potential of *C. militaris* fruiting bodies, especially those cultivated on a drone bee medium, as a novel therapeutic approach for addressing male reproductive concerns related to low testosterone levels. This herbal approach provides a natural alternative to traditional treatments for infertility, potentially reducing the adverse effects associated with synthetic pharmaceuticals [43].

Anti-hyperlipidemic or anti-cholesterolemia property

Hypercholesterolemia, a major contributor to cardiovascular diseases, is characterized by elevated LDL cholesterol levels that promote atherosclerosis and vascular dysfunction, often linked to hypertension, obesity, and diabetes. Recent studies have highlighted the lipid-lowering potential of *Cordyceps* species, which reduce serum cholesterol and triglyceride levels while improving the HDL/LDL ratio, offering a promising alternative to conventional therapies with fewer side effects. Cordycepin, a bioactive compound from *Cordyceps militaris*, has shown anti-atherosclerotic effects in preclinical models by enhancing vascular function, regulating smooth muscle cell activity, and significantly lowering total cholesterol, LDL, VLDL, and triglycerides. These effects are mediated through inhibition of hepatic lipase and activation of AMP-activated protein kinase (AMPK), a key regulator of lipid metabolism [44].

Entomopathogenic activity

Cordyceps militaris, a fungus known for its entomopathogenic properties, infects various insect species in nature: Upon infection, the fruiting body of *C. militaris* grows over the infected insect, reaching heights between 1 to 8 cm: The infected insect gradually loses mobility and becomes mummified as the mycelia of *C. militaris* grow intercellularly inside, ultimately leading to the insect's death. The fruiting body of *C. militaris* emerges as a bright orange-colored club-like structure over the deceased insect [45].

Studies have revealed that secondary metabolites produced by *Cordyceps militaris* possess insecticidal properties, offering eco-friendly solutions for insect control. For instance, by preventing the formation of chitin, the metabolic substance cordycepin obtained from *C. militaris* has insecticidal action against Diamondback moth (*Plutella xylostella*) larvae. Furthermore, by suppressing the expression of genes involved in immune responses, cordycepin can lower the immunological response of insects, as shown by bioassay and qPCR analysis. Also, cordycepin has been demonstrated to raise the death rate of Diamondback moth larvae whether used alone or in conjunction with entomopathogenic fungi [46].

Promising findings have been found from additional research on *Cordyceps militaris*' impact on different insect species. In crawlies like the potato Colorado insect (*Leptinotarsa decemlineata*), it has been seen that changing doses of *C. militaris* affect molting, total hemocyte counts, survival rates, and development time frames. Furthermore, it has been observed that *C. militaris* affects the cuticular enzyme activity of these insects. These results show *C. militaris*'s potential as a biocontrol agent against agricultural pests, providing practical and permanent alternatives for managing insects [47].

Antimicrobial activity

Cordyceps militaris exhibits potent antimicrobial activity, attributed to its diverse bioactive compounds. While its antibacterial and antifungal effects against human pathogens are well-established, emerging evidence suggests its potential in controlling soil-borne plant pathogens remains underexplored [48]. Antifungal efficacy has been demonstrated against *Bipolaris maydis*, *Mycosphaerella arachidicola*, *Rhizoctonia solani*, and *Candida albicans*, primarily due to polysaccharides and cordymin, which inhibit mycelial growth. Additionally, methanol extracts and solvent fractions of *C. militaris* show strong antibacterial effects against *Clostridium spp.*, *Aspergillus*, *Penicillium*, and *Trichoderma species*. These findings highlight *C. militaris* as a promising source of broad-spectrum, eco-friendly antimicrobial agents for both medical and agricultural applications [49].

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