INFORMATICS JOURNALS

Short Review

Journal of Natural Remedies
DOI: 10.18311/jnr/2026/51279

eISSN: 2320-3358 | Vol 26(4), 2026 | pp. 885-896

Cordyceps as a Natural Anticancer Agent: Molecular Mechanisms and Translational Promise

Satya Sree Bandaru*, K. Aishwarya, L. Blessy Jasmin, M. Jasmitha, M. Divya Sri and M. Naga Jyothi

Department of Pharmaceutical Chemistry, V. V. Institute of Pharmaceutical Sciences, Gudlavalleru - 521356, Krishna, Andhra Pradesh, India; satyasree.bandaru@gmail.com

Abstract

Cordyceps is a medicinal genus of entomopathogenic fungi, renowned for its long-standing use in traditional Asian medicine and its growing prominence in modern pharmacological research. Among its bioactive constituents, cordycepin (3'-deoxyadenosine), polysaccharides, and sterols have demonstrated significant anticancer properties across a variety of malignancies, including lung, liver, breast, and leukaemia models. Mechanistically, cordycepin induces apoptosis through mitochondrial and caspase-dependent pathways, inhibits cell proliferation by modulating key signalling cascades such as PI3K/Akt and mTOR, and exerts anti-angiogenic effects by downregulating VEGF. Additionally, *Cordyceps* extracts show potent immunomodulatory activity, enhancing macrophage and natural killer cell functions, which contribute to tumour suppression. *In vitro* and *in vivo* studies consistently support its role in tumour inhibition, while some early-phase clinical trials suggest safety and tolerability in adjunct cancer therapy. However, challenges such as standardisation of extracts, variability in active compound concentrations, and limited clinical data remain. As interest in natural product-based oncology therapies grows, *Cordyceps* represents a promising candidate for integrative cancer treatment strategies. Further molecular and clinical investigations are warranted to validate its therapeutic efficacy and unlock its full potential as a complementary anticancer agent.

Major Findings: *Cordyceps* and its bioactive constituents, particularly cordycepin, exhibit significant anticancer activity through induction of apoptosis, inhibition of proliferation via PI3K/Akt and mTOR pathways, and anti-angiogenic effects. Additionally, strong immunomodulatory properties and consistent preclinical evidence highlight its potential as a complementary cancer therapy, although further clinical validation is required.

Keywords: Anticancer, Apoptosis, Cordycepin, *Cordyceps*, Molecular Mechanisms, Natural Product

(Article Chronicle: Article Received on: 29.08.2025; Revised on: 10.03.2026; Accepted on: 02.04.2026)

1. Introduction

Cordyceps is a genus of entomopathogenic fungi belonging to the family *Clavicipitaceae* and comprises over 500 species that parasitise insects and arthropods. Among them, *Cordyceps sinensis* (currently reclassified as *Ophio Cordyceps sinensis*) and *Cordyceps militaris* (Figure 1) have attracted the greatest scientific interest due to their long-standing use in traditional medicine and their emerging pharmacological significance[1,2]. For centuries, *Cordyceps* has been employed in traditional Chinese and Tibetan medicine as a tonic to enhance vitality, stamina, and longevity, laying the foundation for its continued therapeutic exploration.

Cordyceps sinensis, commonly known as the "caterpillar fungus," naturally occurs in high-altitude Himalayan regions, where it parasitises larvae of ghost moths (*Thitarodes* spp.), ultimately replacing host tissue with fungal mycelium[3]. However, ecological vulnerability and overharvesting have rendered wild *C. sinensis* scarce and costly, prompting increased interest in *C. militaris*, a cultivable and sustainable alternative that contains comparable bioactive constituents[4]. This transition from traditional harvesting to controlled

*Author for correspondence

cultivation has facilitated modern pharmacological and mechanistic studies.

Cordyceps species are rich in biologically active compounds, including cordycepin (3′-deoxyadenosine), adenosine, D-mannitol, ergosterol, and diverse polysaccharides and peptides. These constituents exhibit a wide range of biological activities, such as immunomodulatory, anti-inflammatory, antioxidant, antimicrobial, neuroprotective, and antitumor effects[5-7]. Advances in analytical chemistry and molecular biology have enabled deeper insights into their mechanisms of action. Notably, cordycepin interferes with RNA synthesis, cell proliferation, and key signal transduction pathways, supporting its potential as an anticancer and antiviral agent[8,9].

Beyond oncology, *Cordyceps* extracts have demonstrated beneficial effects in metabolic regulation, enhancement of exercise performance, renal protection, and respiratory health, further validating its traditional use as a systemic tonic[10-12]. To meet increasing demand and ensure consistency, modern biotechnological approaches such as submerged fermentation and genetic engineering are now employed to improve yield, standardise bioactive content, and enhance quality control of *Cordyceps*-based products.

Cancer remains a leading global health burden, with approximately 20 million new cases and 10 million deaths reported annually as of 2023[13]. Although conventional treatments, including chemotherapy, radiotherapy, and immunotherapy, have improved survival outcomes, their clinical utility is often limited by drug resistance, systemic toxicity, and adverse side effects[14]. Consequently, there is an ongoing need for novel anticancer agents that are effective, selective, and better tolerated.



Figure 1. *Cordyceps* species.

Natural products have historically played a pivotal role in oncology drug discovery, with nearly 60% of approved anticancer agents derived from or inspired by natural sources[15]. In this context, *Cordyceps* represents a compelling example of how traditional medicine has informed modern pharmacological research. Bioactive metabolites from *Cordyceps*, particularly cordycepin, polysaccharides, and ergosterol derivatives, have demonstrated anticancer activities through multiple mechanisms, including apoptosis induction, cell cycle arrest, anti-angiogenesis, and immunomodulation[4,6,9,11,16]. The ability of *Cordyceps* to both suppress tumour growth and enhance host immune responses underscores its potential as a complementary agent in integrative cancer therapy. Ongoing research continues to explore its translational and clinical applicability in modern oncology.

2. Bioactive Constituents with Anticancer Potential

The anticancer potential of *Cordyceps* species is primarily attributed to their diverse bioactive constituents, each of which has been shown to exert inhibitory effects on specific cancer types through distinct yet overlapping mechanisms. Major compounds such as cordycepin, polysaccharides, nucleosides, sterols, and peptides (Figure 2) contribute to tumour suppression by modulating cancer cell proliferation, apoptosis, angiogenesis, metastasis, and immune responses.

2.1 Cordycepin (3′-deoxyadenosine)

Cordycepin is the most extensively studied anticancer compound derived from *Cordyceps militaris* and *C. sinensis*. Structurally analogous to adenosine but lacking a hydroxyl group at the 3′ position, cordycepin disrupts RNA synthesis and interferes with DNA repair processes in malignant cells. Substantial evidence demonstrates its efficacy against breast, lung, hepatocellular, colorectal, and haematological cancers, including leukaemia[4,16]. In these models, cordycepin induces apoptosis, inhibits cell proliferation, and suppresses invasion and metastasis. Mechanistically, it modulates multiple oncogenic signalling pathways, including Phosphoinositide 3-kinase/Protein kinase B (PI3K/Akt), AMP-activated protein kinase/Mechanistic (mammalian) target of rapamycin (AMPK/mTOR),

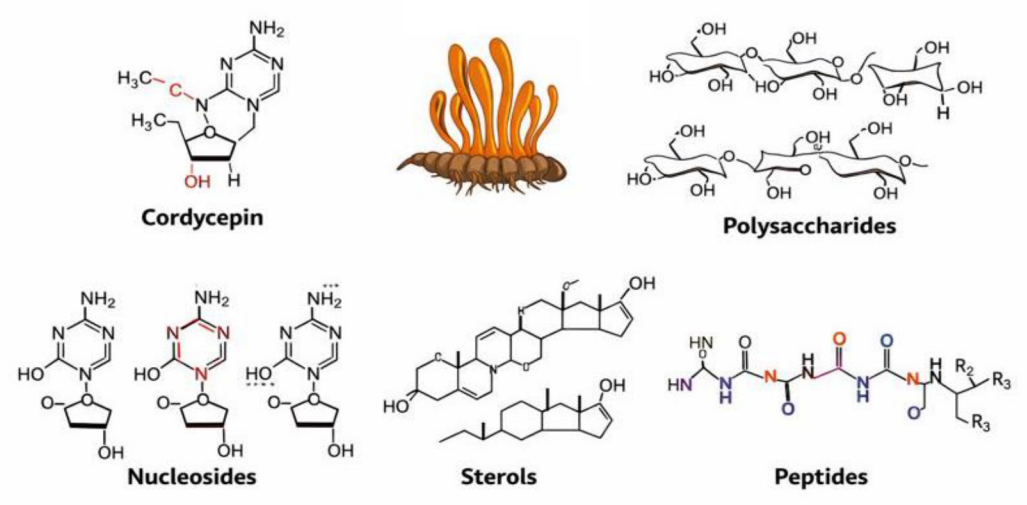


Figure 2. Bioactive compounds in *Cordyceps* mushrooms.

and Mitogen-Activated Protein Kinase (MAPK), highlighting its potential as a multi-targeted agent in cancer therapy[9].

2.2 Polysaccharides

Cordyceps-derived polysaccharides, particularly β-glucans and heteroglycans, exhibit pronounced anticancer effects that are especially relevant to immune-responsive tumours such as gastric, colorectal, lung, and melanoma cancers. These compounds enhance antitumour immunity by activating macrophages, increasing Natural Killer (NK) cell cytotoxicity, and stimulating cytokine production, including interleukin-2 (IL-2) and interferon-γ (IFN-γ)[17]. In addition to immune-mediated tumour suppression, polysaccharides have been reported to directly inhibit tumour growth by inducing apoptosis and suppressing angiogenesis in solid tumour models[18].

2.3 Nucleosides and Nucleobases

Beyond cordycepin, *Cordyceps* species contain several nucleosides and nucleobases, including adenosine, uridine, and guanosine, which influence cancer-related cellular signalling pathways. These compounds exhibit cytostatic effects in various tumour types, particularly in glioma, lung, and liver cancer models. Adenosine plays a dual role in tumour biology by modulating immune checkpoint pathways and contributing to tumour immune evasion, making it a molecule of growing interest in immuno-oncology research[19].

2.4 Sterols and Triterpenoids

Sterols such as ergosterol and ergosterol peroxide isolated from *Cordyceps* have demonstrated significant antiproliferative activity against liver, colon, breast, and prostate cancers. Ergosterol peroxide, in particular, induces apoptosis through Reactive Oxygen Species (ROS) generation, mitochondrial dysfunction, and caspase activation[20]. These lipophilic compounds also modulate inflammatory and lipid metabolic pathways within tumour cells and have been shown to enhance chemosensitivity, suggesting potential utility as adjuvants to conventional chemotherapy[21].

2.5 Peptides and Proteins

Several peptides and small proteins isolated from *Cordyceps* species display anticancer activity against haematological malignancies and solid tumours. Cordymin, a peptide derived from *C. sinensis*, has been reported to inhibit the proliferation of leukaemia and hepatoma cells by inducing cell cycle arrest and apoptosis[22]. Other cyclic peptides exhibit anti-angiogenic and anti-metastatic effects, particularly in aggressive and treatment-resistant cancers.

Collectively, these bioactive constituents target multiple hallmarks of cancer, including uncontrolled proliferation, immune evasion, angiogenesis, and metastasis. The compound-specific and multi-mechanistic actions of *Cordyceps* metabolites not only enhance their overall anticancer efficacy but also reduce the likelihood of resistance development, supporting

their potential role in integrative and adjunctive cancer therapy. Anticancer mechanisms of bioactive compounds from *Cordyceps* are represented in Table 1.

3. Mechanisms of Anticancer Action of *Cordyceps*

The anticancer potential of *Cordyceps* is attributed to its ability to target multiple hallmarks of cancer. Its bioactive components, including cordycepin, polysaccharides, sterols, and peptides, exert a broad range of anticancer effects by modulating key molecular pathways (Figure 3) involved in tumour cell survival, proliferation, angiogenesis, metastasis, and immune evasion. These multitargeted actions support the rationale for exploring *Cordyceps* as a complementary or alternative cancer therapy.

3.1 Induction of Apoptosis

Apoptosis, or programmed cell death, is one of the most critical mechanisms by which *Cordyceps* exerts its anticancer effects. Cordycepin, in particular, activates both intrinsic (mitochondrial) and extrinsic apoptotic pathways. It increases the expression of pro-apoptotic proteins such as Bax while downregulating anti-apoptotic Bcl-2, leading to disruption of mitochondrial membrane potential and cytochrome c release[4,16]. These events trigger the activation of caspase-9 and subsequently executioner caspases-3 and -7, resulting in apoptotic cell death[9]. In parallel, death receptor–mediated pathways involving caspase-8 activation have been observed in several cancer cell lines, suggesting that cordycepin can initiate apoptosis through multiple upstream signals[23]. Sterols and peptides isolated from *Cordyceps* further contribute to apoptosis by inducing oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress, thereby amplifying apoptotic signalling in malignant cells.

3.2 Inhibition of Cell Proliferation

Cordyceps constituents suppress uncontrolled cancer cell growth by interfering with oncogenic signalling pathways that regulate proliferation and cell cycle progression. Cordycepin downregulates the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mechanistic Target of Rapamycin (mTOR) signalling pathways, which are frequently hyperactivated in cancer and are essential for cell survival, protein synthesis, and metabolic reprogramming[5]. Inhibition of the MAPK/ERK pathway further reduces the transcription of genes involved in proliferation and tumour progression. Additionally, cordycepin and related compounds induce cell cycle arrest, predominantly at the G2/M and S phases, through modulation of cyclins (e.g., cyclin B1, cyclin D1) and Cyclin-Dependent Kinases (CDKs), thereby preventing DNA replication and mitotic entry[24]. These effects collectively limit tumour expansion and sensitise cancer cells to additional therapeutic stress. Anticancer mechanisms of *Cordyceps*

Table 1. Bioactive compounds from *Cordyceps* and their anticancer mechanisms

Compound	Anticancer Mechanisms
Cordycepin	- Induces apoptosis via caspase activation - Inhibits mTOR/PI3K/Akt pathway - Inhibits metastasis and cell proliferation
Polysaccharides	- Immunomodulation (↑ NK cells, macrophages, cytokines) - Induces apoptosis - Anti-angiogenic activity
Nucleosides	- Modulation of immune checkpoints - Cytostatic effect on tumour cells - Adenosine receptor-mediated tumour regulation
Ergosterol and Derivatives	- Generation of Reactive Oxygen Species (ROS) - Mitochondrial dysfunction - Caspase-mediated apoptosis
Peptides	- Inhibition of cancer cell proliferation - Potential anti-angiogenic and enzyme inhibitory activity

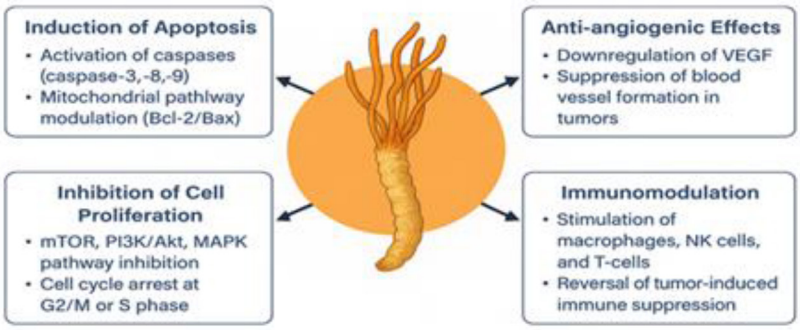


Figure 3. Mechanisms of anticancer action of *Cordyceps*.

Table 2. Anticancer mechanisms of *Cordyceps* bioactive constituents and their synergistic effects with conventional cancer therapies

Bioactive Constituent	Primary Molecular Targets / Pathways	Effects on Cancer Cell Behaviour	Cancer Types Studied (Examples)	Synergistic Effects with Conventional Therapies
Cordycepin (3′-deoxyadenosine)	Caspase cascade (caspase-3, -7, -9); Bax/Bcl-2; PI3K/Akt; mechanistic target of rapamycin (mTOR); MAPK/ERK; DNA repair pathways	Induces intrinsic and extrinsic apoptosis; inhibits proliferation; causes cell cycle arrest (G2/M, S phase); suppresses metastasis and angiogenesis	Breast, lung, liver, colorectal, ovarian, leukaemia	Enhances chemosensitivity to cisplatin and doxorubicin; increases radiosensitivity by impairing DNA repair and pro-survival signalling; may allow dose reduction
Polysaccharides (β-glucans, heteroglycans)	Immune receptors (TLRs); cytokine signaling (IL-2, IFN-γ, TNF-α); VEGF-mediated angiogenesis	Activates macrophages, NK cells, and T lymphocytes; suppresses angiogenesis; induces indirect tumour cell death via immune-mediated mechanisms.	Gastric, colorectal, lung, and melanoma	Restores immune function during chemotherapy/radiotherapy; reduces myelosuppression; improves treatment tolerance and quality of life
Sterols (ergosterol, ergosterol peroxide)	ROS; mitochondrial membrane potential; caspase activation; inflammatory pathways	Induces oxidative stress–mediated apoptosis; inhibits proliferation; modulates lipid metabolism and inflammation	Liver, colon, breast, prostate	Enhances chemotherapeutic efficacy by increasing oxidative stress in tumour cells; may improve chemosensitivity
Peptides and Proteins (e.g., cordymin)	Cell cycle regulators; angiogenesis-related factors; apoptosis-related proteins	Induces cell cycle arrest; inhibits angiogenesis and metastasis; promotes apoptotic signalling	Leukaemia, hepatocellular carcinoma	Potential additive effects with chemotherapy by inhibiting proliferation and metastasis
Whole Cordyceps extracts	Multi-target effects on apoptosis, angiogenesis, immune regulation, and oxidative stress	Tumour growth suppression; reduced angiogenesis; enhanced immune surveillance; improved systemic tolerance	Lung, liver, colorectal, breast, melanoma	Reduces chemotherapy- and radiotherapy-induced toxicity (fatigue, anaemia, mucositis); improves immune markers and patient compliance

bioactive constituents and their synergistic effects with conventional cancer therapies are given in Table 2.

3.3 Anti-Angiogenic Effects

Angiogenesis is essential for tumour growth, invasion, and metastasis. *Cordyceps* extracts inhibit angiogenesis by suppressing the expression of Vascular Endothelial Growth Factor (VEGF) and other pro-angiogenic cytokines within the tumour microenvironment[25]. Cordycepin has been shown to disrupt endothelial cell proliferation, migration, and tube formation *in vitro*, and to reduce microvessel density in tumour xenograft models[16]. These anti-angiogenic effects are mediated through inhibition of the hypoxia-inducible factor-1α (HIF-1α)/VEGF axis and downstream signalling pathways such as ERK and Akt, ultimately restricting nutrient and oxygen supply to growing tumours[26].

3.4 Immunomodulation

The immunomodulatory activity of *Cordyceps* plays a crucial role in its anticancer effects by restoring and enhancing host immune surveillance. Polysaccharides derived from *C. sinensis* and *C. militaris* activate innate and adaptive immune responses by stimulating macrophages, enhancing NK cell cytotoxicity, and promoting T lymphocyte proliferation. This immune activation is accompanied by increased production of antitumour cytokines such as IFN-γ, TNF-α, and IL-2, which facilitate tumour cell recognition and elimination[19,27]. Furthermore, *Cordyceps* modulates the tumour immune microenvironment by reducing regulatory T cell–mediated immunosuppression and promoting dendritic cell maturation, thereby counteracting immune evasion mechanisms employed by cancer cells[28]. Peptide components may further support immune-mediated tumour control by influencing antigen presentation and inflammatory signalling.

4. *In Vitro* and *In Vivo* Studies

Extensive *in vitro* and *in vivo* studies have demonstrated the anticancer potential of *Cordyceps* species and their bioactive compounds across a variety of cancer types. These studies highlight the ability of *Cordyceps* extracts and isolated compounds, particularly cordycepin, to induce apoptosis, inhibit proliferation, suppress metastasis and enhance immune responses against tumour cells. A selection of representative studies is summarised in Table 3, organised by cancer type and model system.

These studies consistently demonstrate that *Cordyceps* extracts and compounds exert significant anticancer effects in a wide range of tumour types, both by direct cytotoxicity to cancer cells and indirect immunomodulatory actions. *In vivo* xenograft models further confirm its tumour volume-reducing and angiogenesis-inhibiting capabilities, suggesting translational potential for therapeutic application.

5. Clinical Evidence

Preclinical investigations have demonstrated the robust anticancer activity of *Cordyceps* species. However, human studies, although limited, have begun to support its use as a complementary therapy in cancer treatment. This section summarises the existing clinical data on *Cordyceps*, including its efficacy, safety and prospects.

5.1 Human Trials and Cohort Studies

A retrospective cohort study conducted in 2013 evaluated the use of *C. sinensis* in patients with advanced Hepatocellular Carcinoma (HCC). Among 27 patients receiving *Cordyceps* as part of a multi-agent naturopathic regimen, the median Overall Survival (OS) was significantly extended to 42.7 months, compared to 15.7 months in the control group ($p < 0.004$). When combined with more than three agents, survival increased to 55.7 months[34].

In Non–Small-Cell Lung Cancer (NSCLC), a meta-analysis of 12 randomised controlled trials (n = 928) assessed the effects of *C. sinensis* as an adjunct to chemotherapy or radiotherapy. Patients receiving *Cordyceps* showed improved tumour response rates (RR = 1.17), enhanced immune markers (CD4, CD8, NK cells, IgA/G/M), better quality of life (Karnofsky Performance Score increase of +8.2), and a reduction in chemotherapy-induced myelosuppression (RR = 0.38)[35].

5.2 Interventional Trials

Several clinical trials have emerged evaluating the role of *Cordyceps* in supportive oncology. A Phase II/III single-arm trial (NCT06598033) is investigating a

Table 3. Summary of preclinical studies on the anticancer effects of *Cordyceps*

Cancer Type	Model System	Key Findings	References
Lung cancer	A549 cells (*in vitro*)	Induced apoptosis via caspase-3 and -9 activation	16
Leukemia	HL-60 cells (*in vitro*)	Cell cycle arrest at G0/G1 phase; caspase-mediated apoptosis	29
Breast cancer	MCF-7 xenograft (*in vivo*)	Reduced tumour volume and angiogenesis	9
Hepatocellular carcinoma	HepG2 cells (*in vitro*)	Suppressed cell migration and invasion by regulating MMPs	30
Prostate cancer	PC-3 and DU145 cells (*in vitro*)	Apoptosis induction via inhibition of the PI3K/Akt pathway	24
Colorectal cancer	CT26 xenograft (*in vivo*)	Tumour growth suppression and immune stimulation	25
Cervical cancer	HeLa cells (*in vitro*)	Cordycepin triggered DNA fragmentation and mitochondrial apoptosis	31
Melanoma	B16F10 melanoma cells (*in vivo*)	Inhibition of metastasis and angiogenesis	11
Gastric cancer	SGC-7901 cells (*in vitro*)	Apoptosis via modulation of Bcl-2/Bax and caspase activation	32
Ovarian cancer	SKOV3 cells (*in vitro*)	Induced apoptosis, inhibited migration and EMT	33

combination of *C. sinensis* (2 g twice daily), *Ganoderma lucidum* (Reishi), and vitamin C alongside gemcitabine/nab-paclitaxel chemotherapy in pancreatic cancer patients. The study aims to assess its effect on quality of life, neuropathy, anaemia and overall survival[36]. A related trial (NCT06601283) is evaluating the same herbal formulation specifically for reducing chemotherapy-induced neuropathy and fatigue in cancer patients[37].

5.3 Recent and Ongoing Clinical Evidence

In recent years, growing clinical interest in *Cordyceps* has led to an increase in registered trials and observational studies exploring its role as an adjunct in oncology. Several recent studies have focused on patient-centred outcomes, including immune recovery, treatment tolerance, fatigue reduction, and quality of life during chemotherapy and radiotherapy. These studies further support earlier findings that *Cordyceps* supplementation may enhance immune parameters, reduce therapy-related adverse effects, and improve functional status in cancer patients. Additionally, emerging clinical investigations involving cordycepin-based formulations and standardised *Cordyceps* extracts are aiming to establish pharmacokinetic profiles, optimal dosing strategies, and safety in combination with conventional anticancer regimens. Although many of these studies are ongoing, their inclusion highlights the increasing translational momentum of *Cordyceps* research and its potential progression from supportive care toward evidence-based integrative oncology. Collectively, these recent and ongoing clinical efforts strengthen the rationale for continued evaluation of *Cordyceps* in cancer treatment and underscore the need for larger, well-controlled randomised trials to confirm its therapeutic efficacy and long-term safety.

5.4 Cordycepin-based Drug Development

One of the most promising advances in *Cordyceps* research is the development of NUC-7738, a cordycepin derivative formulated via ProTide technology to improve bioavailability and stability. In the NuTide:701 Phase I trial, NUC-7738 demonstrated favourable tolerability and early signals of efficacy in patients with advanced treatment-resistant solid tumours, without dose-limiting toxicities[38]. This compound represents a novel approach in translating *Cordyceps*-derived agents into clinical oncology.

5.5 Safety, Toxicity, and Dosage

Clinical studies have shown that *Cordyceps* is generally well tolerated in humans at doses ranging from 3 to

6 g/day, with mild gastrointestinal side effects and occasional dry mouth being the most commonly reported adverse events[39,40].

In preclinical toxicology assessments, oral administration of *Cordyceps* extracts up to 10 g/kg/day in rabbits and 80 g/kg/day intraperitoneally in mice showed no significant toxicity, indicating a high margin of safety[41]. Nonetheless, caution is advised in patients on antidiabetic or antiviral medications, due to potential drug interactions with *Cordyceps*' hypoglycemic and immunomodulatory properties[6].

6. Synergy with Conventional Therapies

The therapeutic potential of *Cordyceps* extends beyond its standalone anticancer activity. Several preclinical and clinical studies have investigated the synergistic effects of *Cordyceps* when used in combination with conventional treatments such as chemotherapy and radiation therapy. These findings highlight its dual role in enhancing anticancer efficacy and ameliorating treatment-related side effects.

6.1 Combination with Chemotherapy Agents

Cordyceps, especially its active component cordycepin, has demonstrated synergy with widely used chemotherapeutic agents, including doxorubicin and cisplatin: *Cordyceps* militaris and Doxorubicin: Co-treatment of cancer cells with *C. militaris* extract and doxorubicin led to enhanced cytotoxicity in breast and liver cancer models, compared to either treatment alone. The combination significantly increased apoptosis via caspase activation and ROS generation[4]. Cordycepin and Cisplatin: In ovarian and lung cancer cells, cordycepin potentiated cisplatin-induced cytotoxicity by suppressing DNA repair pathways and enhancing mitochondrial damage, while also protecting normal cells from oxidative stress[42,43]. Mechanistically, these synergistic effects are attributed to *Cordyceps*-mediated chemosensitisation of tumour cells, achieved through suppression of pro-survival signalling pathways (e.g., PI3K/Akt and NF-κB), impairment of DNA damage repair, and amplification of mitochondrial oxidative stress. At the same time, *Cordyceps* exhibits cytoprotective effects in normal cells by enhancing antioxidant defences, thereby widening the therapeutic window of chemotherapeutic agents. These synergistic interactions may allow for dose reduction of chemotherapeutic agents, potentially minimising systemic toxicity.

6.2 Enhancement of Radiation Therapy

Preclinical studies suggest that *Cordyceps* may sensitise tumour cells to radiation therapy. In hepatoma models, cordycepin was shown to enhance radiosensitivity by impairing DNA repair and inhibiting pro-survival signalling (e.g., PI3K/Akt), thereby improving tumour control[24]. Additionally, *Cordyceps* reduced radiation-induced inflammation and fibrosis in normal tissues, supporting its potential as a radioprotective agent[44]. At the molecular level, *Cordyceps* enhances radiosensitivity by delaying DNA double-strand break repair and inhibiting radiation-activated survival pathways, resulting in prolonged tumour cell damage. Importantly, its anti-inflammatory and antioxidant properties in normal tissues may reduce radiation-induced fibrosis and organ toxicity, highlighting its dual role as a tumour radiosensitizer and normal tissue radioprotectant.

6.3 Reduction of Chemotherapy-induced Side Effects

One of the most clinically relevant applications of *Cordyceps* is its ability to mitigate the adverse effects of conventional therapies. Immune suppression: Chemotherapy often leads to immunosuppression. *Cordyceps sinensis* and *C. militaris* have been shown to restore immune function, enhance NK cell activity, and increase cytokine production (e.g., IL-2, IFN-γ) in immunocompromised hosts[19,28]. Fatigue and anaemia: A clinical trial reported that *Cordyceps sinensis* supplementation significantly improved fatigue, haemoglobin levels, and exercise tolerance in cancer patients undergoing chemotherapy[45]. Gastrointestinal toxicity: Animal models demonstrated that *Cordyceps* extracts reduced chemotherapy-induced intestinal mucositis, likely through antioxidant and anti-inflammatory mechanisms[46]. These protective effects are closely linked to the immunomodulatory and metabolic regulatory properties of *Cordyceps*, which help restore hematopoietic function, maintain mucosal integrity, and reduce systemic inflammation. Clinically, this supportive role may improve treatment

adherence, reduce therapy interruptions, and enhance overall patient outcomes when *Cordyceps* is used as an adjunct to standard cancer therapies. Together, these mechanisms provide a clear biological rationale for the adjunctive use of *Cordyceps* in oncology, as it simultaneously enhances tumour responsiveness to conventional therapies while mitigating treatment-related toxicity.

7. Challenges and Limitations

Despite the promising preclinical and limited clinical data supporting the anticancer potential of *Cordyceps* species, several challenges hinder its widespread integration into mainstream oncology practice. These limitations must be addressed through rigorous research and regulatory oversight.

7.1 Lack of Large-scale Human Trials

Most of the current evidence for the anticancer effects of *Cordyceps* stems from *in vitro*, animal, and small-scale clinical studies. While some retrospective cohort studies and pilot trials suggest improved survival and quality of life, randomised, placebo-controlled clinical trials with large sample sizes are lacking[34,35]. Without such data, it remains difficult to draw definitive conclusions about its clinical efficacy, optimal dosage, or long-term safety in diverse cancer populations.

7.2 Standardisation Issues in Herbal Formulations

A significant barrier to clinical adoption is the lack of standardisation in *Cordyceps*-based products. The content of active compounds such as cordycepin, polysaccharides, and nucleosides can vary widely between wild-harvested, cultured, or fermented preparations[11]. Factors such as strain variability, growth medium, extraction method, and processing conditions contribute to inconsistencies in quality and potency[6]. This variability undermines reproducibility and poses a challenge to regulatory approval and clinical application.

7.3 Variability in Active Compound Concentration

Even among cultivated species like *Cordyceps militaris*, levels of key bioactive constituents such as cordycepin may vary significantly, affecting therapeutic outcomes[47]. In some commercial preparations, cordycepin content has been reported to be up to 10-fold lower than pharmacologically active levels[43]. Ensuring batch-to-batch consistency in clinical-grade products is essential for accurate dosing and efficacy evaluation.

7.4 Potential Drug Interactions

Cordyceps possesses immunomodulatory, hypoglycemic, and antiviral properties, which may interact with immunosuppressants, antidiabetic drugs, or chemotherapy agents[40]. Although severe interactions have not been widely reported, the potential for pharmacodynamic and pharmacokinetic interactions exists and requires careful evaluation, particularly in polypharmacy settings common in cancer patients. Furthermore, cytochrome P450 enzyme modulation by certain *Cordyceps* extracts has been observed *in vitro*, raising concerns about altered metabolism of co-administered drugs[48].

8. Future Directions

To fully harness the anticancer potential of *Cordyceps*, future research must address current gaps through multidisciplinary approaches. There is an urgent need for well-designed randomised controlled trials to validate the efficacy, optimal dosage, and long-term safety of *Cordyceps*-based therapies in diverse cancer populations. Advances in molecular docking, genomics, transcriptomics, and metabolomics offer powerful tools to elucidate the precise mechanisms of bioactive compounds such as cordycepin, enabling targeted drug development. Incorporating nanocarrier systems—including liposomes, nanoparticles, and polymeric micelles—could improve the bioavailability, stability, and tumour-specific delivery of cordycepin, thereby enhancing therapeutic outcomes while minimising systemic toxicity. Additionally, synthetic biology and metabolic engineering approaches hold promise for the high-yield, standardised production of cordycepin and other pharmacologically active metabolites, overcoming challenges related to cultivation and compound variability. Together, these strategies can pave the way for the integration of *Cordyceps* into evidence-based oncology practice.

9. Conclusion

Cordyceps has garnered significant attention as a natural anticancer agent due to its rich profile of bioactive compounds, particularly cordycepin, which exerts diverse mechanisms including apoptosis induction, inhibition of proliferation, and immunomodulation. Preclinical studies across various cancer models, along with emerging clinical evidence, highlight its potential both as a therapeutic agent and as an adjuvant to conventional treatments. Additionally, its role in mitigating chemotherapy-induced side effects adds to its clinical appeal. However, challenges such as inconsistent compound standardisation, limited large-scale human trials, and potential drug interactions must be addressed. Future directions involving randomised clinical trials, nanotechnology-based delivery systems, and synthetic biology for optimised production could pave the way for *Cordyceps* to become a validated and effective option in integrative cancer therapy.

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Author Contribution

Satya Sree Bandaru conceptualized and supervised the review. K. Aishwarya and L. Blessy Jasmin

contributed to literature collection and drafting of the manuscript. M. Jasmitha and M. Divya Sri assisted in data compilation and organization of content. M. Naga Jyothi contributed to critical revision and final editing of the manuscript. All authors have read and agreed to the published version of the manuscript.