Acupuncture and Herbal Medicine

Ophiocordyceps sinensis: decoding its journey—from snowy legends to modern science

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Abstract

Ophiocordyceps sinensis (Berk) Sacc. (*O. sinensis*; Family: Clavicipitaceae; synonym: *Cordyceps sinensis*) is a fungus that is revered in ancient Tibetan folklore as a "miraculous species that becomes a worm in winter and a grass in summer" and renowned as the "elixir of life gifted" by the snow-capped region. Its evolutional awareness and utilization span both traditional Chinese medicine practices and modern biomedical research, rendering it a quintessential example of symbiotic entomo-fungal biological resource development. Extensive research on the biological characteristics, active constituents, pharmacological effects, and underlying mechanisms of *O. sinensis* has generated significant breakthroughs in recent years. From "heavenly elixir" to a vital tonic in imperial cuisine, and from its symbiotic life cycle to its current prominence in modern pharmacological research and clinical applications, this fungus has nurtured both the cultural legends and survival wisdom of the Plateau ancestors and reflected the long journey of contemporary scientific exploration and industrialization. This review traces the journey of *O. sinensis* from traditional empirical applications to scientific validation, focusing on its biological characteristics, extraction and separation techniques for key bioactive constituents, and its pharmacological effects and molecular mechanisms in antitumor activity, immunomodulation, renoprotection, antioxidant properties, and anti-aging effects, and summarizes the current status of its clinical applications. Furthermore, this review examines the challenges confronting current research on *O. sinensis*, including resource conservation and sustainable utilization, quality control and standardization, differences between artificially cultivated and wild-harvested specimens, further elucidating its mechanisms of action and outlining prospects for future research directions.

Keywords: *A*ctive constituents, Clinical applications, Extraction and separation techniques, *Ophiocordyceps sinensis*, Pharmacological effects

Graphical abstract: https://links.lww.com/AHM/A226

Introduction

Ophiocordyceps sinensis (*O. sinensis*; Family: Clavicipitaceae; synonym: *Cordyceps sinensis*), a rare high-altitude fungus endemic to the Qinghai-Tibet Plateau, represents a unique intersection of traditional medicine and contemporary scientific inquiry. Overharvesting and environmental stress have driven the significant decline of wild populations of this prized medicinal and culinary resource, prompting its universal classification as a protected species. Notwithstanding its extensive documentation in time-honored traditional Tibetan and Chinese medicine, particularly for treating pulmonary and renal dysfunctions, the empirical foundations of its therapeutic claims have historically lacked rigorous scientific validation.

Rapid advancement of modern biotechnology and analytical methodologies has enabled a systematic, in-depth investigation of *O. sinensis*, translating its traditional applications into quantifiable and verifiable scientific evidence. Accumulating research bridges empirical knowledge and contemporary science, elucidating the exceptional biological characteristics, complex chemical composition, and extensive pharmacological activities of the fungus.

A review was conducted to identify relevant studies on Ophiocordyceps sinensis (syn. Cordyceps sinensis). A comprehensive literature search was performed in multiple electronic databases, including PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data, and the Chinese Science and Technology Periodical Database (VIP), covering publications from database inception up to December 2025. The search strategy utilized keywords such as "Ophiocordyceps sinensis" "Cordyceps sinensis" "dong chong xia cao" "bioactive constituents" "pharmacological effects" "antitumor" "immunomodulation" "clinical application" and their combinations.This review presents a synthesis of current scientific knowledge on *O. sinensis*: first,

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its historical and traditional significance is contextualized; second, the latest findings regarding its bioactive constituents, demonstrated pharmacological effects, and underlying mechanisms of action are elucidated; and third, the significant challenges and opportunities in its sustainable utilization, including conservation strategies and artificial cultivation, are discussed. Thus, by consolidating existing research and highlighting key knowledge gaps, this review summarizes the field status, aiming to guide future research directions, ultimately contributing to the rational development, conservation, and modern integration of this valuable biological resource.

Historical and traditional perspectives

O. sinensis is primarily distributed in the Qinghai-Tibet Plateau at altitudes >3,000 m, encompassing mainly the Chinese provinces and autonomous regions of Tibet, Gansu, Qinghai, Sichuan, and Yunnan, as well as parts of the Himalayan regions in Bhutan, India, and Nepal. Excessive harvesting, climate change, and ecological damage have caused a significant decline in wild *O. sinensis* populations. The 1999 and 2021 editions of the List of National Key Protected Wild Plants classify this fungus as a National Grade II Protected Species. The *China Biodiversity Red List: Macrofungi Volume* and the IUCN Red List of Threatened Species classify it as "Vulnerable." *O. sinensis* has long been used in Tibetan and traditional Chinese medicine. The oldest extant Tibetan medical text, the "*rGyud bzhi*" (The Four Medical Tantras), first documented the efficacy of *Cordyceps* (dong chong xia cao) for "treating lung diseases" in AD 710. The "Sowa Rigpa" (Traditional Tibetan Medicine) further describes it as "tonifying the lung and kidney, strengthening essence, and resolving phlegm." The "*Ben Cao Cong Xin*" (New Compilation of Materia Medica, 1757) records the following: "For *Cordyceps*, the best quality is produced in the Jiading Prefecture of Sichuan; those from Yunnan and Guizhou are inferior. In winter, it resides in the soil, its body alive like an old silkworm, having hair and capable of movement. By summer, its hair emerges above the earth, and the entire body transforms into a plant." Similarly, the "*Ben Cao Gang Mu Shi Yi*" (Supplements to the Compendium of Materia Medica, 1765) states the following: "Summer-plant Winter-worm (*Cordyceps*) shares similar medicinal properties with ginseng and is capable of treating various deficiency syndromes and consumptive diseases." *Cordyceps* has been included in all editions (1963–2025) of *the Pharmacopoeia of the People's Republic of China*. The 2025 edition records its functions as follows: "Tonifies the kidney and lung, stops bleeding, and resolves phlegm. It is used for patterns such as kidney deficiency with essence depletion, impotence and seminal emission, soreness and weakness of the lumbar region and knees, chronic cough with wheezing due to deficiency, and consumptive cough with bloody sputum."

Biological characteristics of *O. sinensis*

Life cycle: host infection, dormancy, and stroma development

Cordyceps begins its life cycle by infecting a specific insect host: the larva of the ghost moth (*Thitarodes* spp.) The adult moths lay eggs in the alpine meadow or shrubland soil at altitudes of 3,000 to 5,000 m during summer. The hatched larvae feed on tender plant roots, growing slowly underground. The conidia or ascospores of *Cordyceps* are dispersed in the soil. The surfaces of these spores may harbor proteins capable of binding to specific receptors on the larvae's cuticle, endowing them with a highly specific target-host recognition ability and ensuring that infection occurs exclusively in ghost moth larvae. Under suitable temperature and humidity conditions, the spores in contact with the larval surfaces (particularly soft body segments or spiracles) germinate to form highly penetrative germ tubes or infection pegs. These structures secrete chitinase and protease enzymes to dissolve the larval exoskeleton, enabling successful penetration. The transformation of blastospores into invasive hyphae represents the critical initial step for successful colonization. On invading the larval hemocoel, the fungus does not immediately kill the host; rather, it proliferates and disseminates in a yeast-like mycelial form[1–2]. Infected larvae exhibit significantly reduced acetylcholine (ACh) levels in their brains, with elevated choline levels and abnormal acetylcholinesterase (AChE) activity. Subsequently, the larvae are manipulated to migrate to positions near the soil surface and perish with their heads oriented upward, creating optimal conditions for further fungal growth. The larvae's exoskeletons remain largely intact, transforming into mycelium-filled fungal sclerotia[3]. This rigid larva-mycelium complex constitutes the "winter worm" form. The infection strategy of *Cordyceps* involves multi-level regulation. First, during infection, its mycelium may modulate the host's physiological state by activating specific signaling pathways, such as the cAMP-PKA pathway. *Cordyceps* regulates steroid production by inhibiting P450scc enzyme activity, thereby influencing mycelial differentiation and growth. Second, *Cordyceps* exhibits significant fluctuations in bacterial communities during infection, facilitating their rapid invasion and host adaptation. The fungus–host interaction may further regulate hyphal differentiation *via* metabolic pathways, such as the tricarboxylic acid (TCA) cycle[4–5]. Moreover, the RNA editing patterns of fungal mitochondrial genomic characteristics, such as repetitive sequences and methylation patterns, may play crucial roles during infection and differentiation. In the late spring to early summer of the following year, under favorable temperature and humidity conditions, the fungus sprouts a club-shaped stroma from the head of the mummified larva, particularly around its mouthparts ("grass" and "insect" composite). This stroma breaks through the soil surface, growing steadily upward until it emerges above ground, forming the "summer grass." Figure 1 illustrates the life cycle of *O. sinensis*.

Growth environment and characteristics

As a high-altitude endemic entomo-symbiont, *O. sinensis* exhibits distinctive metabolic regulation and genomic evolutionary characteristics under extreme environmental conditions such as low temperature and hypoxia.

The Pharmacopoeia of the People's Republic of China records the following: "The insect body resembles a silkworm, measuring 3 to 5 cm in length and

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0.3 to 0.8 cm in diameter; its surface is deep yellow to yellowish-brown, bearing 20 to 30 annular rings, with those near the head being finer; the head is reddish-brown, possessing eight pairs of legs, the middle four pairs being more conspicuous; it is brittle, easily broken, with a slightly flat fracture surface and a pale yellowish-white color. The stroma is slender and cylindrical, measuring 4 to 7 cm in length and approximately 0.3 cm in diameter. The surface exhibits a dark brown to brownish color with fine longitudinal wrinkles, and the upper part is slightly swollen. The texture is pliable and tough, and the cross-section appears whitish. It has a slightly fishy odor and a mildly bitter taste"[6]. Guo et al.[7] observed the life cycle of the fungus, from parasitic larvae to *O. sinensis*, in the Tibetan High-Altitude Laboratory (directly simulating high-altitude conditions). Experimental evidence indicates that fruiting bodies become more slender in high-altitude environments, developing a darker coloration as an adaptation to intense ultraviolet radiation and low temperatures[7]. Concurrently, high-altitude environments (accompanied by hypoxia) induce significant lipid accumulation in the insect body, enhancing its overall antioxidant capacity of *O. sinensis*, as reflected in the density and coloration of the insect body cross-section[8]. A molecular phylogenetic study of *O. sinensis* from distinct geographical populations (adapted to varying altitudes) revealed that populations from higher altitudes and more hypoxic environments may regulate gene expression to modify their mycelial and fruiting body morphologies (eg, denser structure and darker coloration) to enhance stress resistance[9].

Genome sequencing revealed the significant evolutionary adaptations of *O. sinensis* during its acclimatization to high-altitude environments, with marked expansions in gene families associated with cold tolerance, fungal pathogenicity, and host infection. Mitochondrial genomic analysis revealed widespread DNA methylation modifications, possibly influencing the activity of oxidative phosphorylation enzymes and mitochondrial respiration rates, thereby facilitating adaptation to high-altitude hypoxic conditions. Furthermore, methylation modifications may correlate with transcription factor binding affinity, further regulating gene expression[10]. Transcriptome analysis revealed that key fatty acid metabolism genes (eg, acyl-CoA dehydrogenase and enoyl-CoA hydratase) were significantly upregulated in wild *O. sinensis*[11]. Additionally, the glycerophospholipid metabolism and secondary metabolite biosynthesis pathways in *O. sinensis* are significantly activated under high-altitude conditions, promoting triacylglycerol (TG) degradation and phosphatidylcholine (PC) and phosphatidylethanolamine (PE) synthesis and enhancing its antioxidant capacity and free radical scavenging ability[8]. Moreover, *O. sinensis* upregulates the expression of hypoxia-inducible factor-1α (HIF-1α) and its target genes, such as erythropoietin (*EPO*), glucose transporter type 1 (*GLUT1*), and vascular endothelial growth factor (*VEGF*), under hypoxic conditions, augmenting cellular adaptation to hypoxia[12].

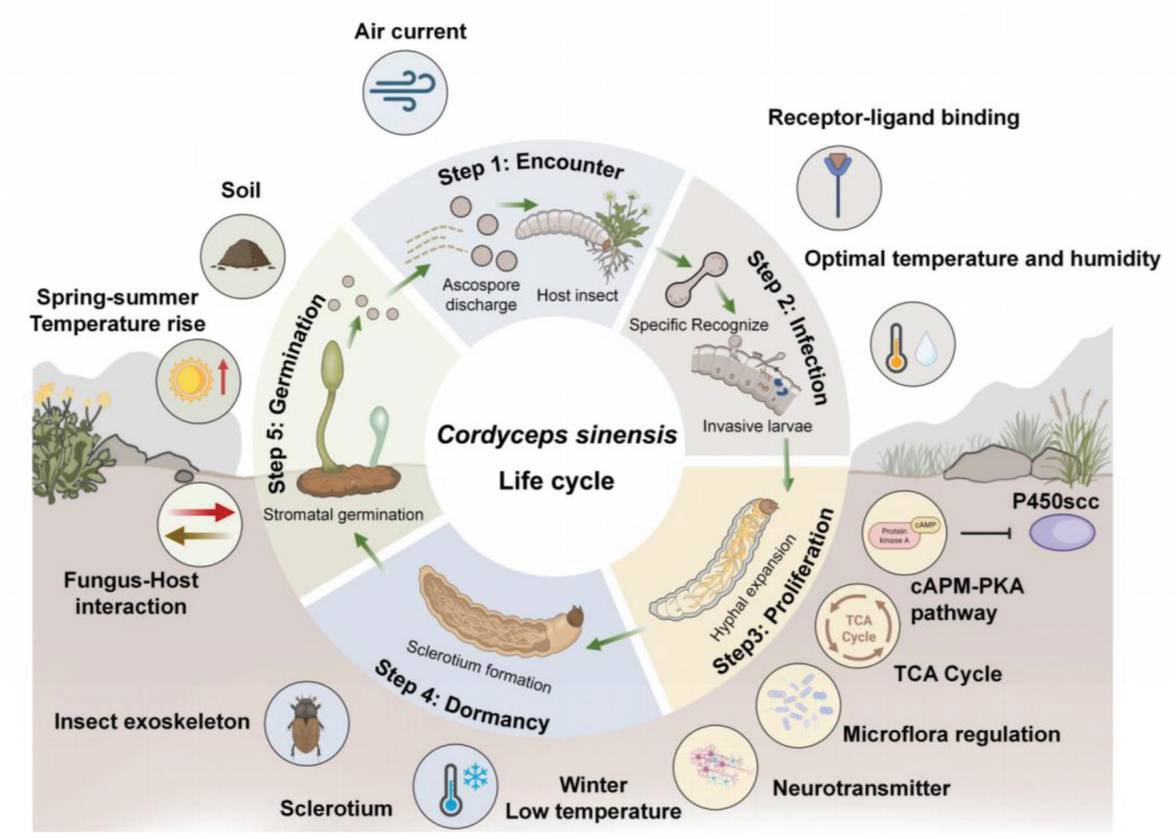


Figure 1. Life cycle of *Ophiocordyceps sinensis*.

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O. sinensis is rich in antioxidants, such as peptides, polyphenols, and nucleosides, which significantly enhance its antioxidant capacity under hypoxic and low-temperature conditions[13]; for example, polypeptides protect against oxidative damage by scavenging reactive oxygen species (ROS) and chelating heavy metal ions[14]. In summary, *O. sinensis* adapts to high-altitude low-temperature hypoxic conditions *via* multiple mechanisms, including stress-related gene family expansions, epigenetic modifications, specific metabolic pathway activation, and enhanced antioxidant capacity (Figure 2). These adaptive traits reveal its survival strategies and provide a scientific ground for developing its medicinal value.

Wild Versus *cultivated* O. sinensis

Wild *O. sinensis* are exceedingly rare and difficult to obtain. The extreme environmental conditions, such as low temperature, hypoxia, and intense ultraviolet radiation, in the Qinghai-Tibet Plateau and its neighboring areas, are considered crucial factors in shaping its unique chemical composition and biological activity[15]. The life cycle (fungal parasitism, stroma formation, and spore release) of wild *O. sinensis* is constrained by natural environmental factors, and typically requires several years for completion. Conversely, cultivated *O. sinensis* has a significantly shortened life cycle in simulated high-altitude environments, including temperature, humidity, and light conditions, which enables large-scale production[16]. The principal distinctions between wild and cultivated *O. sinensis* are described in the following sections.

Components

Both wild and cultivated *O. sinensis* contain nucleosides, polysaccharides, amino acids, sterols, and other constituents, with significant variations observed in certain component levels. Zhang et al.[17] found significant differences in the metabolic profiles of wild and cultivated *O. sinensis*. A total of 256 and 250 differentially expressed metabolites, primarily nucleotides and nucleosides, amino acids and their derivatives, carbohydrates and their derivatives, and phenolic acids, were detected in the fruiting bodies and sclerotia of wild and cultivated *O. sinensis*, respectively. Wang et al.[18] discovered that both wild and cultivated *O. sinensis* exhibit similar fishy odor, albeit originating from different tissues: stroma *versus* sclerotia, respectively. Furthermore, the authors found higher concentrations of volatile compounds such as acetic acid, amyl acetate, and 1-butanol in wild *O. sinensis*, and styrene, isophorone, and 1-pyrrole in cultivated *O. sinensis*.

Pharmacological effects

O. sinensis possesses antitumor activity, immunomodulation, hypoglycemic effects, and antioxidant properties. Gu et al.[19] used 2D nuclear magnetic resonance (NMR)-based metabolomics and *in vitro* assays to compare the chemical composition of wild and cultivated *O. sinensis* and evaluate their pharmacological activity. Cultivated *O. sinensis* was found to contain higher fatty acids (such as linoleic and oleic acids), and wild *O. sinensis*, higher sterols (such as ergosterol, ergosterol

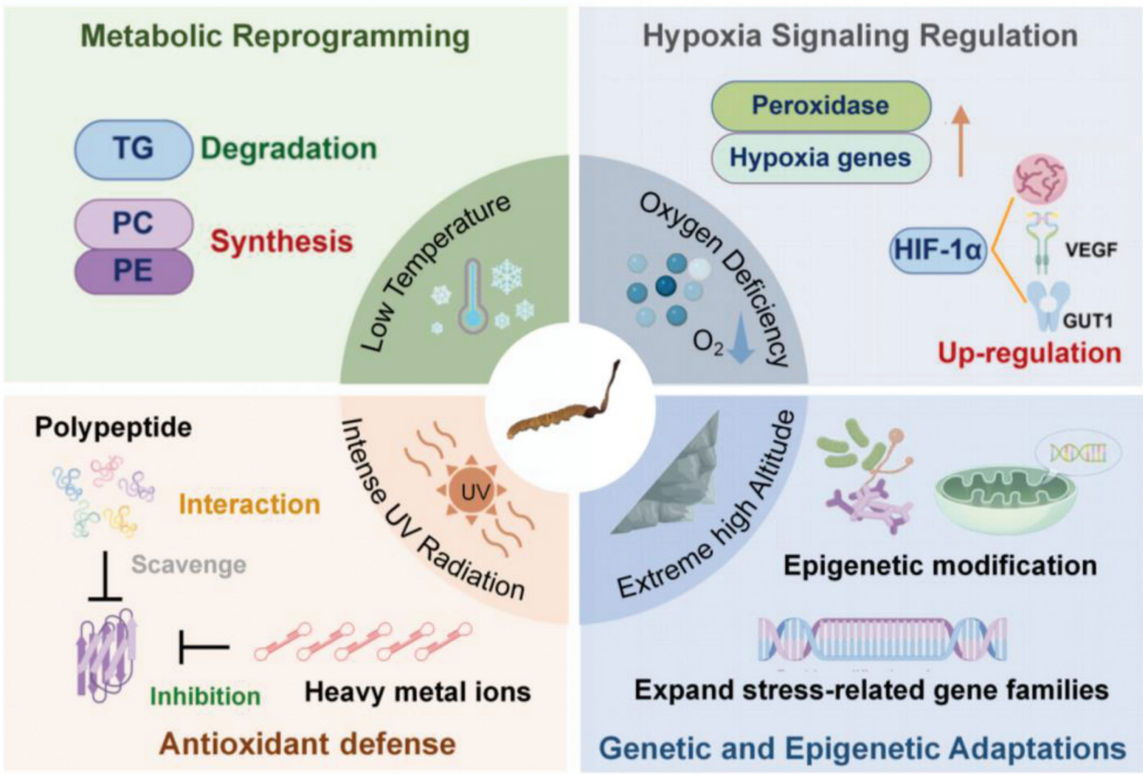


Figure 2. Growth environment and characteristics of *Ophiocordyceps sinensis*. *EPO*: Erythropoietin; *GLUT1*: Glucose transporter type 1; HIF-1α: Hypoxia-inducible factor-1; PC: Phosphatidylcholine; PE: Phosphatidylethanolamine; TG: Triacylglycerols; *VEGF*: Vascular endothelial growth factor.

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peroxide, and β-sitosterol). Cellular assays demonstrated superior antitumor activity in wild *O. sinensis*. Zheng et al.[20] demonstrated that both wild and cultivated *O. sinensis* exhibited comparable pharmacological activity in counteracting cyclophosphamide (CTX)-induced immunosuppression in mice. Furthermore, in aging models, cultivated *O. sinensis* displayed superior antioxidant activity. Dong and Sun[21] quantified 10 nucleosides (cytidine, adenine, guanine, uracil, hypoxanthine, uridine, adenosine, 2′-deoxyadenosine, guanosine, and thymidine) in cultivated *O. sinensis*, with a total content of approximately 2%. Ergosterol and polysaccharide constituted approximately 0.55% and 4.4%, respectively. Furthermore, in a high-glucose-induced rat mesangial cell model, nucleosides, ergosterol, and polysaccharides significantly reduced extracellular matrix (ECM) protein levels, suggesting antifibrotic activity.

Safety

Multiple studies indicate that wild *O. sinensis* exhibits excessive arsenic levels. In 2008, 13 of 14 batches of wild samples exceeded the permissible arsenic limit[22]. In 2017, all 45 batches of commercially available samples exceeded the arsenic limit[23]. Some wild *O. sinensis* specimens have arsenic levels of 6.17 mg/kg, far exceeding international safety standards[24]. In 2016, the erstwhile China Food and Drug Administration monitored and tested *O. sinensis* specimens, *Cordyceps* powder, and pure powder tablets and found arsenic levels of 4.4 to 9.9 mg/kg, indicating that their prolonged consumption may precipitate the significant risk of arsenic accumulation in the human body[25]. The heavy metal profile of cultivated *O. sinensis* or fermented *O. sinensis* products is more readily controlled than that of wild *O. sinensis*. Liu et al.[26] tested for lead, cadmium, mercury, arsenic, and copper and found lower lead, arsenic, and copper levels in cultivated *O. sinensis* specimens than in wild *O. sinensis* specimens.

Despite significant advances in *O. sinensis* cultivation, the full replication of its complex natural environment remains challenging. Moreover, wild *O. sinensis* harbors a rich microbial community. These symbiotic microorganisms may influence the growth, development, and production of the fungal bioactive compounds. However, their precise functions and underlying mechanisms require thorough investigation[27]. Guo et al.[28] isolated the endophytic fungus *Penicillium herquei* from the stroma of *O. sinensis* and induced the production of 3 novel α-pyrone derivatives *via* chemical epigenetics manipulation. This suggests that endophytic fungi may constitute a source of the complex chemical constituents in *O. sinensis*. Li et al.[29] isolated four novel heterocyclic alkanes from the endophytic fungus *Aspergillus fumigatus* in *O. sinensis* and evaluated their cytotoxicity. These studies suggest that the biological characteristics of *O. sinensis* extend far beyond the fungus and its host-insect, with its complex micro-ecosystem warranting attention as well. Successful cultivation and breakthroughs in genomics hold unprecedented opportunities. Future research should continue to focus on the mechanisms of the entomo–fungal interactions, environmental adaptability, and the functions of symbiotic microbial communities to provide a more robust scientific foundation for the conservation, quality control, and sustainable utilization of *O. sinensis*.

The biological characteristics and medicinal value of *O. sinensis* are intrinsically linked to its unique life cycle and environmental adaptations. Although current research has elucidated multiple aspects, from host-specific infection to environmentally driven metabolic regulation, key mechanisms remain unexplored. The molecular signaling pathways *via* which the fungus precisely manipulates host behavior and maintains its "zombie state" remain unexplained. Similarly, systematic analysis of the environmental factors that ultimately shape its morphology and metabolic profile *via* hierarchical networks such as epigenetics is lacking, resulting in cultivated specimens being biologically non-equivalent to their wild counterparts, as they cannot replicate the unique secondary metabolic pathways shaped by natural interactions and extreme environmental stress. Future breakthroughs hinge on emerging technologies: single-cell techniques to decipher host–fungus interface interactions, or synthetic biology strategies to simulate environmental adaptation mechanisms for optimized cultivation. This foundational understanding must be strengthened for advancing the sustainable utilization and scientific development of this valuable resource.

Chemical composition and bioactive compounds

O. sinensis owes its extensive pharmacological activity and multi-target synergistic effects to its complex and diverse bioactive constituents, including nucleosides, polysaccharides, sterols, fatty acids, proteins, amino acids, and inorganic elements.

Primary active constituents

Nucleosides

O. sinensis comprises >30 nucleosides, including adenosine, cytidine, uridine, guanosine, and inosine. Cordycepin (3′-deoxyadenosine) and adenosine are key pharmacological effect drivers[30]. Cordycepin, a unique nucleoside analogue found in both wild and cultivated *O. sinensis*, has been extensively studied for its antitumor[31], antiviral[32], and anti-inflammatory effects[33]. Adenosine, a crucial endogenous nucleoside, regulates various physiological processes, including antioxidant activity[34] and cardiovascular protection[35]. According to the 2025 *Pharmacopoeia of the People's Republic of China*, adenosine content serves as the chemical standard for evaluating *O. sinensis*. Khan et al.[36] determined *via* high-performance liquid chromatography (HPLC) that *O. sinensis* contained 0.71% adenine (w/w); however, cordycepin was not detected, possibly owing to sample origin, processing methods, or detection limits. Zhou et al.[37] found that adenosine and cordycepin levels in cultivated *O. sinensis* were significantly higher than those in its wild counterpart, suggesting that cultivation may enrich specific bioactive compounds. The molecular structural formulae of the principal nucleosides in *O. sinensis* are presented in Figure 3.

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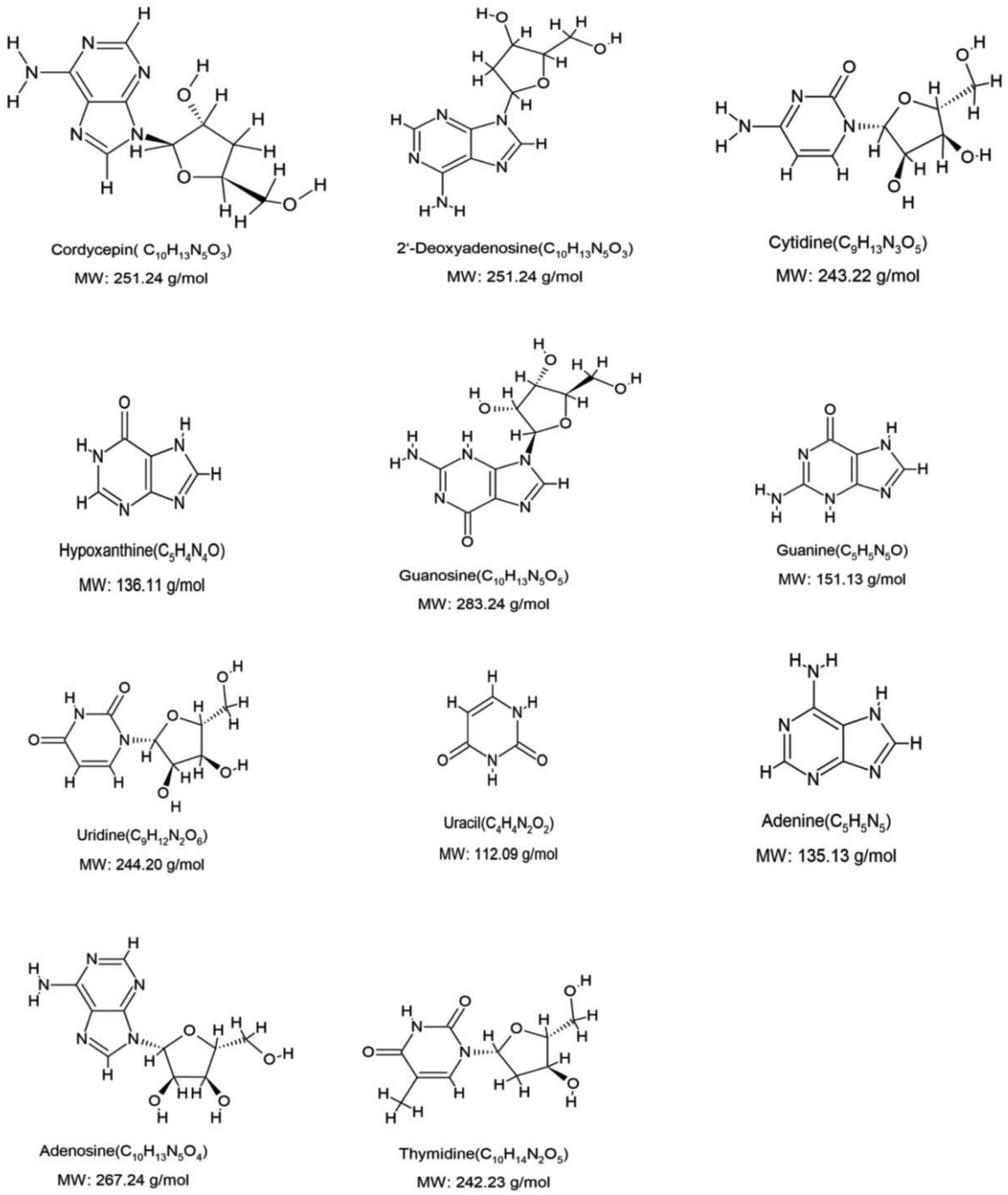


Figure 3. Molecular structural formulae of the principal nucleosides in *Ophiocordyceps sinensis*.

Polysaccharides

Polysaccharides demonstrate immunomodulation[38], antidepressant[39], antitumor[40], and antifibrotic[21] pharmacological effects. The typically water-soluble polysaccharides comprise multiple monosaccharides, and their structural complexity determines the diversity of their biological activities. Jayakumar et al.[41] purified a mycelium-derived novel water-soluble polysaccharide, *Cordyceps militaris* exopolysaccharide-1 (CME-1), and demonstrated its antitumor activity against B16-F10 melanoma cells. Yang and Zhang investigated the production of selenium-enriched polysaccharides and their antioxidant and anti-diabetic activities[42]. Wang[43] proposed using polysaccharides as quality markers for *O. sinensis*, enabling rapid identification *via* powder X-ray diffraction (PXRD). Qian et al.[44] isolated a novel polysaccharide, CSWP-80 (galactomannan, molecular weight [MW]: 26.2 kDa), and confirmed its significant

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antioxidant and immunomodulatory activity in *in vitro* experiments. The molecular structural formulae of the principal polysaccharides in *O. sinensis* are presented in Figure 4.

Sterols

Sterols (free sterols, sterol esters, and sterol glycosides) exhibit antitumor, anti-inflammatory, and antibacterial effects. Wang et al.[45] were the first to analyze sterol compounds in wild and cultivated *O. sinensis* and fermented mycelia of *Trichoderma sinense* and *Penicillium chrysogenum* from bat moths. A total of 141 sterols have been identified, 95 (16 free sterols, 76 sterol esters, and three sterol glycosides) were newly discovered in *O. sinensis*. Ergosterol is a primary active sterol in *O. sinensis*. In cellular and animal models, ergosterol inhibits hepatic stellate cell activation in a dose-dependent manner *via* the upregulation of lysosomal membrane permeability and

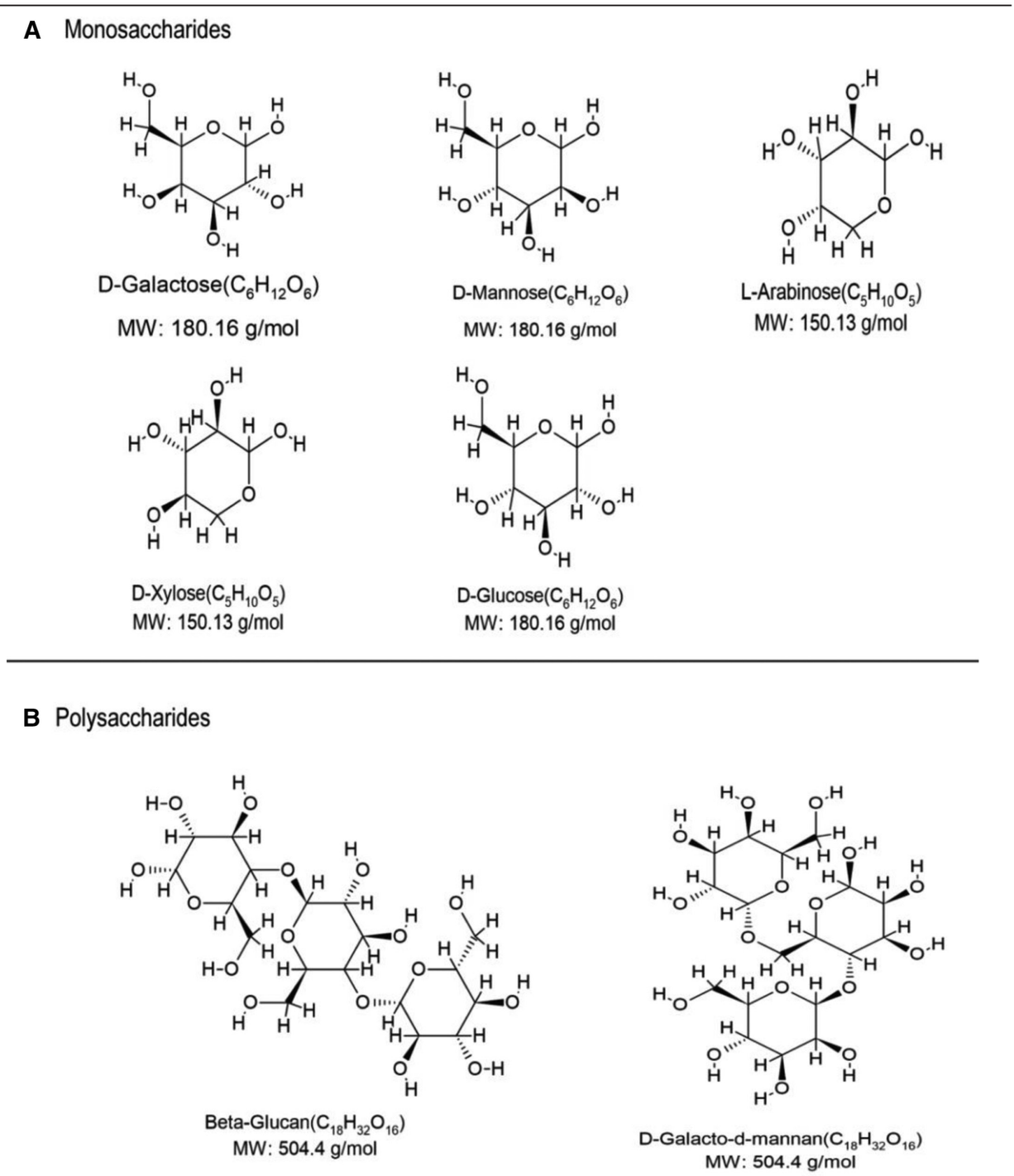


Figure 4. Molecular structural formulae of the principal polysaccharides in *Ophiocordyceps sinensis*. (A) Monosaccharides, (B) polysaccharides.

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downregulation of α-smooth muscle actin (α-SMA) expression, thus exerting an antifibrotic effect[46]. Ergosterol inhibits the nuclear factor kappa-B (NF-κB)/p65 pathway, reducing cigarette smoke extract-induced inflammation, oxidative stress, and apoptosis and alleviating chronic obstructive pulmonary disease (COPD) symptoms[47]. Mycelia-isolated ergosterol peroxides and their glycoside derivatives have exhibited cytotoxic effects against HL-60 (promyelocytic leukemia) and K562 (chronic myeloid leukemia) tumor cell lines, while inducing tumor cell apoptosis[48]. Dihydroergosterol and ergosterol peroxides inhibit the production and release of pro-inflammatory cytokines (tumor necrosis factor-α [TNF-α] and interleukin [IL]-1α/β), alleviating inflammatory responses[49]. Notably, 22,23-dihydroergosterol inhibits tyrosinase activity, reducing melanin formation and achieving skin brightening and lightening; moreover, it promotes collagen synthesis in fibroblasts, improving skin elasticity and diminishing wrinkles[50]. Ergosterol peroxide glycosides such as 5,6-Epoxy-24(R)-methylcholest-7,22-dien-3β-ol and 5α,8α-Epidioxy-24(R)-methylcholest-6,22-dien-3β-ol exhibit antitumor activity[51]. Ergosterol peroxide disrupts mitochondrial function and inhibits tumor growth and metastasis[52–53]. In mouse cancer models, ergosterol peroxides inhibited tumor growth and demonstrated a good tolerability profile[54]. Ergosterol peroxide 3-O-β-D-glucopyranoside exhibits antitumor activity[55]. Similarly, β-sitosterol exhibits proliferation-inhibiting and apoptosis-inducing effects on certain cancer cell lines[56]. It may contribute to cardiovascular health by reducing total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels, by regulating inflammatory mediator production or influencing immune cell function, and by inhibiting cholesterol absorption[57]. Cholesterol, a primary sterol in *O. sinensis*, is a structural component of fungal cell membranes and serves as a precursor for sterol synthesis[58]. The molecular formulae of the primary sterols and their derivatives in *O. sinensis* are presented in Figure 5.

Amino acids

O. sinensis possesses 18 to 19 amino acids, including all eight essential amino acids[59]. These amino acids frequently act synergistically with nucleosides and polysaccharides to exert diverse pharmacological effects *via* multiple pathways. The "calming and tranquilizing" or sedative and hypnotic effects of *O. sinensis* are directly associated with its amino acid composition, primarily tryptophan[60]. Tryptophan and phenylalanine protect against CTX-induced bone marrow suppression[61]. *O. sinensis* extract induces significant airway relaxation *via* the nitric oxide (NO) signaling pathway. Arginine, as a precursor for NO synthesis, mediates airway relaxation *via* both cyclic guanosine monophosphate (cGMP)-dependent and independent NO signaling pathways, thus improving respiratory function[62]. Tyrosine and tryptophan metabolic pathways represent key differentially expressed pathways distinguishing *O. sinensis* from other *Cordyceps* species, possibly associated with its unique cardiovascular protective functions[63]. Correlation analysis revealed that the accumulation of differential metabolites in amino acids and fatty acid acyl derivatives exhibited significant positive correlations with multiple free radical scavenging capacities (DPPH•, FRAP, •OH, O_2•$^-$)[64]. The enrichment of valine, leucine, and isoleucine synthetic and degradation pathways during the development of distinct fungal hyphal morphologies (such as aerial and endophytic hyphae) suggests the close link between amino acid metabolism and fungal reproductive transitions and stress responses[65]. The molecular structural formulae of the principal amino acids are presented in Figure 6.

Other constituents

O. sinensis is rich in proteins, fatty acids, trace elements, and other nutrients. Wang et al. identified carboxylic acids and their derivatives, fatty acyls, organic oxides, benzene and its substituted derivatives, isoprenoid esters, and glycerophospholipids *via* metabolomics and observed variations in their accumulation patterns among *O. sinensis* specimens from different geographical origins, which may contribute to product quality variations[66]. Xiao et al.[67] identified 1,937 metabolites (primarily lipids, lipoid molecules, organic acids and their derivatives, and organic heterocyclic and oxygen compounds) *via* metabolomics and further revealed that different drying methods significantly influenced their content and antioxidant capacity. He et al.[64] comparatively analyzed the metabolic profiles and antioxidant activities of *O. sinensis* and *Paecilomyces hepiali*. They found that differential metabolites were primarily accumulated in organic acids and their derivatives, lipids and lipid-like molecules, and organic heterocyclic compounds and exhibited a positive correlation with antioxidant activity.

Extraction and separation techniques

In-depth research into the active constituents and pharmacological effects of *O. sinensis* requires efficient extraction and separation techniques. Currently, solvent extraction and chromatographic separation are commonly used, each possessing distinct advantages and limitations.

Solvent extraction

Solvent extraction is the most prevalent and fundamental extraction methodology. It operates primarily by exploiting differences in the solubility of target *O. sinensis* constituents across various solvents to achieve separation. Water extraction effectively isolates water-soluble macromolecules such as polysaccharides, proteins, and amino acids. Water is non-toxic and leaves no residues, thus causing no environmental pollution. Moreover, it is readily available at minimal cost. Heating or room-temperature maceration may help extract active components from *O. sinensis* fruiting bodies, mycelium, or related products[68–71]. Water extraction requires simple post-processing; hence, it is primarily employed in the large-scale industrial production of *O. sinensis* polysaccharides, crude nucleoside extracts, and raw materials for health foods.

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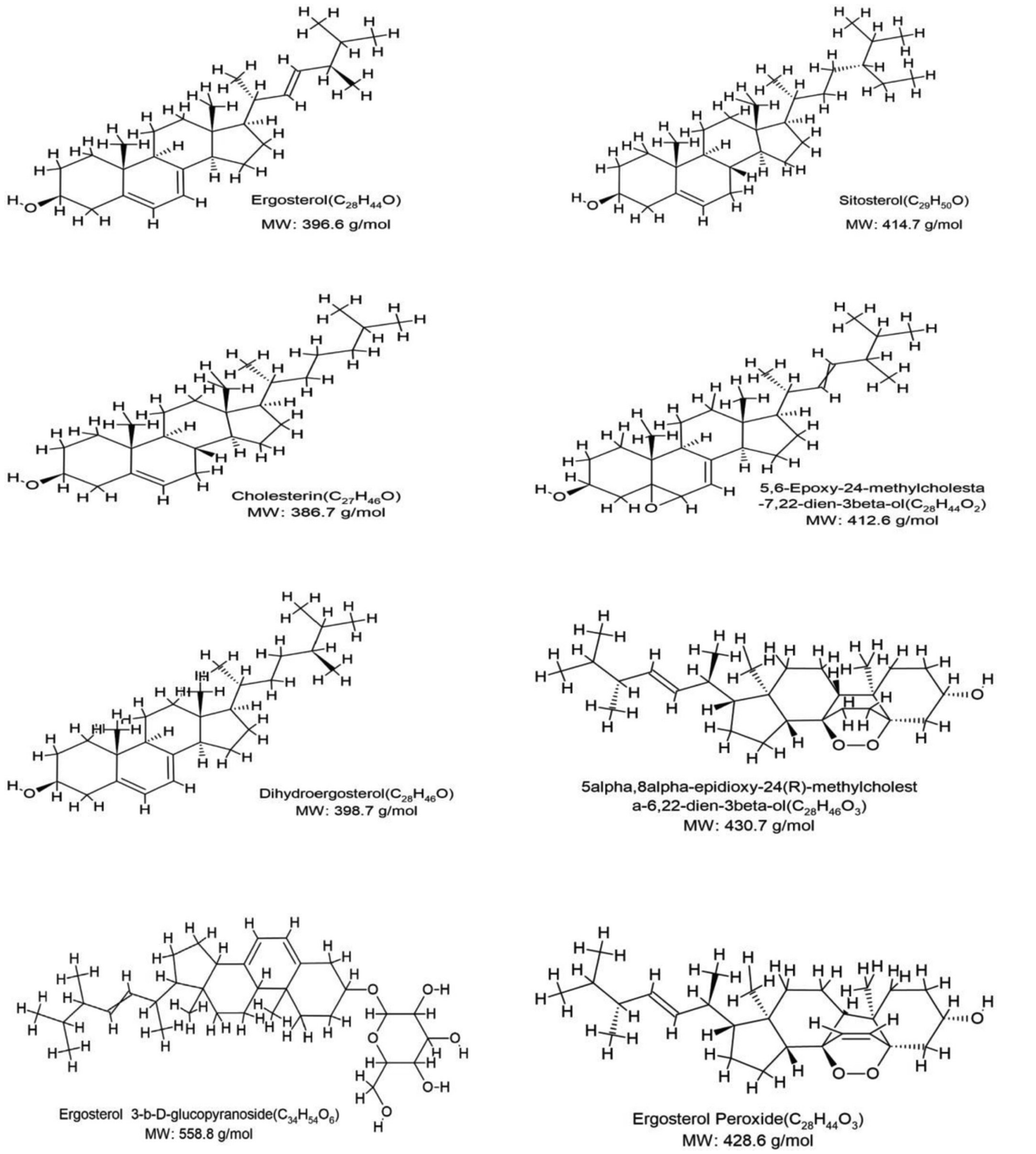


Figure 5. Molecular structural formulae of the primary sterols in *Ophiocordyceps sinensis.*

Alcohol extraction methods (ethanol- or methanol-based) are typically used to extract lipid- or alcohol-soluble constituents (sterols, fatty acids, and certain nucleosides). Organic solvents generally exhibit higher extraction efficiency than water for cordycepin, adenosine, sterols, certain aglycones, and small-molecule alkaloids[72–73]. Solvent extraction offers the advantages of simple operation and relatively low cost, rendering it suitable for large-scale production. Target compounds can be selectively enriched by adjusting ethanol concentration (using low-concentration ethanol to simultaneously extract water- and alcohol-soluble constituents). Furthermore, the low-boiling points of organic solvents facilitate their recovery and removal *via* distillation, simplifying subsequent extract concentration and drying. Solvent extraction is primarily used for extracting high-purity lipophilic active constituents such as cordycepin and sterols, as well as for refining pharmaceutical raw materials.

Chromatographic separation

HPLC, ultra-high-performance liquid chromatography coupled with mass spectrometry (UHPLC-MS/MS), and

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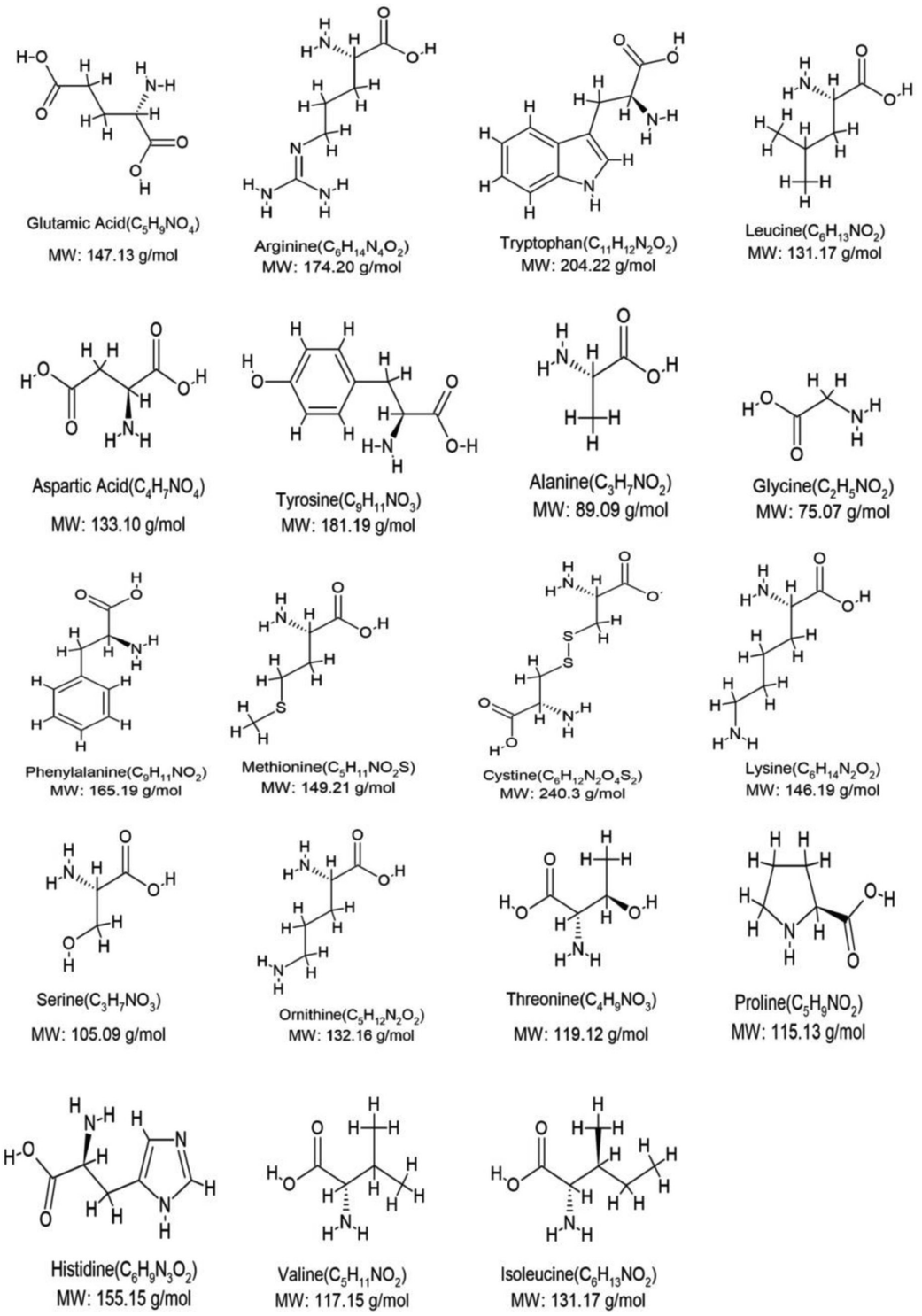


Figure 6. Molecular structural formulae of the principal amino acids in *Ophiocordyceps sinensis*.

gas chromatography coupled with mass spectrometry (GC-MS) constitute the core methodology for the efficient separation and purification of active components in *O. sinensis*. Owing to its high sensitivity, high resolution, and broad applicability, HPLC is an essential tool in the quantitative or chemical composition, analysis of non-volatile or thermally unstable constituents in *O. sinensis*, such as nucleosides, polysaccharides, and amino acids. Khan et al.[36] used HPLC to successfully determine the adenine and adenosine content in *O. sinensis*, noting that it exhibited a favorable linear range, sensitivity, and accuracy, rendering it suitable for routine quality control. Zhou et al.[37] compared the principal constituents, including adenosine, cordycepin, mannitol,

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and polysaccharides, of cultivated and wild *O. sinensis* and *C. militaris via* HPLC-MS and UV spectroscopy. The advantages of HPLC include high separation efficiency and sensitivity and the capability for quantitative analysis, and its disadvantages, relatively high equipment costs and stringent requirements for sample preparation. UHPLC-MS/MS, combining the high resolution of UHPLC and the high sensitivity and structural identification capabilities of MS/MS, is a powerful tool for the analysis of the complex metabolites in *O. sinensis*. Di Lorenzo et al.[34] used UHPLC-Diode Array Detectors for the standardization of cordycepin and adenosine in *O. sinensis* extracts. Tang et al.[63] used the UHPLC Q Exactive™ HF-X system for the metabolomic profiling of diverse *Cordyceps* species, enabling the identification of several metabolites and the characterization of potential biomarkers. The advantage of UHPLC-MS/MS, namely its capacity for comprehensive, high-throughput qualitative and quantitative analysis of complex mixtures, renders it particularly suitable for discovering novel bioactive compounds or conducting metabolomics research. However, its complex data processing requires specialized bioinformatics expertise. GC-MS is primarily used for analyzing volatile or semi-volatile constituents. Zhang et al.[74] developed a simultaneous distillation extraction (SDE) method combined with GC-MS to analyze the volatile constituents of five *C. militaris* mycelium fermentation products. The authors identified 5, 6-dihydro-6-pentyl-2H-pyran-2-one (massoia lactone) as the principal volatile constituent in Jinshuibao capsules and fatty acids as major volatile constituents in the fermentation products. The advantages of GC-MS include its strong separation capability and high sensitivity, with MS providing structural information, and its disadvantages include the requirement for sample derivatization and its limited applicability to only volatile components.

Other separation techniques

Other techniques include macroporous adsorption resins (MARs)[75], gel chromatography (GC) filtration[76], and membrane separation[77]. Zhang et al.[78] used MARs for preliminary separation and purification of *O. sinensis* polysaccharides from cultured material, obtaining active polysaccharide fractions and demonstrating their immunomodulatory and antioxidant activities. GC primarily separates substances based on solute molecule size. Wu et al.[79] used GC to extract and isolate β-glucan from *O. sinensis* mycelium, subsequently purifying it and determining its MW. Membrane separation technology is used in the concentration, impurity removal, and fractionation processes for *O. sinensis* extraction. Li et al.[77] used membrane separation to isolate and partially purify polysaccharides from *O. sinensis* mycelium, effectively boosting polysaccharide purity and recovery rates while avoiding substantial ethanol consumption.

Several novel extraction technologies offer advantages, such as higher extraction efficiency, greater selectivity, and lesser environmental impact, over conventional methods. Deep eutectic solvent (DES) is a mixture of a hydrogen bond acceptor (eg, choline chloride) and a hydrogen bond donor (eg, urea, organic acids, or sugars) in a specific molar ratio with a significantly low melting point. DES is regarded as an ideal alternative to conventional organic solvents owing to its tunable physicochemical properties, low toxicity, and biodegradability, demonstrating significant potential in natural product extraction. A proline-based DES system developed by Gao et al.[80] yielding cordycepin extracts with a 30% higher antioxidant activity than those obtained using conventional solvents. Ultrasonic-assisted extraction (UAE) uses ultrasonic waves to generate cavitation, mechanical, and thermal effects to disrupt plant cell walls and accelerate intracellular transport, significantly enhancing extraction efficiency. The advantages of UAE include short extraction times, high efficiency, no requirement for high temperatures (avoiding degradation of heat-sensitive components), and minimal solvent usage. Wang et al.[81] demonstrated that UAE significantly enhanced cordycepin yield, shortened extraction time by >60% compared with conventional methods. In another study, Wang et al.[82] found that low-temperature (<50°C) UAE of nucleosides from *O. sinensis* had higher rates and greater purity than conventional thermal reflux extraction. Pressurized liquid extraction (PLE), or accelerated solvent extraction (ASE), uses solvents for rapid extraction under high temperature (50–200°C) and pressure (1,000–2,000 psi). PLE enhances solvent solubility and mass transfer rates *via* high temperatures, while pressurization maintains the solvent in liquid form. This enables rapid, efficient extraction, particularly suited to constituents with good thermal stability, such as the polysaccharides and nucleosides in *O. sinensis*[83]. Enzyme-assisted extraction (EAE) uses specific enzymes (eg, cellulase, pectinase, and protease) to degrade the cell wall components (cellulose, pectin, and proteins), disrupting cellular structures and releasing intracellular active substances. The advantages of EAE include mild reaction conditions (30°C–50°C), high specificity, and environmental sustainability with high efficiency[84]. EAE-extracted polysaccharides exhibit a more uniform MW distribution, with potential alterations in monosaccharide composition and glycoside linkage patterns, which may influence their biological activity (such as immunomodulation and hypoglycemic effects), thus rendering this approach crucial for function-directed extraction[85]. These techniques, used either independently or in combination with other techniques, offer efficient, environmentally sound, and intelligent approaches for extracting the active constituents of *O. sinensis*. Their continuous development and refinement will provide robust technical support for the high-value utilization and industrial-scale development of *O. sinensis* resources, while serving as a reference and model for the extraction and separation of other natural products.

Comparison of the advantages and disadvantages of the extraction methods

Various complementary methods are used in the extraction and separation of active components from *O. sinensis*. Solvent extraction is a simple and efficient preliminary technique suitable for crude extraction, although it yields relatively low-purity extracts. Conversely, chromatographic separation techniques, particularly HPLC

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and UHPLC-MS/MS, offer precise separation and structural identification, enabling accurate analysis and quantification of trace active constituents in complex mixtures; however, they require high standards of equipment and operator expertise, and are relatively costly. Notably, between-research team discrepancies, stemming from sample origin (wild *vs*. cultivated and geographical origin), extraction methods, analytical instrumentation, and reference standard purity, may occur in the detection and quantification of the active constituents. Zhou et al.[37] compared the compositional differences between wild and cultivated *O. sinensis* and found that the cultivated specimen contained higher adenosine and cordycepin levels and lower mannitol and polysaccharide levels, suggesting that, in quality control and product development, compositional assessment should be product type and targeted efficacy-based. Liu et al.[86] conducted an *in situ* chemical analysis and imaging of cultivated and wild *O. sinensis* using time-of-flight secondary ion mass spectrometry (TOF-SIMS), revealing that despite a high degree of chemical similarity, the relative content of fatty acids, glycerides, and glycerophospholipids differed between both specimens. This provides a fresh perspective for understanding the subtle differences between wild and cultivated *O. sinensis*. The various extraction methods and their comparisons are summarized in Table 1. Future research should continue to optimize extraction and separation techniques, developing more efficient, environmentally friendly, and selective methods. Integrating multi-omics (eg, metabolomics and proteomics) with bioactivity screening will facilitate a more comprehensive elucidation of the pharmacological basis of *O. sinensis* and the discovery of novel bioactive compounds.

Research into the chemical constituents of *O. sinensis* has systematically revealed its multi-component, multi-targeted material basis. However, existing systems remain constrained in terms of deep correlation and practical application. Despite a predominant research focus on the isolation, identification, and *in vitro* validation of various constituents, the translational pathway from "chemical constituents" to "*in vivo* pharmacological effects" remains unclear. For example, numerous studies have confirmed the significant biological activity of cordycepin, ergosterol, and multiple polysaccharides; however, their bioavailability in complex extracts, metabolic fate, and contribution to the overall pharmacological efficacy remain unknown. The highly heterogeneous research outcomes further highlight the challenges: different origins, cultivation methods, and even drying processes can significantly alter the metabolite profile. Technologically, although emerging techniques (eg, DES and EAE) hold promise in enhancing efficiency and selectivity, their scalability and impact on the structural integrity of the active constituents remain unevaluated. Future research must move toward constructing integrated models linking "chemical profiles-bioactivity-action mechanisms," integrating analytical techniques such as metabolomics with network pharmacology and *in vivo* pharmacokinetic studies to identify truly critical functional constituent clusters. Thereafter, multi-indicator quantitative fingerprinting-based quality control strategies should be established to lay a robust scientific foundation for the precise application and product development of *O. sinensis*.

Modern pharmacological research

O. sinensis has been extensively used in traditional medicine. Modern pharmacological research has further revealed its significant role in multiple physiological and pathological processes: antitumor, immune modulation, renal protection, antioxidant, anti-inflammatory, and anti-aging effects. The complex active constituents in *O. sinensis* exert these effects *via* a synergistic "multi-target, multi-pathway" mechanism.

Antitumor effects

O. sinensis and its bioactive constituents demonstrate significant potential in antitumor applications. The confirmed inhibitory effects on various cancer cells include tumor cell proliferation suppression and apoptosis induction, tumor invasion and metastasis inhibition, and immune function enhancement.

O. sinensis cordycepin inhibits tumor cell proliferation and induces apoptosis. Shao et al.[87] demonstrated its efficacy in apoptosis induction specifically in human HepG2 cells. This mechanism involves both the extrinsic (mediated *via* Fas-related death domain proteins) and the intrinsic (mediated by B-cell lymphoma 2 [Bcl-2] family proteins, leading to altered mitochondrial membrane permeability, cytochrome c release, and caspase cascade activation) pathways. Wu et al.[88] revealed that cordycepin inhibited FGF9-induced proliferation of TM3 mouse mesenchymal progenitor cells by activating autophagy, suggesting that autophagy represented another crucial mechanism underlying cordycepin-induced cell death. *O. sinensis* polysaccharides can inhibit HCT116 colon cancer cell proliferation by blocking the phosphoinositide 3-kinase-protein kinase B-mammalian target of rapamycin (PI3K-AKT-mTOR) signaling pathway and induce autophagy and apoptosis by activating the AMPK-mTOR-ULK1 signaling pathway[40]. In non–small-cell lung cancer, *O. sinensis* significantly reduces VEGF and Ki-67 (antigen identified by the monoclonal antibody Ki-67) expression by inhibiting the mitogen-activated protein kinase (MAPK) pathway and suppressing tumor cell proliferation[89]. Cordycepin enhances radiosensitivity in oral cancer cells by downregulating DNA damage repair-associated proteins such as p-ATM and Chk2 and inducing apoptosis[90]. In summary, *O. sinensis* and its bioactive constituents inhibit tumor cell proliferation and induce apoptosis *via* signaling pathway regulation, apoptosis-related gene activation, and autophagy induction. Although existing research provides the scientific rationale for antitumor therapy applications, further exploration of the clinical efficacy and safety of *O. sinensis* and its bioactive constituents is required.

Tumor invasion and metastasis are major challenges in cancer treatment. Huang et al. reported that their purified *O. sinensis* mycelial polysaccharide, CME-1, inhibited B16-F10 melanoma cell migration in a concentration-dependent manner, possibly by

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Table 1

Extraction methods and comparison of active components in *Ophiocordyceps sinensis*

No.	Method	Primary components extracted	Advantages	Limitations
1	Solvent extraction	Polysaccharides and water-soluble small molecules (such as nucleosides) Lipid- or alcohol-soluble constituents (such as sterols, fatty acids, and certain nucleosides)	Simple to operate; relatively low in cost; suitable for large-scale production	Relatively low selectivity; components require subsequent purification
2	HPLC	Non-volatile or thermally unstable constituents (such as nucleosides, polysaccharides, and amino acids)	High separation efficiency and sensitivity; capable of quantitative analysis	Relatively expensive equipment; rigorous sample preparation procedures
3	UHPLC-MS/MS	Primary constituents and complex metabolites	Comprehensive, high-throughput qualitative and quantitative analysis for novel active ingredients or metabolomics research	Relatively high equipment and personnel requirements; comparatively expensive costs
4	GC-MS	Volatile or semi-volatile components	High separation capability and sensitivity, with mass spectrometry providing structural information	The sample requires derivatization and is only suitable for volatile components
5	MARs	Polysaccharides, cordycepin, adenosine, and other water-soluble to moderately polar small molecules	Significantly enhances purity; combines decolorization, protein removal, and desalination, reducing subsequent processing steps; low cost, renewable, and reusable, thus suitable for large-scale production; simple operation	Non-specific adsorption; requires resin type screening and condition optimization; limited adsorption capacity for high-molecular-weight polysaccharides; increases operational steps and waste liquid treatment requirements
6	GC	Polysaccharides, β-glucans, and polysaccharide-peptide complexes	Yields components with relatively uniform molecular weight; serves as the gold standard for molecular weight and distribution determination; offers high resolution, suitable for structural characterization and fine purification; employs mild conditions, preserving biological activity.	Small processing scale; relatively high-cost, rendering large-scale production challenging; time-consuming, requiring multiple sequential steps or integration with other technologies
7	Membrane separation	Polysaccharides, extracellular polysaccharides, fermentation broth clarification and sterilization, small-molecule impurities, and desalination	Highly efficient and energy-saving; enables integrated concentration, fractionation and clarification, reducing the use of organic solvents (such as ethanol); Suitable for scale-up and continuous operation; Gentle on heat-sensitive components, facilitating the preservation of activity.	Requires regular cleaning and maintenance; membrane selection and pore size design requires high precision, impacting separation efficiency; initial capital investment is substantial; processing capacity for systems with extremely high-molecular-weight or viscosity is limited
8	DES	Polysaccharides, cordycepin, and adenosine; solvent design may be customized to polarity and solubility	Solvent polarity/viscosity/solubility can be adjusted; ultrasonication shortens processing time and enhances yield; room-/low-temperature operation minimizes degradation of heat-sensitive components; can reduce or replace conventional organic solvents, lowering residues and environmental impact	Certain DES exhibit elevated viscosity, impeding mass transfer efficiency; long-term toxicological data remain under accumulation, necessitating assessment for industrial deployment; recovery and regeneration processes require further refinement
9	PLE	Polysaccharides, nucleosides, cordycepin, and other medium-low to medium polarity constituents; suitable for multi-component sequential extraction	Rapid extraction (typically 1520 min); minimal solvent consumption with closed-system operation minimizing volatilization and loss; high automation with excellent reproducibility, suitable for high-throughput applications; interchangeable solvents enabling multi-gradient extraction using water/alcohol systems	High temperatures may cause degradation of certain heat-sensitive components; relatively high equipment costs; stringent requirements exist for equipment safety and maintenance

(Continued)

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Table 1
(Continued)

No.	Method	Primary components extracted	Advantages	Limitations
10	EAE	Polysaccharides, proteins/peptides, and components bound to the cell wall; used for nucleoside release as well	Mild conditions (30°C–50°C) preserve heat-sensitive activity; specifically degrades cell walls to enhance intracellular component release efficiency; minimizes co-extraction of impurities (proteins and pigments), simplifying subsequent purification; synergistic effects achievable when combined with ultrasonication/microwave treatment	Relatively high enzyme costs necessitate optimization of enzyme dosage and incubation time; post-enzymatic digestion requires inactivation treatment, adding an extra step; precise control of pH and temperature is essential, as conditions are highly sensitive

DES: Deep eutectic solvents; EAE: Enzyme-assisted Extraction; GC: Gel chromatography; GC-MS: Gas chromatography coupled with mass spectrometry; HPLC: High-performance liquid chromatography; MARs: Macroporous adsorption resins; PLE: Pressurized liquid extraction; UHPLC-MS/MS: Ultra-high-performance liquid chromatography coupled with mass spectrometry.

downregulating matrix metallopeptidase 1 (MMP-1) expression, inhibiting ERK1/2 and p38 MAPK phosphorylation, and restoring IkB-α degradation. This suggests that CME-1 may suppress tumor cell migration *via* the NF-κB or ERK/p38 MAPK pathways[41]. Lu et al.[89] found that *O. sinensis* improved NSCLC in a mouse cancer model by inhibiting the MAPK pathway. This manifests as a significant reduction in VEGF and Ki-67 expression, alongside a downregulation of *Ras homolog family member A (RhoA)*, *Raf-1 Proto-Oncogene (Raf-1),* and *FBJ murine osteosarcoma viral oncogene homolog (c-fos)* expression, all of which are associated with cell migration and invasion. *O. sinensis* water extract significantly inhibited 4T1 breast cancer cell viability *in vitro* and reduced the number of metastatic nodules in the lungs *in vivo*[91]. The antitumor and metastasis-inhibiting processes of *O. sinensis* are illustrated in Figure 7.

The antitumor effects of *O. sinensis* are closely linked to its regulatory influence on the immune system. *Cordyceps sinensis* polysaccharides (CSP) significantly enhance macrophage, lymphocyte, and dendritic cell activities, while promoting cytokine and chemokine expressions[92]. *O. sinensis* extract mitigates immune-inflammatory responses in acute kidney injury by activating the STING/IRF3 signaling pathway and inhibiting perforin release in natural killer cells[93]. In a mouse model of tuberculosis, the combination of *O. sinensis* and PA-824 significantly reduced pulmonary colony-forming unit counts and inhibited interferon (IFN)-γ and IL-10 secretion[94]. *O. sinensis* polysaccharides regulate intestinal immunity as well. Under simulated microgravity conditions, *O. sinensis* polysaccharides administered in combination with moxifloxacin mitigate abdominal infection-induced intestinal barrier damage *via* anti-inflammatory and immunomodulatory mechanisms[95].

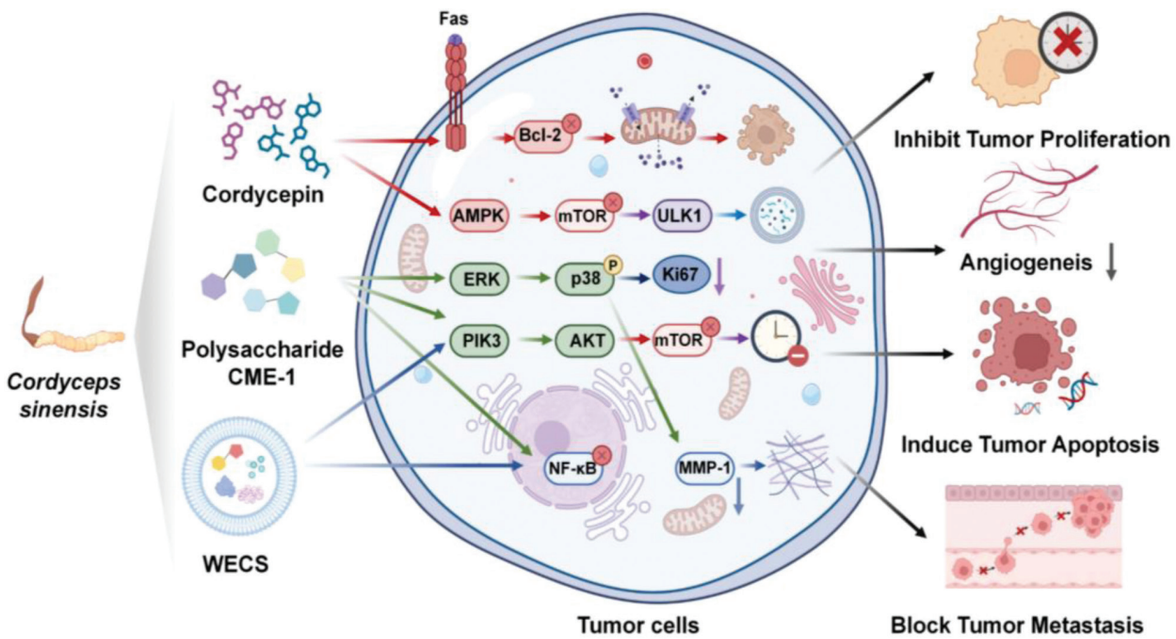


Figure 7. Antitumor and metastasis-inhibiting effects of *Ophiocordyceps sinensis.* Bcl-2: B-cell lymphoma 2; c-fos: FBJ murine osteosarcoma viral oncogene homolog; CME-1: *Cordyceps militaris* exopolysaccharide-1; Fas: Fas-related death domain proteins; Ki-67: Antigen identified by monoclonal antibody Ki-67; MMP-1: Matrix metallopeptidase 1; Raf-1: Raf-1 Proto-Oncogene; RhoA: Ras homolog family member A; VEGF: Vascular endothelial growth factor; WECS: Water extract of *O. sinensis*.

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O. sinensis extract inhibits breast cancer growth by promoting macrophage differentiation toward the M1 phenotype *via* NF-κB pathway activation[96].

O. sinensis exhibits bidirectional effects in immune regulation: enhancing immune function and suppressing excessive inflammatory responses. CSP significantly augments the phagocytic capacity of RAW264.7 macrophages, MAPK and PI3K/Akt signaling pathway activation, while modulating pro- and anti-inflammatory cytokine expression to bolster immune responses[97]. Furthermore, CSP increased and decreased the abundance of probiotic (*Lactobacillus*, *Bifidobacterium*, and *Bacteroides*) and pathogenic (*Clostridium* and *Fusobacterium*) bacteria, respectively. Thus, CSP may function as a prebiotic to mitigate the adverse effects of CTX on intestinal mucosal immunity and the gut microbiota[98]. The anti-inflammatory effects of *O. sinensis* are primarily achieved by inhibiting inflammatory mediator release and modulating inflammatory signaling pathways. For example, cordycepin significantly suppresses NF-κB and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) activation, thereby reducing IL-6, IL-1β, and TNF-α expression and alleviating inflammatory responses[99]. *O. sinensis* polysaccharides demonstrate significant anti-inflammatory effects in intestinal inflammation models. By inhibiting the Toll-like receptor 4 (TLR4)/MyD88 signaling pathway, CSP can block inflammatory signal transmission, reduce oxidative damage, and alleviate inflammatory responses[100]. Chen et al.[101] revealed that *O. sinensis* ameliorated sepsis-associated acute kidney injury by reprogramming mitochondrial energy metabolism and macrophage polarization (M1–M2 shift, a key regulatory mechanism of the inflammatory response). Li et al.[93] found that *O. sinensis* 2′-deoxyadenosine protected against acute kidney injury by inhibiting perforin expression in natural killer cells *via* the STING/IRF3 pathway, suggesting its potential in modulating immune cell function to mitigate inflammatory damage. Huang et al. found that *Hirsutella sinensis* alleviated bleomycin-induced pulmonary inflammation and fibrosis by inhibiting transforming growth factor-beta 1 (TGF-β1)–induced fibroblast activation, restoring superoxide dismutase expression, suppressing ROS production, and reducing inflammatory cell infiltration and pro-inflammatory cytokine levels in lung tissue while diminishing NLRP3 and P2X7R expression[102]. Tao et al.[103] demonstrated that Bailing Capsules (a *O. sinensis* preparation) can reduce hs-CRP, IL-6, and TNF-α in chronic kidney disease. The immunomodulatory effects of *O. sinensis* are illustrated in Figure 8. In summary, the immune-enhancing and anti-inflammatory properties of *O. sinensis via* gene expression modulation of immune cells, inflammatory signaling pathways inhibition, and antioxidant capacity enhancement form the crucial basis for its extensive clinical applications.

Antioxidant and anti-aging effects

The pronounced antioxidant properties of *O. sinensis* have recently garnered significant attention. Singh et al. found that *O. sinensis* water extract significantly reduced hypoxia-induced ROS production, lipid peroxidation, and protein oxidation inducing heme oxygenase-1 (HO-1), metallothionein (MT), and nuclear factor erythroid 2–related factor 2 (Nrf 2) activation, thus improving tolerance to hypoxia[12]. Zhang et al.[104] found that *O. sinensis* ameliorated idiopathic pulmonary fibrosis (IPF) in a mouse model by inhibiting mitochondrial-mediated oxidative stress by regulating mitochondrial complex expression and activity, suppressing bleomycin-induced excessive mitochondrial ROS production and safeguarding mitochondrial

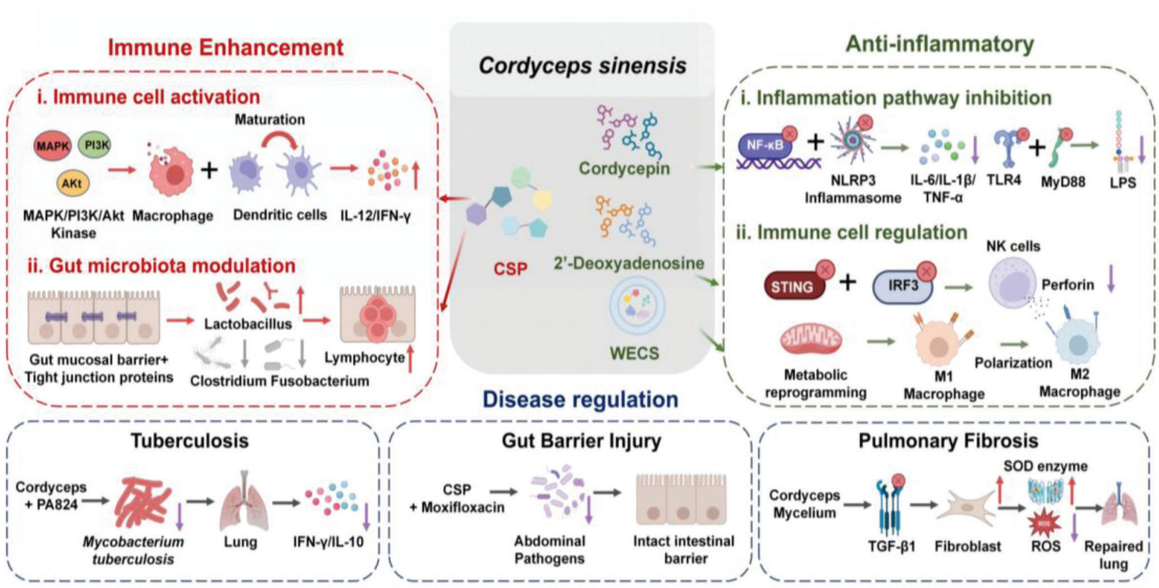


Figure 8. *Ophiocordyceps sinensis* and its immunomodulatory effects. CSP: *Cordyceps sinensis* polysaccharides; IL-1β: Interleukin-1 beta; IL-10: Interleukin-10; IL-12: Interleukin-12; INF-γ: Interferon-gamma; IRF3: Interferon regulatory factor 3; LPS: Lipopolysaccharide; M1: M1 macrophages; M2: M2 macrophages; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TGF-β1: Transforming growth factor-beta 1; TLR4: Toll-like receptor 4; WECS: Water extract of *O. sinensis*.

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integrity and function. Wu et al.[105] found that fermented *O. sinensis* significantly increased polyphenolic activity and reduced malondialdehyde levels in cardiac and hepatic tissues, demonstrating cardiac and hepatic antioxidant effects. *O. sinensis* exopolysaccharide-selenium nanoparticles (EPS-SeNPs) significantly inhibit H_2O_2-induced oxidative stress in human HepG2 cells, enhance cellular viability, reduce lactate dehydrogenase (LDH) levels, and increase SOD and catalase activity[106]. *O. sinensis* extract can alleviate lipopolysaccharide (LPS)-induced inflammation and oxidative stress damage by upregulating the Nrf2/HO-1 signaling pathway[107]. The antioxidant effects of *O. sinensis* in chronic diseases have been extensively explored as well. For example, in a rat model of COPD, *O. sinensis* significantly reduced oxidative stress markers (malondialdehyde and glutathione-*S*-transferase) and elevated SOD and glutathione (GSH) levels by regulating glycerophospholipid, glutathione, and tryptophan metabolism[108]. *O. sinensis* and its bioactive constituents have demonstrated significant efficacy in antioxidant activity and the treatment of chronic diseases, primarily *via* free radical scavenging, antioxidant enzyme activity enhancement, and relevant metabolic pathway modulation.

Moreover, *O. sinensis* has demonstrated a significant anti-aging potential. *O. sinensis* oral solution extended the lifespan of fruit flies by modulating antioxidant stress pathways, including upregulating SOD1 and catalase activity and inhibiting lipofuscin (LF) accumulation[109]. Di Lorenzo et al.[34] investigated the adaptogenic potential of *O. sinensis* mycelium hydroethanolic extract in promoting skin longevity and revealed that it significantly increased sirtuin (SirT1, SirT3, and SirT6) expression and NAD+ synthesis in HaCat cells, enhanced adenosine triphosphate (ATP) production in skin cells, reduced cytoplasmic ROS, and promoted collagen synthesis, thus markedly reducing wrinkles. This indicates the positive effects of *O. sinensis* on skin aging *via* cellular energy metabolism and antioxidant pathway regulation. Although its clinical application requires further investigation, existing research indicates that *O. sinensis* and its bioactive constituents hold promise for anti-aging drugs or functional foods. The antioxidant and anti-aging effects of *O. sinensis* are illustrated in Figure 9.

Neuroprotective effects

O. sinensis and its active constituents exert neuroprotective effects *via* multiple mechanisms, demonstrating significant therapeutic potential across various neurodegenerative disease and brain injury models. Ethanol extracts of *O. sinensis* exhibited marked neuroprotective effects in cerebral ischemia/reperfusion models, reducing infarct volume, improving neurological behavioral function, and suppressing inflammatory cytokine expression[110]. *O. sinensis* fermented powder exhibited preventive and therapeutic effects in vascular dementia models, improving learning and memory functions, restoring blood-brain barrier function, and reducing white matter damage[111]. Cerebral ischemia is a common refractory brain disorder caused by reduced cerebral blood flow. Mitochondrial dysfunction contributes to ischemic stroke and brain injury. *O. sinensis* extract improved

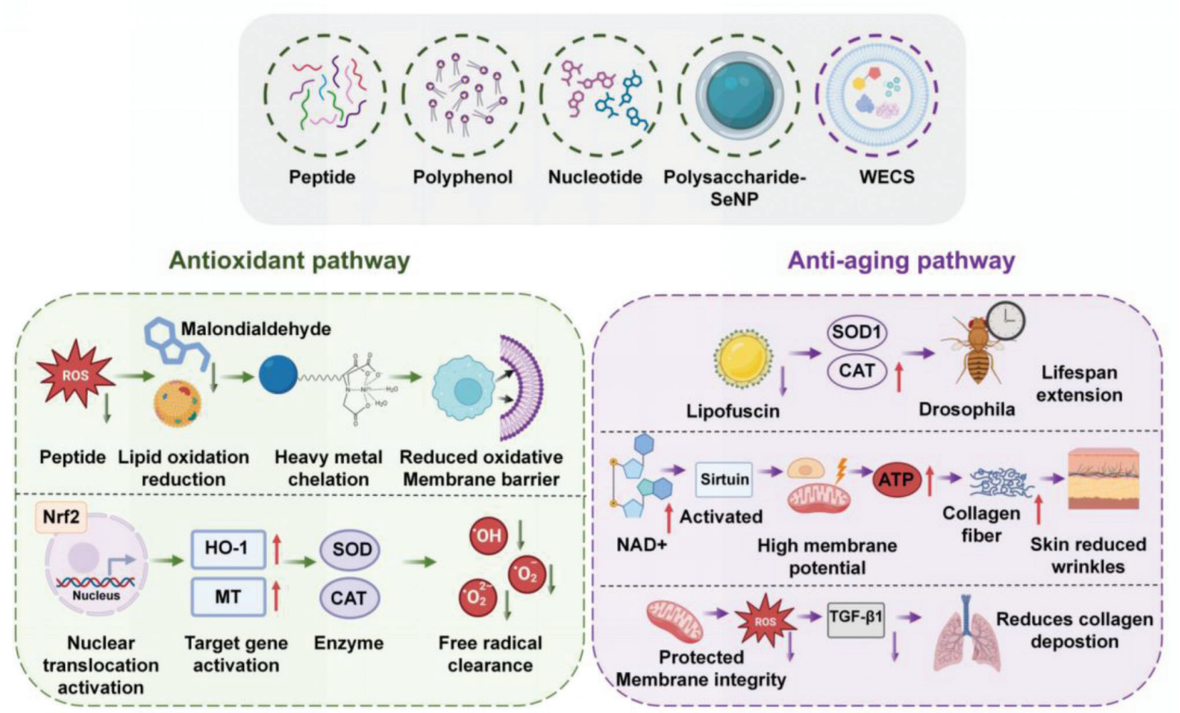


Figure 9. Antioxidant and anti-aging effects of *O. sinensis*. ATP: Adenosine triphosphate; CAT: Catalase; HO-1: heme oxygenase-1; LDH: Lactate dehydrogenase; LF: Lipofuscin; LPS: Lipopolysaccharide; MT: metallothionein; Nrf2: nuclear factor erythroid 2–related factor 2; ROS: Reactive oxygen species; SOD: Superoxide dismutase; WECS: Water extract of *Cordyceps sinensis*.

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mitochondrial respiratory chain function, increased ATP production, and inhibited mitochondrial apoptosis pathways, thus protecting neurons from ischemic injury in a mouse model of middle cerebral artery occlusion[112]. Cordycepin has demonstrated potential neuroprotective effects in Huntington disease (HD) and Parkinson disease (PD) models. Cordycepin reduced the aggregation of mutant proteins and enhanced neuronal survival in the HD model[113], and inhibited the TLR/NF-κB signaling pathway, protected dopamine neurons, and alleviated neuroinflammation and oxidative stress in the PD model[114]. In summary, the neuroprotective effects of *O. sinensis* (Figure 10) provide a theoretical basis for its application in various neurological disorders. However, current research remains predominantly focused on animal models and *in vitro* experiments, and clinical trial data remains limited. Future studies should validate the safety and efficacy of *O. sinensis* while exploring its combined application with other therapeutic approaches.

Improvement in COPD

O. sinensis treatment significantly reduced airway wall thickening in a rat model of COPD. These effects included diminished collagen deposition, airway wall fibrosis, smooth muscle hypertrophy, epithelial hyperplasia, and inflammatory cytokine production[115]. *O. sinensis* treatment significantly alleviated pulmonary tissue damage in rat models of COPD, reduced lung tissue and serum TNF-α, IL-8, and matrix metalloproteinase-9 (MMP-9) levels. It further exerts effects by influencing the phosphoinositide 3-kinase-protein kinase B (PI3K-AKT) signaling pathway and targeting PLA2G4E and B4GALT4 proteins to influence glycerophospholipid and sphingolipid metabolism, thus mitigating inflammation and pulmonary tissue damage[116]. *O. sinensis* has demonstrated beneficial effects in the prevention and treatment of pulmonary fibrosis. It reduced inflammatory cell infiltration, collagen deposition, and oxidative stress in rat models of bleomycin-induced pulmonary fibrosis by regulating the balance between MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1), thus alleviating fibrosis. Cordycepin can reverse epithelial-mesenchymal transition, further inhibiting pulmonary fibrosis progression[117]. Shu et al.[118] conducted a randomized, double-blind, placebo-controlled clinical trial and demonstrated that Bailing Capsules significantly reduced the frequency of acute exacerbations in patients with chronic bronchitis and improved the severity of acute exacerbation of chronic bronchitis and chronic bronchitis symptoms. In summary, the amelioration of pulmonary system disorders by *O. sinensis* (Figure 11) involves multiple signaling pathways and metabolic processes; however, further high-quality clinical studies are required to validate its long-term efficacy and safety.

Other pharmacological effects

O. sinensis has demonstrated several other pharmacological activities (Figure 12).

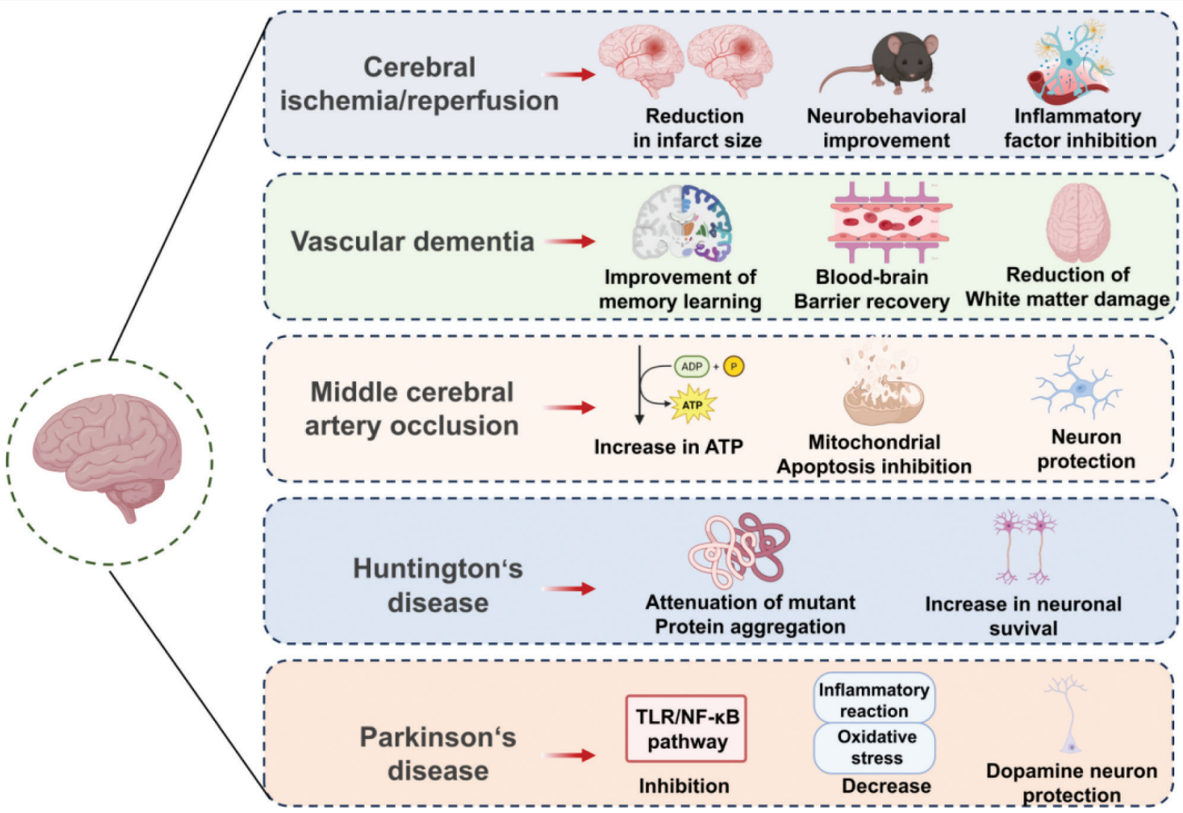


Figure 10. Neuroprotective effects of *Ophiocordyceps sinensis.* ATP: Adenosine triphosphate; NF-κB: nuclear factor kappa-B; TLR4: Toll-like receptor 4.

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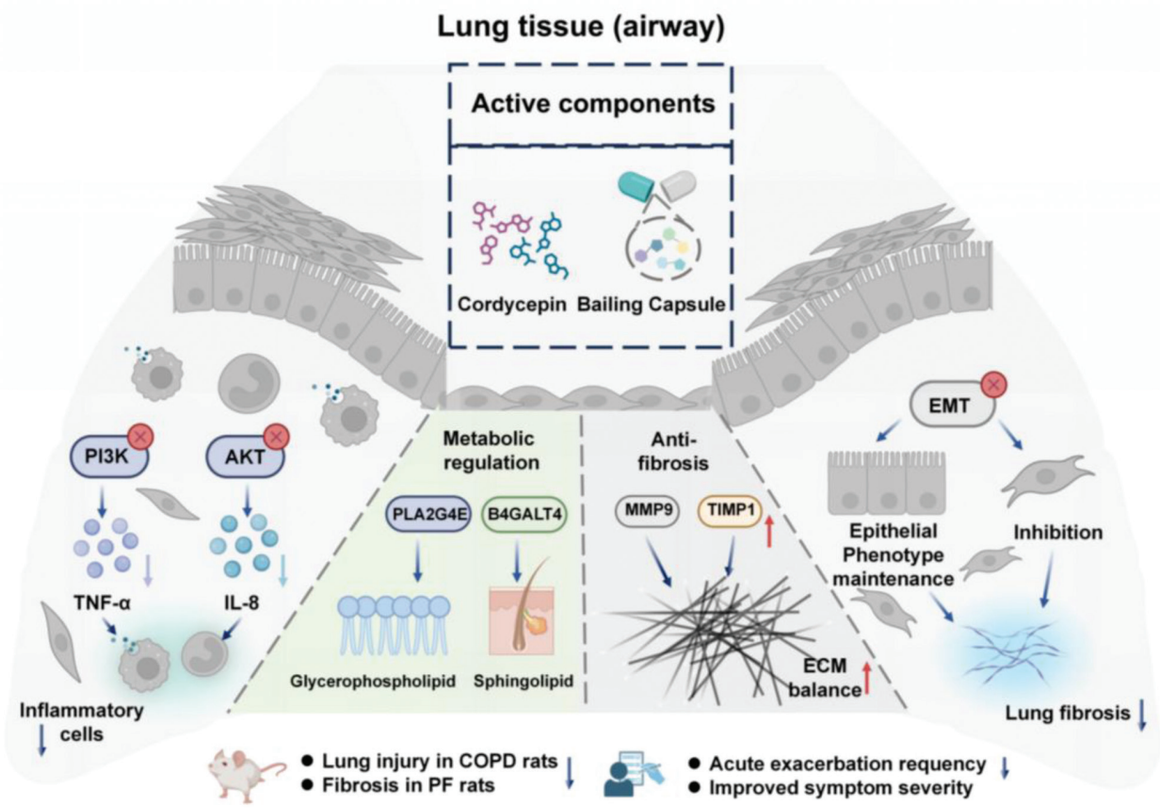


Figure 11. Ameliorative effects of *Ophiocordyceps sinensis* on COPD. COPD: Chronic obstructive pulmonary disease; ECM: Extracellular matrix; IL-8: Interleukin-8; MMP-9: Matrix metalloproteinase-9; PF: Pulmonary fibrosis; TIMP-1: Tissue inhibitor of metalloproteinase-1; TNF-α: Tumor necrosis factor-α.

Hypolipidemic effects

O. sinensis modulates blood lipid levels *via* multiple pathways. Its water extract alleviated glucose and lipid metabolism disorders and inflammation in high-fat diet mice by regulating the gut microbiota, particularly *via* a reduction of the abundance of bile salt hydrolase-producing microorganisms such as *Enterococcus cecorum*, thus influencing bile acid metabolism[119]. Li et al.[120] investigated the biotransformation of ginsenoside Rb1 by wild *O. sinensis* and *Ascomycota* strains, and its hypolipidemic effects in dietary hypercholesterolemic zebrafish and found that ginsenoside Rb1 ameliorated hypercholesterolemia by downregulating cholesterol synthesis and lipoprotein assembly/secretion, simultaneously upregulating cholesterol transport and efflux. In fermented *Cordyceps*, structural characteristics such as the MW of polysaccharides, monosaccharide composition, and glycosidic bond types are closely linked to its hypolipidemic activity. Specific polysaccharides can enhance antioxidant and immunomodulatory functions, indirectly influencing lipid metabolism[121]. Bailing Capsules reduced TG accumulation in the kidneys of diabetic rats *via* peroxisome proliferator-activated receptor alpha (PPARα) pathway modulation[122]. *O. sinensis* demonstrated significant hypolipidemic effects by regulating lipid metabolism and improving the gut microbiota. Future research should explore its specific mechanisms of action and potential for clinical application.

Muscle injury repair

In a study examining high-intensity interval training, participants who consumed pre-exercise *O. sinensis* supplements exhibited a significant increase in both $CD34^+$ (stem cell marker) and $Pax7^+$ (muscle stem cells) cells over the subsequent 3 hours, indicating accelerated exercise-induced muscle damage repair; thus, *O. sinensis* significantly promotes muscle regeneration by hastening stem cells recruitment to injured sites[123]. *O. sinensis* is frequently combined with other herbal medicines such as deer antler, *Rhodiola rosea*, and ginseng. The compound herbal preparation M3P, containing *O. sinensis*, significantly enhanced mice's swimming endurance while simultaneously increasing hepatic glycogen and serum cortisol levels[124].

Hepato- and renoprotective effects

O. sinensis improves liver function by reversing metabolic disturbances (oxidative stress, energy metabolism, and choline metabolism), significantly alleviating liver injury in rat models[125]. Cordycepin protects the liver from ischemia-reperfusion injury by inhibiting the p38/JNK signaling pathway and reducing inflammation and apoptosis[126]. In kidney transplant recipients, *O. sinensis* significantly reduced serum creatinine and blood urea nitrogen levels, decreased proteinuria incidence, markedly lowered hepatic toxicity occurrence, and improved

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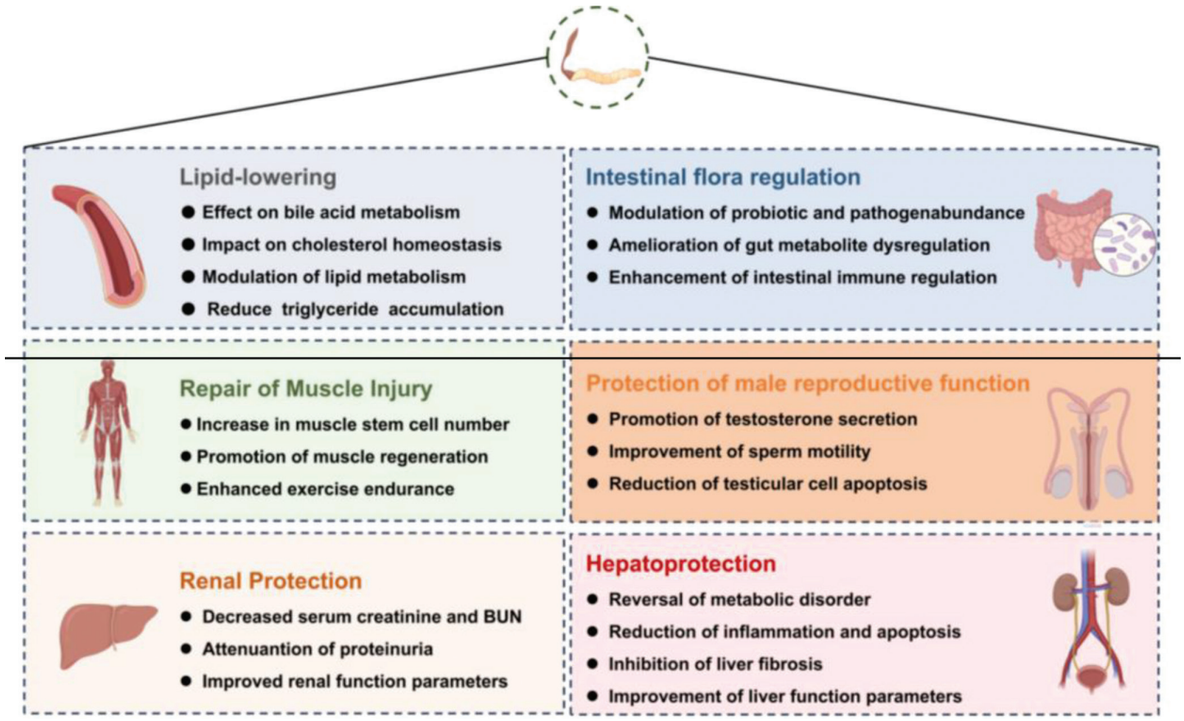


Figure 12. Other pharmacological effects of *Ophiocordyceps sinensis*.

liver function parameters[127]. *O. sinensis* polysaccharides exert an antifibrotic effect on the liver by inhibiting hepatic stellate cell activation, TGF-β1/Smad signaling pathway, and matrix metalloproteinases and tissue metalloproteinase inhibitor expression[128]. In summary, *O. sinensis* demonstrates significant hepato- and renoprotective potential. Its clinical application improves patients' quality of life and reduces medication-related adverse reactions; however, further high-quality research should validate its long-term efficacy and safety.

Gut microbiota modulation

O. sinensis significantly enhances gut microbiota diversity and structure. For example, in a CTX-induced intestinal immunosuppression model, CSP restored both gut microbiota α- and β-diversity, concurrently increasing and decreasing the abundance of probiotic (*Lactobacillus* and *Bifidobacterium*) and pathogenic *Clostridium* and *Campylobacter*) bacteria, respectively[98]. In colitis-associated cancer models, *O. sinensis* significantly modulated the gut microbiota by increasing *Parabacteroides goldsteinii* and *Bifidobacterium pseudolongum* PV8-2 abundance[129]. In obesity models, *O. sinensis* significantly reduced weight gain and metabolic disorders by increasing *Parabacteroides goldsteinii* abundance, suggesting its potential to prevent diet-induced obesity and type 2 diabetes *via* gut microbiota modulation[130]. *O. sinensis* polysaccharides regulate the gut microbiota, reducing *Enterococcus cecorum* abundance, thus improving bile acid metabolism and glucose/lipid metabolic disorders[119]. The combined use of *O. sinensis* with other fungi enhances the effects on gut microbiota regulation. For example, *O. sinensis* and *Ganoderma lucidum* polysaccharides significantly increase butyrate production and restore Treg/Th17 immune balance, improving colonic immune function[131]. In summary, *O. sinensis* has multiple roles in gut health, offering both scientific justification for its traditional medicinal applications and potential avenues for developing novel therapeutic strategies based on the gut microbiota.

Male reproductive function protection

O. sinensis and its extracts (eg, cordycepin) can synthesize compounds that promote the proliferation of mesenchymal cells and stimulate testosterone secretion[132]. In experimental models, *O. sinensis* extract significantly increased sperm count, improved sperm motility, and reduced morphologically abnormal sperm count[133]. *H. sinensis*, the anamorphic mycelium of *O. sinensis*, mitigates testicular damage caused by high-fat diets or CTX treatment, restores normal testicular morphology, and protects testicular function by reducing testicular cell apoptosis *via* apoptosis-related protein (Bax/Bcl-xl ratio and cleaved caspase 3) inhibition[134].

In summary, *O. sinensis* and its bioactive constituents exert their extensive pharmacological effects by regulating a highly interconnected signaling network. As summarized in Table 2, its core mechanisms center on the precise modulation of key signaling pathways, including MAPK, PI3K/Akt/mTOR, NF-κB, and Nrf2. For example, cordycepin and CSP synergistically exert anti-inflammatory and antitumor effects by inhibiting MAPK and NF-κB pathways, while Nrf2 pathway activation and NLRP3 inflammasome suppression constitute the core molecular basis for its antioxidant and anti-inflammatory properties. This multi-component,

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multi-pathway synergy and interaction constitutes the systems biology essence of the multi-effect pharmacology of *O. sinensis*.

The extent of modern pharmacological research on *O. sinensis* is notable. Its antitumor, immunomodulatory, antioxidant, and multi-organ protective effects have been validated across multiple levels, systematically supporting its traditional "tonifying" and "strengthening the body's vital energy" theories. Nevertheless, a significant limitation persists: the various pharmacological domains remain relatively isolated, lacking an integrated interpretation and placing its "multifunctionality" in a unified biological framework. For example, cordycepin has antitumor, anti-inflammatory, and neuroprotective effects. However, whether these seemingly distinct actions share common underlying mechanisms, such as cellular energy metabolism regulation (eg, AMPK/mTOR pathways), abnormal cell death inhibition (apoptosis/pyroptosis), or immune microenvironment remodeling remains moot. Similarly, its antioxidant, anti-aging, and metabolic disease-improving effects (eg, COPD, hyperlipidemia) may form intrinsic networks *via* the Nrf2 pathway and the gut microbiota-metabolite axis. Current research largely remains confined to linear "phenomenon-pathway" descriptions, neglecting to intwine the scattered evidence of efficacy into a coherent "network map of actions" or elucidate the ultimate integration of its "multicomponent" nature into holistic regulatory effects at the organismal level *via* synergistic or antagonistic interactions. Future research should integrate systems pharmacology and computational biology methodologies to construct quantitative predictive models linking chemical constituents to multi-organ therapeutic effects. This should be complemented by designing clinical studies (e.g., in chronic inflammatory diseases or aging-related syndromes) to validate its holistic intervention value. These initiatives will propel *O. sinensis* from a "multi-functional" natural resource to a modern drug with a clearly defined "systemic regulatory" mechanism.

Current status of medicinal preparations and clinical applications of *O. sinensis*

O. sinensis has a long history of clinical application in traditional medicine, both as a treatment for various ailments and as a tonic. Table 3 lists the medicinal preparations containing *O. sinensis* constituents. With the advancement of modern scientific research, scientific evidence has offered support for its clinical value.

Bailing Capsules (*O. sinensis* Powder [Cs-C-Q80]) nourish the lungs and kidneys and enhance vital essence and energy. Its principal active constituents include adenosine, guanosine, uridine, cordycepin, ergosterol, and mannitol[25]. Following its marketing approval in 1991, numerous clinical studies have reported its efficacy in treating COPD, chronic bronchitis, and bronchial asthma and preventing radiation-induced lung injury. Its active ingredients alleviate inflammatory responses and airway hyperresponsiveness in patients with asthma by modulating key targets and signaling pathways[135]. Its combination with traditional Chinese medicine formulations such as Yupingfeng Granules and Buzhong Yiqi Decoction for COPD management effectively improves patients' pulmonary function and quality of life. When integrated with non-pharmacological therapies (acupoint application, electroacupuncture, and Tai Chi). It further enhances clinical efficacy. The core therapeutic targets of Bailing Capsules include SRC, HIF1A, NFKB1, HDAC2, and PRKACA1, which are closely associated with inflammatory responses, oxidative stress, and immune regulation[136]. *O. sinensis* cordycepin, polysaccharides, and nucleosides can significantly suppress airway inflammatory responses and reduce the frequency of acute exacerbations in patients with COPD[72]. A systematic review and meta-analysis of patients with stable COPD (GOLD stages 2–3) demonstrated that oral *O. sinensis* preparations or their compound formulations can improve pulmonary function indicators such as forced expiratory volume in 1 s (FEV_1) and the FEV_1/forced vital capacity ratio. Furthermore, they enhanced the 6-minute walk distance (6MWD) and increased exercise endurance[137]. A meta-analysis of Bailin Capsules confirmed its significant benefits in improving FEV_1 and 6MWD results[135]. A significant reduction in the frequency of AECB was noted after 48 weeks of treatment with Bailing Capsules. This therapy improved the severity of both AECB and chronic bronchitis symptoms, effectively alleviating coughing with sputum production and wheezing. The therapeutic advantage persisted throughout the follow-up period[118]. Cigarette smoke is a primary cause of COPD. CSE induces cellular senescence in human airway epithelial cells (16HBE) by activating the ROS/PI3K/AKT/mTOR signaling pathway. *O. sinensis* effectively reduces CSE-induced senescence marker (p16 and p21) expression and inhibits excessive ROS/PI3K/AKT/mTOR pathway activation, thus delaying airway cellular senescence[138]. Apoptosis leads to destruction of alveolar walls and the formation of pulmonary emphysema in COPD. *O. sinensis* ergosterol effectively inhibits CSE-induced activation of the NF-κB/p65 pathway in cellular and animal models, reducing apoptosis-related protein (cleaved caspase 3/7/9 and cleaved PARP expression, significantly alleviating inflammation, oxidative stress, and apoptosis[47]. *O. sinensis* reduced the expression of TGF-β1 and its receptors and phosphorylated Smad2/3 in lung tissue in a model of COPD. Concurrently, it increased inhibitory Smad7 expression, suppressing pro-fibrotic signaling and significantly ameliorating airway wall thickening[115]. In COPD pathogenesis, *O. sinensis* exerts regulatory effects on multiple proteins and signaling pathways, alleviating its symptoms by inhibiting inflammation, apoptosis, and oxidative stress, suggesting a novel therapeutic potential[139]. These mechanisms collectively provide a robust pharmacological basis for alleviating COPD symptoms and delaying its progression.

O. sinensis has properties that "tonify the lungs and kidneys." Its therapeutic effects include multiple aspects: improving renal function indicators, reducing proteinuria, and exhibiting anti-inflammatory, antioxidant, antifibrotic, and immunomodulatory properties[140]. Multiple meta-analyses and clinical studies indicate that *O. sinensis*, when used as an adjunct, can significantly improve renal function and reduce inflammation in patients with CKD. A systematic review (22 studies including 1,746 participants) demonstrated that *O. sinensis* preparations significantly reduced serum creatinine, increased

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Table 2

Key signaling pathways regulated by *Ophiocordyceps sinensis* components

No.	Pathway	Active components	Key targets/action	Main effects	Pharmacological outcome	Refs.
1	MAPK (ERK, p38, JNK)	Cordycepin, Cordyceps polysaccharides (CME-1)	Inhibits ERK/p38 phosphorylation	Inhibits proliferation, migration, invasion	Antitumor	[41, 89]
		CSP	Activates MAPK	Enhances macrophage activity	Immunoenhancement	[97]
		Cordycepin, extracts	Inhibits JNK/p38	Reduces inflammation, apoptosis	Anti-inflammatory, organ protection	[126]
2	PI3K/Akt/mTOR	Polysaccharides	Inhibits PI3K/Akt/mTOR	Induces apoptosis, autophagy.	Antitumor	[40]
		CSP	Activates PI3K/Akt	Promotes immune cell function	Immunoenhancement	[97]
3	NF-κB	Cordycepin, Polysaccharides	Inhibits IκB-α degradation, NF-κB nuclear translocation	Downregulates TNF-α, IL-1β, IL-6, MMPs	Anti-inflammatory, antitumor	[41, 96, 99]
4	NLRP3 inflammasome	Cordycepin, *Hirsutella sinensis* mycelium	Inhibits NLRP3/ASC/ caspase-1 assembly	Reduces IL-1β, IL-18 release	Anti-inflammatory	[99, 102]
5	Nrf2/ARE	Water/ethanol extracts	Activates Nrf2 nuclear translocation	Upregulates HO-1, NQO1; scavenges ROS	Antioxidant, anti-aging	[12, 107]
6	Mitochondrial apoptosis	Cordycepin	↑Bax/Bak, ↓Bcl-2/Bcl-xl, ↑Cytochrome c.	Activates caspase-9/-3 cascade	Antitumor (apoptosis)	[87]
7	AMPK/mTOR/ Autophagy	Cordycepin, polysaccharides	Activates AMPK, inhibits mTOR, ↑ULK1	Induces autophagy	Antitumor, metabolic regulation	[40, 88]
8	TGF-β1/Smad	Polysaccharides, *H. sinensis* mycelium	Inhibits TGF-β1 signaling, ↓p-Smad2/3	Inhibits fibroblast/HSC activation; reduces ECM deposition	Anti-fibrosis (lung/ liver)	[102, 128]
9	TLR4/MyD88	Polysaccharides	Inhibits TLR4/MyD88 activation	Blocks NF-κB signaling	Anti-inflammatory (gut)	[100]
10	STING/IRF3	Extracts (2′-deoxyadenosine)	Activates STING-IRF3 axis	Modulates NK cell function (↓perforin)	Immunomodulation, renoprotective	[93]

ASC: Apoptosis-associated speck-Like protein containing a CARD; AMPK: AMP-activated protein kinase; CM1: Cordyceps militaris exo-polysaccharide-1; CSP: Cordyceps sinensis polysaccharides; ECM: Extracellular matrix; ERK: Extracellular signal-regulated kinase; HO-1: Heme oxygenase-1; HSC: Hepatic stellate cell; IL-1β: Interleukin-1β; IL-6: Interleukin-6; IκB-α: Inhibitor of kappa B alpha; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; MMPs: Matrix metallopeptidase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NK: Natural killer cell; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; Nrf2/ARE: Nuclear factor erythroid 2–related factor 2; NQO1: NAD(P)H: quinone oxidoreductase 1; p38: p38 mitogen-activated protein kinase; PI3K/ AKt/mTOR: phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; ROS: Reactive oxygen species; STING/IRF3: Stimulator of interferon genes/Interferon regulatory factor 3; TGF-β1: Transforming growth factor-beta 1; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor-α;

creatinine clearance, and decreased 24-hour urinary protein (24UP) in non-dialysis patients. Furthermore, these preparations alleviated CKD-related complications, such as elevating hemoglobin and serum albumin levels[140]. A meta-analysis of Bailing Capsules confirmed that the treatment group exhibited lower 24UP, blood urea nitrogen, and serum creatinine levels than the control group. Additionally, high-sensitivity C-reactive protein, IL-6, and TNF-α levels were significantly lower than those in the control group[103]. The combination of Bailing Capsules and α-keto acid tablets can delay disease progression in patients with stage 3 CKD while improving fatigue and loss of appetite, as well as renal function[141]. Diabetic kidney disease (DKD) is the primary cause of end-stage renal failure (ESRF) in CKD. *O. sinensis* and its preparations are frequently used in the treatment of DKD, yielding considerable therapeutic efficacy[142]. A large meta-analysis (60 trials involving 4,288 participants) demonstrated that co-administration of *O. sinensis* with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) proved more effective than monotherapy with ACEIs/ ARBs in reducing proteinuria (including 24UP and urinary albumin excretion rate), improving renal function (lower blood urea nitrogen and serum creatinine), optimizing lipid profiles (reduce TG and TC), and mitigating inflammation (lower C-reactive protein)[143]. Yan et al.[144] found that *O. sinensis* preparations combined with ACEI/ARB demonstrated beneficial effects on renal function, proteinuria, dyslipidemia, and even oxidative stress and inflammation in patients with DKD. *O. sinensis* promotes proliferation and inhibits apoptosis in renal tubular epithelial cells (HK-2 cells) under hyperglycemic conditions by downregulating pro-apoptotic proteins, Bax and Caspase-3, and modulating signaling protein (PTEN, VEGFA, p-AKT, and p-ERK) expression, suggesting a potential role in repairing renal tubular damage[145]. Furthermore, in diabetic and HK-2 mouse models exposed to high glucose, an extract rich in *O. sinensis* nucleosides/nucleobases (CS-N) counteracted renal fibrosis in diabetic nephropathy by inhibiting the p38/ERK signaling pathway and mitigating epithelial-mesenchymal transition and ECM deposition[146]. In a rat model of diabetic nephropathy, *O. sinensis* reduced the overexpression of HIF-1α and VEGF in the kidneys, suggesting its amelioration of chronic renal hypoxic conditions[147]. Bailing Capsules activate the PPARα pathway to promote renal lipolysis and inhibit lipid synthesis, reducing TG accumulation in diabetic rat kidneys and alleviating lipotoxicity damage[122].

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Table 3

Formulated preparations containing *Ophiocordyceps sinensis*

No.	Chinese herbal preparations	Source	Composition	Functions
1	Bailing Capsules	Pharmacopoeia of the PRC	Fermented *O. sinensis* Powder (Cs-C-Q80)	Tonifies the lungs and kidneys, nourishes essence and *qi*; indicated for cough, wheezing, hemoptysis, lumbar and waist soreness, face and eye puffiness, and copious clear urine at night due to deficiency of both lung and kidney *qi*; adjunctive treatment for chronic bronchitis and chronic renal insufficiency
2	Yisui Granules (Yisui Chongji)	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 4 WS3-B-0823-91	Deer antler velvet, prepared Rehmannia root, cornelian cherry, morinda root, fresh bovine spinal cord, goji berries, *O. sinensis*, polygonatum rhizome, ginseng, astragalus root, angelica root, chicken-blood vine, ginseng, and fresh bovine spinal cord	Nourishes essence and replenishes marrow, fortifies the kidneys and invigorates *yang*; indicated for lumbar soreness and leg weakness, muscular atrophy and pain, impaired cold and heat sensitivity, dizziness and tinnitus due to syringomyelia and other spinal disorders
3	Luwei Bushen Pills	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 4 WS3-B-0831-91	Pilose antler (hair removed), deer aelvet antler (steamed with wine), glue of tortoise shell, glue of deer antler, morinda root (steamed with salt), eucommia bark (slightly stir-fried), mantis egg-case (steamed with salt), lotus stamen, *O. sinensis*, gecko (head and scales removed), codonopsis Root (steamed), *Astragalus* Root, Chinese angelica (steamed with wine), and 11 other medicinal materials (totaling 24 ingredients)	Nourishes the kidneys and replenishes essence, strengthens sinews and bones, and invigorates *qi* and blood; indicated for kidney deficiency with essence depletion, *qi* and blood deficiency, dizziness and blurred vision, forgetfulness and seminal emission, lumbar soreness and leg pain
4	Gejie Zhilao Pills	National Drug Standards of the National Medical Products Administration WS3-B-0850-91	Gecko, *O. sinensis*, Stemmona root (honey-fried), *Fritillaria thunbergii*, *Bletilla striata*, *Ginkgo biloba*, Chinese plum	Nourishes the kidneys and tonifies the lungs, alleviates coughing and combats phlegm; indicated for pulmonary tuberculosis, tidal fevers, night sweats, coughing, and hemoptysis
5	Mie'ao Ling Tablets	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 8 WS3-B-1521-93	Banlangen, *Eleutherococcus senticosus*, honeysuckle, *O. sinensis*	Clears heat and detoxifies, nourishes the liver and tonifies the kidneys; indicated for acute and chronic hepatitis B, and for carriers of the surface antigen
6	Lifei Tablets	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 11 WS3-B-21527-96	Stemona root, *Bletilla striata*, gecko, oyster shell, loquat leaf, schisandra berry, lily bulb, *O. sinensis*, licorice root	Expels phlegm and fortifies the lungs; suppresses cough and dissolves phlegm; indicated for pulmonary tuberculosis with cough, expectoration of phlegm, hemoptysis, asthma due to *qi* deficiency, and chronic bronchitis
7	Zhiling Capsules	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 12 WS3-B-2312-97	*O. sinensis*	Tonifies the lungs and nourishes the kidneys; indicated for coughing, wheezing, and edema due to both lung and kidney *qi* deficiency; adjunctive treatment for various kidney disorders, chronic bronchial asthma, chronic hepatitis, and tumors
8	Wenshen Quanlu Pills	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 12 WS3-B-2442-97	Ginseng, *O. sinensis*, deer antler, deer penis, fresh venison (with bone), *Cynomorium songaricum*, processed *Morinda officinalis*, charred *Eucommia ulmoides*, prepared *Rehmannia glutinosa*, *Lycium barbarum*, *Angelica sinensis*, longan arils, and other medicinal materials (totaling 59 ingredients)	Warms the kidneys and consolidates essence; tonifies *qi* and nourishes blood; indicated for kidney *yang* deficiency and *qi* insufficiency and blood manifesting as: dizziness and forgetfulness, dim vision, and tinnitus, lumbar and knee soreness and weakness, lethargy and excessive sleepiness, impotence and seminal emission, uterine cold with leukorrhea, and habitual miscarriage

(Continued)

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Table 3
(Continued)

No.	Chinese herbal preparations	Source	Composition	Functions
9	Guben Qiangshen Capsules	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 13 WS3-B-2542-97	Ginseng, *O. sinensis*, Goji berries, Epimedium, Pollen, *Polygonum multiflorum*, Black-boned chicken (defeathered, de-clawed, gutted)	Replenish deficiency and invigorate *qi*, moisten the lungs, and protect the liver. Delay aging, benefit the brain and invigorate the spirit, enhance sexual function
10	Zibu Shuiya Decoction	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 19 WS3-B-3700-98	Duck meat, *O. sinensis*, prepared rehmannia root, goji berries, *Cistanche deserticola*, *Ligustrum lucidum*, *Eclipta prostrata*, *Astragalus membranaceus*, ginger	Tonifies *qi* and nourishes blood, replenishes *yin*. Indicated for generalized weakness, insomnia with frequent dreams, poor appetite, and postpartum or convalescent physical debility
11	Fangshuai Yishou Pills	Drug Standards of Ministry of Health PRC: Chinese Patent Medicine Formulations, Vol. 20 WS3-B-3833-98	Ginseng, Prepared Rehmannia root, White Fungus, Mussel, Aquilaria Wood, Turtle Shell (scorched with sand and quenched in vinegar), Deer Tendon, *O. sinensis*, Astragalus Root, Cornus Fruit (wine-roasted), Epimedium (roasted in mutton fat), Deer Antler, and other medicinal materials (totaling 59 ingredients)	For complexion lacking luster, shortness of breath with reluctance to speak, fatigue and listlessness, aversion to cold with cold limbs, forgetfulness and insomnia, frequent dreaming, heat in the palms and soles, night sweats or spontaneous sweating, dizziness and vertigo, poor appetite, loose stools or constipation, irregular menstruation, frequent urination or excessive nocturnal urination, arising from deficiency of *qi*, blood, and *yin* and *yang*.

O. sinensis may serve as an adjunct immunosuppressant in renal transplantation. Supplementing conventional immunosuppressive regimens (eg, cyclosporine A) with *O. sinensis* may reduce their dosage and blood concentration without increasing the risk of acute rejection, thus lowering the incidence of associated side effects, including hepatotoxicity, nephrotoxicity, and hyperuricemia[127,148]. A retrospective clinical study spanning 3 to 5 years revealed that the 5-year transplanted kidney survival rate was significantly higher in the Bailing Capsules group than in the control group, suggesting a potential beneficial effect on long-term graft survival[149]. A study on patients with chronic allograft nephropathy (CAN) revealed that after 6 months of treatment with Bailin Capsules, significant improvements were observed in serum creatinine, creatinine clearance, urinary protein, and urinary transforming growth factor-β1 levels, demonstrating potential in slowing the progression of CAN[150]. In summary, *O. sinensis* demonstrates potential value in reducing the dosage of conventional immunosuppressants, mitigating drug toxicity, improving transplanted kidney function, and enhancing patients' overall condition.

As an adjunctive therapy, Bailing Capsules may enhance the clinical response rate in lupus nephritis and improve indicators such as the systemic lupus erythematosus disease activity index, serum albumin, 24UP, and serum creatinine[151–152]. Furthermore, for autoimmune thyroiditis, Bailing Capsules plus levothyroxine sodium treatment yielded superior efficacy compared with levothyroxine sodium monotherapy, demonstrating greater effectiveness in improving thyroid function, reducing thyroid autoantibody (TPOAb and TgAb) and inflammatory cytokine (IL-6 and IL-17) levels, without increasing adverse reactions[153].

O. sinensis is frequently used as an adjunct to conventional drug therapies in cancer treatment, with preliminary clinical observations suggesting its potential in tumor adjuvant therapy. Niwa et al.[154] conducted a retrospective analysis to evaluate the impact of natural therapies, including *O. sinensis*, on survival duration in patients with hepatocellular carcinoma. They found that patients treated with at least four natural therapies (including *O. sinensis*) demonstrated significantly longer survival than those treated with ≤3 natural products (40.2 *vs*. 6.4 months). This survival prolongation was independent of liver disease severity or tumor stage, and no toxic side effects were observed, providing preliminary clinical support for the potential of *O. sinensis* as an adjunctive tumor therapy. *O. sinensis* has demonstrated significant efficacy in the adjuvant treatment of lung cancer. Compared to conventional therapy, *O. sinensis* enhances tumor response rate and markedly improves immune function, including increased CD4, CD8, and NK cell levels and immunoglobulin (Ig) A, IgG, and IgM expression; Moreover, *O. sinensis* can enhance patients' quality of life, significantly reducing bone marrow suppression, leukopenia, and thrombocytopenia incidence and radiation pneumonitis risk[155]. Owing to the rapid metabolism of cordycepin, its clinical application has been limited. Poly(lactic-co-glycolic acid) (PLGA) nanoparticles have been developed as a delivery system for cordycepin. These nanoparticles enhance cordycepin's cellular uptake rate and cytotoxicity and markedly reduce its hemolytic toxicity, offering a safer and more effective option for breast cancer treatment[156]. Thus, *O. sinensis*, as a natural product, has demonstrated significant efficacy in the adjunctive treatment of cancer, particularly in improving immune function and quality of life and mitigating adverse drug reactions.

Di Lorenzo et al.[34] evaluated the role of *O. sinensis* mycelium hydroalcoholic extract in promoting skin longevity in 40 participants and revealed that the extract

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significantly elevated skin energy levels and stimulated collagen production, markedly reducing wrinkles. These clinical findings align with mechanisms observed *in vitro*, including increased sirtuin expression, NAD^+ synthesis, and ATP production and decreased ROS. A clinical trial involving patients with melasma demonstrated that the combination of an *O. sinensis* extract serum with oral tranexamic acid significantly improved both the melasma area and severity index (MASI) of melasma lesions, concurrently reducing the incidence of adverse reactions[157].

Chen et al.[158] found that *Cordyceps sinensis* mycelium extract (Cs4) demonstrated efficacy in alleviating long COVID-19 symptoms in a study including 110 patients. Zhao et al.[159] conducted a randomized double-blind trial including 90 patients with primary insomnia who received fermentation broth of *Cordyceps sinensis* (FBCS) and found that FBCS improved the overall sleep quality of patients with primary insomnia. Wei et al.[160] conducted a systematic review and meta-analysis (14 clinical studies including 1,014 patients) to evaluate the efficacy and safety of *O. sinensis* preparations for Hashimoto thyroiditis (HT). The findings indicated that *O. sinensis* preparations, when combined with other treatments (low-iodine diet or levothyroxine), reduced thyroid autoantibodies and inflammatory responses in patients with HT. Furthermore, in patients with HT with hypothyroidism, the combination of *O. sinensis* preparations and levothyroxine improved symptoms. Welch et al.[161] conducted a systematic review and meta-analysis and found that *O. sinensis* supplements in healthy individuals can improve quality of life, alleviate fatigue, and enhance immune responses.

O. sinensis and its pharmaceutical preparations exhibit multi-target regulatory properties. Their therapeutic efficacy is supported by several clinical studies and meta-analyses (Table 4). The primary diseases treated are illustrated in Figure 13. The mechanism of action of *O. sinensis* encompasses metabolic regulation, anti-inflammatory, immunomodulation, and antioxidant properties. Further high-quality, large-scale randomized controlled trials are required to confirm its long-term benefits and safety profile.

Challenges and the future: discussions on sustainable development

O. sinensis, as a valuable Chinese herbal medicine resource, has long garnered considerable attention owing to its unique pharmacological effects and rarity. However, with increasing market demand and ecological changes, the research and development of *O. sinensis* is facing numerous challenges while presenting new opportunities for its future advancement.

Challenges to sustainable development

Resource scarcity and sustainability concerns

Wild *O. sinensis* thrives in highly specialized habitats with stringent climatic and ecological requirements. Global warming has precipitated significant habitat alterations, with the Tianshan and Kunlun mountain ranges and southwestern Qinghai-Tibet Plateau regions facing substantial reductions in viable distribution areas in the near future[162]. Robust market demand and excessive harvesting have increasingly depleted the wild species, with prices remaining persistently high, placing it at the brink of extinction[163]. This scarcity limits its widespread application and poses challenges in securing sufficient and stable wild *O. sinensis* sample sources for scientific research. Although cultivation techniques (such as liquid culture and solid-state fermentation) have advanced, the medicinal and active constituents in cultivated *O. sinensis* differ from those found in wild *O. sinensis*[16], thus requiring more in-depth comparative research. Other *Cordyceps* species (eg, *C. militaris* and *C. cicadae*) have been explored as *O. sinensis* substitutes; however, their metabolite profiles differ from those of *O. sinensis*, and their medicinal value is yet to be fully recognized[164].

Comprehensive elucidation of the complex mechanisms of action

The pharmacological effects of *O. sinensis* involve multiple active constituents, including polysaccharides, nucleosides, amino acids, lipids, and others, which exert synergistic effects through multi-targeted, multi-pathway mechanisms. Although existing research in antitumor, renoprotective, and immunomodulation effects has revealed partial molecular mechanisms (eg, MAPK pathways, sirtuin activation, mitochondrial energy metabolism, and macrophage polarization), a systematic and thorough understanding of the synergistic function of these intrinsic networks and the variations in dominant mechanisms across different disease states remains lacking. For example, Li et al.[165] used network pharmacology to elucidate the multi-target and multi-pathway mechanisms *via* which *O. sinensis* helps treat diabetic nephropathy; however, these predicted mechanisms require more rigorous experimental validation. The pharmacological effects of *O. sinensis* involve the cross-regulation of multiple signaling pathways, rendering a comprehensive and clear investigation of its mechanism of action challenging.

Insufficient clinical positioning and evidence-based research

Although *O. sinensis* is widely used as a therapeutic and dietary supplement in traditional Chinese medicine, demonstrating potential effects across multiple disease models, high-quality, large-scale, randomized, double-blind, placebo-controlled clinical studies are relatively lacking, limiting the promotion and application of *O. sinensis* in the modern medical system. For example, despite numerous randomized controlled trials investigating the application of *O. sinensis* in patients undergoing dialysis, evidence regarding its effects on C-reactive protein, creatinine, and blood urea nitrogen, while suggesting some degree of improvement, remains of low certainty[166].

Controversy over the equivalence of cultivated and wild O. sinensis *products*

Although Li et al.[167] indicate that cultivated *O. sinensis* specimens exhibit no significant differences in chemical

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Table 4

Clinical research on the primary diseases treated using *Cordyceps* preparations

No.	Usage format	Types of disease	Primary function	Sample size	Study design	Source
1	Cordyceps Preparations and Compound Formulations	COPD	Improve lung function	1,238	Meta-analysis	[137]
2	Bailing Capsules	COPD	Improve lung function	27	RCT + meta-analysis	[135]
3	Bailing Capsules	CB	Reduce the frequency of AECB occurrences	238	RCT	[118]
4	*Ophiocordyceps sinensis* preparations	CKD	Improve renal function indicators	1,746	Random-effects model statistical analysis	[140]
5	Bailing Capsules	CKD	Improve renal function indicators; reduce levels of inflammatory cytokines	/	Meta-analysis	[103]
6	Combination therapy with Bailing Capsules and α-keto acid Tablets	CKD	Delay the progression of the disease	72	RCT	[141]
7	Combination therapy of *O. sinensis* with ACEs or ARBs	DKD	Improve kidney function and reduce inflammation	4,288	Meta-analysis	[143]
8	Combination therapy of *O. sinensis* with ACEs or ARBs	DKD	Aids in improving renal function, reduces proteinuria, and ameliorates dyslipidemia and oxidative stress	3,167	Systematic review + meta-analysis	[144]
9	Bailing Capsules	Kidney transplant	Significantly improved 5-year kidney transplant survival rates;	180	Retrospective clinical study	[149]
10	Bailing Capsules	CAN	Improve renal function indicators; delay disease progression	231	RCT	[150]
11	Bailing Capsules in combination with levothyroxine sodium	Autoimmune thyroiditis	Improve thyroid function; reduce immune-inflammatory responses	70	Retrospective clinical study	[153]
12	*O. sinensis*	HCC	Significant increase in survival time; no toxic side effects	101	Retrospective clinical study	[154]
13	*O. sinensis* mycelium hydroalcoholic extract	Skin aging	Promotes collagen production, significantly reducing wrinkles	40	Double-blind placebo-controlled clinical trial	[34]
14	*O. sinensis* extract combined with TXA	Melasma	Significantly reduces the area of melasma; minimizes adverse reactions	62	RCT	[157]
15	*Cordyceps sinensis* mycelium culture extract (Cs4)	Long COVID symptoms	Significantly improve quality of life, reducing symptoms of fatigue and breathlessness	110	RCT	[158]
16	FBCS	Primary insomnia	Significantly improve sleep quality	90	Randomized, double-blind, placebo-controlled trial	[159]
17	*O. sinensis* preparations	Hashimoto Thyroiditis	As an adjunct therapy to improve clinical condition	1,014	Systematic review + meta-analysis	[160]
18	*O. sinensis*	Healthy individuals	Enhance quality of life, reduce fatigue, and strengthen immune response	286	Systematic review + meta-analyses	[161]

ACE: Angiotensin-converting enzyme inhibitor; AECB: Acute exacerbation of chronic bronchitis; ARB: Angiotensin II receptor blocker; CAN: Chronic allograft nephropathy; CB: Chronic bronchitis; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; DKD: Diabetic kidney disease; FBCS: Fermentation broth of Cordyceps sinensis; HCC: Hepatocellular carcinoma; RCT: Randomized controlled trial; TXA: Tranexamic acid.

composition compared with wild specimens, and that it can avoid heavy metal contamination[167], a comparative study by Zhou et al.[37] revealed differences in adenosine, cordycepin, mannitol, and polysaccharide content between both specimens. Liu et al.[86] observed differences in the relative content of fatty acids, glycerides, and glycerophospholipids between cultivated and wild *O. sinensis via* an *in situ* chemical analysis using TOF-SIMS. The chemical composition and biological activity of wild *O. sinensis* are significantly influenced by its growth environment, such as climate and altitude. Despite cultivation under controlled conditions, complete replication of natural growth conditions is difficult, potentially leading to variations in certain constituents. For example, an analysis of volatile compounds indicates that cultivated *O. sinensis* may exhibit differences in odor characteristics. These variations may result in subtle differences in their pharmacological activity and clinical efficacy. Consequently, the scientific evaluation of the equivalence of cultivated *O. sinensis* products with

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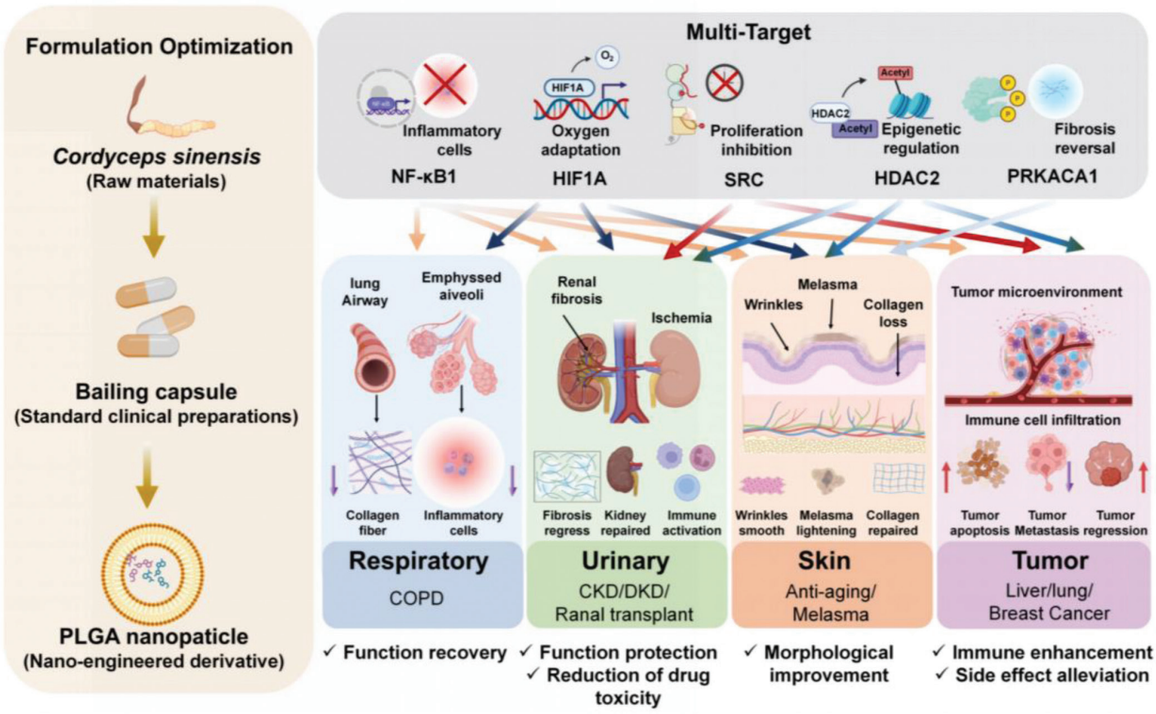


Figure 13. Clinical applications of *Ophiocordyceps sinensis* and its derivatives. CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; DKD: Diabetic kidney disease; HCC: Hepatocellular carcinoma; PLGA: Poly(lactic-co-glycolic acid).

their wild counterparts, and widespread acceptance from both the market and consumers, hinders their industrial development.

Quality control and regulatory science challenges

The quality of *O. sinensis* is influenced by its origin, harvesting time, processing methods, storage conditions, and the fungal strains, causing significant fluctuations in active constituent content and inconsistent product quality[168]. Zhou et al.[169] have revealed issues regarding bioavailability and risk assessment of heavy metals (eg, arsenic, lead, cadmium, and mercury) in *O. sinensis*. Although its inorganic arsenic content is relatively low, excessive heavy metal levels remain a quality and safety concern for wild *O. sinensis*. Moreover, the composition and pharmacological activity of different commercialized products (such as fermented mycelium products) vary. The establishment of scientific, unified quality evaluation standards and methodologies poses a key challenge for the strong development of the *O. sinensis* industry[170]. Currently, standardized testing techniques for *O. sinensis* are lacking. Although surface-enhanced Raman spectroscopy combined with machine learning algorithms can rapidly distinguish wild from cultivated *O. sinensis*[171], and TOF-SIMS enables *in situ* chemical analysis and imaging of the chemical constituents in *O. sinensis*[86], further research and promotion remain needed. Quality control and standardization of *O. sinensis* demand multidisciplinary collaboration and concerted efforts for effective resolution. Refining the quality standards and evaluation systems for *O. sinensis* and its products while clearly distinguishing their classification as medicinal "products," "health supplements," or "foodstuffs" helps prevent efficacy-related confusions.

Recommendations for sustainable future development strategies

Strengthening resource conservation and sustainable utilization

O. sinensis has immense economic and medicinal value. However, global warming and human activities have rapidly diminished its habitats[162], and over-exploitation has led to a sharp decline in its wild populations, further exacerbating the resource crisis[172]. Measures for advancing the establishment of an ecological conservation framework for the Qinghai-Tibet Plateau include a dynamic monitoring and early warning mechanism for *O. sinensis*, ecological restoration and sustainable harvesting techniques, and coordinated biodiversity protection, which may help explore novel pathways for the sustainable conservation and utilization of *O. sinensis* resources. Cultivation techniques are crucial to addressing the scarcity of wild *O. sinensis*. Currently, liquid culture techniques (eg, submerged and surface/static cultures) are regarded as a viable industrial method owing to their short cultivation cycles and high cordycepin yields[164]. Furthermore, the government and relevant agencies should enhance training in harvesting techniques, effectively mitigate inter-harvester competition *via* co-management models in nature reserves, and disseminate market information to increase local communities' income and awareness of resource conservation.

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Custom hybridization enrichment probes from 94 production zones across Asia alongside market-grade *Cordyceps* samples (dating back up to 30 years) were used to distinguish specimens from primary production areas, enabling product verification and enhancing oversight of this transnational trade route, curbing illicit exports and other forms of economic exploitation, and promoting fair trade, thereby bolstering urgently needed cross-border conservation efforts for this natural commodity[173].

Establishing a robust quality control system

Future research should focus on developing more comprehensive and precise quality assessment methodologies to evaluate *O. sinensis* and its products *via* multidimensional, holistic quality evaluations. A robust quality control system will ensure medicinal efficacy, safety, and market standardization. Polysaccharides serve as quality markers for *O. sinensis*. PXRD technology enables effective analysis of polysaccharide composition, establishing characteristic diffraction peak fingerprint patterns to distinguish *O. sinensis* from different geographical origins[43]. Specific metabolic markers such as adenosine, riboflavin, and tyrosine can be identified *via* MS-based metabolomics analysis in wild versus cultivated *O. sinensis*. These markers aid in distinguishing *O. sinensis* from different sources and provide support for multi-target quality control[174]. Heavy metals such as arsenic, lead, and cadmium in *O. sinensis* pose potential threats to human health. Inductively coupled plasma MS enables the precise determination of heavy metal content in *O. sinensis* and facilitates the establishment of metal elemental profiles for identifying anomalous samples[175]. Moreover, DNA detection based on nucleic acid hybridization lateral flow test strips enables rapid authentication of *O. sinensis*, offering high efficiency and convenience[176]. Currently, quality standards for *O. sinensis* and its fermented products remain inconsistent. Further standardization in product nomenclature, unified management of approval number categories, and the introduction of specific quality control attributes may elevate overall quality standards.

Conducting an in-depth analysis of the synergistic mechanisms of multiple components

Future pharmacological research should shift from single components or simple extracts to multi-component formulations and holistic mechanisms of action. Complex networks linking the active constituents of *O. sinensis* with disease targets that are constructed using systems biology, network pharmacology, and multi-omics technologies can help elucidate the molecular mechanisms of its multi-component synergistic effects. Concurrently, genomic analyses indicate that the genomic architecture and protein families of *O. sinensis* are closely linked with its ecological and nutritional heterogeneity. Its symbiotic microbiota, comprising bacteria and other fungi, form intricate mutualistic relationships that facilitate its colonization and reproduction in the insect host. These microorganisms may further promote infection by producing specific metabolites or modulating the host's immune response[177]. Research on the endophytic fungi and symbiotic microbial communities in *O. sinensis* could be strengthened to investigate their contribution to the production of active constituents and its pharmacological effects.

Innovative product development and application expansion

In 2016, the erstwhile China Food and Drug Administration halted the pilot program for using *O. sinensis* in health foods, and further restrictions have since been imposed on the development and utilization of related products. Fundamental research should be strengthened to conduct comprehensive evaluations of the edible and ecological safety and resource security of *O. sinensis*. Rigorous scientific conclusions should be drawn through meticulous research data to establish national standards for *O. sinensis*, providing reference for its further application in health supplements, nutritional foods, and similar products. Building upon an in-depth understanding of the active constituents of *O. sinensis* and their mechanisms of action, future development may yield more functional foods, health supplements, and novel pharmaceuticals with clearly defined efficacy and controllable quality. Łysakowska et al.[178] indicated that *O. sinensis* Powder may serve as a functional food additive, enhancing the nutritional value and antioxidant capacity of bread. Furthermore, the application of *O. sinensis* in fields such as biotransformation and bioengineering has garnered research attention. For example, Li et al.[120] investigated the biotransformation of ginsenoside Rb1 by wild *O. sinensis*, offering insights for the development of novel functional products. In summary, *O. sinensis* research is ongoing, and the numerous challenges notwithstanding, with continuous advances in science and technology and in-depth investigations, the immense potential of *O. sinensis* will be more fully explored and harnessed, thus contributing significantly to the cause of human health.

Conclusions and prospects

O. sinensis is a rare and valuable medicinal and economic resource endemic to the Qinghai-Tibet Plateau. In recent years, multiple factors have progressively diminished its distribution range, with resource reserves declining markedly, posing severe challenges to sustainable utilization. Concurrently, despite the progress of cultivation techniques, quality control and market recognition issues persist. *O. sinensis* possesses complex constituents with multi-targeted mechanisms of action, necessitating further elucidation of its pharmacokinetic characteristics and multi-component synergistic effects. Moreover, limited high-quality, large-scale, multi-center randomized controlled clinical trials constrains its widespread application in modern medicine and the accumulation of evidence-based data. Currently, both national and local authorities are increasingly prioritizing the conservation and sustainable utilization of *O. sinensis* resources. This review has systematically elucidated the unique biological characteristics, active constituents, pharmacological actions, and clinical applications of *O. sinensis*. It introduces novel technical approaches, providing fresh

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research perspectives while exploring existing challenges and future research directions. Future studies and applications should focus on resource conservation and sustainable utilization, cultivation and substitute development, establishment of quality standards, elucidation of action mechanisms, and product development and promotion. *O. sinensis* research is transitioning from traditional understanding to scientific elucidation. Enhanced multidisciplinary collaboration integrating traditional knowledge with modern technology can further reveal its scientific essence, driving in-depth human health-contributory research.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Guiyu Li drafted the original manuscript. Ziwei Chen revised the figures. Weiwei Tian revised the manuscript. Yang Liu, Siye Yang, and Li Liu contributed to figure preparation. Ping Wei provided writing suggestions. Hua Hua and Junning Zhao supervised and guided the review. All the authors have read and approved the final version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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