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Review Article

# Comparative Analysis of Bioactive Ingredients and Medicinal Functions of Natural and Cultivated *Ophiocordyceps sinensis* (Berk.)

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## Abstract

The Chinese caterpillar fungus *Ophiocordyceps sinensis* (Berk.) is a valuable traditional medicine, also known throughout Asia by its Tibetan name དབྱར་རྩྭ་དགུན་འབུ (Yartsa Gunbu), meaning "summer grass, winter worm". The mature fungus *O. sinensis* contains abundant active biological components, including polysaccharides, alkaloids, amino acids, inorganic elements, and others. Studies have previously confirmed that *O. sinensis* possesses multiple pharmacological activities. Therefore, it holds high value in the commercial market and is in increasing demand. However, the unique formation process and harsh growth environment contribute to the preciousness and scarcity of the species. To meet market demand, multiple mycelium types have been isolated from natural *O. sinensis* and cultivated artificially using fermentation technology. Currently, both natural and cultivated *O. sinensis* products are available as healthy Chinese herbal medicines on the market. However, there is a lack of comparative reviews on the two types of *O. sinensis* in terms of their compositions and medicinal functions. This mini-review will focus on the bioactive ingredients and medicinal functions of both natural and cultivated *O. sinensis*, intending to elucidate their medical values as traditional Chinese medicines for human use.

## Introduction

Chinese caterpillar fungus *Ophiocordyceps sinensis* (Berk.) is a well-known entomopathogenic fungus with high medicinal values.[1] In China, it is colloquially known as Dong Chong Xia Cao, derived from the Tibetan name དབྱར་རྩྭ་དགུན་འབུ (Yartsa Gunbu), meaning "summer grass, winter worm". The fungus is endemic to the Tibetan Plateau and its surroundings, including Tibet, Qinghai, Sichuan, and Yunnan provinces in China, as well as the Himalayas, such as Bhutan, India, and Nepal.[2] *O. sinensis* is an aggregation of larvae and parasitic fungi associated with lepidopteran hosts. More than 400 species of *Ophiocordyceps spp.* exist worldwide, and approximately 90 species of *Ophiocordyceps spp.* have been recorded in China.[3,4] The most commonly used and extensively investigated species are *O. sinensis* and *Cordyceps militaris* (orange caterpillar fungus),[5,6] with *O. sinensis* being more commonly used as a medicinal product. *O. sinensis* has been used as a traditional medicine in China for over 700 years.[7] As a renowned traditional Chinese medicine, it has long been known to boost the human immune system. *O. sinensis* enhances the immune response by increasing the production of interleukin (IL) and tumor necrosis factor, inducing macrophage phagocytosis, and stimulating the inflammatory response through the mitogen-activated protein kinase

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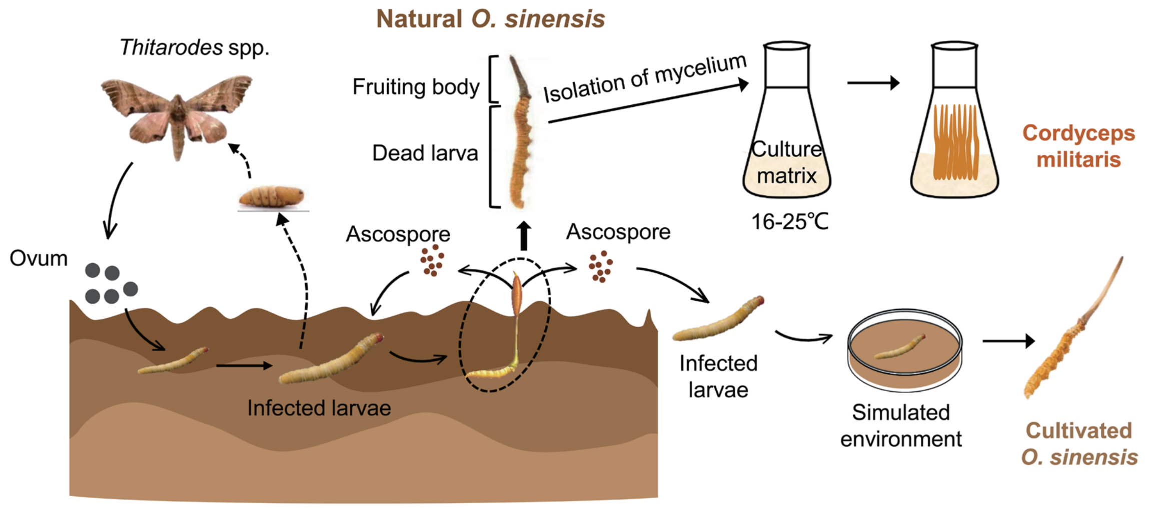


**Fig. 1. Schematic illustration of the formation process of natural and cultivated *O. sinensis*.** The whole process is a complex cycle, including the fungus invading the host and the infected larvae moving 2-5 cm below the soil surface. After the larvae gradually harden, the interstitial buds grow from the head of the parasitic larva in the spring to form a stalked fruiting body filled with ascospores. Under the right conditions, the ascospores spread and infect other larvae.

pathway, playing a role in regulating the immune response and helping to resist bacterial infections.[3] In addition, modern pharmacological research has revealed its therapeutic effects on various diseases and conditions, including respiratory, renal, liver, nervous system, and cardiovascular diseases.[8] It has also shown potential as an anti-tumor, cholesterol-reducing, and antioxidant agent.[9,10] The pharmacological effects are attributed to the active ingredients in *O. sinensis*.[11] The chemical components of *O. sinensis* include polysaccharides, nucleosides, amino acids, sterols, alkaloids, and other nutrients and bioactive ingredients.[12] It has been reported that changes in growth conditions and environmental factors may alter the composition of these components, leading to differences in their pharmacological effects.

*O. sinensis* has a restricted geographical distribution, with a preference for high altitudes. The long-term interaction between the fungus and the larvae has resulted in the complex composition of *O. sinensis*.[13] Furthermore, the precious pharmacological effects of wild *O. sinensis* have led to increasing market demand and over-exploitation, which has severely endangered its wild population and jeopardized its sustainability. Therefore, artificially cultivated *O. sinensis* has been gradually developed as an alternative.[14] Various methods have been introduced to understand the biological characteristics of natural and cultivated *O. sinensis* through component comparisons, including mass spectrometry-based metabolomics, transcriptomics, surface-enhanced Raman spectroscopy combined with machine learning algorithms, proteomics, and others.[15–17] These methods have facilitated extensive research on the similarities and differences in pharmacologically active ingredients and functions between natural and cultivated *O. sinensis*, promoting the market application of the latter in artificial cultivation.[18]

In conclusion, a deeper understanding of the differences in the content of active ingredients between cultivated and wild *O. sinensis* is essential for clarifying its growth, development, and pharmacological activity. This review summarizes and explains in detail the differences in bioactive components and medicinal functions between natural and cultivated *O. sinensis*, aiming to facilitate the understanding of the alternative value of cultivated *O. sinensis* as a substitute for natural *O. sinensis*.

## Research progress on natural and cultivated *O. sinensis*

The fungus *O. sinensis* has been regarded as a highly valuable traditional Chinese medicine for centuries, as documented in numerous ancient texts. According to reports, this distinctive and precious fungus is predominantly found in alpine meadows situated at elevations ranging from 3,000 to 5,000 meters across the Qinghai-Tibetan Plateau in southwest China, as well as in the Himalayas of Bhutan and Nepal.[7] These regions experience extremely low temperatures and significant fluctuations between day and night, creating particularly challenging conditions.[19] Additionally, *O. sinensis* fungus is a fascinating organism that grows parasitically on the larvae of specific ghost moth species, *Thitarodes* spp. This entomopathogenic fungus continues multiplying within the larvae until the entire worm is digested and filled with fungal hyphae.[6] When the nutrition in the infected larvae is exhausted, the worm dies during winter but remains intact and is known as a "winter worm". In the following year, as the weather warms during late spring and early summer, the fruiting body of *O. sinensis* grows out from the head of the dead worm, resembling the appearance of summer grass.[20] Figure 1 illustrates the distinct steps involved in the formation of the Chinese caterpillar fungus. *O. sinensis* comprises two parts: the fruiting body and the dead larva. The fruiting body is the part above the head of the insect that grows out of the body of the larva parasitized by the fungus, while the dead larva is the body of the insect larva that died after being parasitized. There are clear and visible rings on the surface of the larva's body, as well as eight pairs of feet under the abdomen of the dead larva. Terrain, climate, soil, and other factors restrict the distribution and formation of *O. sinensis*, which is why its availability is limited. Its reliance on specific moth species as hosts, as well as its long growth cycle and restricted geographical range, contribute to this scarcity.

The unique bioactive metabolites and components with medicinal values in natural *O. sinensis* have undoubtedly increased its demand in the commercial market, leading to its high price and overharvesting. Research has shown that techniques have been developed to cultivate and feiment *O. sinensis* mycelium products, such as the cultivation of asexual mycelium from *O. sinensis* harvested in nature, the asexual reproduction of *O. sinensis*, and the growth of mycelium in culture media.[21,22] Currently, the culture

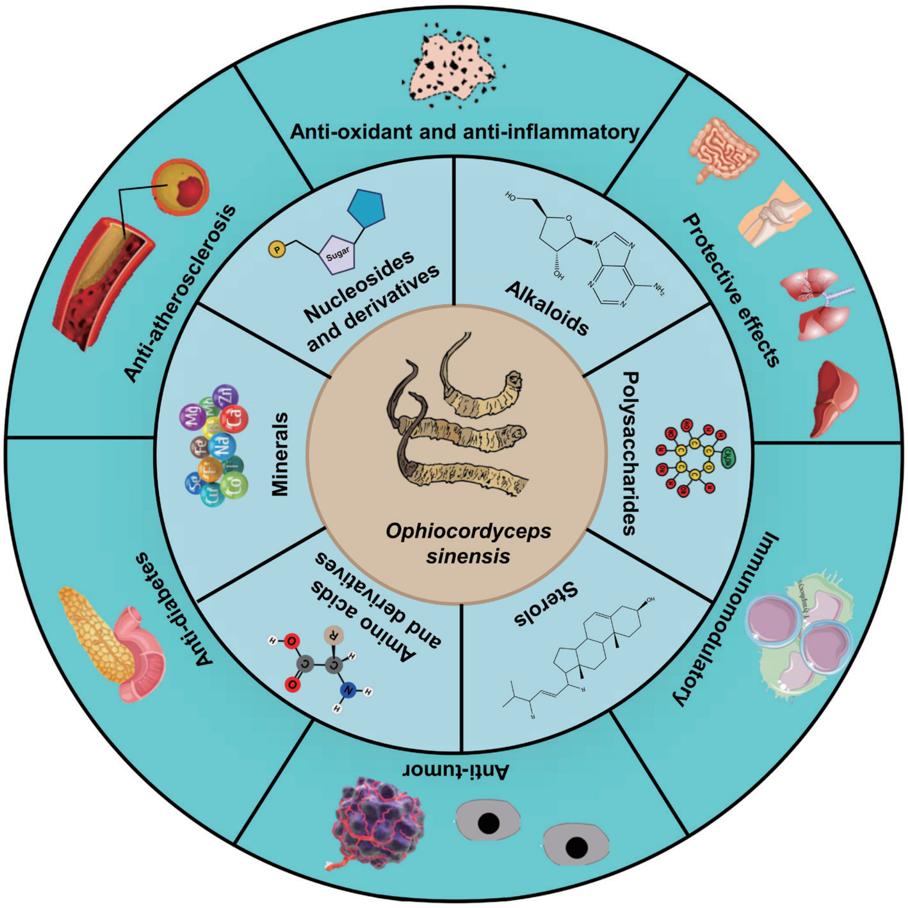


**Fig. 2. Major component composition and their functions of Chinese caterpillar fungus.**

medium temperature is maintained at 16–25°C, and large-scale cultivation takes only about 30 days to obtain *Cordyceps militaris*.[23,24] Significant progress has also been made in isolating the fungus and rearing the cultured larvae. The isolated spores are injected into the parasitic larvae, enabling large-scale cultivation of artificially cultivated Cordyceps sinensis under controlled conditions. The fungi have been identified as *O. sinensis* and *Hepialus xiaojinensis Y.Q.*[25] It is worth noting that the fungus can be isolated from various tissues and organs at different developmental stages of *O. sinensis*, such as fruiting bodies, dead caterpillars, living larvae, and ascospores.[21] Although natural and cultivated *O. sinensis* are similar in appearance, the composition and content of cultivated *O. sinensis* may differ from those of natural *O. sinensis* due to the lack of multiple environmental factors. This discrepancy may lead to a preference for natural *O. sinensis* in terms of medicinal value and health functions. Additionally, consumers are concerned about whether cultivated and natural *O. sinensis* have the same medicinal effects. Therefore, a comprehensive understanding of the pharmacological components and functional similarities and differences between natural and cultivated *O. sinensis* is essential, providing a theoretical basis for using cultivated *O. sinensis* as a reliable Chinese medicinal.

## Composition of natural and cultivated *Ophiocordyceps sinensis*

Natural and cultivated *O. sinensis* have a unique combination of metabolites, including polysaccharides, nucleosides, sterols, alkaloids, and amino acids. In addition, they also contain a variety of minerals, vitamins, and other nutrients (Fig. 2).[26] Comparison of natural *O. sinensis* with cultivated *O. sinensis* showed that the metabolite compositions of these two are similar.[27] Similarly, the Nuclear Magnetic Resonance (NMR) fingerprint of natural *O. sinensis* is consistent with that of cultivated *O. sinensis*.[27] However, there are still some differences in the content of certain ingredients. For example, during the cultivation process, carbon sources are usually added as nutrients, so the carbohydrate content in natural *O. sinensis* is slightly lower than that in cultivated *O. sinensis*.[28] In addition, the nucleoside content in natural *O. sinensis* is increased to cope with the harsh growth environment, as the accumulation of nucleosides is essential for enhancing the stress resistance of plants during growth.[29] Therefore, we summarized the similarities and differences in the contents of active compounds in natural and cultivated *O. sinensis*, providing a basis for determining whether cultivated O. sinensis can be used as an alternative.

### *Carbohydrates*

The carbohydrates in *O. sinensis* consist of free saccharides, polymerized saccharides, sugar alcohols, and sugar acids, which are important compounds with multiple pharmacological activities.[30] Polysaccharides are a group of essential ingredients with biological activities in *O. sinensis*,[13,31] and the content of polysaccharides is approximately 3–8% of the total weight.[32] Polysaccharides might be used as markers for the quality evaluation of *O. sinensis*. Previous studies have shown that the polysaccharides in *O. sinensis* exhibit antioxidant, anti-cancer, immune-enhancing, and liver-protective biological activities.[33–36] At the same time, structural studies show a close relationship between the structure of *O. sinensis* polysaccharides and their pharmacological activities.[37] Currently, polysaccharides with different molecular weights have been discovered in *O. sinensis*. However, due to the structural diversity and complexity of polysaccharide molecules, variations in monosaccharide composition, molecular weight, and configuration may be key factors affecting their pharmacological activities.

The carbohydrate compounds in natural Cordyceps are mainly α-1,4, α-1,3, and α-1,6 linked glucans, with small amounts of galactose, arabinose, mannose, and galacturonic acid. The structural composition of carbohydrate compounds is complex, and different monosaccharide compositions, glycosidic bond connection methods, and the presence of straight chains and branches may result in different biological activities.

In recent years, studies have extracted four types of polysaccharides from both natural *O. sinensis* and artificially cultivated *O. sinensis*, indicating that the main chain of polysaccharides in natural *O. sinensis* is composed mainly of α-1,4, α-1,3, and α-1,6 linked glucans, with small amounts of galactose, arabinose, mannose, and galacturonic acid.[38] In contrast, the polysaccharide structure in cultivated *O. sinensis* is very complex, mainly composed of glucose, galactose, and mannose, with 1,4-glucose and 1,4-galactose as the main chains, and the average molecular weight is much lower than that of natural cordyceps.[39] Studies have shown that mannitol has a content more than twice that of natural *O. sinensis* compared to cultivated *O. sinensis*.[40] In addition, studies have demonstrated that the content of trehalose is higher in natural *O. sinensis*, while the content of D-arabitol, D-xylitol, D-xylose, gluconic acid, and 6-phosphogluconic acid is higher in cultivated *O. sinensis*.[15]

In general, *O. sinensis* polysaccharides can be divided into two types based on their location: intracellular polysaccharides (IPSs) and extracellular polysaccharides (EPSs). IPSs are mainly extracted from the fruiting bodies (or worms) and mycelium by heating.[41] To extract EPS, they are obtained by concentration followed by ethanol precipitation.[31] Previous research on the polysaccharide structure in *O. sinensis* found that IPSs in *O. sinensis* are usually composed of glucose, mannose, and galactose with 1-4(6)-glucopyranosyl, 1-6-mannopyranosyl, and 1-4(6)-galactopyranosyl,[42] indicating that IPS has a multi-branched chain structure, consisting of small rings and helical structures, while EPS is prone to forming large interaction networks in aqueous solutions.[31] It should be noted that the pharmacological activity of polysaccharide molecules is related to their molecular weight, chemical structure, and conformation. For example, the higher the content of high molecular weight IPS, the higher the anti-tumor activity,[43] only polysaccharides with a molecular weight greater than 16,000 have effective anti-tumor activity.[44] Therefore, the relationship between the structure of polysaccharides and the pharmacological effects of *O. sinensis* deserves further research. In a recent study, Liu *et al*.[45] isolated and purified biological macromolecular glycogen from *O. sinensis* using the sucrose gradient method for the first time and characterized the particle size distribution and chain length distribution of glycogen particles, providing a new direction for the subsequent exploration of the biological activity of polysaccharides in *O. sinensis*.

### *Nucleosides*

Nucleosides are the principal components in *O. sinensis*, playing a key role in regulating various physiological processes in the body and exhibiting effective anti-viral, anti-inflammatory, antioxidant activities, as well as neuroprotective functions.[46] Currently, more than ten nucleosides, nucleobases, and related compounds have been isolated and identified from *O. sinensis* through various analytical methods (Fig. 1). Nucleosides are the principal components that ensure the authenticity of *O. sinensis*. Cordycepin and adenosine are important nucleosides in *O. sinensis*.[4,47] As early as the 1950s, cordycepin was first isolated from Cordyceps militaris, with the structural formula determined as 3′-deoxyadenosine. The content of cordycepin in cultivated *O. sinensis* is higher than that in natural *O. sinensis*.[48] Additionally, adenosine is the main nucleoside in *O. sinensis* and has been used as a quality control indicator. It is also the main bioactive component in *O. sinensis* and plays multiple roles in regulating inflammation and tissue remodeling.[44,49–52] Research has confirmed that the adenosine content in cultivated *O. sinensis* is much higher than that in natural *O. sinensis*. *O. sinensis* also contains many other adenosine analogs, such as 2′-deoxyadenosine, 2′,3′-dideoxyadenosine, cordycepin triphosphate, and 3′-amino-3′-deoxyadenosine. So far, six nucleobases have been identified from natural and cultivated *O. sinensis*, including cytosine, guanine, uracil, thymine, hypoxanthine, and adenine.[53] Additionally, four nucleotides were isolated by reverse-phase liquid chromatography-mass spectrometry, including uridine 5′-monophosphate, adenosine 5′-monophosphate, guanosine 5′-monophosphate, and cytidine 5′-monophosphate. Among these, guanosine and uridine were found to be high in content, and there was no significant difference in guanosine content between cultivated and natural *O. sinensis*, as reported in previous studies.[40] *O. sinensis* also contains many specific nucleotides, such as adenosine, 2′,3′-dideoxyadenosine, hydroxyethyl adenosine, cordycepin triphosphate, guanidine, and deoxyguanidine. Adenosine and cordycepin (3′-deoxyadenosine), have several different deoxyguanosine structures.[46] Non-targeted UPLC-MS-based metabolomics identified that the contents of 11 nucleotides were higher in natural *O. sinensis*, about 2.22–104.36 times that of cultivated samples.[15] Currently, the identification and detection of nucleoside components in *O. sinensis* is a hot research topic, aiming to develop a fast, sensitive, and selective method for the quality evaluation of *O. sinensis*.

### *Proteins and nitrogenous compounds*

Amino acids play an important role in maintaining internal balance and are key precursors for synthesizing plant hormones, as well as acting as amino group donors to form nitrogen-containing compounds.[54] It has been proven that *O. sinensis* contains all essential amino acids and some non-essential amino acids (including pyroglutamic acid, glutamic acid, histidine, arginine, and tyrosine), as well as abundant and vital peptides, proteins, and polyamines.[3,40] In a comparative analysis, Wang and his colleagues examined the amino acid composition of cultivated and natural *O. sinensis*.[39] The results demonstrated a marked increase in the total amino acid content in cultivated samples. Specifically, compared to cultivated *O. sinensis*, natural *O. sinensis* contains higher levels of glutamic acid, arginine, pyroglutamic acid, valine, histidine, phenylalanine, and tyrosine, while the content of leucine and aspartic acid is lower.[40,55,56] Glutamic acid was the most dominant amino acid across all samples. However, arginine was the second most prevalent amino acid in natural samples, while cultivated samples had a higher concentration of aspartic acid and leucine.[40] Additionally, *O. sinensis* contains several rare cyclic dipeptides, including cyclo-[Gly-Pro], cyclo-[Leu-Pro], cyclo-[Val-Pro], cyclo-[Ala-Leu], and cyclo-[Thr-Leu]. Significant quantities of polyamines, such as 1,3-diamino propane, cadaverine, spermidine, spermine, and putrescine, were also detected. Other nitrogenous compounds, like putrescine, were also identified.

#### *Sterol*

Furthermore, the steroids in *O. sinensis* have critical physiological functions. They exist in two forms: free ergosterol and esterified ergosterol. Various sterols have been isolated from *O. sinensis*, including ergosterol and four ergosterol derivatives (ergosteryl-3-O-β-D-glucopyranoside, 22,23-dihydroergosteryl-3-O-β-D-glucopyranoside, 5α, 8α-epidioxy-24(R)-methylcholesta-6,22-dien-3β-D-glucopyranoside, 5α, 6α-epoxy-24(R)-methylcho lesta-7,22-dien-3β-ol).[57] Studies have shown that the ergosterol content in different natural *O. sinensis* samples varies and is higher than that in cultivated *O. sinensis*.[11] Different sterol compounds are involved in various physiological processes. Among the four ergosterol derivatives, a large number of experiments have confirmed that the latter two have anticancer activity, while the first two do not.[58] Studies have determined the sterols in *O. sinensis* fruiting bodies (CsA) and parasitic caterpillars (CsB) separately and found that CsA and CsB have similar ergosterol compositions, but the content of ergosterol in CsA is much higher than that in CsB, indicating that CsA and CsB may be in different growth stages or have different physiological functions related to ergosterol growth and reproduction.[59]

For example, anti-tumor compounds and ergosterol derivatives can induce apoptosis in human liver cancer HepG2 cells,[60] while ergosterol compounds have significant cytotoxic activity.[58,61]

#### *Alkaloids*

Alkaloids can improve blood circulation and regulate endocrine functions.[62] $^1$H-NMR identification of *O. sinensis* metabolites revealed that the betaine content in cultivated *O. sinensis* is relatively high. Two new pyrrole alkaloid derivatives, 2-carboxaldehyde-1-(4-aminobutyl)-5-(methoxymethyl)-1H-pyrrole (14) and 2-carboxaldehyde-5-(methoxymethyl)-1-(2-oxo-3-piperidinyl)-1H-pyrrole (15), were isolated from *O. sinensis*, and the anti-inflammatory results showed no significant inhibitory activity.[55] Recently, in the study of the chemical components of *O. sinensis*, a thiazole alkaloid was isolated and identified, which has glucosidase inhibitory activity and is a potential anti-diabetes compound.[63]

#### *Other components*

In addition, three different lipid metabolites, namely linolenic acid, linoleic acid, and oleic acid, were isolated from *O. sinensis*.[55] Among them, linolenic acid was only detected in natural *O. sinensis*. *O. sinensis* is rich in minerals, with five macro-elements and eighteen trace minerals detected (Table 1).[15,40,48,53,55,57,64–66] The contents of K and P among the five macro-elements are significantly higher in cultivated *O. sinensis*. The Se, Zn, Cu, and Co contents in natural *O. sinensis* are higher than those in cultivated samples, while the Ni content is three to five times higher than that in natural *O. sinensis* samples. Interestingly, as natural *O. sinensis* grows at higher altitudes, the content of toxic elements Ni, Pb, Hg, and As decreases.[40] At the same time, *O. sinensis* is also rich in vitamins B1 and B2, which help promote blood circulation and primary metabolism in the human body. Taken together, the rich active ingredients in *O. sinensis* determine its important pharmacological activity. Therefore, more in-depth research is needed on the biological components and content of *O. sinensis* to cultivate more effective alternatives to it.

### Medicinal functions of *Ophiocordyceps sinensis*

Current research has confirmed the pharmacological effects of *O. sinensis* in anti-diabetes, antioxidants, anti-inflammatory, immunomodulatory, liver protection, and anti-atherosclerosis (Fig. 2).[65] Diabetes is a metabolic disease characterized by hyperglycemia, and persistent hyperglycemia has become an increasingly serious public health problem. Previous studies have found that a variety of traditional Chinese medicines have been used to lower blood glucose, such as berberine, astragalus, *Panax notoginseng*, and *Pueraria lobata*.[67–70] At the same time, polysaccharides extracted from *O. sinensis* have been shown to alleviate diabetic metabolic disorders by regulating glucose metabolism and modulating intestinal flora and metabolites.[71] The mycelium of *O. sinensis* and the polysaccharide components in the extract exhibit strong antioxidant activity. For example, previous studies have reported that water-soluble polysaccharides isolated from *O. sinensis* demonstrate effective *in vitro* antioxidant activity, including scavenging hydroxyl and superoxide radicals and inhibiting hemolysis caused by hydrogen peroxide.[72] Studies have shown that the monosaccharide composition of polysaccharides can significantly influence their antioxidant activity. It has been reported that a higher glucose content in the monosaccharide composition correlates with stronger antioxidant activity.[73] Moreover, acidic polysaccharides mainly composed of glucose (88.4%) not only exhibit free radical scavenging effects *in vitro* but also enhance antioxidant enzyme activity in type 2 diabetic mice.[74]

Xu *et al*.[75] first described the enhancement of natural killer cell activity *in vivo* and *in vitro* by the ethanol extract of *O. sinensis*, as well as the reduction of melanoma formation in the lungs of mice, suggesting the immune-enhancing effect of *O. sinensis* on immune-deficient organisms. Currently, several compounds with immunomodulatory activity have been isolated from *O. sinensis*, among which polysaccharides are the main component. *O. sinensis* polysaccharides induces T lymphocyte proliferation and secretion of IL-β and IL-6. In addition, they can enhance the phagocytosis of macrophages, demonstrating their important role in immune response, and can be used as a natural immune regulator.[76] Bi *et al*.[77] reported that low molecular weight polysaccharides obtained from cultivated *O. sinensis* fruiting bodies exerted immunostimulatory effects. Inflammation is a protective mechanism that defends against tissue damage caused by various stimuli and harmful factors, such as ultraviolet radiation, infection, and cell damage. Studies have shown that *O. sinensis* polysaccharides enhance the immunity of mice exposed to ionizing radiation by reducing oxidative damage and regulating the secretion of cytokines (IL-4, IL-5, and IL-17).[78] Recent studies have shown that *O. sinensis* polysaccharides can alleviate acute liver injury by upregulating vascular endothelial growth factor, stromal cell-derived factor-1α, proliferating cell nuclear antigen, and downregulating IL-12 and caspase-1 to promote hepatocyte proliferation and liver tissue repair.[79] Notably, *O. sinensis* polysaccharides can increase the abundance of *Akkermansia* and *Lachnospiraceae*, reduce the abundance of *Bacteroides*, *Parabacteroides*, and *Blautiae*, improve intestinal barrier function, and inhibit intestinal inflammation.[80] In addition, many studies have demonstrated the potential of cordycepin from *Cordyceps militaris* in anti-inflammatory treatment. For example, cordycepin effectively alleviates lipopolysaccharide induced acute lung injury by inhibiting inflammation and oxidative stress.[81] Cordycepin significantly decreased the expression of cyclooxygenase-2 and inducible nitric oxide synthase in RAW 264.7 cells.[82]

Compounds in *O. sinensis*, including polysaccharides, sterols, and adenosine, have been shown to inhibit tumor cell growth and metastasis by inducing tumor cell apoptosis, cell cycle arrest, and

**Table 1. Comparison of the bioactive compound composition of natural and cultivated *O. sinensis***

| Chemical name | Chemical formula | Classification | Change direction | Reference |
|---|---|---|---|---|
| 6-phosphogluconic acid | $C_6H_{13}O_{10}P$ | Carbohydrates | ↓ | 15 |
| D-arabitol | $C_5H_{12}O_5$ | | ↓ | 15 |
| D-xylitol | $C_5H_{12}O_5$ | | ↓ | 15 |
| D-xylose | $C_5H_{10}O_5$ | | ↓ | 15 |
| Gluconic acid | $C_6H_{12}O_7$ | | ↓ | 15 |
| Mannitol | $C_6H_{14}O_6$ | | ↑ | 40 |
| Trehalose | $C_{12}H_{22}O_{11}$ | | ↑ | 64 |
| 2′-deoxyadenosine | $C_9H_{15}N_3O_5$ | Nucleoside | ↑ | 15 |
| 2′,3′-dideoxyadenosine | $C_{10}H_{13}N_5O_2$ | | – | 53 |
| 3′-amino-3′- deoxyadenosine | $C_{10}H_{14}N_6O_3$ | | – | 53 |
| Adenosine | $C_{10}H_{13}N_5O_4$ | | ↑ | 65 |
| Adenine | $C_5H_5N_5$ | | ↑ | 15 |
| Cordycepic acid | $C_6H_{14}O_6$ | | ↓ | 40 |
| Cordycepin | $C_{10}H_{13}N_5O_3$ | | ↓ | 48 |
| Cordycepin triphosphate | $C_{10}H_{16}N_5O_{12}P_3$ | | – | 53 |
| Cytidine | $C_9H_{13}N_3O_5$ | | – | 53 |
| Cytosine | $C_4H_5N_3O$ | | – | 53 |
| Guanosine | $C_{10}H_{13}N_5O_5$ | | NS | 40 |
| Guanine | $C_5H_5N_5O$ | | ↑ | 15 |
| Hypoxanthine | $C_5H_4N_4O$ | | ↑ | 15 |
| Thymine | $C_5H_6N_2O_2$ | | ↑ | 15 |
| Xanthine | $C_5H_4N_4O_2$ | | ↑ | 15 |
| Uracil | $C_4H_4N_2O_2$ | | ↑ | 15 |
| Uridine | $C_9H_{12}N_2O_6$ | | ↑ | 15 |
| Alanine | $C_3H_7NO_2$ | Amino acids | ↓ | 40 |
| Arginine | $C_6H_{14}N_4O_2$ | | ↑ | 40 |
| Aspartic acid | $C_4H_7NO_4$ | | ↓ | 40 |
| Cysteine | $C_3H_7NO_2S$ | | NS | 40 |
| Glycine | $C_2H_5NO_2$ | | ↓ | 66 |
| Glutamic acid | $C_5H_9NO_4$ | | ↑ | 40 |
| Histidine | $C_6H_9N_3O_2$ | | ↑ | 40 |
| Isoleucine | $C_6H_{13}NO_2$ | | ↓ | 40 |
| Leucine | $C_6H_{13}NO_2$ | | ↓ | 40 |
| Lysine | $C_6H_{14}N_2O_2$ | | ↓ | 66 |
| Methionine | $C_5H_{11}NO_2S$ | | ↓ | 40 |
| Phenylalanine | $C_9H_{11}NO_2$ | | ↑ | 40 |
| Proline | $C_5H_9NO_2$ | | ↓ | 40 |
| Pyroglutamic acid | $C_5H_7NO_3$ | | ↑ | 55 |
| Serine | $C_3H_7NO_3$ | | NS | 40 |
| Threonine | $C_4H_9NO_3$ | | NS | 40 |

*(continued)*

**Table 1.** *(continued)*

| Chemical name | Chemical formula | Classification | Change direction | Reference |
|---|---|---|---|---|
| Tryptophan | $C_{11}H_{12}N_2O_2$ | | – | 40 |
| Tyrosine | $C_9H_{11}NO_3$ | | ↑ | 40 |
| Valine | $C_5H_{11}NO_2$ | | ↑ | 40 |
| Ergosterol | $C_{28}H_{44}O$ | Sterol | ↑ | 57 |
| Ergosteryl-3-O-β-D-glucopyranoside | $C_{34}H_{54}O_6$ | | – | 57 |
| 22,23-dihydroergosteryl-3-O- β- D-glucopyranoside | $C_{34}H_{54}O_8$ | | – | 57 |
| 5α, 8α- Epidioxy-24 (R) - methylcholesta-6,22 dien-3β- D-glucopyranoside | $C_{28}H_{44}O_3$ | | – | 57 |
| 5α, 6α- Epoxy 24 (R) - methylcholesta-7,22 dien-3β-ol | $C_{28}H_{44}O_2$ | | – | 57 |
| Betaine | $C_5HNO_2$ | Alkaloids | ↓ | 64 |
| Linoleic acid | $C_{18}H_{32}O_2$ | Other components (fatty acid) | – | 55 |
| Linolenic acid | $C_{18}H_{30}O_2$ | | ↑ | 55 |
| Oleic acid | $C_{18}H_{34}O_2$ | | – | 55 |
| Aluminum | Al | Other components (mineral) | ↑ | 40 |
| Arsenic | As | | ↑ | 40 |
| Barium | Ba | | ↑ | 40 |
| Cadmium | Cd | | NS | 40 |
| Calcium | Ca | | ↑ | 40 |
| Chromium | Cr | | NS | 40 |
| Cobalt | Co | | ↑ | 40 |
| Copper | Cu | | ↑ | 40 |
| Hydrargyrum | Hg | | NS | 40 |
| Iron | Fe | | ↑ | 40 |
| Lead | Pb | | ↑ | 40 |
| Magnesium | Mg | | ↑ | 40 |
| Manganese | Mn | | ↑ | 40 |
| Molybdenum | Mo | | NS | 40 |
| Niccolum | Ni | | ↓ | 40 |
| Phosphorusb | P | | ↓ | 40 |
| Potassium | K | | ↓ | 40 |
| Selenium | Se | | ↑ | 40 |
| Sodium | Na | | ↑ | 40 |
| Stannum | Sn | | ↑ | 40 |
| Strontium | Sr | | ↓ | 40 |
| Vanadium | V | | NS | 40 |
| Zinc | Zn | | ↑ | 40 |

Arrows represent changes in the content of a certain component in natural *O. sinensis* compared to cultivated *O. sinensis*. "NS" represents no significant difference in content between the two, while "–" represents that the comparison of the compound content between the two is not yet clear.

inhibiting angiogenesis.[83] Previous studies have found that *O. sinensis* polysaccharides have a strong regulatory effect on mouse liver cancer.[84] Ergosterol can reduce the proliferation of various tumor cells, and cordycepin inhibits the proliferation of cancer cells by triggering the Wnt signaling pathway. For example, in human colon cancer cells, it induces apoptosis by increasing pro-apoptotic molecules.[85] Additionally, it could enhance exercise and improve memory and learning ability, as supported by various clinical studies.[86] It has also shown reliable results in improving organ malfunctioning by regulating cytokines, chemokines, and oxidative stress-induced protein changes.

An increasing number of studies have concentrated on the pharmacological activities of cultivated *O. sinensis*, including antioxidant, anti-inflammatory, anticancer, immunomodulatory, hypoglycemic, and the ability to delay the progression of kidney disease.[87–89] Dong *et al*.[90] evaluated the *in vitro* antioxidant activity of aqueous extracts of natural and cultivated *O. sinensis* mycelium and confirmed that both had effective antioxidant activity. Wang *et al*.[91] compared the protective effects of natural and cultivated *O. sinensis* against hepatotoxicity. The results showed that both play a liver-protective role by preventing liver cells from oxidative damage. Therefore, the pharmacological functions of natural and cultivated *O. sinensis* are similar, and there is no significant difference in pharmacological activity.

Despite these advances, there remains a need for further research to comprehensively understand the molecular mechanisms underlying these effects and to explore the full spectrum of pharmacological activities. Similarly, new drug delivery systems should be developed to enhance the effects of *O. sinensis* active ingredients, compensating for the limitations of traditional drug delivery methods and better elucidating the bioactive compounds of *O. sinensis* and their therapeutic potential.

## Conclusions

The chemical composition and bioactive compounds of *O. sinensis* have been increasingly elucidated, with key components such as cordycepin, adenosine, polysaccharides, and sterols recognized for their pharmacological properties. These compounds have demonstrated a range of health benefits, including immunomodulatory, anti-inflammatory, antioxidant, and antitumor activities. Beyond the traditional harvesting of wild *O. sinensis* from their native, harsh environments, significant advancements have been made in the large-scale artificial cultivation of *O. sinensis*. This method is particularly advantageous as it allows for more sustainable production while mitigating the environmental impact associated with wild harvesting. However, the market is currently flooded with numerous low-quality substitutes, which may not only fail to deliver the therapeutic benefits associated with genuine *O. sinensis* but may also pose safety risks. To ensure clarity, precision, and a deeper understanding of the medicinal potential of *O. sinensis*, a multifaceted approach to its production and quality control is imperative. Thus, it is essential to establish rigorous identification and standardization protocols. These should include a detailed analysis of morphological characteristics and comprehensive profiling of active ingredients to distinguish between natural *O. sinensis*, its fermented counterparts, and inferior substitutes. Current research is mainly through comparative analysis of natural and cultivated *O. sinensis* metabolites. It is generally believed that the components and pharmacological activities of the two are similar, but there are differences in the content of some specific components. Accurate identification and quality control are crucial to ensuring that the therapeutic potential of *O. sinensis* is fully harnessed. Therefore, a more profound and systematic understanding of the health benefits and therapeutic potential of *O. sinensis* will significantly contribute to its future medicinal applications. Such knowledge will not only enhance its utilization in traditional medicine but also pave the way for its integration into modern therapeutic practices, potentially leading to the development of novel drugs and health supplements derived from this precious fungus.

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## Conflict of interest

LW has been an editorial board member of *Future Integrative Medicine* since October 2021. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Author contributions

Topic conception, logical framework, student supervision, project administration (LW), discussions (YRT), investigation, image visualization (ZWM), writing of the original draft, and performing the literature review (ZWM, QHL, YXH, JC, JWT). All the authors approved the final version and publication of the manuscript.

## References

[1] Lo HC, Hsieh C, Lin FY, Hsu TH. A Systematic Review of the Mysterious Caterpillar Fungus Ophiocordyceps sinensis in Dong-ChongXiaCao (Dōng Chóng Xià Cǎo) and Related Bioactive Ingredients. J Tradit Complement Med 2013;3(1):16–32. doi:10.4103/2225-4110.106538, PMID:24716152.

[2] Yan Y, Li Y, Wang WJ, He JS, Yang RH, Wu HJ, *et al*. Range shifts in response to climate change of Ophiocordyceps sinensis, a fungus endemic to the Tibetan Plateau. Biol Conserv 2017;206:143–150. doi:10.1016/j.biocon.2016.12.023.

[3] Das G, Shin HS, Leyva-Gómez G, Prado-Audelo MLD, Cortes H, Singh YD, *et al*. Cordyceps spp.: A Review on Its Immune-Stimulatory and Other Biological Potentials. Front Pharmacol 2020;11:602364. doi:10.3389/fphar.2020.602364, PMID:33628175.

[4] Xu C, Wu F, Zou Z, Mao L, Lin S. Discovery of the chemical constituents, structural characteristics, and pharmacological functions of Chinese caterpillar fungus. Open Chem 2023;21(1):20220337. doi:10.1515/chem-2022-0337.

[5] Shrestha B, Zhang W, Zhang Y, Liu X. The medicinal fungus Cordyceps militaris: research and development. Mycol Prog 2012;11(3):599–614. doi:10.1007/s11557-012-0825-y.

[6] Olatunji OJ, Tang J, Tola A, Auberon F, Oluwaniyi O, Ouyang Z. The genus Cordyceps: An extensive review of its traditional uses, phytochemistry and pharmacology. Fitoterapia 2018;129:293–316. doi:10.1016/j.fitote.2018.05.010, PMID:29775778.

[7] Wei Y, Zhang L, Wang J, Wang W, Niyati N, Guo Y, *et al*. Chinese caterpillar fungus (Ophiocordyceps sinensis) in China: Current distribution, trading, and futures under climate change and overexploitation. Sci Total Environ 2021;755(Pt 1):142548. doi:10.1016/j.scitotenv.2020.142548, PMID:33035977.

[8] Das SK, Masuda M, Sakurai A, Sakakibara M. Medicinal uses of the mushroom Cordyceps militaris: current state and prospects. Fitoterapia 2010;81(8):961–968. doi:10.1016/j.fitote.2010.07.010, PMID:20650308.

[9] Dai Y, Wu C, Yuan F, Wang Y, Huang L, Chen Z, *et al*. Evolutionary biogeography on Ophiocordyceps sinensis: An indicator of molecular phylogeny to geochronological and ecological exchanges. Geosci Front 2020;11(3):807–820. doi:10.1016/j.gsf.2019.09.001.

[10] Winkler D. Yartsa Gunbu (Cordyceps sinensis) and the Fungal Commodification of Tibet's Rural Economy. Economic Botany 2008;62(3):291–305. doi:10.1007/s12231-008-9038-3.

[11] Zhou X, Gong Z, Su Y, Lin J, Tang K. Cordyceps fungi: natural products,

pharmacological functions and developmental products. J Pharm Pharmacol 2009;61(3):279–291. doi:10.1211/jpp/61.03.0002, PMID:19222900.
[12] Xu J, Huang Y, Chen XX, Zheng SC, Chen P, Mo MH. The Mechanisms of Pharmacological Activities of Ophiocordyceps sinensis Fungi. Phytother Res 2016;30(10):1572–1583. doi:10.1002/ptr.5673, PMID:27373780.
[13] Jędrejko KJ, Lazur J, Muszyńska B. Cordyceps militaris: An Overview of Its Chemical Constituents in Relation to Biological Activity. Foods 2021;10(11):2634. doi:10.3390/foods10112634, PMID:34828915.
[14] Tan W, Wang Y, Dai H, Deng J, Wu Z, Lin L, *et al*. Potential Therapeutic Strategies for Renal Fibrosis: Cordyceps and Related Products. Front Pharmacol 2022;13:932172. doi:10.3389/fphar.2022.932172, PMID:35873549.
[15] Zhang J, Wang N, Chen W, Zhang W, Zhang H, Yu H, *et al*. Integrated metabolomics and transcriptomics reveal metabolites difference between wild and cultivated Ophiocordyceps sinensis. Food Res Int 2023;163:112275. doi:10.1016/j.foodres.2022.112275, PMID:36596185.
[16] Zhang B, Li B, Men XH, Xu ZW, Wu H, Qin XT, *et al*. Proteome sequencing and analysis of Ophiocordyceps sinensis at different culture periods. BMC Genomics 2020;21(1):886. doi:10.1186/s12864-020-07298-z, PMID:33308160.
[17] Liu QH, Tang JW, Ma ZW, Hong YX, Yuan Q, Chen J, *et al*. Rapid discrimination between wild and cultivated Ophiocordyceps sinensis through comparative analysis of label-free SERS technique and mass spectrometry. Curr Res Food Sci 2024;9:100820. doi:10.1016/j.crfs.2024.100820, PMID:39263205.
[18] Yue K, Ye M, Lin X, Zhou Z. The artificial cultivation of medicinal Caterpillar Fungus, Ophiocordyceps sinensis (Ascomycetes): a review. Int J Med Mushrooms 2013;15(5):425–434. doi:10.1615/intjmedmushr.v15.i5.10, PMID:24266368.
[19] Li Y, Wang XL, Jiao L, Jiang Y, Li H, Jiang SP, *et al*. A survey of the geographic distribution of Ophiocordyceps sinensis. J Microbiol 2011;49(6):913–919. doi:10.1007/s12275-011-1193-z, PMID:22203553.
[20] Paterson RR. Cordyceps: a traditional Chinese medicine and another fungal therapeutic biofactory? Phytochemistry 2008;69(7):1469–1495. doi:10.1016/j.phytochem.2008.01.027, PMID:18343466.
[21] Zhou XW, Li LJ, Tian EW. Advances in research of the artificial cultivation of Ophiocordyceps sinensis in China. Crit Rev Biotechnol 2014;34(3):233–243. doi:10.3109/07388551.2013.791245, PMID:23875938.
[22] Ko YF, Liau JC, Lee CS, Chiu CY, Martel J, Lin CS, *et al*. Isolation, Culture and Characterization of Hirsutella sinensis Mycelium from Caterpillar Fungus Fruiting Body. PLoS One 2017;12(1):e0168734. doi:10.1371/journal.pone.0168734, PMID:28046129.
[23] Jang SH, Kim SH, Lee HY, Jang SH, Jang H, Chae SW, *et al*. Immune-Modulating Activity of Extract Prepared from Mycelial Culture of Chinese Caterpillar Mushroom, Ophiocordyceps sinensis (Ascomycetes). Int J Med Mushrooms 2015;17(12):1189–1199. doi:10.1615/intjmedmushrooms.v17.i12.90, PMID:26854106.
[24] Kaushik V, Arya A, Sindhu A, Singh A. Identification, Optimization of Culture Conditions, and Bioactive Potential of Chinese Caterpillar Mushroom Ophiocordyceps sinensis (Ascomycetes) Mycelium Isolated from Fruiting Body. Int J Med Mushrooms 2019;21(9):931–942. doi:10.1615/IntJMedMushrooms.2019031841, PMID:32450031.
[25] Li WJ, Dong CH, Liu XZ, Li QP, Xia JM, Liang L. Research advances in artificial cultivation of Chinese cordyceps. Mycosystema 2016;35(4):375–387. doi:10.13346/j.mycosystema.160003.
[26] Zhou Y, Wang M, Zhang H, Huang Z, Ma J. Comparative study of the composition of cultivated, naturally grown Cordyceps sinensis, and stiff worms across different sampling years. PLoS One 2019;14(12):e0225750. doi:10.1371/journal.pone.0225750, PMID:31800596.
[27] Zhang X, Liu Q, Zhou W, Li P, Alolga RN, Qi LW, *et al*. A comparative proteomic characterization and nutritional assessment of naturally- and artificially-cultivated Cordyceps sinensis. J Proteomics 2018;181:24–35. doi:10.1016/j.jprot.2018.03.029, PMID:29609095.
[28] Sharma A, Ranout AS, Nadda G. Insights into cultivation strategies, bioactive components, therapeutic potential, patents, and market products of Ophiocordyceps sinensis: A comprehensive review. S Afr J Bot 2024;171:546–570. doi:10.1016/j.sajb.2024.06.036.
[29] Lu C, Wang Q, Jiang Y, Zhang M, Meng X, Li Y, *et al*. Discovery of a novel nucleoside immune signaling molecule 2′-deoxyguanosine in microbes and plants. J Adv Res 2023;46:1–15. doi:10.1016/j.jare.2022.06.014, PMID:35811061.
[30] Chen H, Chen H, Lu H, Tang X, Zhang H, Chen YQ, *et al*. Carbohydrate analysis of Mortierella alpina by colorimetry and HPLC-ELSD to reveal accumulation differences of sugar and lipid. Biotechnol Lett 2021;43(7):1289–1301. doi:10.1007/s10529-021-03120-2, PMID:33864523.
[31] Yan JK, Wang WQ, Wu JY. Recent advances in Cordyceps sinensis polysaccharides: Mycelial fermentation, isolation, structure, and bioactivities: A review. J Funct Foods 2014;6:33–47. doi:10.1016/j.jff.2013.11.024, PMID:32362940.
[32] Li SP, Su ZR, Dong TT, Tsim KW. The fruiting body and its caterpillar host of Cordyceps sinensis show close resemblance in main constituents and anti-oxidation activity. Phytomedicine 2002;9(4):319–324. doi:10.1078/0944-7113-00134, PMID:12120813.
[33] Cai Y, Guo J, Kang Y. Future prospect of polysaccharide as a potential therapy in hepatocellular carcinoma: A review. Int J Biol Macromol 2024;270(Pt 1):132300. doi:10.1016/j.ijbiomac.2024.132300, PMID:38735616.
[34] Bai C, Su F, Zhang W, Kuang H. A Systematic Review on the Research Progress on Polysaccharides from Fungal Traditional Chinese Medicine. Molecules 2023;28(19):6816. doi:10.3390/molecules28196816, PMID:37836659.
[35] Ohta Y, Lee JB, Hayashi K, Fujita A, Park DK, Hayashi T. In vivo anti-influenza virus activity of an immunomodulatory acidic polysaccharide isolated from Cordyceps militaris grown on germinated soybeans. J Agric Food Chem 2007;55(25):10194–10199. doi:10.1021/jf0721287, PMID:17988090.
[36] Koh JH, Kim JM, Chang UJ, Suh HJ. Hypocholesterolemic effect of hot-water extract from mycelia of Cordyceps sinensis. Biol Pharm Bull 2003;26(1):84–87. doi:10.1248/bpb.26.84, PMID:12520179.
[37] Zeng P, Li J, Chen Y, Zhang L. The structures and biological functions of polysaccharides from traditional Chinese herbs. Prog Mol Biol Transl Sci 2019;163:423–444. doi:10.1016/bs.pmbts.2019.03.003, PMID:31030757.
[38] Wang J, Nie S, Chen S, Phillips AO, Phillips GO, Li Y, *et al*. Structural characterization of an α-1, 6-linked galactomannan from natural Cordyceps sinensis. Food Hydrocoll 2018;78:77–91. doi:10.1016/j.foodhyd.2017.07.024.
[39] Ying M, Yu Q, Zheng B, Wang H, Wang J, Chen S, *et al*. Cultured Cordyceps sinensis polysaccharides attenuate cyclophosphamide-induced intestinal barrier injury in mice. J Funct Foods 2019;62:103523. doi:10.1016/j.jff.2019.103523.
[40] Wang J, Kan L, Nie S, Chen H, Cui SW, Phillips AO, *et al*. A comparison of chemical composition, bioactive components and antioxidant activity of natural and cultured Cordyceps sinensis. LWT-Food Sci Technol 2015;63(1):2–7. doi:10.1016/j.lwt.2015.03.109.
[41] Guan J, Zhao J, Feng K, Hu DJ, Li SP. Comparison and characterization of polysaccharides from natural and cultured Cordyceps using saccharide mapping. Anal Bioanal Chem 2011;399(10):3465–3474. doi:10.1007/s00216-010-4396-y, PMID:21152906.
[42] Nie S, Cui SW, Xie M, Phillips AO, Phillips GO. Bioactive polysaccharides from *Cordyceps sinensis*: Isolation, structure features and bioactivities. Bioact Carbohydr Diet Fibre 2013;1(1):38–52. doi:10.1016/j.bcdf.2012.12.002.
[43] Zhu ZY, Liu XC, Tang YL, Dong FY, Sun HQ, Chen L, *et al*. Effects of cultural medium on the formation and antitumor activity of polysaccharides by Cordyceps gunnii. J Biosci Bioeng 2016;122(4):494–498. doi:10.1016/j.jbiosc.2016.03.015, PMID:27074949.
[44] Zhou Y, Schneider DJ, Blackburn MR. Adenosine signaling and the regulation of chronic lung disease. Pharmacol Ther 2009;123(1):105–116. doi:10.1016/j.pharmthera.2009.04.003, PMID:19426761.
[45] Liu QH, Zhang YD, Ma ZW, Qian ZM, Jiang ZH, Zhang W, *et al*. Fractional extraction and structural characterization of glycogen particles from the whole cultivated caterpillar fungus Ophiocordyceps sinensis. Int J Biol Macromol 2023;229:507–514. doi:10.1016/j.ijbiomac.2022.12.319, PMID:36603712.
[46] Liu Y, Wang J, Wang W, Zhang H, Zhang X, Han C. The Chemical

Constituents and Pharmacological Actions of Cordyceps sinensis. Evid Based Complement Alternat Med 2015;2015:575063. doi:10.1155/2015/575063, PMID:25960753.
[47] Li X, Liu Q, Li W, Li Q, Qian Z, Liu X, *et al*. A breakthrough in the artificial cultivation of Chinese cordyceps on a large-scale and its impact on science, the economy, and industry. Crit Rev Biotechnol 2019;39(2):181–191. doi:10.1080/07388551.2018.1531820, PMID:30394122.
[48] Duan X, Yang H, Wang C, Liu H, Lu X, Tian Y. Microbial synthesis of cordycepin, current systems and future perspectives. Trends Food Sci Technol 2023;132:162–170. doi:10.1016/j.tifs.2023.01.006.
[49] Kim J, Shin JY, Choi YH, Lee SY, Jin MH, Kim CD, *et al*. Adenosine and Cordycepin Accelerate Tissue Remodeling Process through Adenosine Receptor Mediated Wnt/β-Catenin Pathway Stimulation by Regulating GSK3b Activity. Int J Mol Sci 2021;22(11):5571. doi:10.3390/ijms22115571, PMID:34070360.
[50] Vincenzi F, Pasquini S, Contri C, Cappello M, Nigro M, Travagli A, *et al*. Pharmacology of Adenosine Receptors: Recent Advancements. Biomolecules 2023;13(9):1387. doi:10.3390/biom13091387, PMID:37759787.
[51] Kitakaze M, Hori M. Adenosine therapy: a new approach to chronic heart failure. Expert Opin Investig Drugs 2000;9(11):2519–2535. doi:10.1517/13543784.9.11.2519, PMID:11060817.
[52] Nakav S, Chaimovitz C, Sufaro Y, Lewis EC, Shaked G, Czeiger D, *et al*. Anti-inflammatory preconditioning by agonists of adenosine A1 receptor. PLoS One 2008;3(5):e2107. doi:10.1371/journal.pone.0002107, PMID:18461129.
[53] Zong SY, Han H, Wang B, Li N, Dong TT, Zhang T, *et al*. Fast Simultaneous Determination of 13 Nucleosides and Nucleobases in Cordyceps sinensis by UHPLC-ESI-MS/MS. Molecules 2015;20(12):21816–21825. doi:10.3390/molecules201219807, PMID:26690105.
[54] Torres N, Tobón-Cornejo S, Velazquez-Villegas LA, Noriega LG, Alemán-Escondrillas G, Tovar AR. Amino Acid Catabolism: An Overlooked Area of Metabolism. Nutrients 2023;15(15):3378. doi:10.3390/nu15153378, PMID:37571315.
[55] Chen L, Liu Y, Guo Q, Zheng Q, Zhang W. Metabolomic comparison between wild Ophiocordyceps sinensis and artificial cultured Cordyceps militaris. Biomed Chromatogr 2018;32(9):e4279. doi:10.1002/bmc.4279, PMID:29752731.
[56] Wu G. Amino acids: metabolism, functions, and nutrition. Amino Acids 2009;37(1):1–17. doi:10.1007/s00726-009-0269-0, PMID:19301095.
[57] Zhao J, Shi T, Zhu W, Chen L, Guan Y, Jin C. Quality control method of sterols in fermented Cordyceps sinensis based on combined fingerprint and quantitative analysis of multicomponents by single marker. J Food Sci 2020;85(10):2994–3002. doi:10.1111/1750-3841.15412, PMID:32918296.
[58] Matsuda H, Akaki J, Nakamura S, Okazaki Y, Kojima H, Tamesada M, *et al*. Apoptosis-inducing effects of sterols from the dried powder of cultured mycelium of Cordyceps sinensis. Chem Pharm Bull (Tokyo) 2009;57(4):411–414. doi:10.1248/cpb.57.411, PMID:19336939.
[59] Yuan JP, Wang JH, Liu X, Kuang HC, Zhao SY. Simultaneous determination of free ergosterol and ergosteryl esters in Cordyceps sinensis by HPLC. Food Chem 2007;105(4):1755–1759. doi:10.1016/j.foodchem.2007.04.070.
[60] Zhao YY, Shen X, Chao X, Ho CC, Cheng XL, Zhang Y, *et al*. Ergosta-4,6,8(14),22-tetraen-3-one induces G2/M cell cycle arrest and apoptosis in human hepatocellular carcinoma HepG2 cells. Biochim Biophys Acta 2011;1810(4):384–390. doi:10.1016/j.bbagen.2010.12.005, PMID:21241775.
[61] Zhabinskii VN, Drasar P, Khripach VA. Structure and Biological Activity of Ergostane-Type Steroids from Fungi. Molecules 2022;27(7):2103. doi:10.3390/molecules27072103, PMID:35408501.
[62] Belwal T, Bhatt ID, Kashyap D, Sak K, Tuli HS, Pathak R, *et al*. Nabavi SM, Silva AS. Ophiocordyceps sinensis. Nonvitamin and Nonmineral Nutritional Supplements. Academic Press; 2019:527–537. doi:10.1016/B978-0-12-812491-8.00069-2.
[63] Han X, Liu LH, Fang XY, Jiang ST, Zhao H, Qian ZM, *et al*. Cordythiazole A, the first member of thiazole alkaloids from Chinese cordyceps, with α-glucosidase inhibitory activity. J Nat Med 2023;77(4):986–991. doi:10.1007/s11418-023-01732-8, PMID:37515674.
[64] Zhang J, Zhong X, Li S, Zhang G, Liu X. Metabolic characterization of natural and cultured Ophicordyceps sinensis from different origins by 1H NMR spectroscopy. J Pharm Biomed Anal 2015;115:395–401. doi:10.1016/j.jpba.2015.07.035, PMID:26279370.
[65] Krishna KV, Ulhas RS, Malaviya A. Bioactive compounds from Cordyceps and their therapeutic potential. Crit Rev Biotechnol 2024;44(5):753–773. doi:10.1080/07388551.2023.2231139, PMID:37518188.
[66] Wang T, Tang C, Xiao M, Cao Z, He H, He M, *et al*. Analysis of metabolic spectrum characteristics of naturally and cultivated Ophiocordyceps sinensis based on non-targeted metabolomics. Sci Rep 2024;14(1):17425. doi:10.1038/s41598-024-68306-w, PMID:39075220.
[67] Yang L, Chen J, Lu H, Lai J, He Y, Liu S, *et al*. Pueraria lobata for Diabetes Mellitus: Past, Present and Future. Am J Chin Med 2019;47(7):1419–1444. doi:10.1142/S0192415X19500733, PMID:31659910.
[68] Zhang Z, Zhang L, Xu H. Effect of Astragalus polysaccharide in treatment of diabetes mellitus: a narrative review. J Tradit Chin Med 2019;39(1):133–138. PMID:32186034.
[69] Baska A, Leis K, Gałązka P. Berberine in the Treatment of Diabetes Mellitus: A Review. Endocr Metab Immune Disord Drug Targets 2021;21(8):1379–1386. doi:10.2174/1568026620666201022144405, PMID:33092516.
[70] An X, Xu Y, Gui D. Combination of Astragalus membranaceus and Panax notoginseng as Main Components in the Treatment of Diabetic Nephropathy: A Systematic Review and Meta-Analysis. Evid Based Complement Alternat Med 2023;2023:2945234. doi:10.1155/2023/2945234, PMID:37101717.
[71] Sun H, Yu X, Li T, Zhu Z. Structure and hypoglycemic activity of a novel exopolysaccharide of Cordyceps militaris. Int J Biol Macromol 2021;166:496–508. doi:10.1016/j.ijbiomac.2020.10.207, PMID:33129900.
[72] Wang Y, Wang M, Ling Y, Fan W, Wang Y, Yin H. Structural determination and antioxidant activity of a polysaccharide from the fruiting bodies of cultured Cordyceps sinensis. Am J Chin Med 2009;37(5):977–989. doi:10.1142/S0192415X09007387, PMID:19885957.
[73] Wu F, Yan H, Ma X, Jia J, Zhang G, Guo X, *et al*. Comparison of the structural characterization and biological activity of acidic polysaccharides from Cordyceps militaris cultured with different media. World J Microbiol Biotechnol 2012;28(5):2029–2038. doi:10.1007/s11274-012-1005-6, PMID:22806024.
[74] Zhao H, Lai Q, Zhang J, Huang C, Jia L. Antioxidant and Hypoglycemic Effects of Acidic-Extractable Polysaccharides from Cordyceps militaris on Type 2 Diabetes Mice. Oxid Med Cell Longev 2018;2018:9150807. doi:10.1155/2018/9150807, PMID:30595798.
[75] Xu RH, Peng XE, Chen GZ, Chen GL. Effects of cordyceps sinensis on natural killer activity and colony formation of B16 melanoma. Chin Med J (Engl) 1992;105(2):97–101. PMID:1597083.
[76] Rong L, Li G, Zhang Y, Xiao Y, Qiao Y, Yang M, *et al*. Structure and immunomodulatory activity of a water-soluble α-glucan from Hirsutella sinensis mycelia. Int J Biol Macromol 2021;189:857–868. doi:10.1016/j.ijbiomac.2021.08.185, PMID:34464642.
[77] Bi S, Jing Y, Zhou Q, Hu X, Zhu J, Guo Z, *et al*. Structural elucidation and immunostimulatory activity of a new polysaccharide from Cordyceps militaris. Food Funct 2018;9(1):279–293. doi:10.1039/c7fo01147d, PMID:29168868.
[78] Zhang J, Yu Y, Zhang Z, Ding Y, Dai X, Li Y. Effect of polysaccharide from cultured Cordyceps sinensis on immune function and antioxidation activity of mice exposed to 60Co. Int Immunopharmacol 2011;11(12):2251–2257. doi:10.1016/j.intimp.2011.09.019, PMID:22001898.
[79] Gu L, Yu T, Liu J, Lu Y. Evaluation of the mechanism of cordyceps polysaccharide action on rat acute liver failure. Arch Med Sci 2020;16(5):1218–1225. doi:10.5114/aoms.2020.94236, PMID:32864011.
[80] Lee BH, Chen CH, Hsu YY, Chuang PT, Shih MK, Hsu WH. Polysaccharides Obtained from Cordyceps militaris Alleviate Hyperglycemia by Regulating Gut Microbiota in Mice Fed a High-Fat/Sucrose Diet. Foods 2021;10(8):1870. doi:10.3390/foods10081870, PMID:34441649.
[81] Lei J, Wei Y, Song P, Li Y, Zhang T, Feng Q, *et al*. Cordycepin inhibits LPS-induced acute lung injury by inhibiting inflammation and

oxidative stress. Eur J Pharmacol 2018;818:110–114. doi:10.1016/j.ejphar.2017.10.029, PMID:29054740.
[82] Kim HG, Shrestha B, Lim SY, Yoon DH, Chang WC, Shin DJ, *et al*. Cordycepin inhibits lipopolysaccharide-induced inflammation by the suppression of NF-kappaB through Akt and p38 inhibition in RAW 264.7 macrophage cells. Eur J Pharmacol 2006;545(2-3):192–199. doi:10.1016/j.ejphar.2006.06.047, PMID:16899239.
[83] Liu Y, Guo ZJ, Zhou XW. Chinese Cordyceps: Bioactive Components, Antitumor Effects and Underlying Mechanism-A Review. Molecules 2022;27(19):6576. doi:10.3390/molecules27196576, PMID:36235111.
[84] Tan L, Liu S, Li X, He J, He L, Li Y, *et al*. The Large Molecular Weight Polysaccharide from Wild Cordyceps and Its Antitumor Activity on H22 Tumor-Bearing Mice. Molecules 2023;28(8):3351. doi:10.3390/molecules28083351, PMID:37110586.
[85] He W, Zhang MF, Ye J, Jiang TT, Fang X, Song Y. Cordycepin induces apoptosis by enhancing JNK and p38 kinase activity and increasing the protein expression of Bcl-2 pro-apoptotic molecules. J Zhejiang Univ Sci B 2010;11(9):654–660. doi:10.1631/jzus.B1000081, PMID:20803769.
[86] Yuan Q, Xie F, Tan J, Yuan Y, Mei H, Zheng Y, *et al*. Extraction, structure and pharmacological effects of the polysaccharides from Cordyceps sinensis: A review. J Funct Foods 2022;89:104909. doi:10.1016/j.jff.2021.104909.
[87] Wen Z, Du X, Meng N, Li Y, Mi R, Li X, *et al*. Tussah silkmoth pupae improve anti-tumor properties of Cordyceps militaris (L.) Link by increasing the levels of major metabolite cordycepin. RSC Adv 2019;9(10):5480–5491. doi:10.1039/c8ra09491h, PMID:35515955.
[88] Ma S, Sun Y, Wang F, Mi R, Wen Z, Li X, *et al*. Effects of tussah immunoreactive substances on growth, immunity, disease resistance against Vibrio splendidus and gut microbiota profile of Apostichopus japonicus. Fish Shellfish Immunol 2017;63:471–479. doi:10.1016/j.fsi.2017.02.045, PMID:28254498.
[89] Shweta, Abdullah S, Komal, Kumar A. A brief review on the medicinal uses of Cordyceps militaris. Pharmacol Res - Mod Chin Med 2023;7:100228. doi:10.1016/j.prmcm.2023.100228.
[90] Dong CH, Yao YJ. In vitro evaluation of antioxidant activities of aqueous extracts from natural and cultured mycelia of Cordyceps sinensis. Lebensm Wiss Technol 2008;41(4):669–677. doi:10.1016/j.lwt.2007.05.002, PMID:32287390.
[91] Wang BS, Lee CP, Chen ZT, Yu HM, Duh PD. Comparison of the hepatoprotective activity between cultured Cordyceps militaris and natural Cordyceps sinensis. J Funct Foods 2012;4(2):489–495. doi:10.1016/j.jff.2012.02.009.