International Journal of Pharma and Biosciences
Content Available at www.lapinjournals.com ISSN: 0975-6299

CORDYCEPIN AS A LEAD BIOACTIVE MOLECULE FROM CORDYCEPS: MOLECULAR MECHANISMS AND CLINICAL PROSPECTS

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Article History: Received: 04.Sept.2025 Revised: 25.Oct.2025 Accepted: 30.Nov.2025

Abstract

Cordycepin (3′-deoxyadenosine), a naturally occurring nucleoside analog predominantly isolated from *Cordyceps* species, has attracted significant scientific interest as a lead bioactive molecule with broad pharmacological potential. Structurally analogous to adenosine but lacking a 3′-hydroxyl group, cordycepin interferes with nucleic acid synthesis, RNA polyadenylation, and multiple intracellular signaling pathways. Extensive preclinical evidence demonstrates that cordycepin exerts diverse biological activities, including anticancer, anti-inflammatory, immunomodulatory, metabolic, cardioprotective, and neuroprotective effects. These actions are mediated through modulation of key molecular pathways such as AMP-activated protein kinase (AMPK), NF-κB, MAPKs, PI3K/Akt, mTOR, and mitochondrial signaling networks. Despite robust mechanistic and experimental support, clinical translation of cordycepin remains limited due to challenges including poor oral bioavailability, rapid degradation by adenosine deaminase, lack of standardized formulations, and scarcity of well-controlled human clinical trials using purified compound. Recent advances in biosynthesis, formulation strategies, and delivery systems offer promising avenues to overcome these limitations. This review critically summarizes the chemical characteristics, biosynthesis, molecular mechanisms, pharmacological activities, clinical prospects, and translational challenges of cordycepin, highlighting future research directions required to advance it from a promising natural product to a clinically viable therapeutic agent for complex chronic diseases.

***Keywords*:** Cordycepin; Cordyceps; bioactive nucleoside; molecular mechanisms; anticancer activity; anti-inflammatory activity; AMPK; pharmacological potential; clinical translation; natural product drug discover.

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DOI: https://doi.org/10.22376/ijpbs.v17i1.137

INTRODUCTION

Medicinal mushrooms have long been used in traditional medicine systems, particularly in East Asian therapeutics, owing to their wide range of bioactive constituents and health-promoting properties. Among these, *Cordyceps sinensis* and *Cordyceps militaris* have received considerable scientific attention for their pharmacological potential [1,2].

Representative species of *Cordyceps* are shown in Fig. 01

Figure 01: Representative species of *Cordyceps* (*Cordyceps sinensis* and *Cordyceps militaris*) Adapted from Ref. [2].

Cordycepin (3′-deoxyadenosine), a naturally occurring nucleoside analog isolated predominantly from Cordyceps species, is regarded as the principal bioactive metabolite responsible for many of their therapeutic effects[3,4].Structurally, cordycepin closely resembles adenosine but lacks a hydroxyl group at the 3′ position of the ribose moiety, a modification that enables it to interfere with nucleic acid synthesis, RNA

polyadenylation, and key cellular signaling pathways[5].Through these mechanisms, cordycepin exerts diverse biological activities, including anticancer, anti-inflammatory, immunomodulatory, and metabolic regulatory effects[6].Accumulating experimental and translational evidence increasingly supports cordycepin as a promising lead compound for drug discovery and development, particularly for complex chronic diseases requiring multi-target therapeutic strategies[7].

2. CHEMICAL STRUCTURE AND BIOSYNTHESIS

Cordycepin is a purine nucleoside analog characterized by the absence of a hydroxyl group at the 3′ position of its ribose moiety, a structural feature responsible for its biological activity, as shown in Fig. 2.[8]. This modification enables cordycepin to disrupt RNA chain elongation and inhibit polyadenylation during nucleic acid synthesis [9]. In *Cordyceps* species, cordycepin biosynthesis is regulated by specific gene clusters associated with purine metabolism and nucleoside transport, as illustrated in Fig. 3 [9]. Recent advances in submerged fermentation, strain improvement, and biotechnological optimization have significantly enhanced cordycepin yield, facilitating its scalable production for pharmacological and therapeutic research[10,11].

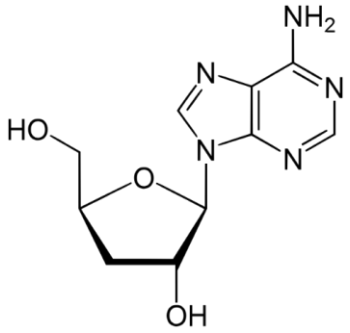

Figure 02. Chemical structure of cordycepin (3′-deoxyadenosine)Adapted from Ref. [8].

3. MOLECULAR MECHANISMS OF ACTION

3.1 Regulation of Apoptosis and Cell Cycle

Cordycepin induces apoptosis in cancer cells through both intrinsic and extrinsic pathways. It activates caspase cascades, promotes mitochondrial membrane depolarization, and downregulates anti-apoptotic proteins such as Bcl-2[12].

3.2 Modulation of Inflammatory Signaling

Anti-inflammatory effects of cordycepin are primarily mediated through inhibition of NF-κB and MAPK signaling pathways.Cordycepin suppresses pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, thereby reducing chronic inflammation implicated in metabolic and autoimmune disorders [13].

3.3 Metabolic and Endocrine Regulation

Cordycepin activates AMP-activated protein kinase (AMPK), a central regulator of cellular energy homeostasis. Through AMPK activation, cordycepin improves insulin sensitivity, enhances lipid metabolism, and reduces adipogenesis, highlighting its therapeutic relevance in metabolic syndrome and endocrine disorders[7,14,15].

3.4 Immunomodulatory Effects

Cordycepin modulates both innate and adaptive immune responses by regulating macrophage polarization, T-cell activation, and cytokine balance. These properties contribute to its protective effects against inflammatory and immune-mediated diseases[16].

4 PHARMACOLOGICAL ACTIVITIES

4.1 Anticancer Activity

Extensive in vitro and in vivo studies have demonstrated the anticancer potential of cordycepin against breast, lung, liver, colorectal, prostate, and hematological malignancies. Cordycepin exerts anticancer effects through induction of apoptosis, cell cycle arrest, inhibition of tumor cell proliferation, and suppression of metastasis and angiogenesis[4,6]. At the molecular level, cordycepin modulates key oncogenic signaling pathways, including PI3K/Akt, MAPK/ERK, mTOR, and Wnt/β-catenin pathways, and interferes with RNA synthesis and polyadenylation[14].Owing to its multitarget activity and comparatively low toxicity toward normal cells, cordycepin has been proposed as a potential adjuvant to conventional chemotherapy [4,6].

4.2 Anti-Inflammatory and Antioxidant Effects

Cordycepin exhibits marked anti-inflammatory and antioxidant properties relevant to chronic inflammatory disorders[17]. It suppresses pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, nitric oxide, and prostaglandins, primarily through inhibition of NF-κB and MAPK signaling pathways[18]. In parallel, cordycepin reduces oxidative stress by scavenging reactive oxygen species and enhancing endogenous antioxidant defense systems such as superoxide dismutase, catalase, and glutathione peroxidase[19].

4.3 Metabolic and Cardioprotective Effects

Cordycepin has emerged as a promising agent for metabolic and cardiovascular disorders[20]. Through activation of AMP-activated protein kinase (AMPK), cordycepin improves glucose uptake, insulin sensitivity, and lipid metabolism by inhibiting lipogenesis and promoting fatty-acid oxidation[15].Additionally, cordycepin exerts cardioprotective effects by improving mitochondrial function, reducing oxidative stress, and attenuating inflammatory responses in cardiovascular tissues[20].

4.4 Neuroprotective Activity

Cordycepin exhibits neuroprotective effects by attenuating inflammatory signaling and oxidative stress, thereby reducing neuronal damage. Experimental and review evidence indicates beneficial effects in neurodegenerative and neuroinflammatory conditions through modulation of inflammatory pathways and cellular homeostasis[6].

5 CLINICAL EVIDENCE AND THERAPEUTIC PROSPECTS

Despite extensive preclinical research, direct clinical evidence for cordycepin as a purified therapeutic agent in humans remains limited, as most available data are derived from *in vitro* and animal studies, with no large, well-controlled human clinical trials reported to date [21]. Most human-related evidence is based on studies involving Cordyceps-derived formulations and nutraceuticals, in which cordycepin represents only one of several bioactive constituents, thereby limiting definitive attribution of clinical effects to cordycepin alone [4].

Nevertheless, systematic and narrative reviews consistently report robust preclinical efficacy of cordycepin, demonstrating anti-inflammatory, metabolic, cardioprotective, and neuroprotective effects through modulation of key molecular pathways, including AMP-activated protein kinase (AMPK), NF-κB, MAPKs, and mitochondrial signaling [4,21]. From a therapeutic perspective, the pleiotropic and multitarget pharmacological profile of cordycepin supports its potential as a lead bioactive molecule for complex chronic diseases such as metabolic syndrome, cardiovascular disorders, inflammatory conditions, and neurodegeneration[22].

However, clinical translation is constrained by pharmacokinetic and formulation challenges, including limited oral bioavailability, rapid metabolic degradation, and the absence of long-term safety data, underscoring the need for optimized delivery strategies and rigorous clinical evaluation[4]. In summary, while cordycepin is supported by strong mechanistic and preclinical evidence, well-designed human clinical trials are essential to establish its efficacy, safety, and translational viability[21].

6 CHALLENGES AND LIMITATIONS

Despite compelling preclinical evidence, several challenges limit the clinical translation of cordycepin as a therapeutic agent. A major limitation is its poor oral bioavailability, largely attributed to rapid degradation by adenosine deaminase (ADA), which converts cordycepin into inactive metabolites, thereby reducing its systemic exposure and therapeutic efficacy [4,21].

Another important challenge is the scarcity of well-controlled human clinical trials using purified cordycepin. Most available human data are derived from Cordyceps-based formulations or nutraceuticals, in which cordycepin represents only one of several bioactive constituents, making it difficult to attribute clinical outcomes specifically to cordycepin. Furthermore, the lack of standardized formulations, dosing regimens, and long-term safety data hampers regulatory approval and clinical translation [6,23].

Given that cordycepin interferes with nucleic acid metabolism, potential off-target effects and toxicity at higher doses require careful evaluation. Collectively, these limitations highlight the need for improved pharmacokinetic profiles, standardized preparations, and rigorous clinical assessment [21,24]

7 FUTURE PERSPECTIVES

Future research on cordycepin should prioritize strategies that bridge the gap between robust preclinical evidence and clinical translation. A key direction involves pharmacokinetic optimization, including the development of adenosine deaminase (ADA)–resistant analogs, prodrug approaches, and advanced delivery systems such as nanoparticles, liposomes, and polymer-based carriers to enhance bioavailability, stability, and tissue targeting [2,23,25].These approaches may substantially improve systemic exposure and therapeutic efficacy while minimizing off-target effects.

Another important area is the standardization of cordycepin formulations and dosing regimens. Establishing consistent quality-control parameters, validated analytical methods, and well-defined dose–response relationships will be essential for regulatory approval and reproducibility across studiesThe genus *Cordyceps*: A chemical and pharmacological review [1,2].In parallel, comprehensive toxicological and long-term safety evaluations are required to define therapeutic windows and assess potential risks associated with chronic administration.

From a mechanistic standpoint, integration of systems biology, network pharmacology, and multi-omics approaches may further elucidate cordycepin's pleiotropic actions and identify predictive biomarkers of response. Such insights could facilitate patient stratification and precision medicine approaches, particularly for complex chronic diseases involving inflammation, metabolic dysregulation, and immune dysfunction.

Importantly, future efforts must include well-designed, randomized, controlled human clinical trials using purified cordycepin, rather than Cordyceps-based formulations, to definitively establish clinical efficacy, safety, and pharmacokinetics [2]. Collectively, these advances will be critical for translating cordycepin from a promising bioactive natural product into a clinically viable therapeutic agent.

8 CONCLUSION

Cordycepin, a prominent bioactive nucleoside derived from Cordyceps species, has emerged as a multifunctional lead compound with broad pharmacological potential. Extensive preclinical evidence demonstrates its ability to modulate key molecular pathways involved in apoptosis, inflammation, metabolism, immunity, and oxidative stress, underpinning its anticancer, anti-inflammatory, metabolic, cardioprotective, and neuroprotective activities.

Despite these promising findings, clinical translation remains limited by pharmacokinetic constraints and insufficient clinical validation. Advances in formulation science, structural modification, and targeted delivery systems provide viable opportunities to overcome these challenges and enhance the therapeutic applicability of cordycepin. Importantly, well-designed human clinical trials using purified cordycepin are essential to establish its efficacy, safety, and

translational viability. Continued integration of mechanistic insights, pharmacokinetic optimization, and clinical evaluation will be critical for advancing cordycepin toward clinical application in complex chronic diseases.

9 FUNDING ACKNOWLEDGEMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors solely contributed to the conception, design, and preparation of this work.

10 AUTHOR CONTRIBUTION

Conceptualization.and data curation, Rakesh S A, formal analysis investigation and methodology Bhagya V H, Bhumika B C ,Gagan H S.; writing-original draft, Anusha B N writing and editing, Pratiksha CC and Mohd Yusuf Damani. All authors have read and agreed to the published version of the manuscript.

11 Conflict of interest

No conflict of interest from all the authors.

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