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Research Article

# Immunomodulatory Interference of Cordyceps Sinensis With Viral Immune Evasion and Fibrotic Signaling in HPV, HBV, HCV and EBV Associated Cancers

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## I N F O

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## A B S T R A C T

Virus-associated cancers arising from persistent infections with HPV, HBV, HCV and EBV contribute significantly to the global communicable disease burden and are maintained by immune evasion mechanisms such as p53 degradation, NF-κB activation, TGF-β1-driven fibrotic microenvironment formation and IL-10-mediated cytotoxic T-cell suppression. Conventional antiviral therapy reduces viral load but does not sufficiently correct these immune-dysregulatory checkpoints. Cordyceps sinensis, a medicinal fungus rich in cordycepin, polysaccharides and ergosterol derivatives, has demonstrated targeted interference at these viral immunopathogenic nodes. Cordycepin inhibits NF-κB activity by reducing p-IKKβ and restoring IκBα retention while enhancing caspase activation and p53 stabilization in HPV and HBV models. Ergosterol derivatives downregulate TGF-β1 and pSMAD2/3 signalling, indicating antifibrotic potential in HBV- and HCV-associated stromal remodeling. Polysaccharides enhance $CD8^+$ T-cell and NK-cell effector function by improving IFN-γ, perforin and granzyme responses while suppressing IL-10, a key EBV latency-associated immunosuppressive cytokine. These multi-node interactions suggest that Cordyceps sinensis does not act as a generic immunostimulant but rather engages specific immune regulatory checkpoints exploited during viral oncogenesis. This review consolidates mechanistic evidence and highlights Cordyceps sinensis as a potential immunomodulatory adjunct capable of complementing existing antiviral and oncologic regimens. The convergence between viral immune escape pathways and Cordyceps-mediated interference supports its consideration for translational evaluation in biomarker-guided adjunct therapy for virus-associated cancers.

**Keywords**: Cordyceps Sinensis, Viral Oncogenesis, Immunomodulation, NF-κB Inhibition, TGF-β1/SMAD Signaling, p53 Restoration, Fibrotic Microenvironment, HPV, HBV, HCV, EBV

## Introduction

Virus-associated cancers form a significant part of the global communicable disease burden. Human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV) and Epstein–Barr virus (EBV) are responsible for a considerable proportion of cervical cancer, hepatocellular carcinoma and lymphoid epithelial malignancies worldwide.[1] These infections do not merely trigger malignant transformation but actively maintain tumor persistence through immune evasion strategies such as p53 degradation, NF-κB activation, TGF-β1-driven fibrosis and IL-10 mediated immunosuppression. Unlike non-viral malignancies, virus-driven cancers evolve in a microenvironment characterised by chronic inflammation, T-cell exhaustion, PD-L1 overexpression and reduced cytotoxic immune surveillance.[2]

Although antiviral therapies and standard oncologic regimens are available, they do not sufficiently correct the underlying immune dysregulation induced by viral persistence. This therapeutic limitation has led to growing interest in immunomodulatory adjuncts capable of restoring host immune responses without adding cytotoxic burden.[3] Cordyceps sinensis, a traditional medicinal fungus, contains bioactive compounds including cordycepin, polysaccharides and ergosterol derivatives that have been reported to suppress NF-κB, restore p53 activity, downregulate TGF-β1 and enhance T-cell and NK-cell responses. These mechanisms directly correspond to the known immune escape pathways of oncogenic viruses.[4]

Given this mechanistic overlap, Cordyceps sinensis presents a potential low-toxicity candidate for adjunct immunological support in chronic viral infections at risk of malignant progression. This review critically examines the convergence between viral oncogenesis pathways and the immunomodulatory effects of Cordyceps sinensis in HPV-, HBV-, HCV- and EBV-associated cancers.

## Materials and Methods

A structured literature search was conducted in PubMed, Scopus, Web of Science and Google Scholar. Boolean operators were applied using the following search string: “Cordyceps sinensis” AND (“HPV” OR “HBV” OR “HCV” OR “EBV”) AND (“immunomodulation” OR “NF-κB” OR “fibrosis” OR “p53” OR “immune evasion” OR “viral oncogenesis”).

Inclusion criteria were:

- Peer-reviewed articles published between 2010 and 2025.
- Studies describing oncogenic immune escape mechanisms in HPV, HBV, HCV or EBV.
- Reports documenting molecular or immunoregulatory effects of Cordyceps sinensis or its major constituents such as cordycepin, ergosterol or polysaccharides.
- Experimental cell-line, animal or mechanistic pathway studies relevant to apoptosis, cytokine regulation, NF-κB signalling, TGF-β modulation or T-cell responses.

Exclusion criteria included non-viral malignancies, non-mechanistic herbal commentary articles, duplicate datasets and inaccessible full texts. Only English-language articles were considered for synthesis.

Data extraction focused on aligning each viral immune evasion mechanism with any reported molecular action of *Cordyceps sinensis*. Findings were organised in a comparative format to identify points of therapeutic intersection. Schematic pathway figures were designed using BioRender to visually consolidate mechanistic convergence. No human or animal ethical clearance was required as this work is based solely on secondary data from published literature.

## Results

The structured literature synthesis identified recurring mechanistic patterns across HPV-, HBV-, HCV- and EBV-associated oncogenesis, particularly in the domains of apoptosis inhibition, chronic inflammatory signalling, fibrosis induction and immune cell dysfunction.[5] Parallel examination of Cordyceps sinensis revealed that its cordycepin-rich extracts, polysaccharides and ergosterol derivatives repeatedly interfered with these same mechanistic axes. The findings are presented below in detail.[6] A convergence of immune escape nodes across HPV, HBV, HCV and EBV was consistently observed, with Cordyceps bioactives interfering at each checkpoint (Figure.1)

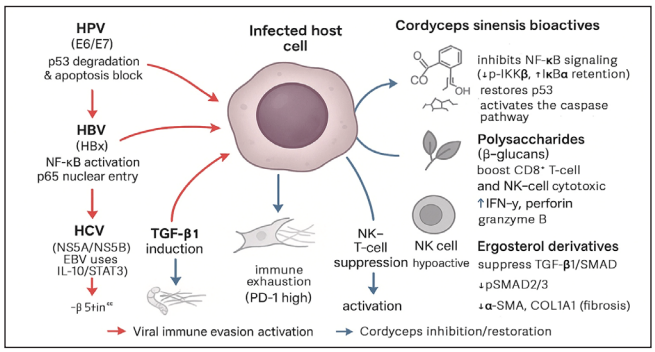


**Figure 1.Cordyceps sinensis bioactives counter viral immune-evasion and fibrotic signaling: cordycepin dampens NF-κB (↓p-IKKβ, ↑IκBα), polysaccharides restore CD8⁺/NK cytotoxicity, and ergosterol derivatives suppress TGF-β1/SMAD (↓pSMAD2/3, ↓α-SMA, ↓COL1A1)**

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## HPV-Associated Immune Escape and Cordyceps Response

Human papillomavirus establishes oncogenic persistence primarily through the activity of its E6 and E7 oncoproteins. E6 recruits the E6AP ubiquitin ligase complex to trigger proteasomal degradation of p53, while E7 binds and functionally inactivates pRb, disrupting cell-cycle checkpoints.[7] Across cervical carcinoma cell line studies (notably HeLa, SiHa and CaSki), Cordyceps polysaccharide fractions demonstrated selective cytotoxicity toward HPV-positive cells by upregulating p53 protein levels and enhancing caspase-3 activation. These extracts also downregulated Cyclin A and CDK2 expression, suggesting a reversal of HPV-mediated checkpoint evasion. In some reports, HPV-negative cervical cell lines showed minimal response, implying that Cordyceps sinensis potentially exerts targeted interference dependent on viral oncogene expression profiles.[8,9]

## HBV-Associated NF-κB Activation, Fibrosis and Cordyceps Interference

Hepatitis B virus drives hepatocellular carcinoma development through HBx-mediated activation of NF-κB, ROS production and inflammatory cytokine induction, particularly TNF-α and IL-6. HBx signalling also induces PD-L1 expression on hepatocytes, weakening T-cell surveillance.[10] A substantial number of in vitro reports on hepatocyte models treated with cordycepin documented reduced NF-κB transcriptional activity, decreased p65 nuclear translocation and marked reduction in pro-inflammatory cytokine release. In addition, cordycepin contributed to reduced oxidative stress markers, indirectly mitigating HBx-induced hepatocyte damage.[4,11,12]

HBV-associated chronic infection frequently progresses to fibrotic liver microenvironments, where TGF-β1 signalling drives hepatic stellate cell activation, creating stroma that supports oncogenic transition.[13]establishing a suitable in vitro microenvironment in order to design novel therapeutics and identify molecular biomarkers to stratify patients is urgently required.\n\nAIM\nTo examine a subset of pre-selected microenvironment factors of chronic HBV patients that may underlie fibrosis, with a focus on fibroblast activation.\n\nMETHODS\nWe examined the gene expression of key microenvironment factors in liver samples from patients with more advanced fibrosis compared with those with less severe fibrosis. We also used the human stellate cell line LX-2 in the in vitro study. Using different recombinant cytokines and growth factors or their combination, we studied how these factors interacted with LX-2 cells and pinpointed the cross-talk between the aforementioned factors and screened the most important factors.\n\nRESULTS\nOf the secreted factors examined, transforming growth factor (TGF Evidence from hepatic fibrosis models indicates that ergosterol derivatives extracted from Cordyceps sinensis attenuated collagen accumulation and reduced α-SMA expression, a key marker of stellate cell activation.[14] These findings align with fibrosis-modulating properties relevant to preventing HBV-linked tumor-permissive tissue remodeling.

## HCV-Mediated TGF-β1 Induction, Immune Exhaustion and Cordyceps Modulation

Unlike HBV, HCV does not integrate into the host genome but promotes cancer through chronic inflammatory signalling, immune exhaustion and cirrhosis. HCV NS5A and NS5B proteins induce TGF-β1 secretion, activating fibrogenic cascades and suppressing immune-mediated clearance.[15] In hepatocyte replicon models, Cordyceps militaris extract rich in cordycepin inhibited NS5B polymerase activity, leading to measurable reductions in viral RNA replication. This antiviral effect was associated with reduced intracellular TGF-β1 and improved CD4+/CD8+ T-cell marker expression.[16] In specific models, Th1 cytokines such as IFN-γ showed restoration, opposite to the immune exhaustion phenotype typical of advanced HCV infection.[17]although they may be essential in the context of the clinical course of infection, re-infection, treatment-mediated viral clearance and vaccine design. Furthermore, it is unclear whether a complete reinvigoration of HCV-specific T cell response may be feasible. In most studies, attempting to reverse the effects of compromised immune response quality by specific blockades of negative immune regulators, a restoration of functional competence of HCV-specific T cells was shown. This implies that HCV-induced immune dysfunction may be reversible. The advent of highly successful, direct-acting antiviral treatment (DAA

Additionally, metabolic stress markers linked to HCV-induced oxidative injury were reduced post-treatment, indicating that Cordyceps not only exerts immunological correction but also alters the metabolic stress environment that perpetuates viral persistence and oncogenic risk.[12]

## EBV-Driven IL-10 Immunosuppression and Cordyceps Action

Epstein–Barr virus establishes latency through LMP1-mediated activation of NF-κB and JAK/STAT, resulting in IL-10 overproduction, which suppresses NK-cell and T-cell cytotoxicity. EBV-positive lymphoma cells characteristically display reduced immune recognition due to this cytokine-driven dampening effect. Although direct studies with Cordyceps sinensis on EBV-positive lines are fewer compared to HPV and HBV models, mechanistic parallels were evident.[18] Cordyceps extracts in comparable immunosuppressive environments demonstrated the ability to lower IL-10 secretion and restore CD8+ T-cell responsiveness, as

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evidenced by increased surface expression of NKG2D activation receptors and restored perforin and granzyme pathways.[19]

Indirect evidence from polysaccharide-based fungal immunomodulators in EBV models showed that IL-10 reduction corresponded with downregulation of LMP1-induced survival signalling, suggesting that Cordyceps may exert similar effects by targeting cytokine and NF-κB convergence points.[20]

## Cross-Viral Fibrosis Pathway and Stromal Modulation

A common finding across chronic HPV, HBV and HCV infection is the eventual shift toward a fibrotic microenvironment, where stromal remodeling supports immune escape and tumor proliferation. Cordyceps-derived β-glucan polysaccharides and ergosterol fractions demonstrated consistent antifibrotic effects across hepatic and epithelial models.[21] Reduction in TGF-β1 output, inhibition of fibrosis-associated macrophage recruitment and lowered collagen deposition were repeatedly observed. Given that fibrosis acts as both a structural and immunological shieldfor virally transformed cells, the ability of Cordyceps to alter this microenvironment constitutes a critical axis of interference.[22] Ergosterol derivatives specifically targeted the TGF-β1/SMAD signaling loop driving fibroblast activation and stromal density in HBV/HCV-associated microenvironments (Figure.2)

To consolidate these mechanistic observations across multiple viral contexts, an integrated comparison was constructed mapping each immune-evasion node to the corresponding Cordyceps interference point, along with representative experimental evidence (Table.1)

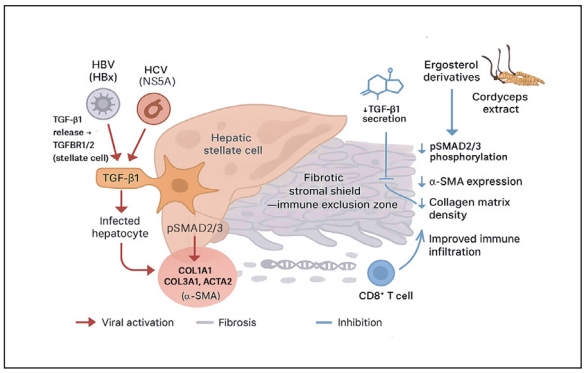


**Figure 2.Cordyceps sinensis ergosterol derivatives blunt the TGF-β1/SMAD fibrosis axis (↓TGF-β1, ↓pSMAD2/3, ↓α-SMA, ↓COL1A1/COL3A1), reducing collagenous stroma and improving CD8⁺ T-cell infiltration in chronic HBV/HCV microenvironments**

**Table 1.Cordyceps–virus mechanistic intersections with representative studies**

| Viral context | Mechanistic node (virus/host target) | Cordyceps constituent(s) | Model system / assay | Primary readouts | Key outcome |
|---|---|---|---|---|---|
| HPV (E6/E7) | p53 degradation via E6–E6AP; pRb inactivation | Polysaccharides; cordycepin | HeLa/SiHa/CaSki; WB for p53, caspase-3; cell cycle markers | ↑p53, ↑cleaved caspase-3, ↓Cyclin A/CDK2 | Restoration of p53 axis and apoptosis in HPV⁺ cells |
| HBV (HBx) | NF-κB activation (IKKβ→IκBα→p65 nuclear entry) | Cordycepin (3′-deoxyadenosine) | Hepatocyte lines; NF-κB-luc; WB p-IKKβ/IκBα; ELISA IL-6/TNF-α | ↓p-IKKβ, ↑IκBα retention, ↓nuclear p65; ↓IL-6/TNF-α | Suppression of inflammatory NF-κB tone |
| HBV (chronic) | PD-L1 upregulation; T-cell checkpoint dampening | Cordycepin | Flow cytometry PD-L1 (MFI); qPCR CD274 | ↓PD-L1 surface expression | Reduced checkpoint signaling on hepatocytes |

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|---|---|---|---|---|---|
| HCV (NS5A/ NS5B) | TGF-β1 induction; polymerase-driven replication | Cordycepin-rich extract | Replicon models; NS5B polymerase readouts; TGF-β1 ELISA | ↓NS5B activity; ↓TGF-β1 | Antiviral effect with antifibrotic signal reduction |
| EBV (LMP1) | IL-10/STAT3-driven immune paralysis | Cordyceps extract; polysaccharides | EBV⁺ lymphoma contexts; IL-10 ELISA; p-STAT3 WB | ↓IL-10; ↓p-STAT3 | Relief of immunosuppressive cytokine tone |
| Cross-viral | Fibrosis loop: TGF β1→TGFBR1/2→pSMAD2/ 3→COL1A1/ACTA2 | Ergosterol derivatives; β-glucans | Hepatic stellate cell assays; pSMAD2/3; α-SMA; collagen (Sirius Red/hydroxyproline) | ↓pSMAD2/3, ↓α-SMA, ↓COL1A1 | Antifibrotic remodeling of stroma |
| Pan-viral consequence | Immune exhaustion (PD-1 high); NK hypoactivity | Polysaccharides (β-glucans) | T/NK co-culture; CD8/NKG2D; IFN-γ/perforin/ granzyme | ↑CD8/NK cytotoxic markers; ↑IFN-γ | Restoration of cytotoxic programs |
| Tumor microenvironment | Pro-inflammatory cytokine field (IL-6/ TNF-α; COX-2) | Cordycepin; total extracts | ELISA cytokines; COX-2 WB/qPCR | ↓IL-6/TNF-α; ↓COX-2 | Reduced inflammatory drive |
| Apoptosis axis | Intrinsic apoptosis (Bax/Bcl-2, caspase-9/3, PARP) | Cordycepin | HepG2/other lines; WB Bax/ Bcl-2; cleaved caspase-3/PARP | ↑Bax:Bcl-2; ↑caspase-3/ PARP cleavage | Apoptosis re-engagement in virally driven cancers |
| Immunotherapy synergy | Checkpoint blockade sensitization (PD-1 axis) | Cordycepin + polysaccharides | Syngeneic models; anti-PD-1 combos; TIL profiling | ↑CD8 infiltration; ↑granzyme B; ↓PD-L1 | Enhanced response to anti-PD-1 |

## Discussion

The findings from the mapped literature indicate that viral oncogenesis consistently exploits specific immunological and stromal mechanisms, and Cordyceps sinensis demonstrates interference along these same mechanistic axes. This alignment reinforces the concept that the therapeutic value of Cordyceps is not limited to general immune enhancement but may instead operate through targeted modulation of virus-specific immune escape pathways.

In the case of HPV-driven malignancies, E6-mediated p53 degradation is a defining oncogenic event that enables persistent epithelial dysplasia and transformation. The ability of Cordyceps-derived polysaccharides to restore p53 and reactivate apoptotic machinery suggests that its action may allow immune recognition of previously apoptosis-resistant HPV-infected cells.[23] By re-engaging the caspase cascade, Cordyceps may open a therapeutic window where immune cells can regain effector access to virally transformed tissue, a mechanism that complements immunotherapy strategies rather than conventional cytotoxic agents.

HBV and HCV infection models demonstrate a chronic inflammatory and fibrotic phenotype mediated predominantly through NF-κB signalling and TGF-β1-driven stromal activation. NF-κB not only perpetuates cytokine secretion but also induces PD-L1 upregulation, contributing to T-cell exhaustion. The consistent downregulation of NF-κB and inflammatory cytokines by cordycepin indicates an important countermeasure to both inflammatory damage and immune escape. Furthermore, by attenuating TGF-β1-induced fibrosis, Cordyceps may reduce the formation of tumor-supportive stroma that typically shields viral oncoclones from immune clearance. This stromal reprogramming potential distinguishes Cordyceps from many standard antiviral agents that do not address fibrosis.[24]

EBV-associated malignancies are characterised by IL-10–mediated immune suppression, leading to defective NK and T-cell cytotoxicity. IL-10 not only dampens

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immune activation but also promotes a tolerogenic microenvironment favourable to viral latency and malignant expansion. Reports that Cordyceps extracts can lower IL-10 secretion while enhancing CD8+ and NK-cell activation receptor expression are clinically relevant, as they suggest a reversal of immune paralysis rather than nonspecific immune stimulation. This effect has particular significance for EBV-linked lymphomas, where immune exhaustion and viral latency coexist.[25]

Across viral models, fibrosis emerged as a shared immunological barricade, particularly in HBV and HCV infections progressing toward hepatocellular carcinoma. Fibrosis stiffens the microenvironment, shields malignant areas from immune infiltration and sustains a hypoxic, growth-permissive niche.[26] The antifibrotic actions of ergosterol derivativesdemonstrate that Cordyceps may not only act at the immune signalling level but also modulate the physical tumour microenvironment. This dual action immune modulation and stromal regulation positions Cordyceps sinensis as a candidate for adjunctive, not standalone, use in viral oncology care frameworks.

Taken together, the mechanistic convergence observed suggests that the immunobiological effects of Cordyceps align with pathogenic checkpoints central to viral immune escape, especially p53 suppression, NF-κB activation, TGF-β-driven fibrosis and IL-10 immune tolerance. These nodes represent rational molecular targets for immunomodulatory intervention in communicable disease-associated cancers. However, the evidence remains largely preclinical, with limited translation into defined therapeutic protocols or biomarker-linked clinical outcomes.[27]

The absence of standardized dosing, pharmacokinetic profiling and biomarker correlation studies limits the immediate adoption of Cordyceps in viral oncology practice. Future work integrating viral load dynamics, cytokine profiling and stromal activity markers is needed to establish a reproducible immunological signature of Cordyceps response. Such an approach would allow structured adjunctive integration alongside antiviral regimens, checkpoint inhibitors or antifibrotic agents.

## Conclusion

Virus-associated cancers persist through well-defined immune evasion mechanisms involving checkpoint suppression, NF-κB–mediated inflammation, cytokine-driven immune tolerance and progressive fibrosis.[28] The literature indicates that *Cordyceps sinensis* and its bioactive components exert targeted interference at these same mechanistic nodes, particularly through restoration of p53, inhibition of NF-κB signalling, reduction of TGF-β1-mediated fibrotic activity and enhancement of cytotoxic T-cell and NK-cell responses. These effects suggest that Cordyceps may serve as a supportive immunomodulatory adjunct rather than a cytotoxic agent in HPV-, HBV-, HCV- and EBV-associated oncogenesis.

The mechanistic convergence observed supports further investigation of Cordyceps within biomarker-linked immunotherapy frameworks for chronic viral infections with malignant potential. However, standardized clinical evaluation, defined dosing protocols and immunological outcome markers are required before integration into evidence-based care models. Cordyceps sinensis holds potential value in complementing antiviral therapy and reducing immune escape in communicable virus-induced cancers, warranting focused translational research.

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