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REVIEW

Anti-Inflammatory Mechanisms and Translational Relevance of *Cordyceps sinensis* and Its Bioactive Constituents

Jiahao Xie*, Jingwen Xu*, Qi Fan, Yuchi Chen

School of Medical Technology and Information Engineering, Zhejiang Chinese Medical University, Hangzhou, 310053, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yuchi Chen, School of Medical Technology and Information Engineering, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, People's Republic of China, Email btcyc@sina.com

Abstract: *Cordyceps sinensis*, an important medicinal fungus in traditional Chinese medicine, has gained increasing attention for its diverse pharmacological activities, particularly its anti-inflammatory properties. Its principal bioactive components, including cordycepin, cordycepic acid, polysaccharides, and sterols, exert significant protective effects in a wide range of inflammation-related diseases, primarily covering respiratory diseases, autoimmune disorders, neuroinflammatory conditions, and metabolic and gastrointestinal syndromes. These compounds act mainly by modulating key signaling pathways, including NF-κB, MAPK, TLR4/MyD88, PI3K/Akt, JAK/STAT, and Nrf2/HO-1. This review summarizes recent progress in the identification of anti-inflammatory components of *Cordyceps sinensis* and their mechanisms of action, highlights current challenges in clinical translation, and outlines future research directions. Collectively, these findings emphasize the broad potential of *Cordyceps sinensis* as a multi-target natural product–based anti-inflammatory therapy.

Keywords: *Cordyceps sinensis*, bioactive components, anti-inflammatory mechanisms, inflammation-related diseases

Introduction

Cordyceps sinensis (Berk). Sacc., an important medicinal fungus in traditional Chinese medicine belonging to the family Clavicipitaceae, parasitizes larvae of insects in the family Hepialidae, producing a natural complex composed of the fungal fruiting body and the larval cadaver. After harvesting and drying, this complex is used as the medicinal material commonly referred to as "Cordyceps" in Chinese medicine. The species is mainly distributed in the Qinghai–Tibet Plateau and adjacent high-altitude regions of China. Although recent taxonomy has reclassified it as *Ophiocordyceps sinensis*, most pharmacological studies, including this review, follow the nomenclature of the Chinese Pharmacopoeia.[1] In this review, the scope encompasses both the wild fungus-caterpillar complex and its major fermented mycelial products, distinguishing between them where specific pharmacological differences are noted. The life cycle of *Cordyceps sinensis* is typical of an insect–fungus complex. Spores infect larvae of Hepialus/Thitarodes by air dissemination or direct contact. Hyphae then proliferate inside the larvae, eroding host tissues and absorbing nutrients, thereby entering the parasitic stage. During winter, the hyphae continue to grow, leading to larval death and the formation of "mummified insects", known as the "winter-worm" stage. In the following summer, stromata (fruiting bodies) develop from the heads of the stiffened larvae, break through the soil surface, and release spores, thereby entering the reproductive stage—the "summer-plant" stage. These spores then infect new hosts, completing the life cycle.[2]

In China, *Cordyceps sinensis* has a long history of documented use. Its traditional functions of protecting the lungs and tonifying the kidneys were already documented in Bencao Congxin (New Compilation of Materia Medica) approximately 300 years ago. In recent years, *Cordyceps sinensis* has received increasing attention owing to its pharmacological properties, including anti-inflammatory,[3] antioxidant,[4] immunomodulatory,[5] and anti-tumor[6] effects,

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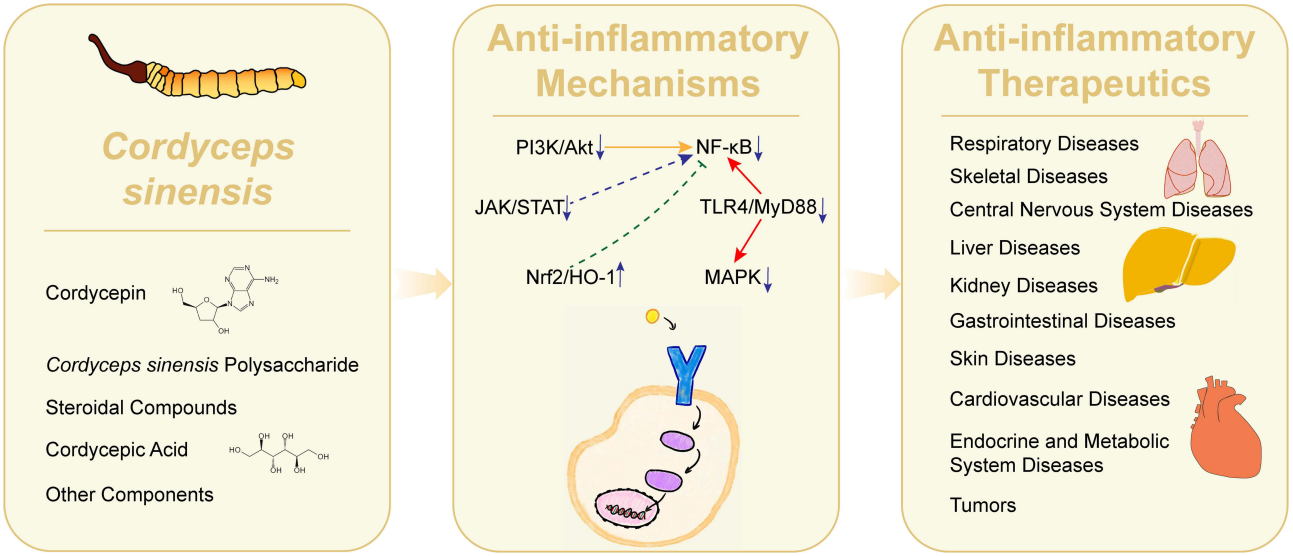
Graphical Abstract



among others. The therapeutic efficacy of *Cordyceps sinensis* is fundamentally underpinned by its diverse bioactive constituents, most notably cordycepin, polysaccharides, and sterols. By regulating distinct signaling nodes—such as NF-κB, MAPK, and TLR pathways—these co-existing components provide the molecular basis for a broad, multi-target immunomodulatory strategy. Consistent with this broad bioactivity, a growing body of research has confirmed its significant anti-inflammatory activity across multiple cell types, such as glomerular mesangial cells[7] and liver sinusoidal endothelial cells.[8] Moreover, its anti-inflammatory effects have been demonstrated in several disease models, including liver inflammation and fibrosis,[9] pulmonary inflammation and fibrosis,[10] thyroiditis,[11] and neuroinflammation after traumatic brain injury.[12] Although numerous studies have examined the anti-inflammatory activities of bioactive components from *Cordyceps sinensis*, most existing summaries focus on single agents. Consequently, there is still a lack of an integrated evaluation covering the broad range of these components. This review therefore highlights the latest findings on the anti-inflammatory constituents of *Cordyceps sinensis* and explores their mechanisms of action in different diseases.

This article presents a comprehensive narrative review focusing on the anti-inflammatory activities of the bioactive components of *Cordyceps sinensis*. To ensure a robust evaluation of the literature, we conducted a systematic search across multiple electronic databases, including PubMed, Web of Science, and Google Scholar. The search was performed to identify relevant studies published up to November 2025. The search strategy employed a combination of keywords including "*Cordyceps sinensis*", "anti-inflammatory", "inflammation", "cordycepin", "polysaccharides", and other relevant bioactive compounds. We primarily included peer-reviewed experimental studies and reviews published in English. Articles were selected based on their relevance to the anti-inflammatory mechanisms and efficacy of *Cordyceps sinensis* components.

Anti-Inflammatory Components of *Cordyceps sinensis*

Cordyceps sinensis contains multiple bioactive components with anti-inflammatory properties, including cordycepin, cordycepic acid, polysaccharides, steroidal compounds, and other constituents. These compounds differ in chemical structure and mechanisms of action. The principal structures are shown in Figure 1. The following subsections describe each component.

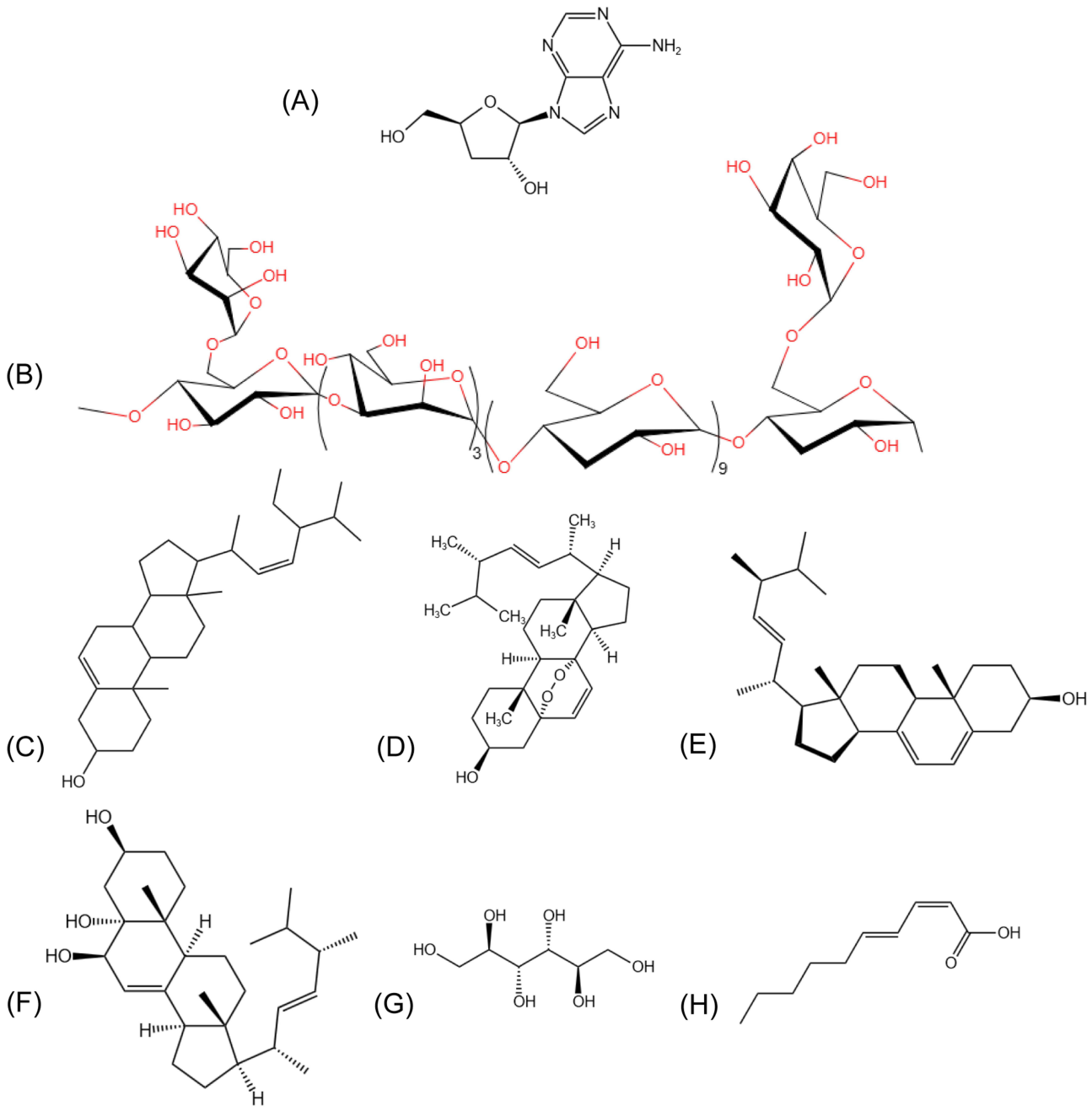


Figure 1 Chemical structures of anti-inflammatory components in *Cordyceps sinensis*. Cordycepin (**A**), *Cordyceps sinensis* Polysaccharide CPS-2 (**B**), Stigmasterol (**C**), Ergosterol peroxide (**D**), Ergosterol (**E**), Cerevisterol (**F**), Cordycepic Acid (**G**), (2Z,4E)-deca-2,4-dienoic acid (DDEA) (**H**).

Cordycepin

Cordycepin is one of the most important bioactive constituents of *Cordyceps sinensis*. Its chemical structure, 9-(3-deoxy-β-D-ribofuranosyl) adenine, is structurally similar to adenosine, which underlies its wide range of biological activities. Cordycepin exerts anti-inflammatory effects by regulating the expression of inflammation-related proteins and reducing the production of inflammatory mediators. For example, cordycepin decreases Ang II–induced expression of IL-6, TNF-α, and IL-1β, whereas lowering the levels of oxidative stress markers ROS and MDA.[13] Mechanistically, cordycepin inhibits the TLR4 signaling pathway by interfering with the interaction between LPS and TLR4 in RAW264.7 cells, thereby blocking LPS-induced NF-κB/p65 nuclear translocation and MAPK phosphorylation (ERK, JNK, and p38). It also reduces the expression of TLR4 and its downstream adaptor MyD88, suppressing inflammatory signal transduction and attenuating the inflammatory response.[14]

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Cordyceps sinensis Polysaccharide

Polysaccharides are the main water-soluble bioactive constituents of *Cordyceps sinensis* and exert pronounced anti-inflammatory effects. They are typically composed of various glycosyl residues, including mannose, galactose, glucose, arabinose, rhamnose, xylose, and sorbitol, with diverse molar ratios, glycosidic linkages, and branched structures.[15] Structural features such as molecular weight, degree of branching, and chain conformation are closely associated with biological activity.[16] In 2017, a water-soluble polysaccharide was extracted from natural *Cordyceps sinensis*,[17] and in 2018, an α-1,6-linked galactomannan was further isolated and structurally characterized.[18] Advances in structural characterization techniques have recently enabled more detailed studies of isolation, purification, and biological activities, particularly anti-inflammatory effects. For example, a highly active homogeneous polysaccharide (EPS-LM-1, molecular weight 360 kDa) was identified from exopolysaccharides produced by Cs-HK1 mycelial fermentation. EPS-LM-1 significantly inhibited secretion of NO and IL-1β in LPS-induced THP-1 cells, likely by regulating the NF-κB pathway through suppression of IκBα phosphorylation.[19] Additional studies have shown that *Cordyceps sinensis* polysaccharides inhibit α-SMA expression (a fibrosis marker) and regulate TGF-β1 and downstream signaling molecules, thereby suppressing both pro-inflammatory and pro-fibrotic factors.[20]

Steroidal Compounds

Steroidal compounds from *Cordyceps sinensis* have been used to treat inflammatory diseases such as arthritis and asthma, where they show significant efficacy. The principal compounds include ergosterol, ergosterol peroxide, and cerevisterol.[21] These compounds inhibit the release of inflammatory mediators and mitigate inflammatory responses. For example, ergosterol,[22] stigmasterol,[23] and related steroidal compounds reduce prostaglandin production by inflammatory cells, thereby relieving inflammatory symptoms.

Cordycepic Acid

Cordycepic acid, also known as D-mannitol, is a major bioactive component of *Cordyceps sinensis*. As a six-carbon straight-chain polyol, it exhibits both anti-inflammatory and other biological activities. In studies of renal ischemia/reperfusion injury, cordycepic acid acted through multiple targets and pathways. It inhibited the MAPK pathway, thereby reducing the release of pro-inflammatory factors such as TNF-α and IL-6; activated the HIF-1 pathway, alleviating ischemia/reperfusion-induced inflammation; and reduced oxidative stress via the cAMP–PKA–CREB pathway. Protein–protein interaction network analysis further indicated that IL-10 plays a central role in mediating its effects, highlighting its importance in inflammatory regulation.[24] However, it is important to note that these mechanistic insights are largely derived from network pharmacology predictions and limited experimental models. Further extensive validation is required to confirm these specific pathways in broader biological contexts.

Other Components

Cordyceps sinensis also contains a variety of amino acids and peptides, including 7 essential amino acids required by humans, which may enhance immune function. In addition, several bioactive fatty acids have been identified. A novel fatty acid, (2Z,4E)-deca-2,4-dienoic acid (DDEA), was isolated from *Cordyceps sinensis*. Although DDEA did not directly inhibit H1N1 viral replication, it significantly reduced expression of inflammatory factors induced by infection, including TNF-α, IFN-α, IFN-β, IL-6, CXCL-8/IL-8, CCL-2/MCP-1, CXCL-10/IP-10, CCL-3/MIP-1α, and CCL-4/MIP-1β. It also downregulated TLR-3 and RIG-I expression, inhibited phosphorylation of downstream signaling molecules IRF-3, p65, and STAT2, and reduced excessive activation of NF-κB, JAK–STAT, and IRF pathways.[25] Nevertheless, these findings regarding DDEA represent novel observations from a single preliminary study. Independent replication and broader investigation are necessary to establish it as a definitive anti-inflammatory constituent of *Cordyceps sinensis*.

Anti-Inflammatory Effects and Mechanisms of *Cordyceps sinensis*

Cordyceps sinensis and its bioactive components exhibit therapeutic potential across a wide range of inflammation-related diseases, including respiratory, skeletal, central nervous system (CNS), liver, kidney, gastrointestinal, skin,

cardiovascular, endocrine and metabolic disorders, as well as tumors. The spectrum of diseases targeted by *Cordyceps sinensis* and its active constituents is shown in Figure 2. Its anti-inflammatory mechanisms are summarized in Figure 3, and detailed information on these mechanisms in different disease models is presented in Table 1. The following subsections describe representative diseases and mechanisms in detail.

Respiratory Diseases

Respiratory diseases, such as Chronic Obstructive Pulmonary Disease (COPD), Acute Lung Injury (ALI), and coronavirus disease 2019 (COVID-19), are among the leading causes of disability and mortality worldwide, with their incidence and death rates continuing to rise.[54]

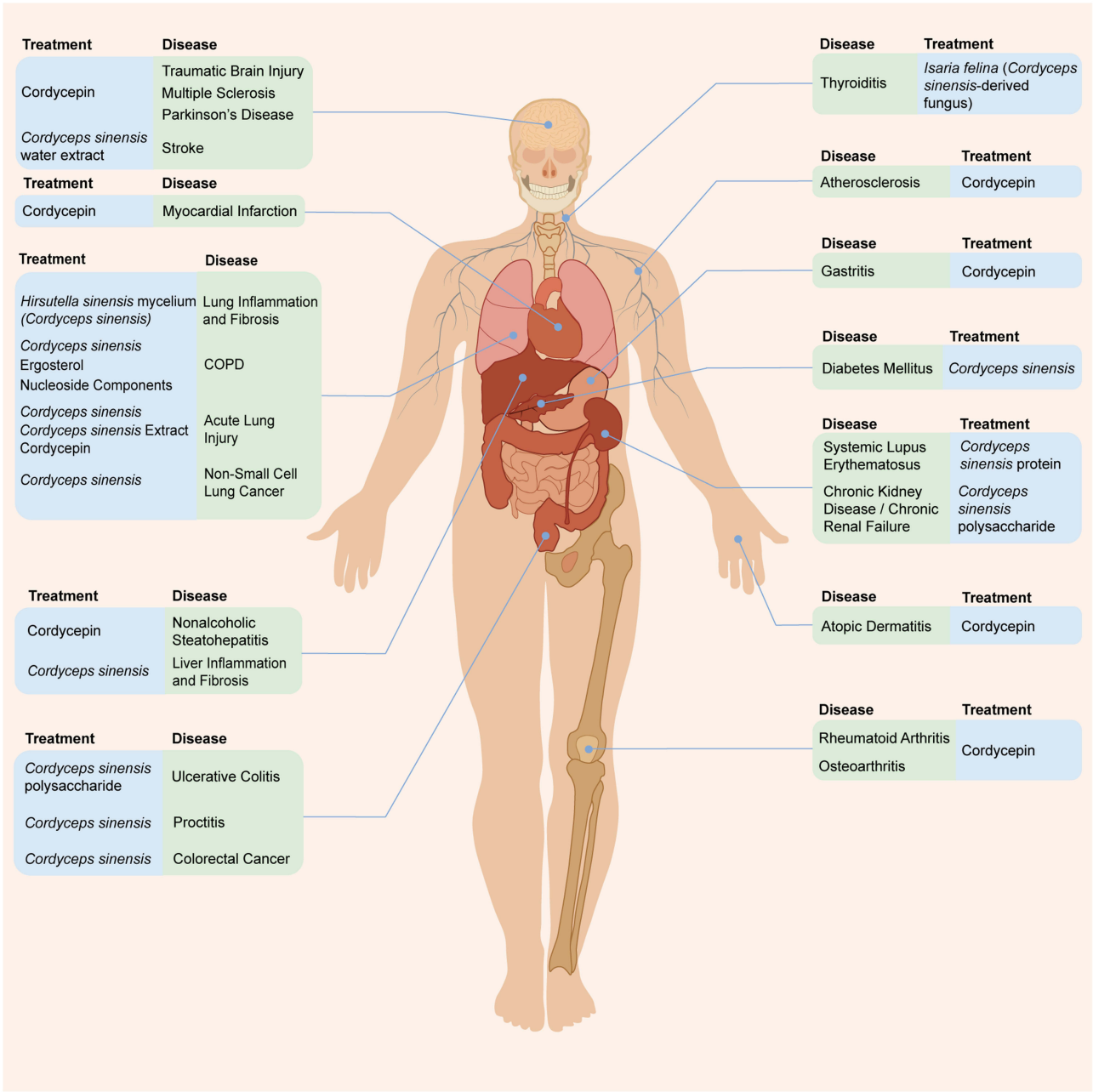

Figure 2 Systemic therapeutic effects of *Cordyceps sinensis* and its bioactive components across major inflammation-related diseases. The diagram summarizes the protective roles of *Cordyceps sinensis* in multiple organ systems, including the Respiratory system (COPD, ALI), Skeletal system (Rheumatoid arthritis, Osteoarthritis), Central Nervous System (Parkinson's disease, Stroke), Digestive system (Liver inflammation and fibrosis, NASH), Urinary system (Systemic lupus erythematosus, Chronic kidney disease), and Cardiovascular system (Myocardial infarction, Atherosclerosis).

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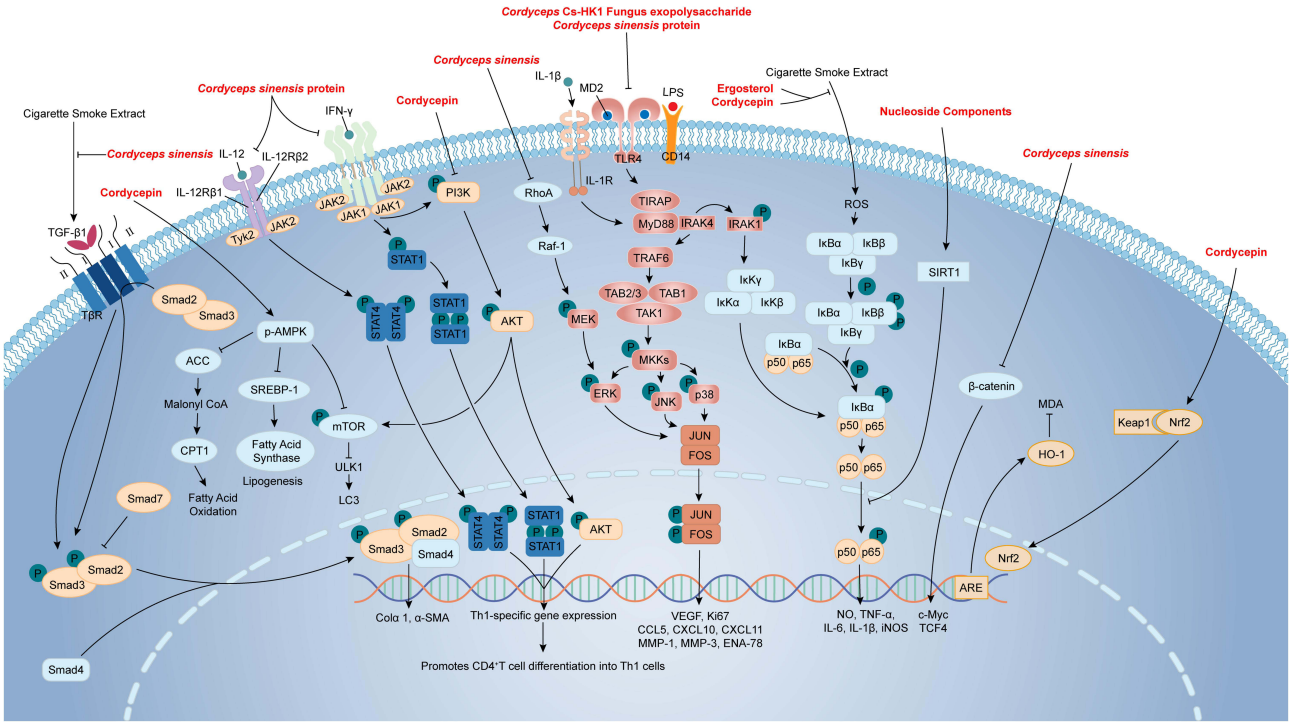

Figure 3 Recognized molecular mechanisms of *Cordyceps sinensis* in inflammation modulation. The schematic illustrates the key signaling pathways targeted by *Cordyceps sinensis* and its bioactive components, including the inhibition of TLR4/NF-κB nuclear translocation, suppression of MAPK phosphorylation, and activation of the Nrf2/HO-1 antioxidant axis. These molecular events collectively lead to reduced secretion of pro-inflammatory cytokines and enhanced tissue protection.

COPD is a chronic respiratory disorder caused primarily by exposure to harmful particles such as tobacco smoke and air pollutants. It is characterized by persistent respiratory symptoms and progressive airflow limitation, with high prevalence and mortality.[55–57] The core pathology is chronic inflammation of the lung parenchyma and airways, marked by infiltration of macrophages, lymphocytes, and neutrophils, abnormal release of pro-inflammatory factors (eg, TNF-α, IL-6, CXCL8), and activation of matrix metalloproteinases (MMPs), which together drive tissue destruction and airway remodeling.[58] *Cordyceps sinensis* intervenes in the pathogenesis of COPD through multiple mechanisms. First, it suppresses the inflammatory cascade by lowering levels of pro-inflammatory mediators such as TNF-α and IL-8, whereas inhibiting MMP-9 activity. This regulation extends to glutathione metabolism, glycerophospholipid metabolism, and tryptophan metabolism, thereby alleviating oxidative stress.[26] Second, it attenuates inflammatory fibrosis by inhibiting the TGF-β1/Smad pathway: it downregulates TβR I and TβR II, reduces Smad2/3 phosphorylation, and upregulates Smad7 expression, ultimately lowering cytokine production (TNF-α, IL-8, TGF-β1) and relieving airway inflammation.[27] Oxidative stress plays a central role in COPD by activating inflammatory genes. NF-κB, a redox-sensitive transcription factor, is pivotal in the inflammatory network regulating cytokine activity in airway pathology.[59] Targeting NF-κB is therefore a promising strategy. A recent study[28] demonstrated that ergosterol treatment of 16HBE cells and Balb/c mice suppressed cigarette smoke extract (CSE)-induced inflammatory responses, oxidative stress, and apoptosis by inhibiting NF-κB/p65 activation. Similarly, nucleoside components from *Cordyceps sinensis* reduced the activation of NF-κB/p65 and the expression of inflammatory mediators (NO, TNF-α, IL-6, IL-1β, iNOS), whereas significantly upregulating mRNA and protein expression of SIRT1, thereby enhancing anti-inflammatory activity.[29] Conventional drugs for COPD, including inhaled corticosteroids and phosphodiesterase-4 inhibitors, have notable limitations. Corticosteroids increase the risk of pneumonia and may elevate mortality risk when used alone, whereas phosphodiesterase-4 inhibitors often cause adverse gastrointestinal effects such as nausea, weight loss, and discomfort.[60] In contrast, *Cordyceps sinensis* has demonstrated benefits in improving lung function, exercise tolerance, quality of life, and symptom relief without serious adverse effects reported in clinical studies, highlighting its potential as an oral therapeutic option for COPD.[61]

Table 1 Mechanisms of Action of Anti-Inflammatory Components of *Cordyceps sinensis* in Different Disease Models

Disease	Pharmacodynamic Substances	Models	Mechanisms of Action/ Pharmacological Effects	Refs.
Respiratory Diseases				
Lung Inflammation and Fibrosis	*Hirsutella sinensis* mycelium (*Cordyceps sinensis*)	Bleomycin-induced pulmonary fibrosis mouse model/ TGF-β1-stimulated human lung fibroblasts (MRC-5) / BLM-stimulated mouse lung epithelial cells (MLE12)	↓IL-1β, IL-18, IL-6, TNF-α, Caspase-1 activation, NLRP3 inflammasome, ASC, P2X7R, ROS, ↑SOD, ↓Smad2/3 phosphorylation, Akt phosphorylation	[10]
Chronic Obstructive Pulmonary Disease	*Cordyceps sinensis*	Exposure to cigarette smoke and LPS-induced COPD rat model	↓TNF-α, IL-8, MMP-9	[26]
	Cordyceps sinensis	Exposure to cigarette smoke and LPS-Induced COPD rat model	↓TGF-β1/Smad, TβR I, TβR II, Smad2&Smad3 phosphorylation, ↑Smad7, ↓TNF-α, IL-8, TGF-β1	[27]
	Ergosterol	Intraperitoneal injection of cigarette smoke extract-induced COPD mouse model and 5% cigarette smoke extract treatment for 1 hour in 16HBE cell model	↓NF-κB/p65	[28]
	Nucleoside Components	CSE-stimulated RAW264.7 macrophages and mouse models	↓NF-κB/p65, NO, TNF-α, IL-6, IL-1β, iNOS, ↑SIRT1	[29]
Acute Lung Injury	*Cordyceps sinensis*	Renal ischemia-reperfusion injury-induced ALI rat model	↓IL-1β, TNF-α, MDA, MPO, ↑SOD	[30]
	Cordyceps sinensis Extract	Intratracheal instillation of LPS-induced ALI mouse model	↓total cell counts, neutrophil counts, macrophage counts, TNF-α, IL-6, IL-1β, NO, MPO	[31]
	Cordycepin	Intratracheal instillation of LPS-induced ALI mouse model	↓MPO, NF-κB, MDA, ↑Nrf2/HO-1, Nrf2 nuclear translocation, HO-1	[32]
	Cordycepin	Intratracheal instillation of LPS-induced ALI mouse model	↓PARP-1, phosphorylation of p65 subunit, ICAM-1, VCAM-1	[33]
Bone Diseases				
Rheumatoid Arthritis	Cordycepin	IL-1β-stimulated RASFs	↓IL-1β induced MMP-1, MMP-3, ENA-78, p38/JNK/AP-1	[34]
Osteoarthritis	Cordycepin	Surgical-induced medial meniscus instability and Sodium Iodoacetate-induced osteoarthritis rat model	↓IκB-α phosphorylation, NF-κB p65 nuclear translocation, IL-1β, TNF-α, VEGF	[35]
	Cordycepin	IL-1β stimulated human OA chondrocytes	↓NO, PGE_2, iNOS, COX-2, MMP-13, IL-6	[36]
	Cordycepin	IL-1β stimulation-induced ferroptosis mouse chondrocyte model and surgical transection of mouse ACL-induced osteoarthritis model	↓ADAMTS-5, ↑Col2a1&Aggrecan synthesis, ↓Nrf2 degradation, ↑Nrf2 nuclear translocation, GPX4, SLC7A11, ↓ROS, Fe^{2+}, MDA	[37]
Central Nervous System Diseases				
Traumatic Brain Injury	Cordycepin	Controlled cortical impact (CCI)-induced TBI mouse model	↓neurological deficits, neuronal tissue loss, CD16+, IL-17a, BBB leakage, MMP-2, MMP-9, Ly6G+, TNF-α, IL-1β, CCL3, A2a receptor, ↑CD206+, IL-10, ZO-1, CAPs	[12]
Multiple Sclerosis	Cordycepin	Cuprizone-induced demyelination mouse model	↓Iba1, GFAP, IL-1β, IL-6, ↑IL-4	[38]
Parkinson's Disease	Cordycepin	MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced Parkinson's disease mouse model and MPP+ (1-methyl-4-phenylpyridinium) treated BV2 microglial cells	↓PI3K/AKT/mTOR, ↑ERK/JNK	[39]
Stroke	*Cordyceps sinensis* water extract	Rat middle cerebral artery occlusion (MCAO) model of cerebral ischemia injury and oxygen-glucose deprivation (OGD) in brain microvascular endothelial cells (BMECs) under ischemic conditions	↑ATP, COX, ↓ROS, Bax, Cyt c, Caspase-3, NF-κB, TNF-α, IL-6, Caspase-3, Caspase-8, Caspase-9	[40]
Liver Diseases				
Liver Inflammation and Fibrosis	*Cordyceps sinensis*	CCl_4 (carbon tetrachloride)-induced hepatic inflammation and fibrosis mouse model	↓ALT, AST, T.Bil, Hyp, α-SMA, TGF-β, desmin, inflammation (mononuclear infiltration), fibrosis (collagen deposition); ↑Alb, hepatic NK cells (NK1.1 +CD3-), NKG2D, RAE-1δ, RAE-1ε, TUNEL (HSC apoptosis)	[9]
Nonalcoholic Steatohepatitis	Cordycepin	High-fat diet-induced mouse model	↓NF-κB, ↑AMPK phosphorylation	[41]
	Cordycepin	High-fat diet-induced mouse model	↓TNF-α, IL-6, IL-1β, MCP-1, MIP-2, ICAM-1, ↑AMPK, ↓SREBP1-c, ACC, CD36, ↑CPT-1, PPARα	[42]

(*Continued*)

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Table 1 (Continued).

Disease	Pharmacodynamic Substances	Models	Mechanisms of Action/ Pharmacological Effects	Refs.
Kidney Disease				
Systemic Lupus Erythematosus	*Cordyceps sinensis* protein	MRL/lpr spontaneous lupus mice (a spontaneous mutation mouse model prone to systemic lupus erythematosus)	↓IFN-γ, IL-12, RANTES, infiltration of $CD4^+$ and $CD8^+$ T cells, IL-12-STAT4, IFN-γ-STAT1, Th1, PI3K-AKT, p-PI3K, p-AKT	[43]
Chronic Kidney Disease/ Chronic Renal Failure	*Cordyceps sinensis* polysaccharide	Renal fulguration-induced chronic renal failure rat model	↓BUN, SCr	[44]
Gastrointestinal Diseases				
Gastritis	Cordycepin	*Helicobacter pylori*-induced gastritis mouse model	↓IL-6, IL-1β, ↑IL-10, ↓Th17, IL-17, ROR-γt, ↑SOCS3	[45]
Ulcerative Colitis	*Cordyceps sinensis* polysaccharide	DSS-induced ulcerative colitis mouse model	↓NF-κB, NF-κB p65, p-IκBα, TNF-α, IL-1β, ↑Occludin, Claudin-1, SCFAs	[46]
Proctitis	*Cordyceps sinensis*	Linear accelerator 6-MV X-ray irradiation of the lower abdomen-induced acute radiation proctitis mouse model	↓TNF-α, IL-6, IL-1β, ROS, MDA, Fe^{2+}	[47]
Skin Disease				
Atopic Dermatitis	Cordycepin	DNFB-induced atopic dermatitis mouse model	↓histamine, IgE, TSLP, MIP-2, ICAM-1, IL-4, IL-6, TNF-α, Caspase-1	[48]
Cardiovascular Diseases				
Arrhythmia	Cordycepin	Brief ligation of the left anterior descending artery (LAD)-induced myocardial ischemia/reperfusion (I/R) injury mouse model	↑Bcl-2, ↓Bax, Caspase-3, ROS, ↑LC3-II, ↓p62, ↑p-AMPK, AMPK, ↓p-mTOR, mTOR	[49]
Atherosclerosis	Cordycepin	PA-induced HUVECs injury model	↓ROS, ↑PI3K/Akt/eNOS, ↓NF-κB	[50]
Endocrine and Metabolic System Diseases				
Thyroiditis	*Isaria felina* (*Cordyceps sinensis*-derived fungus)	Nal-induced experimental autoimmune thyroiditis mouse model	↓TSH, TGAb, TPOAb, WBC, IFN-γ, TNF-α, IL-6, cleaved caspase-3, ↑Bcl-2	[11]
Diabetes Mellitus	*Cordyceps sinensis*	Non-Obese Diabetic mouse model	↓Th17 to Treg cell ratio, IL-6, TNF-α	[51]
Cancer				
Colorectal Cancer	*Cordyceps sinensis*	AOM/DSS-induced colitis-associated tumor mouse model	↓IL-1β, IL-6, TNF-α, IFN-γ, ↑IL-2, IL-10, ↓Wnt/β-catenin, β-catenin, TCF4, ↑SCFAs, Parabacteroides goldsteinii, Bifidobacterium pseudolongum PV8-2	[52]
Non-Small Cell Lung Cancer	*Cordyceps sinensis*	Lewis lung cancer cell-induced orthotopic non-small cell lung cancer (NSCLC) mouse model	↓RhoA, Raf-1, c-fos, MAPK, TNF-α, IL-6, ↑IL-10, ↓MDA, ↑SOD, GSH-Px, ↓VEGF, Ki67	[53]

ALI is a clinical syndrome caused by factors such as acute pneumonia, sepsis, and severe trauma. Its core pathology is a cytokine storm (eg, IFN-γ, IL-1β, TNF-α) triggered by excessive immune activation, together with dysregulation of multiple pathways, including mTOR, NF-κB, TLR, MAPK, and JAK–STAT.[62,63] These processes ultimately lead to vascular leakage and multi-organ failure. A key driver of ALI progression is the oxidative–inflammatory vicious cycle: ferroptosis-induced oxidative marker MDA exacerbates lung injury via positive feedback,[64] whereas neutrophil-derived MPO activates complement, promotes neutrophil extracellular trap (NET) formation and fibrosis through MPO–ANCA antibodies, and directly damages alveolar epithelium through its oxidative products.[65] *Cordyceps sinensis* regulates both inflammation and oxidative stress in ALI. It reduces the levels of pro-inflammatory cytokines (IL-1β, TNF-α) and oxidative stress markers (MDA, MPO), whereas enhancing superoxide dismutase (SOD) activity, thereby interrupting the oxidative–inflammatory cycle.[30] Extracts of *Cordyceps sinensis* lower total cell counts, neutrophils, and macrophages in bronchoalveolar lavage fluid (BALF), inhibit the expression of TNF-α, IL-6, IL-1β, and NO, and suppress MPO activity,

collectively reducing inflammatory infiltration and oxidative stress.[31] Cordycepin, a major bioactive component, exerts synergistic effects through multiple pathways. It decreases MPO activity and suppresses NF-κB signaling, whereas lowering MDA levels, activating the Nrf2/HO-1 pathway, promoting Nrf2 nuclear translocation, and upregulating HO-1, thereby enhancing antioxidant defense.[32] In addition, cordycepin directly inhibits PARP-1 activity, blocking its regulation of NF-κB signaling and preventing phosphorylation of the p65 subunit. This downregulates ICAM-1 and VCAM-1, reduces neutrophil pulmonary infiltration, and produces a significant anti-inflammatory effect.[33] Currently, no clinically approved drugs effectively reduce ALI mortality. Although corticosteroids and phosphodiesterase-4 inhibitors can relieve symptoms, they are associated with increased pneumonia risk and gastrointestinal side effects.[66] In contrast, *Cordyceps sinensis* exerts multi-target effects on inflammatory and oxidative pathways, providing a potential multi-mechanism therapeutic strategy for ALI.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is believed to have originated from an animal reservoir and spreads rapidly among humans via respiratory droplets and direct contact.[67] After binding to the ACE2 receptor, the virus enters host cells and activates innate immune pathways such as TLR and RLR. These initiate NF-κB and IRF cascades, leading to the release of pro-inflammatory cytokines (eg, IL-6, TNF-α). Concurrently, NLRP3 inflammasome assembly promotes IL-1β secretion and pyroptosis, further amplifying local inflammation. The JAK–STAT pathway amplifies cytokine signaling, culminating in a cytokine storm characterized by high systemic levels of pro-inflammatory mediators.[68] Emerging evidence suggests that traditional Chinese medicines possess notable immunomodulatory and anti-inflammatory properties; for example, a systematic review has demonstrated that the classic formula Yupingfengsan exhibits potential efficacy in the prevention of COVID-19.[69] In this context, *Cordyceps sinensis* and its bioactive components further complement therapeutic potential by exhibiting both anti-inflammatory and antiviral activities. Extracts suppress IL-6 and IL-8 overexpression, reduce abnormal proliferation of airway smooth muscle cells, and thereby mitigate airway remodeling.[70] Its exopolysaccharides inhibit the TLR4/MyD88/NF-κB pathway, reduce nuclear translocation of NF-κB p65, downregulate TLR4 and MyD88 expression, and lower ROS production.[71] Cordycepin, in particular, is associated with anti-inflammatory and apoptosis-related proteins (IL-10, Caspase-3, Caspase-8, Caspase-9) in network pharmacology analysis. It directly inhibits the SARS-CoV-2 main protease (Mpro) and spike protein, blocking viral replication and host cell entry. In addition, cordycepin interferes with the poly(A) tail of viral RNA, destabilizing viral RNA and accelerating degradation, which further reduces replication efficiency.[72] Clinically approved COVID-19 drugs such as remdesivir, nirmatrelvir/ritonavir, and sotrovimab reduce hospitalization and mortality risk[73] but are associated with adverse effects: remdesivir may cause nausea and liver dysfunction; lopinavir/ritonavir increases gastrointestinal toxicity;[74] and sotrovimab commonly induces headache, diarrhea, and rash. By contrast, *Cordyceps sinensis* and its bioactive compounds show favorable safety profiles. They alleviate acute respiratory symptoms and improve long COVID manifestations such as fatigue and insomnia, significantly enhancing quality of life.[75] In summary, through multi-target anti-inflammatory mechanisms and direct inhibition of viral replication, *Cordyceps sinensis* offers a promising adjuvant strategy for COVID-19 management, warranting further clinical investigation.

However, it is worth noting that most current findings are derived from rodent models of inflammation (eg, LPS or ovalbumin induction). Whether these anti-inflammatory effects can be fully translated to chronic, complex human respiratory conditions (such as COPD or severe asthma), which involve extensive tissue remodeling and distinct immune phenotypes, requires further validation through rigorous, long-term clinical trials.

Skeletal Diseases

Skeletal diseases, such as Rheumatoid Arthritis (RA) and Osteoarthritis (OA), are major causes of pain, functional impairment, and reduced quality of life. The incidence of these diseases has been increasing annually worldwide, imposing a substantial burden on patients and society.

RA is a severe, systemic autoimmune inflammatory disease that primarily targets joints and periarticular tissues. It affects approximately 1% of the global population and is associated with high morbidity and mortality.[76,77] Pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-17, are central mediators of joint inflammation and tissue destruction. These cytokines are regulated by signaling pathways such as JAK–STAT and NF-κB, which represent critical

therapeutic targets.[78] Cordycepin demonstrates potent anti-inflammatory activity in RA. It significantly inhibits IL-1β-induced expression of matrix metalloproteinases MMP-1 and MMP-3, enzymes central to joint destruction. In addition, cordycepin selectively suppresses IL-1β-induced production of the chemokine ENA-78 (CXCL5), reducing inflammatory cell recruitment. Mechanistically, it inhibits phosphorylation of p38 and JNK, thereby suppressing the p38/JNK/AP-1 signaling pathway and decreasing inflammatory factor expression. Collectively, by targeting MMPs, chemokines, and key signaling cascades, cordycepin attenuates RA-related inflammation.[34] Current therapies for RA, including methotrexate, glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs), are effective but limited by safety concerns. Methotrexate, the first-line treatment, often causes gastrointestinal discomfort and fatigue.[79] Glucocorticoids provide rapid relief but, even at low doses, carry risks of cardiovascular events, infections, metabolic disorders, and osteoporosis.[80] DMARDs are associated with severe infections, malignancy, cardiovascular disease, venous thromboembolism, and gastrointestinal perforation, particularly during early treatment or at higher doses.[81] By contrast, cordycepin shows promising anti-inflammatory efficacy with fewer reported adverse effects, although research remains limited. Further studies are needed to confirm its biological activity and clinical potential in RA management.

OA is an age-related degenerative joint disorder characterized by cartilage degradation, low-grade synovial inflammation, and subchondral bone remodeling, leading to chronic pain and functional decline.[82] During pathogenesis, mechanical stress and damage-associated molecular patterns (DAMPs) activate the TLR/NF-κB pathway, inducing pro-inflammatory cytokines (IL-1β, TNF-α) and matrix-degrading enzymes that damage the cartilage matrix. The NLRP3 inflammasome amplifies IL-1β release and suppresses matrix synthesis through NF-κB/MAPK signaling. Concurrently, ROS accumulation triggered by IL-1β and TNF-α would normally activate the Nrf2 antioxidant pathway, but chronic inflammation often causes Nrf2 dysfunction, impairing ROS clearance. This reciprocal amplification of inflammation and oxidative damage accelerates joint degeneration.[83] Cordycepin exhibits multi-target anti-inflammatory and chondroprotective effects in both in vitro and in vivo models. First, it inhibits IκB-α phosphorylation and degradation, blocks NF-κB p65 nuclear translocation, and downregulates IL-1β and TNF-α expression, thereby reducing synovial inflammation, macrophage infiltration, and VEGF expression.[35] Second, cordycepin inhibits IL-1β-induced overproduction of NO and PGE2 in chondrocytes, and downregulates matrix-degrading enzymes (iNOS, COX-2, MMP-13, IL-6) at mRNA and protein levels.[36] It also protects against proteoglycan degradation by reducing ADAMTS-5 expression, whereas promoting matrix repair through increased synthesis of Col2a1 and Aggrecan. Cordycepin further modulates oxidative stress and ferroptosis through the Keap1/Nrf2 axis. By inhibiting Keap1-mediated Nrf2 degradation, it enhances Nrf2 nuclear translocation and upregulates antioxidant genes such as GPX4 and SLC7A11, thereby reducing ROS accumulation and lipid peroxidation. It also lowers IL-1β-induced Fe^{2+} and MDA levels, restoring iron metabolism homeostasis. In mouse OA models, cordycepin treatment improved cartilage structure and significantly reduced OARSI scores. These effects were partially reversed by the Nrf2 inhibitor Brusatol, confirming the role of the Keap1/Nrf2 axis.[37] Conventional OA treatments, including bisphosphonates, hyaluronic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids, remain limited. Bisphosphonates reduce bone resorption but show uncertain efficacy in hip OA; hyaluronic acid provides only transient analgesia; NSAIDs relieve pain but may worsen cartilage damage; and intra-articular glucocorticoids, though rapidly effective, accelerate cartilage degeneration at high doses.[84] By contrast, cordycepin acts on multiple key pathways (TLR/NF-κB, NLRP3, Keap1/Nrf2), reduces inflammation and oxidative damage, and promotes matrix repair, offering a new direction and theoretical basis for multi-target OA therapy.

Despite these promising findings, specific limitations in this domain must be acknowledged. Most data are drawn from chemically induced arthritis or surgical osteoarthritis models in rodents. These models often fail to fully recapitulate the chronic, age-related, and mechanically driven pathogenesis of human skeletal disorders. Future research warrants validation in larger animal models that better mimic human biomechanics and long-term clinical trials targeting structural preservation endpoints.

Central Nervous System Diseases

CNS diseases, including Multiple Sclerosis (MS), Parkinson's Disease (PD), and Stroke, are characterized by complex pathological mechanisms. These disorders lead to cognitive decline and motor dysfunction, severely affecting quality of life and imposing major challenges on healthcare systems.

MS is a chronic demyelinating disease of the CNS marked by myelin loss, inflammatory responses, neuronal degeneration, and glial scarring.[85] Demyelination in the brain and spinal cord slows or blocks nerve conduction, causing diverse neurological symptoms that impair quality of life and may result in permanent disability.[86] In a cuprizone-induced demyelination mouse model, cordycepin significantly reduced activation of Iba1-positive microglia and GFAP-positive astrocytes, indicating inhibition of neuroinflammation. It also decreased IL-1β and IL-6 expression in the corpus callosum and hippocampus, whereas upregulating IL-4, an anti-inflammatory cytokine, thereby alleviating neuroinflammatory responses.[38]

PD is a progressive neurodegenerative disorder, with pathogenesis closely associated with abnormal α-synuclein aggregation and neuroinflammation.[87] In PD patients, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) are elevated, whereas anti-inflammatory cytokines with neurorepair functions, such as IL-9, are reduced. This imbalance, driven by microglial activation, α-synuclein propagation, and viral infection, establishes a self-perpetuating inflammatory loop that accelerates dopaminergic neuronal damage.[88] Cordycepin alleviates MPTP-induced behavioral deficits and neuronal apoptosis, reduces dopaminergic neuron loss in the nigrostriatal pathway, increases monoamines and their metabolites in the striatum, and inhibits microglial polarization and pro-inflammatory cytokine expression. Mechanistically, cordycepin suppresses PI3K/AKT/mTOR and ERK/JNK signaling whereas enhancing autophagic protein expression in the striatum and substantia nigra, contributing to its neuroprotective effects.[39]

Stroke is the most common and severe cerebrovascular disease and a leading cause of long-term disability.[89] Ischemic Stroke (IS), the predominant type, imposes a particularly heavy disease burden.[90] IS disrupts brain energy metabolism by impairing mitochondrial oxidative phosphorylation, reducing ATP production, and compromising cytochrome COX and mitochondrial complex function. Abnormal mitochondrial fission promotes Bax-mediated outer membrane permeabilization, Cyt c release, and activation of apoptotic pathways.[91] Aqueous extracts of *Cordyceps sinensis* exhibit pronounced mitochondrial protective effects in ischemic injury. They elevate ATP levels, enhance COX activity, and improve the function of respiratory chain complexes I–IV, thereby increasing mitochondrial efficiency, reducing electron leakage, lowering ROS production, and alleviating inflammatory responses. These extracts also downregulate pro-apoptotic genes (Bax, Cyt c, Caspase-3), suggesting protection against inflammation-induced neuronal apoptosis through inhibition of mitochondria-mediated pathways. Additionally, they suppress NF-κB signaling and decrease TNF-α and IL-6 release, further mitigating neuroinflammation. In brain microvascular endothelial cells under hypoxia and nutrient deprivation, aqueous extracts reduce apoptosis, restore mitochondrial membrane potential, and decrease Caspase-3, Caspase-8, and Caspase-9 activity, thereby protecting against inflammation-mediated cellular injury.[40]

A critical gap in this area is the limited understanding of the blood-brain barrier (BBB) permeability of these bioactive macromolecules. Future pharmacokinetics studies must verify whether effective concentrations of polysaccharides or adenosine can physically reach the central nervous system sites of inflammation to exert direct neuroprotection, rather than relying solely on peripheral immunomodulation.

Liver Diseases

Non-Alcoholic Fatty Liver Disease (NAFLD) includes a spectrum ranging from Non-Alcoholic Fatty Liver (NAFL) to Non-Alcoholic Steatohepatitis (NASH) and is often associated with progressive fibrosis.[92] AMPK plays a protective role in NASH progression by directly phosphorylating pro-Caspase-6, thereby preventing its cleavage and activation. Since Caspase-6 activation depends on upstream Caspase-3/7 and perpetuates a positive feedback loop for apoptosis through mitochondrial Cyt c release, AMPK activation reduces Caspase-6 activity and alleviates liver injury. Targeting the AMPK–Caspase-6 axis may therefore provide a therapeutic strategy for NASH.[93] Cordycepin has shown efficacy in reducing lipid accumulation, inflammatory responses, and lipotoxicity in hepatocytes under metabolic stress. In diet-induced NASH mice, cordycepin lowers serum transaminase levels in a dose-dependent manner and reduces hepatic triglyceride deposition, inflammatory infiltration, and fibrosis. Mechanistically, it inhibits NF-κB activation in hepatocytes whereas enhancing AMPK phosphorylation, collectively suppressing pro-inflammatory cytokine secretion in both in vitro and in vivo NASH models.[41] Using a high-fat diet mouse model, it was further demonstrated that cordycepin exerts anti-inflammatory and lipid-regulatory effects: it inhibits inflammatory mediators (TNF-α, IL-6, IL-1β, MCP-1) and reduces expression of macrophage-associated activity markers (MIP-2, ICAM-1). These effects may be attributable

to decreased macrophage number or activity. Concurrently, cordycepin activates AMPK signaling, downregulates lipid synthesis genes (SREBP1-c, ACC, CD36), and upregulates β-oxidation genes (CPT-1, PPARα), thereby lowering hepatic lipid content and indirectly alleviating inflammation.[42] In contrast, although obeticholic acid has shown promise in improving liver fibrosis in Phase III trials, its use is associated with high rates of pruritus (51%) and elevated LDL-C, which increases cardiovascular risk.[94] Cordycepin, through multi-target activation of AMPK and inhibition of inflammatory responses, offers a safer therapeutic prospect and provides a theoretical basis for the treatment of NASH.

Currently, the majority of hepatic studies focus on phenotypic improvements in fibrosis or steatosis markers. There is a pressing need for more in-depth investigations into the specific signaling crosstalk between lipid metabolism pathways and inflammatory cascades to fully elucidate the underlying hepatoprotective mechanisms distinguishing them from standard lipid-lowering agents.

Kidney Diseases

Systemic Lupus Erythematosus (SLE) is a common autoimmune disorder that affects multiple organs, with kidney damage being particularly prevalent. Lupus Nephritis (LN) is one of the most frequent complications, occurring in about 40% of adult and up to 80% of pediatric patients.[95–97] *Cordyceps sinensis* protein shows therapeutic potential in LN, largely through modulation of inflammatory responses. It significantly lowers serum levels of IFN-γ, IL-12, and RANTES—key mediators of LN-related immune dysregulation and renal injury. In MRL/lpr mice, *Cordyceps sinensis* protein reduces renal infiltration of $CD4^+$ and $CD8^+$ T cells, suggesting that it suppresses T cell recruitment and inflammatory injury. Mechanistically, it attenuates Th1-mediated inflammation by inhibiting IL-12–STAT4 and IFN-γ–STAT1 signaling. It also downregulates PI3K–AKT signaling, suppressing p-PI3K and p-AKT expression, thereby reducing Th1 differentiation and activation.[43]

Chronic Kidney Disease (CKD) refers to persistent functional or structural abnormalities of the kidney, strongly associated with accelerated cardiovascular disease, infection risk, and premature mortality.[98] In the past, chronic renal failure (CRF) was used as a related term, though CKD includes earlier disease stages. A homogeneous polysaccharide, CPS-2 (4.39×10^4 Da), was isolated from *Cordyceps sinensis*. In a CRF model, CPS-2 significantly reduced blood urea nitrogen (BUN) and serum creatinine (SCr) levels, and alleviated glomerular sclerosis and tubular injury, demonstrating both nephroprotective and anti-inflammatory effects. These benefits were associated with alleviation of oxidative stress and regulation of the TGF-β1 pathway, thereby inhibiting inflammation and fibrosis. CPS-2 thus represents a potential therapeutic candidate for CKD prevention and treatment.[44]

Despite these promising preclinical results, the precise molecular targets of *Cordyceps sinensis* components within specific renal cell types (eg, podocytes versus tubular epithelial cells) remain largely undefined. Future studies need to rigorously distinguish between direct nephroprotective effects and secondary benefits arising from systemic immunomodulation.

Gastrointestinal Diseases

Chronic gastritis is a prevalent digestive disorder worldwide, with Helicobacter pylori recognized as its primary causative factor.[99] It is characterized by long-term gastric mucosal inflammation and atrophy, which in severe cases may progress to achlorhydria. This pathological progression not only increases the risk of gastric cancer and peptic ulcers but also impairs nutrient absorption.[100] Cordycepin significantly alleviates gastric mucosal inflammation. Cordycepin was reported to reduce inflammatory cell infiltration and markedly attenuate mucosal injury. Mechanistically, cordycepin downregulated pro-inflammatory cytokines IL-6 and IL-1β, whereas upregulating the anti-inflammatory cytokine IL-10. It also decreased Th17 cell numbers and suppressed IL-17 secretion, indicating an inhibitory effect on Th17-mediated inflammation. Further analysis showed that cordycepin reduced expression of ROR-γt, a transcription factor critical for Th17 differentiation, whereas upregulating SOCS3, a negative regulator. These findings suggest that cordycepin modulates the SOCS3/ROR-γt axis to inhibit Th17 differentiation and exert anti-inflammatory activity.[45]

Ulcerative colitis (UC) is a chronic, lifelong inflammatory disease that primarily affects the rectum and colon and can extend to the entire colon, substantially impairing quality of life. As of 2023, the global prevalence of UC is estimated at 5 million cases, with incidence continuing to rise.[101] UC is a form of inflammatory bowel disease (IBD) with a complex

pathogenesis driven by interactions among host genetics, intestinal immune responses, environmental factors, and the gut microbiota. Among these, the NF-κB transcription factor family has a central role in regulating immune responses and driving abnormal intestinal inflammation.[102] *Cordyceps sinensis* polysaccharides show strong therapeutic potential in UC. They inhibit NF-κB activation, reducing expression of NF-κB p65 and p-IκBα. This suppression is accompanied by decreased levels of TNF-α and IL-1β, confirming their anti-inflammatory effects. Furthermore, polysaccharide treatment upregulates tight junction proteins such as Occludin and Claudin-1, strengthening intestinal barrier function and limiting the entry of inflammatory mediators into the bloodstream. These polysaccharides also promote production of short-chain fatty acids (SCFAs), including acetic acid and butyric acid. Mechanistically, these SCFAs exert anti-inflammatory effects by activating G-protein-coupled receptors (GPR43) and inhibiting histone deacetylases (HDACs), thereby blocking NF-κB signaling.[46] Thus, *Cordyceps sinensis* polysaccharides improve UC pathology by simultaneously inhibiting inflammatory pathways, enhancing barrier integrity, and modulating the gut microbiota and its metabolites.

Proctitis, defined as inflammation of the anus and/or rectum,[103] can also benefit from *Cordyceps sinensis*. In radiation-induced proctitis, treatment reduces inflammatory mediators such as TNF-α, IL-6, and IL-1β. It decreases ROS and the lipid peroxidation marker MDA, thereby improving systemic redox balance and antioxidant capacity. In addition, *Cordyceps sinensis* regulates ferroptosis by modulating SLC7A11, GPX4, and ACSL4 expression, whereas reducing Fe^{2+} accumulation. These mechanisms protect intestinal cells from oxidative and ferroptotic injury.[47]

Despite these extensive mechanistic insights ranging from Th17 modulation in gastritis to ferroptosis inhibition in proctitis, the current research landscape remains relatively fragmented. Most findings rely on chemically induced (eg, DSS) or radiation-induced acute injury models, which may not fully capture the complex, chronic, and relapsing-remitting nature of human IBD. Furthermore, definitive evidence distinguishing whether the observed benefits arise from direct mucosal repair or are secondary to microbiota reshaping remains to be established via rigorous germ-free systems or patient-derived organoid models.

Skin Diseases

Atopic dermatitis (AD) is a chronic, recurrent, non-infectious inflammatory skin disorder characterized primarily by persistent pruritus.[104] Its pathogenesis is multifactorial, driven by epidermal barrier dysfunction, skin microbiota dysbiosis, and Th2-dominated immune imbalance. These processes interact to reduce filaggrin expression, promote abnormal Staphylococcus aureus colonization, and elevate local inflammatory mediators (eg, IL-4, IL-13, IL-31). This cascade results in barrier disruption, itching, and chronic inflammation, establishing a self-perpetuating cycle of disease progression.[105] Cordycepin exerts significant therapeutic effects in AD models. It lowers serum histamine and IgE levels, indicating potential anti-allergic activity, and reduces mast cell and eosinophil infiltration in AD-like lesions. Cordycepin also suppresses thymic stromal lymphopoietin (TSLP), macrophage inflammatory protein-2 (MIP-2), and intercellular adhesion molecule-1 (ICAM-1) expression in skin tissue, whereas decreasing serum concentrations of IL-4, IL-6, and TNF-α. Through these actions, it inhibits multiple inflammatory signaling pathways relevant to AD. Furthermore, cordycepin reduces Caspase-1 expression and activity, thereby limiting inflammatory responses in AD-like lesions.[48] In summary, cordycepin shows considerable promise as a therapeutic agent for AD by modulating inflammatory mediators and signaling pathways. However, its mechanisms of action and clinical applications remain insufficiently characterized, highlighting the need for further systematic investigation.

Although cordycepin shows promise in reducing pruritus and inflammation in murine models, clinical data on its dermatological application are virtually nonexistent. Future research needs to optimize topical delivery systems to enhance skin penetration and conduct human trials to assess its safety and efficacy compared to standard corticosteroids.

Cardiovascular Diseases

Myocardial Infarction (MI) and Atherosclerosis are common cardiovascular disorders with strong inflammatory components. Following MI, processes such as inflammation, fibrosis, and angiogenesis overlap within the damaged myocardium. Ischemia and hypoxia induce widespread cardiomyocyte apoptosis within hours to days, and the necrotic tissue triggers inflammatory responses accompanied by immune cell infiltration. These infiltrating cells release pro-inflammatory cytokines and chemokines that drive tissue remodeling.[106] Atherosclerosis, by contrast, is primarily

initiated by abnormal cholesterol accumulation, which activates inflammasomes, mediates IL-1β activation, and promotes pro-inflammatory cytokine release.[107]

Acute MI is usually caused by coronary artery occlusion. Timely reperfusion remains the gold standard treatment; however, reperfusion itself can aggravate myocardial injury due to sudden pH shifts, Ca^{2+} overload, and hyperoxia. These changes trigger oxidative stress and a cascade of inflammatory responses.[108] During I/R, the restoration of blood flow and oxygen supply produces excessive ROS, which directly damage cardiomyocytes and amplify inflammatory signaling. Within this network, AMPK and mTOR play pivotal roles: AMPK activation suppresses ROS and inflammation, whereas abnormal mTOR activation exacerbates injury. AMPK exerts cardioprotective effects partly by inhibiting mTOR.[109] Cordycepin mitigates I/R injury by regulating apoptosis, oxidative stress, and autophagy. It upregulates Bcl-2 and downregulates Bax and Caspase-3, thereby suppressing apoptosis. Cordycepin also reduces ROS production, alleviating oxidative damage, and enhances autophagy by increasing LC3-II expression and autophagosome formation whereas reducing p62 accumulation. Through these actions, it activates autophagic clearance, reduces inflammatory responses, and protects myocardial tissue. Additionally, cordycepin increases p-AMPK and decreases p-mTOR, indicating that it regulates autophagy by activating AMPK signaling and inhibiting mTOR, which collectively attenuate I/R-induced injury.[49] Despite the availability of antiarrhythmic agents, clinical management remains limited by safety concerns. Sodium channel blockers such as flecainide increase mortality; amiodarone causes multi-organ toxicity; dronedarone is contraindicated in advanced heart failure; and sotalol may induce QT prolongation and torsades de pointes.[110] By contrast, treatment with *Cordyceps sinensis* preparations significantly improves arrhythmia response rates without serious adverse effects, highlighting its potential as a safer therapeutic alternative.[111]

Atherosclerosis is a lipid-driven inflammatory disease.[112] Its pathogenesis is driven by complex interactions among immune cells, inflammatory mediators, and vascular components. Oxidized low-density lipoprotein (ox-LDL) activates endothelial cells, induces monocyte adhesion and migration into the intima, and promotes differentiation into macrophages that form foam cells. Pro-inflammatory mediators such as TNF-α and IFN-γ, together with activated T cells, accelerate plaque formation, whereas regulatory T cells (Tregs) and anti-inflammatory cytokines such as IL-10 provide partial protection. Oxidative stress, activation of innate immune pathways, and dysregulated adaptive immunity collectively drive plaque progression and instability.[113] Cordycepin has been shown to exert potent antioxidant and anti-inflammatory effects in this context.[50] It inhibits ROS production, enhances cellular antioxidant capacity, and alleviates oxidative stress-induced endothelial injury. Cordycepin activates the PI3K/Akt/eNOS pathway, thereby maintaining endothelial function, and simultaneously suppresses NF-κB activation and downstream inflammatory mediator expression. It also prevents palmitic acid-induced calcium overload, stabilizes mitochondrial membrane potential, and inhibits mitochondria-dependent apoptosis. Currently, lipid-lowering drugs such as statins and PCSK9 inhibitors remain the mainstay of therapy, but their effectiveness is limited by adherence issues and adverse reactions in some patients.[114] Cordycepin provides multi-target protection through antioxidation, regulation of signaling pathways, and suppression of inflammation, making it a promising therapeutic candidate for atherosclerosis. These findings provide new mechanistic insights and a theoretical basis for developing innovative strategies in cardiovascular disease prevention and treatment.

Although endothelial protection has been consistently observed in animal models, high-quality clinical evidence regarding the effects of *Cordyceps sinensis* on hard cardiovascular endpoints (such as mortality or myocardial infarction rates) in humans is currently lacking. Future research should prioritize translational studies to verify these vascular benefits in clinical settings.

Endocrine and Metabolic System Diseases

Thyroiditis is an inflammatory disorder of the thyroid gland that typically progresses through three clinical phases: an initial hyperthyroid phase caused by excessive hormone release, a subsequent hypothyroid phase, and eventual recovery of normal thyroid function in most patients. However, some cases progress to permanent hypothyroidism.[115] *Isaria felina*, derived from *Cordyceps sinensis*, has been shown to ameliorate experimental autoimmune thyroiditis (EAT) through multi-target mechanisms. It reduces pro-inflammatory factors (TNF-α, IFN-γ, IL-6) as well as TSH, TGAb, TPOAb, and WBC counts, thereby modulating autoimmune responses, decreasing inflammatory infiltration, and

preserving follicular structure. In addition, *Isaria felina* regulates apoptosis via the Bcl-2/Caspase-3 pathway, upregulating Bcl-2 and reducing cleaved Caspase-3 activation, which together decrease apoptosis and limit inflammatory thyroid injury.[11]

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from varying degrees of insulin resistance and impaired insulin secretion.[116] Chronic low-grade inflammation plays a central role in its pathogenesis: obesity promotes immune cell release of TNF-α, IL-6, and IL-1β, which activate inflammatory pathways and drive insulin resistance.[117] The effects of *Cordyceps sinensis* in delaying the onset of type 1 diabetes were investigated using a Non-Obese Diabetic (NOD) mouse model. Oral administration of *Cordyceps sinensis* delayed disease onset and reduced incidence. Histological analysis revealed alleviated pancreatic islet infiltration and reduced inflammatory responses in treated mice. Mechanistically, *Cordyceps sinensis* restored immune tolerance by modulating T cell subsets, notably increasing the Treg/Th17 ratio. By inhibiting IL-6 and TNF-α expression, it promoted Treg differentiation and suppressed Th17-driven inflammatory responses. Collectively, these findings suggest that *Cordyceps sinensis* may provide early intervention benefits in type 1 diabetes through regulation of T cell balance and inflammatory signaling.

It is important to acknowledge that many mechanisms reported in metabolic contexts overlap significantly with general antioxidant pathways. Future work should aim to identify specific molecular targets that distinguish the action of *Cordyceps sinensis* from standard hypoglycemic agents to better position its unique therapeutic value in metabolic regulation.

Tumors

Tumors includes a group of diseases characterized by uncontrolled and continuous cell division, growth, and spread into surrounding tissues.[118] Increasing basic and clinical evidence indicates that inflammatory factors and their signaling pathways play central roles in tumor initiation and progression.[119] Pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, together with the transcription factors NF-κB and STAT3, are key regulators in this process. Activated by pro-inflammatory signals, NF-κB and STAT3 induce the expression of oncogenic target genes that enhance tumor cell survival, proliferation, invasion, and metastasis.[120] Chronic inflammation, a pivotal link in this process, can be significantly driven or exacerbated by prolonged environmental exposures to carcinogens, such as air pollutants, occupational toxins, and chemical contaminants, which promote oxidative stress, DNA damage, epigenetic alterations, and a pro-tumorigenic microenvironment.[121] These findings highlight the importance of inflammatory mechanisms in tumorigenesis and provide a rationale for targeting inflammation in cancer therapy. In recent years, the intestinal microbiota has emerged as an important factor in cancer prevention and treatment. *Cordyceps sinensis* has been shown to downregulate IL-1β, IL-6, TNF-α, and IFN-γ whereas upregulating anti-inflammatory cytokines IL-2 and IL-10, thereby alleviating intestinal inflammation.[52] Mechanistically, *Cordyceps sinensis* inhibits the Wnt/β-catenin signaling pathway, reducing β-catenin and TCF4 expression, suppressing abnormal intestinal epithelial cell proliferation, and limiting inflammatory damage. It also reshapes the gut microbiota by increasing probiotic abundance and stimulating the production of SCFAs, which further inhibit inflammatory mediator release and improve intestinal barrier function. Fecal microbiota transplantation experiments confirmed that microbiota derived from *Cordyceps sinensis*-treated mice alleviated inflammatory symptoms in recipients, promoting enrichment of probiotics such as *Parabacteroides goldsteinii* and *Bifidobacterium pseudolongum* PV8-2. These strains degrade inflammation-associated metabolites, reduce oxidative stress, inhibit pathogenic bacteria, and prevent overactivation of the immune system. Beyond intestinal regulation, *Cordyceps sinensis* also exerts direct anti-tumor effects by blocking the MAPK signaling pathway. It was demonstrated that RhoA, Raf-1, c-fos, and phosphorylated ERK1/2 and MEK1/2 are downregulated, thereby inhibiting tumor cell proliferation and associated inflammatory responses. It also reduces TNF-α and IL-6 levels whereas increasing IL-10, indicating suppression of the chronic inflammatory state. In parallel, *Cordyceps sinensis* mitigates oxidative stress by lowering MDA concentrations and enhancing antioxidant enzymes such as SOD and GSH-Px. These antioxidant activities protect against inflammation-driven tumor progression. Furthermore, by downregulating VEGF and Ki67 expression, *Cordyceps sinensis* inhibits angiogenesis and tumor cell proliferation, thereby improving the tumor inflammatory microenvironment. Together, these findings suggest that *Cordyceps sinensis* exerts multi-dimensional anti-tumor

effects through inhibition of inflammatory signaling, regulation of the gut microbiota, suppression of oxidative stress, and reduction of angiogenesis. Its broad activity highlights its potential as both an anti-inflammatory and anti-cancer therapeutic candidate.

Nevertheless, the complexity of the tumor microenvironment (TME) poses a significant challenge. Most current studies focus on the direct cytotoxicity of *Cordyceps sinensis* against cancer cell lines in vitro, while research elucidating its impact on the complex immune landscape (eg, TAMs repolarization or T-cell exhaustion) within the TME in vivo is still relatively scarce.

Discussion

As a key representative of traditional Chinese medicine, *Cordyceps sinensis* has been used clinically for centuries in the management of inflammation-related disorders, including chronic respiratory inflammation,[122] kidney diseases,[123] and fatigue syndrome.[75] Historical records and modern clinical observations consistently demonstrate good safety[124] and measurable anti-inflammatory efficacy,[21] providing a solid foundation for contemporary pharmacological research. However, mechanistic studies remain largely confined to rodent models and in vitro experiments, limiting the translational value of current findings. For clinical application, it is essential to adopt disease models that more closely recapitulate human pathophysiology or conduct systematic early-phase clinical trials to evaluate the predictability and applicability of preclinical results. Pharmacokinetic limitations of key bioactive components also pose a major challenge. For example, cordycepin is rapidly degraded by adenosine deaminase, resulting in a short half-life and low bioavailability. Future work should focus on novel delivery systems such as lipid nanoparticles and exosome carriers to improve in vivo stability, enhance bioavailability, and achieve tissue-specific targeting. Equally important is the implementation of rigorous, large-sample, and long-term follow-up clinical trials in well-defined patient populations (eg, RA, NAFLD) to systematically evaluate safety and preliminary efficacy, drawing on historical evidence of safe use whereas adhering to modern evidence-based standards.

Systemic challenges in the field also warrant explicit consideration. Publication bias remains a concern, as the underreporting of null results may overestimate overall efficacy. Reproducibility is further complicated by the biological variability inherent to natural products (eg, diverse strains and origins). Finally, clinical translation is often hindered by pharmacokinetic discrepancies, where high effective in vitro concentrations are difficult to achieve in human tissues due to rapid metabolism and poor membrane permeability.

Current research on the anti-inflammatory pharmacology of *Cordyceps sinensis* also faces conceptual and methodological limitations. A primary concern is the homogeneity in reported mechanisms. As noted in this review, the majority of studies attribute efficacy to the modulation of classical pathways, particularly NF-κB and MAPK, and the suppression of common cytokines. While this underscores a conserved mode of action, it also exposes a lack of depth regarding disease-specific upstream triggers or distinct molecular targets beyond these "hub" pathways. Future research must move beyond phenotypic descriptions to elucidate precise molecular interactions within specific tissue microenvironments. In parallel with this mechanistic redundancy, there is a limitation in the scope of study materials: Many studies focus on single components such as cordycepin or polysaccharides, but these cannot reproduce the comprehensive, multi-target pharmacodynamics of the whole fungus.[125,126] Studies using crude extracts more closely reflect real-world use but are limited by compositional complexity, batch variability, and lack of standardization, which hinder mechanistic clarification and quality control.[127,128] Notably, many studies fail to specify the content of main bioactive components, resulting in insufficient comparability of results among different investigations and hindering strict mechanistic clarification. The "component-target-effect" of *Cordyceps sinensis* is likely derived from the interaction and synergy of multiple bioactive components, including cordycepin, polysaccharides, sterols, and cyclic peptides, rather than from a single compound. However, current research lacks sufficient experimental data on the specific synergistic mechanisms between these components. Consequently, identifying and optimizing a "Core Active Compound Combination (CACC)" that can achieve multi-target synergy, maximize efficacy, and minimize adverse effects will be central to future innovation. To this end, systematic application of multi-omics technologies (metabolomics, proteomics, transcriptomics), combined with bioinformatics, artificial intelligence-assisted molecular docking, and network pharmacology, offers powerful tools for elucidating synergistic interactions and predicting action networks. These predictions can then be validated through

multi-level in vitro and in vivo experiments. Such integrative approaches are expected to overcome the respective limitations of single-component and crude-extract studies, enabling scientific optimization and standardization of bioactive combinations, and laying the groundwork for subsequent drug development.

The regulatory potential of *Cordyceps sinensis* in complex immune–microenvironment interactions, such as inflammation resolution and tissue repair, also remains underexplored.[129] High-resolution techniques, including single-cell omics and spatial transcriptomics,[130] together with patient-derived organoids,[131] will allow detailed mapping of cell-specific mechanisms, such as macrophage polarization and fibroblast activation. Gene-editing tools such as CRISPR–Cas9 can further pinpoint core targets (eg, the NLRP3 inflammasome) in humanized models, providing direct evidence of pharmacodynamic action. Leveraging these insights, future studies may explore the synergistic use of *Cordyceps sinensis* bioactive combinations with immunotherapies, such as immune checkpoint inhibitors or targeted small-molecule anti-inflammatory drugs, to develop more effective and less toxic therapeutic strategies. Finally, the potential of *Cordyceps sinensis* in emerging chronic inflammatory contexts, such as long COVID-19, merits systematic evaluation. By capitalizing on its multi-target, multi-pathway activity, *Cordyceps sinensis* holds promise as a platform for next-generation natural product-based anti-inflammatory therapies.

Conclusion

Cordyceps sinensis, with its long history of clinical application, has shown broad therapeutic potential and favorable safety in both traditional Chinese medicine practice for inflammation-related diseases and preliminary modern clinical studies. Contemporary pharmacological research, predominantly derived from in vitro and animal models, confirms that its anti-inflammatory effects are mediated through multi-target, multi-pathway regulatory networks, providing a rich foundation for developing novel anti-inflammatory agents from natural products. Nevertheless, a critical evaluation of the literature suggests that while the therapeutic scope is extensive, the mechanistic depth in specific disease contexts requires strengthening. Current studies often rely on the modulation of conserved inflammatory pathways (eg, NF-κB and MAPK) to explain efficacy across disparate conditions, which may limit the precision of translational applications. Beyond these mechanistic gaps, the field faces critical translational bottlenecks, including the lack of standardization in *Cordyceps* preparations and bioactive quantification, the significant variability introduced by diverse sources and processing methods, and the uncertain pharmacokinetics of key compounds (notably cordycepin). Future work should therefore prioritize shifting from breadth to depth. To make these findings actionable, research efforts must focus on three specific directions: (1) the strict utilization of chemically characterized extracts to ensure reproducibility; (2) the implementation of comparative dose/exposure mapping across studies to define optimal therapeutic windows; and (3) the execution of indication-specific, adequately powered clinical trials with validated inflammatory endpoints. Such systematic efforts will accelerate the transformation of *Cordyceps sinensis* into a strong candidate for next-generation natural product-based anti-inflammatory therapies.

Abbreviations

ACC, Acetyl-CoA Carboxylase; ACSL4, Acyl-CoA Synthetase Long-Chain Family Member 4; AMPK, AMP-Activated Protein Kinase; AP-1, Activator Protein-1; ASC, Apoptosis-associated speck-like protein containing a CARD; CAPs, Compound Action Potentials; CCL, C-C Motif Chemokine Ligand; COX-2, Cyclooxygenase-2; CXCL, C-X-C Motif Chemokine Ligand; DAMPs, Damage-Associated Molecular Patterns; GPX4, Glutathione Peroxidase 4; HO-1, Heme Oxygenase-1; ICAM-1, Intercellular Adhesion Molecule-1; IFN, Interferon; IL, Interleukin; iNOS, Inducible Nitric Oxide Synthase; IκBα, Inhibitor of Nuclear Factor kappa B alpha; JAK, Janus Kinase; JNK, c-Jun N-terminal Kinase; Keap1, Kelch-like ECH-associated Protein 1; LPS, Lipopolysaccharide; MAPK, Mitogen-Activated Protein Kinase; MCP-1, Monocyte Chemoattractant Protein-1; MIP, Macrophage Inflammatory Protein; MMP, Matrix Metalloproteinase; mTOR, Mechanistic Target of Rapamycin; MyD88, Myeloid Differentiation Primary Response 88; NET, Neutrophil Extracellular Trap; NF-κB, Nuclear Factor Kappa B; NKG2D, Natural Killer Group 2, Member D; NLRP3, NOD-, LRR- and Pyrin Domain-Containing Protein 3; Nrf2, Nuclear Factor Erythroid 2–Related Factor 2; PARP-1, Poly(ADP-ribose) Polymerase 1; PI3K, Phosphoinositide 3-Kinase; PPARα, Peroxisome Proliferator-Activated Receptor Alpha; RANTES, Regulated on Activation, Normal T Cell Expressed and Secreted; RIG-I, Retinoic Acid–Inducible Gene I; ROR-γt,

Retinoic Acid-Related Orphan Receptor Gamma t; ROS, Reactive Oxygen Species; SCFAs, Short-Chain Fatty Acids; SIRT1, Sirtuin 1; SOCS3, Suppressor of Cytokine Signaling 3; STAT, Signal Transducer and Activator of Transcription; TGF-β1, Transforming Growth Factor-beta 1; TLR, Toll-like Receptor; TNF-α, Tumor Necrosis Factor-alpha.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

Jiahao Xie: Data curation, Investigation, Writing – original draft; Jingwen Xu: Data curation, Writing – original draft; Qi Fan: Formal analysis, Writing – original draft; Yuchi Chen: Conceptualization, Writing – review and editing, Supervision. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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