In vitro cultivation & applications of a medicinal mushroom cordyceps militaris: from traditional medicine to modern therapeutics

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Abstract :

Cordyceps militaris is a well-recognised medicinal fungus that has gained significant scientific attention as a sustainable alternative to the rare and endangered *Ophiocordyceps sinensis.* Advances in *in vitro* cultivation technologies have enabled large scale production, facilitating detailed investigations into its bioactive metabolites, pharmacological activities and biosynthetic pathways. Among its metabolites, cordycepin, polysaccharides and sterols have been extensively studied for anticancer, immunomodulatory and antioxidant effects. However, substantial variability in cultivation methods, metabolites profiles and experimental models has resulted in inconsistent findings across studies. Recent developments in genomics, metabolomics and quality control methodologies have improved species authentication and standardisation, yet translational challenges remain due to limited clinical validation and regulatory harmonization. This review critically synthesizes current knowledge on taxonomy, ecology, cultivation, metabolite biosynthesis, pharmacological activities, safety, quality control and future perspectives of *C. militaris*, highlighting key research gaps and directions for clinical and industrial translation.

Keywords : *Cordyceps militaris*, *Ophiocordyceps sinensis*, Cordycepin, entomopathogenic fungus, medicinal mushroom, immunomodulatory, antioxidant.

Introduction :

Medicinal fungi have long been integral to traditional medicine systems, particularly in East Asia where they are valued for their therapeutic and tonic properties. Among these, *Cordyceps* species occupy a unique ecological and pharmacological niche due to their entomopathogenic lifestyle and production of bioactive secondary metabolites (Olatunji et al., 2018). *C. militaris* has emerged as the most extensively studied and commercially cultivated species within the genus, primarily because of its ability to complete its life cycle under artificial conditions. In contrast to *Ophiocordyceps sinensis*, which is restricted to alpine ecosystems and faces overharvesting pressures, *C. militaris* offers a renewable and controllable source of cordycepin and related compounds (Wasser, 2010). The growing global demand for functional foods,

nutraceuticals and natural therapeutics has accelerated research into *C. militaris*. However, despite extensive biochemical and pharmacological studies, challenges persist in standardization, reproducibility and clinical translation. A comprehensive synthesis integrating taxonomy biology, genomics and applied research is therefore essential to guide development.

The objective of this review is to critically integrate current knowledge on the taxonomy, genomics, in vitro cultivation strategies, bioactive metabolites, pharmacological activities, safety and quality control of *Cordyceps militaris*. The review further aims to identify key research gaps limiting clinical translation and industrial standardisation and to propose future directions for translational and bioprocess-oriented research.

Context :

1.Taxonomy, Phylogeny and Species Authentication

The taxonomy of Cordyceps has undergone major revisions following the integration of molecular phylogenetics. Traditionally classified under the genus Cordyceps (family Cordycipitaceae, order Hypocreales) many species were reclassified into Ophiocordyceps, Metacordyceps and Elaphocordyceps based on multigenetic analyses. (Shrestha et al., 2017). C. militaris remains within the core Cordyceps clade and is taxonomically distinct from O. sinensis despite historical conflation in commercial products. Phylogenetic analyses using ITS, LSY, SSU and TEF1-α markers consistently place C. militaris in a monophyletic group closely related to C. cicadae and C. tenuipes (Quandt et al., 2014). Species authentication has become increasingly important due to widespread adulteration of Cordyceps based products. DNA Barcoding, particularly using the ITS region, has proven effective for species level identification and detection of substitution or contamination. (Meng et al., 2025). Combining molecular tools with chemical fingerprinting is now considered best practice for authentication.

2. Ecology and Life cycle

C. militaris is an entomopathogenic fungus that naturally parasitizes lepidopteran larvae and pupae. Its ecological role involves regulating insect populations and contributing to nutrient cycling within forest ecosystems (Tian et al., 2010). Unlike O. sinensis, which exhibits strict host and habitat specificity, C. militaris displays broader host adaptability. Life cycle begins with spore attachment and germination on the insect cuticle, followed by hyphal penetration and internal colonization. Mycelial growth eventually leads to host death and the emergence of stromata from the insect cadaver under favourable environmental conditions. (Shrestha et al., 2012). Environmental factors such as temperature, humidity and light strongly influence

stromatal development and sporulation. These biological traits underpin the species amenability to artificial cultivation and have informed modern cultivation technologies. (Li et al., 2019).

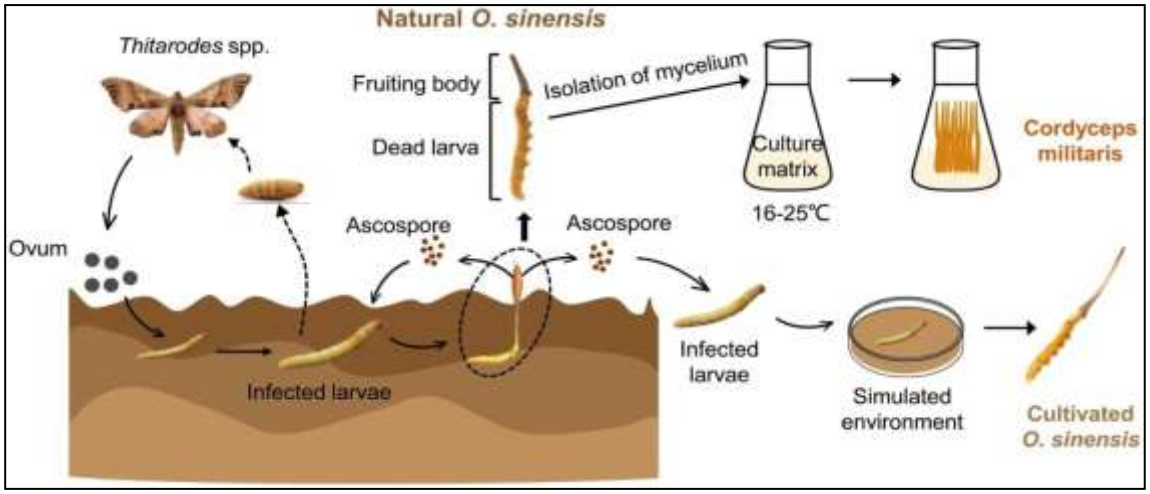
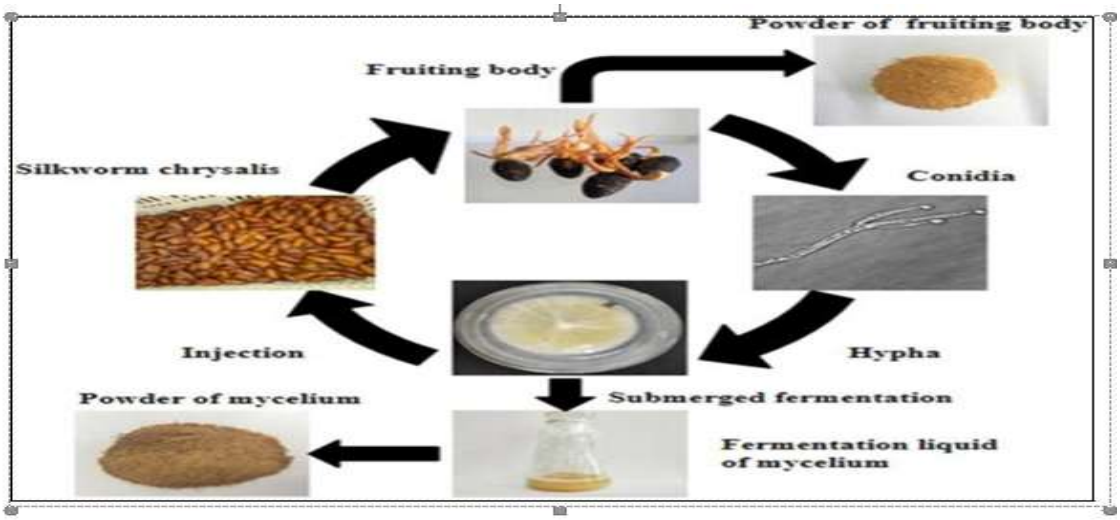


Fig 1: Schematic illustration of the formation process of natural and cultivated O. sinensis. The whole process is a complex cycle, including the fungus invading the host and the infected larvae moving 2-5 cm below the soil surface. After the larvae gradually harden, the interstitial buds grow from the head of the parasitic larva in the spring to form a stalked fruiting body filled with ascospores. Under the right conditions, the ascospores spread and infect other larvae. (Zhangwen Ma et al. (2024))

3. Genomics and Biosynthetic Potential

The availability of whole genome sequences has significantly advanced understanding of the biosynthetic capacity of C. militaris. The genome (~32-34 Mb) encodes numerous gene clusters associated with secondary metabolite production, including non-ribosomal peptide synthetases (NRPS), polyketide synthases (PKS) and hybrid clusters. (Zheng et al., 2011). Genomic and transcriptomic studies have identified gene clusters directly involved in cordycepin biosynthesis, revealing coordinated regulation of purine metabolism and transport pathways. (Zhang et al., 2024). These findings explain the influence of environmental and nutritional factors on cordycepin yield observed in cultivation studies. Comparative genomics indicates that C. militaris possesses greater biosynthetic plasticity than O. sinensis, supporting its suitability for metabolic engineering and industrial exploitation. (Kramer & Nodwell, 2017). However, many represent an untapped reservoir of novel metabolites.



4. Cultivation Technologies of C. militaris

Early cultivation systems relied on Solid state fermentation (SSF) using cereal grains such as rice, wheat and millet. These substrates support mycelial growth and fruiting body formation but show variability in yields and metabolite contents depending on grain composition and moisture levels.(Wen et al., 2016) To address this, insect free and protein supplemented substrates were developed, allowing ethical and scalable production without host insects. (Borde & Singh, 2023). Light is a critical morphological factor for fruiting body induction in C. militaris. Blue and white light (400-500 nm) regulate stromata formation and pigmentation through photoreceptor mediated pathways, while complete darkness favours only mycelial biomass. Optimised photoperiods (12-16 h/day) significantly enhance cordycepin accumulation in fruiting bodies. (Lin et al., 2024).

Fig 2: Cultivation process of C.sinensis (Lingran et al, (2020))

4. Bioactive Metabolites of C. militaris

The therapeutic value of C. militaris is attributed to a diverse array of primary and secondary metabolites, with nucleoside analogues being the most extensively studied. Cordycepin (3`-deoxyadenosine) is the signature compound, first isolated in 1950 and subsequently identified as a key pharmacologically active molecule (Cunningham, 1951). Cordycepin biosynthesis occurs via modified purine metabolism and its accumulation is strongly influenced by cultivation conditions, particularly oxygen availability and nitrogen sources. (Xia et al., 2017). Alongside cordycepin, adenosine and related nucleosides contribute synergistically to biological activity (Tuli et al., 2013). Polysaccharides isolated from C. militaris fruiting bodies and mycelia exhibit β-glucan-rich structures with immunomodulatory and antioxidant properties. Structural characterisation studies indicate that branching degree and molecular

weight critically determine bioactivity. (Li et al., 2022). Other bioactive constituents include ergosterol and ergosterol derivatives, which exhibit anti-inflammatory and anti-cancer properties as well as minor metabolites such as mannitol, peptides and phenolics (Wang et al., 2021). Advanced LC-MS based metabolomics has revealed significant metabolic diversity between cultivation methods, reinforcing the need for standardised production (Ma et al., 2023).

BIOMOLECULE	BIOACTIVE COMPONENT	BIOLOGICAL ACTIVITY / THERAPEUTIC EFFECT
Nucleoside	Cordycepin	Antitumor, anti-diabetic, anti-inflammatory, antimicrobial, inhibit platelet aggregation, hypolipidemic, analgesic, immunomodulatory
	Adenosine	Anticonvulsant, Anti-inflammatory, Anti-tumor
Polysaccharides	Exopolysaccharide Fraction (EPSF)	Anti-tumor, antioxidant, anti-inflammatory, Immunomodulatory
	Acid polysaccharides (APS)	Antioxidant, Immunomodulatory effect
	CPS-1/2	Cell proliferation inhibition
	PS-A	Inhibitory activity against cholesterol esterase
	Cordyglucan	Anti-tumor
	D-mannitol or Cordycepic acid	Diuretic, anti-tussive and anti-free radical activities
Sterols	Ergosterol	Antimicrobial, antiviral, anti-arrhythmic effects, Helps in bone development
	β-Sitosterol	Protect from breast, colon and prostate cancer
	H1-A	Immunoregulation
Proteins, Amino acids & Polypeptides	Tryptophan	Serves as precursor for the synthesis of the neurotransmitters serotonin and tryptamine
	CSDNase	DNA hydrolysis, nucleolytic properties
	Cordymin	Anti-diabetic effect, antifungal
Others	Exopolysaccharides	Nutraceutical, pharmaceutical

	Vit B1,2,12,E,K	Antioxidant, Help in formation of blood cells, muscles, lung and nerve tissues, Increase immunity
	Phenolic compounds	Antioxidant, antimicrobial, anti-arthritic, anti-carcinogenic, anti-hypertensive, cardio-protective, anti-inflammatory and anti-allergic
	Proteoglucans	Enhanced anticancer effect on bladder cancer cells
	Fibrinolytic enzyme	Treatment of thrombosis

Table 1: List of bioactive components present in Cordyceps with their biological activities and implication in therapeutics. (Sayyed et al, 2020)

5. Pharmacological Activities

Pharmacological investigations demonstrate that C. militaris exhibit multifunctional bioactivity, largely mediated by cordycepin and polysaccharides. Anticancer activity is among the most documented, with cordycepin inducing apoptosis through caspase activation, mitochondrial membrane depolarization and inhibition of mTOR and AMPK signalling pathways. (Nakamura et al., 2006). Immunomodulatory effects include enhancement of macrophage phagocytosis, regulation of cytokine secretion and activation of natural killer cells, primarily attributed to polysaccharide fractions. (Kim et al., 2022). Anti-inflammatory effects are mediated through suppression of NF-KB and MAPK pathways, resulting in decreased production of pro-inflammatory mediators such as TNF-α and IL-6. (Won et al., 2010). Additionally, antioxidant activity arises from free-radical scavenging and upregulation of endogenous antioxidant enzymes. Neuroprotective and antidiabetic effects have also been reported, although these require further mechanistic validation. (Lee et al., 2020).

PRODUCT NAME	HEALTH BENEFIT CLAIM	MANUFACTURER
Mycoformulas Endurance™	Enhancement of intracellular energy exchange, increases oxygenation and natural endurance	Myco Formulas, USA
Nutricafe-organic	Increases physical endurance and helps to remove toxins from your body	Aloha Medicinals USA
Mushroom Plus	Supporting immune system, energy levels and cognition	Link Nutrition Ltd., UK

Dragon Herbs	Increases the primary stimulating force for life activity	Iherb Holdings LLC, USA
OM™ Maitake	Supports weight control and blood sugar balancing	Yukiguni Maitake CO., LTD, Japan
Host Defense Mushrooms	Energy support	Host Defense, USA
CaféCeps® Packets	Numbers of health-enhancing properties,	Madre Labs LLC, France
Bhutan *Cordyceps* Tea	Immunity booster, Anticancer, Anti-aging, Antioxidant, Improve kidney and gastrointestinal systems	Bhutan Natural, Singapore
MRM *Cordyceps* CS-4 Strain	It strengthens the immune system, respiratory system and cardiovascular system and strengthens the natural metabolism of energy	All Star Health, USA
Ultra *Cordyceps* Plus	Help boost physical energy and stamina, improve vitality, support lung health, liver function, memory and mental ability	Doctor's Best, USA
Now Foods *Cordyceps*	Immune health support	Now Foods, USA
Exploding Buds *Cordyceps Sinensis*	Immune health support	Iherb Holdings LLC, USA
Fungiology from California Gold Nutrition	For healthy immunity and health promotion of the entire body	California Gold Nutrition, USA
Planetary Herbals *Cordyceps* POWER CS-4	Energy support	Michael Tierra, USA
Cordyceps Capsules, Extracts or Powders	Energy support and stamina	Host Defense Mushrooms, USA
Cordyceps active	Promotes mental health, Ensure perfect oxygenation of the heart and vascular system	Terezia, Czech
Collagen C ReLift Capsules	For less wrinkles and improved complexion	Zein Pharma, Germany
MycoNutri *Cordyceps* Organic	Immune system support	The Really Healthy, UK

Table 2: Nutraceutical products from Cordyceps available on the global market (Sayyed et al, 2020)

6. Safety and Toxicology

Despite its long history of traditional use, systematic toxicological evaluation of C. militaris is essential for pharmaceutical and nutraceutical applications. Acute and sub-chronic toxicity studies in rodents indicate no significant adverse effects at therapeutically relevant doses, supporting its general safety profile. (Long et al., 2021). Genotoxicity and mutagenicity assessments, including Ames and micronucleus tests, have shown negative results, suggesting low genetic risk. (Dutta et al.), However, safety concerns primarily arise from contaminant accumulation, particularly heavy metals absorbed from substrates during cultivation. (Paul & Pradhan, 2024). Therefore, cultivation conditions, substrate quality and post-harvest processing are critical determinants of product safety.

7. Quality Control and Standardisation

Quality control of C. militaris products remains challenging due to chemical variability across strains and cultivation systems. Marker-based quantification of cordycepin and adenosine using HPLC or UPLC is the most widely adopted approach. (Hu et al., 2015). Advanced chromatographic fingerprinting combined with chemometric analysis provides comprehensive quality assessment and batch consistency evaluation. (Zhang et al., 2018). Molecular authentication using DNA barcoding ensures species-level identification and prevents adulteration. (Xiang et al., 2013). The inclusion of C. militaris monographs in the Chinese Pharmacopoeia has accelerated efforts toward international standardization; however, harmonized international guidelines further exacerbate these limitations.

8. Future Perspectives and Translational Challenges

Future research on C. militaris must prioritize translational consistency, moving beyond descriptive bioactivity studies towards mechanism-driven and clinically relevant investigations. One promising direction is the integration of systems biology approaches, including transcriptomics and metabolomics, to link cultivation conditions directly with metabolite biosynthesis and pharmacological outcomes. (Tang et al., 2021). Advances in bioprocess engineering, such as continuous fermentation and metabolic pathway engineering, offer potential for enhanced cordycepin production with reduced batch variability. (Xia et al., 2017). Genetic and synthetic biology tools could further enable strain improvement; however, regulatory acceptance of genetically modified fungal products remains a challenge. (Krishna et al., 2025).

From a translational standpoint, standardized formulations and dosage determination are critical bottlenecks. The lack of consensus on therapeutic dosing, bioavailability and pharmacokinetics hinders progression from nutraceuticals to evidence-based therapeutics. (Tuli et al., 2014). Additionally, variability in national regulatory frameworks complicates global commercialization (Meshram et al., 2025).

Clinical translation will require well-designed, randomized controlled trials, particularly for oncology, metabolic disorders and immune-related conditions. Collaborative efforts between academia, industry and regulatory bodies are essential to bridge the gap between traditional use and modern medicine.

1. Take black rice in Jar

2. Add nutrient solutions

3. Sterilize the Jars

4. Inoculate with liquid culture

5. Mycelium run at dark condition

6.Exposing in light, mycelium turn orange

7. Pinhead formation

8. Keep in proper light, temp., R.H.

Discussion :

The literature on Cordyceps militaris demonstrates clear progress in its development as a sustainable medicinal fungus but also highlights substantial heterogeneity in cultivation methods, analytical pipelines and biological validation models. Comparative evaluation shows that solid-state fermentation (SSF) on cereal substrates is widely used for fruiting body production due to simplicity and low cost, with enhanced cordycepin accumulation under optimized moisture and blue/white light conditions. However, SSF exhibits pronounced batch-to-batch variability due to inconsistent substrate composition and limited environmental control. In contrast, submerged liquid fermentation (SmF) and bioreactor-based systems provide greater reproducibility through precise control of pH, oxygen and nutrients, making them more suitable for standardized extract production with reduced fruiting body formation and metabolite complexity. These trade-offs indicate that cultivation strategies must be aligned with the intended nutraceutical or pharmaceutical application.

Comparative metabolomic studies show that cultivation mode, substrate, photoperiod and strain selection strongly influence nucleoside and polysaccharide profiles, with multi-omics analyses linking cordycepin biosynthesis to purine metabolism and oxygen availability. However, variability in extraction methods and marker selection limits cross-study comparability, underscoring the need for harmonized analytical frameworks and quality benchmarks.

Pharmacological evidence from in vitro and animal models supports anticancer, immunomodulatory, anti-inflammatory and antioxidant activities mediated primarily by cordycepin and polysaccharides, yet translational relevance is constrained by inconsistent extract composition and limited pharmacokinetic standardization. Chemically characterized, cordycepin-enriched preparations show greater reproducibility but lack robust clinical validation.

Several critical research gaps continue to impede translational progress. Foremost are the limitations of well-designed human clinical trials employing chemically standardized C. militaris formulations, which limits evidence-based dose determination, safety profiling, and therapeutic positioning; this can be addressed through multicentric, randomized controlled trials using rigorously characterized preparations. Persistent batch-to-batch variability in metabolite profiles arising from non-uniform substrates, strain drift and poorly controlled cultivation environments undermines reproducibility and regulatory confidence; implementation of closed-system bioreactors, strain authentication protocols, and metabolite-

guided release specifications is therefore essential. In addition, the mechanistic basis of synergistic interactions between nucleosides, polysaccharides and minor metabolites remains inadequately resolved, restricting rational formulation design. Integrated multi-omics, network pharmacology and target-validation studies can provide mechanistic clarity. Finally, regulatory heterogeneity across jurisdictions creates uncertainty for product development and global commercialization; alignment of pharmacopeial standards, harmonized quality control frameworks and clear regulatory pathways distinguishing nutraceutical and therapeutic claims are required to facilitate clinical translation and industrial scalability.

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