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# Computational Investigation Of Cordycepin As A Potential SARS-Cov-2 Inhibitor: A Step Toward Efficient Antiviral Therapy

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**Abstract**
The outbreak of COVID-19 pandemic causing virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) underscores the urgent need for affordable and effective antiviral agents. Natural nucleoside analogues such as cordycepin (3′-deoxyadenosine) have emerged as promising candidates due to their structural similarity to adenosine and broad biological activities. In this study, an integrated *in-silico* approach was employed to evaluate the therapeutic potential of cordycepin against SARS-CoV-2. Molecular docking demonstrated stable binding of cordycepin within the catalytic site of the viral main protease (Mpro), a key enzyme in viral replication, with a predicted binding affinity of -6.3 kcal $mol^{-1}$, indicating a moderate yet biologically relevant interaction consistent with competitive inhibition. Complementary ADMET and drug-likeness analyses revealed favorable physicochemical and pharmacokinetic properties, including optimal molecular weight, balanced hydrogen-bonding profile, high gastrointestinal absorption, absence of P-glycoprotein substrate liability, and non-inhibitory behavior toward major cytochrome P450 isoforms. Cordycepin complied with multiple drug-likeness filters, lacked structural alerts for toxicity, and exhibited a moderate bioavailability score with reasonable synthetic accessibility. Collectively, these computational findings support cordycepin as a promising natural lead compound for anti-SARS-CoV-2 drug development. Nevertheless, experimental validation through enzymatic inhibition assays and *in-vitro* studies is warranted to confirm its efficacy and safety, thereby establishing a rational basis for its advancement into *in-vivo* and preclinical development.
**Keywords**: *Cordycepin, 3′-Deoxyadenosine, SARS-CoV-2, COVID-19, Molecular docking, In silico analysis, Antiviral therapy*

## 1.INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has produced an unprecedented global health and socio-economic burden since its emergence in late 2019. Continued waves, the emergence of variants, and gaps in worldwide vaccine access have kept antiviral therapeutics a central pillar of pandemic response and preparedness (Patil et.al, 2025).

Since its first emergence in late 2019, SARS-CoV-2 has infected hundreds of millions of people worldwide, resulting in significant morbidity, mortality, and long-term health, social, and economic consequences. The virus is a positive-sense single-strand RNA virus of the *Coronaviridae* family; its genome encodes several nonstructural proteins, structural proteins (spike, envelope, membrane, nucleocapsid), and accessory proteins that are essential for entry, replication, assembly, and egress. Key steps in its infection cycle includes binding to host receptors (primarily angiotensin-converting enzyme 2, ACE2), entry mediated by proteases such as TMPRSS2, replication via RNA-dependent RNA polymerase (RdRp), and proteolytic processing of large polyproteins by main protease (Mpro / 3CLpro) and papain-like protease (PLpro). Among these, the RNA-dependent RNA polymerase (RdRp, nsp12) and the main protease (Mpro, 3CLpro) are essential for viral genome replication and polyprotein processing, respectively; inhibition of either enzyme can potently suppress viral replication, making them high-value targets for both de-novo drug design and repurposing efforts (Duan, 2022).

Nucleoside and nucleotide analogues that target RdRp have been particularly successful as broad-spectrum antivirals. Remdesivir and Molnupiravir both targeting viral polymerases through distinct incorporation or mutagenic mechanisms demonstrated that small-molecule modulation of RdRp can translate into clinical benefit, and they set a pharmacological precedent for exploring other nucleoside

analogues against SARS-CoV-2. While vaccines have proven transformative, variants of concern (with mutations in spike protein or elsewhere), vaccine distribution inequities, waning immunity, and breakthrough infections mean that efficacious antiviral therapeutics remain critically important. Still, challenges such as drug resistance, side-effects, cost, and logistical considerations make ongoing search for alternative or complementary treatments essential (Khan et.al, 2021).

**Benefits of Natural Drug-Based Treatments in COVID-19**

Natural products (including small molecules derived from plants, fungi, or other organisms, herbal extracts, and traditional medicines) offer several advantages in the context of emerging viral diseases such as COVID-19:

1. **Rich chemical diversity**: Natural compounds often have complex scaffolds and unique chemical functionalities evolved through natural selection, which can interact with biological targets in ways synthetic libraries may not readily encompass.
2. **Multifunctional / pleiotropic effects**: Beyond direct antiviral activity, many natural compounds exhibit immunomodulatory, anti-inflammatory, antioxidant, and even pro-resolving properties. In COVID-19, where severe disease involves dysregulated immune responses (cytokine storm), lung inflammation, and oxidative damage, compounds that modulate more than one pathway may offer therapeutic benefits. Reviews have identified plant-derived bioactive compounds (flavonoids, terpenoids, alkaloids, polyphenols etc.) that inhibit viral entry, replication, protease activities, or mitigate host inflammation (Al-kuraishy et.al, 2022).
3. **Accessibility, cost, and scalability**: Especially in low- and middle-income regions, natural products or traditional medicines may be more accessible or affordable than novel synthesized drugs. If safety and efficacy are validated, they may help fill gaps where commercial antivirals are scarce (Low et.al, 2023).
4. **Complementary or adjunctive use**: Natural drug-based therapies may serve alongside standard of care to improve symptom relief, reduce disease severity, or reduce progression to severe disease. Some randomized controlled trials of herbal medicine added to conventional COVID-19 therapy have shown improvements in total effective rate, symptom resolution, imaging findings, hospital stay duration, and reduced progression to severe disease, although quality of evidence is still variable (Ang et.al, 2022)

However, there are challenges: natural compounds often have variable potency, bioavailability, metabolic stability, sometimes toxicity, and the need for high-quality clinical trials to establish efficacy and dosing.

**Cordycepin: Its Origin, Mechanisms, and Antiviral Effects**

Cordycepin (3′-deoxyadenosine) is a naturally occurring nucleoside analogue isolated primarily from fungi of the *Cordyceps* genus (notably *Cordyceps militaris* and *Cordyceps sinensis*). Structurally similar to adenosine but lacking a 3′ hydroxyl group on the ribose (Rawat et.al, 2025). Cordycepin (3′-deoxyadenosine), a natural adenosine analogue isolated from Cordyceps species, has a long history of reported antimicrobial, anti-inflammatory and anticancer activities. Mechanistically, cordycepin can act as a chain terminator after phosphorylation to its active triphosphate form, and it has shown antiviral activity across several RNA viruses in preclinical studies. Importantly, multiple recent pharmacological and molecular simulation studies indicate that cordycepin binds to and may inhibit SARS-CoV-2 replication machinery, with some in vitro reports suggesting potent anti-SARS-CoV-2 activity at low micromolar concentrations. These cumulative findings position cordycepin as a promising candidate for further mechanistic and drug-development investigation against COVID-19 (Rabie, 2022).

Its known pharmacological effects include antimicrobial, antitumor, anti-inflammatory, immunomodulatory, and antiviral activities against several viruses. Importantly, recent studies have begun to explore its specific activity against SARS-CoV-2:

In studies of SARS-CoV-2 proteases (e.g. Mpro / 3CLpro) and spike protein mediated entry, computational and lab-based evidence suggest cordycepin may interfere with viral entry pathways or protease activity. For example, assays demonstrated suppression of syncytia formation (which is driven by spike/ACE2 interactions) in the presence of cordycepin (He et.al 2022).

Beyond direct antiviral activity, cordycepin has also been found to reduce expression of certain host factors implicated in COVID-19 pathology, such as ADAM17, which may be relevant to inflammation and tissue damage (He et.al 2022).

Computational approaches including molecular docking, molecular dynamics (MD) simulations, and free-energy calculations have played a crucial role throughout the COVID-19 era, accelerating hit

identification, clarifying binding modes, and prioritizing molecules for in vitro testing. Structure-based virtual screening and MD refinement have been widely used to triage natural products and repurposed drugs against RdRp and Mpro, enabling efficient, cost-effective exploration of molecular interactions before committing resources to biochemical assays (AbouYoussef et.al, 2025).

Despite encouraging preclinical signals, several pharmacological challenges must be addressed for cordycepin to become a viable antiviral: (i) metabolic instability due to rapid deamination by adenosine deaminase (ADA), (ii) efficient intracellular phosphorylation to the active triphosphate form, and (iii) selectivity for viral versus host polymerases to avoid toxicity. Recent medicinal chemistry efforts including ProTide prodrug strategies and structural modification of the nucleoside scaffold aim to overcome metabolic and delivery hurdles and have renewed interest in cordycepin derivatives as drug candidates (Thiraporn et.al, 2025)

Given (a) the mechanistic plausibility of RdRp inhibition by adenosine analogues, (b) experimental reports of cordycepin's antiviral and anti-inflammatory effects, and (c) the demonstrated utility of computational pipelines to prioritize antiviral leads, a focused computational investigation of cordycepin against key SARS-CoV-2 targets is justified. Such an approach can (i) define probable binding modes and interaction hotspots with RdRp and other viral targets (e.g., Mpro, entry cofactors), (ii) estimate relative binding affinities and dynamic stability, (iii) suggest modifications to improve potency and metabolic stability, and (iv) prioritize analogues or prodrug forms for biochemical and cellular testing (Bibi et.al, 2022)

This study therefore undertakes an integrated in-silico analysis of cordycepin and selected derivatives against validated SARS-CoV-2 targets. Using molecular docking, we aim to (1) characterize the structural basis of cordycepin–target interactions, (2) compare cordycepin's predicted binding to that of known nucleoside inhibitors, and (3) identify chemical or prodrug modifications likely to improve antiviral potential and drug-like properties. Results from this computational pipeline are intended to generate testable hypotheses for subsequent in vitro and in vivo evaluation, and to inform rational design of cordycepin-based antivirals for COVID-19 and related RNA viruses (Xu and Zhang, 2023)

## MATERIAL AND METHODS:

### In Silico Analysis

#### Protein Preparation

The crystal structure of the viral protein was retrieved from the Protein Data Bank (PDB). The SARS-CoV-2 main protease (Mpro) (PDB ID: 7BRO) was prepared by adding polar hydrogen atoms, removing water molecules, and assigning Kollman charges using AutoDock Tools. The processed protein structure was then saved in PDBQT format for molecular docking.

#### Ligand Preparation

The canonical SMILES and 3D structure of the bioactive compound cordycepin (PubChem ID: 6303) were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The SDF file was converted into PDB format using Open Babel. Ligand optimization was carried out, and the final structure was saved in PDBQT format using AutoDock Tools for docking studies.

#### Molecular Docking Analysis

Molecular docking was performed using AutoDock Vina (Version 1.5.7). The prepared protein and ligand structures were utilized for docking simulations. The CASTp server was employed to predict the active site residues, and the docking grid was defined accordingly. Docking parameters were set with an exhaustiveness of 8, generating multiple binding poses with varying affinities. The docking results were obtained in PDBQT format, converted to PDB format using Open Babel, and subsequently visualized and analyzed with PyMOL. (O. Trott et.al, 2010)

#### ADMET Analysis

The pharmacokinetic and drug-likeness properties of cordycepin were evaluated using the SwissADME web server (http://www.swissadme.ch/). The analysis included physicochemical parameters, lipophilicity, water solubility, pharmacokinetics, and drug-likeness predictions. Additional toxicity and structural alert assessments were performed using the ADMETlab 2.0 server. The results provided insights into absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles to evaluate the compound's suitability as a potential therapeutic candidate. (Nagamalla et.al, 2021)

## RESULTS

### Molecular Docking Analysis

In the present study, molecular docking was conducted as shown in figure 1. to evaluate the binding interaction between cordycepin and the main protease (Mpro) of SARS-CoV-2, a critical enzyme responsible for viral polyprotein processing and replication. Docking simulations revealed that cordycepin binds to the active site of Mpro with a binding affinity of −6.3 kcal/mol, suggesting a moderate yet potentially significant interaction.

Visual inspection of the docking pose indicated that cordycepin is stabilized within the active site, implying that cordycepin may act as a competitive inhibitor of Mpro. The observed binding affinity indicates a plausible inhibitory potential, warranting further investigation through in-vitro experimental studies.

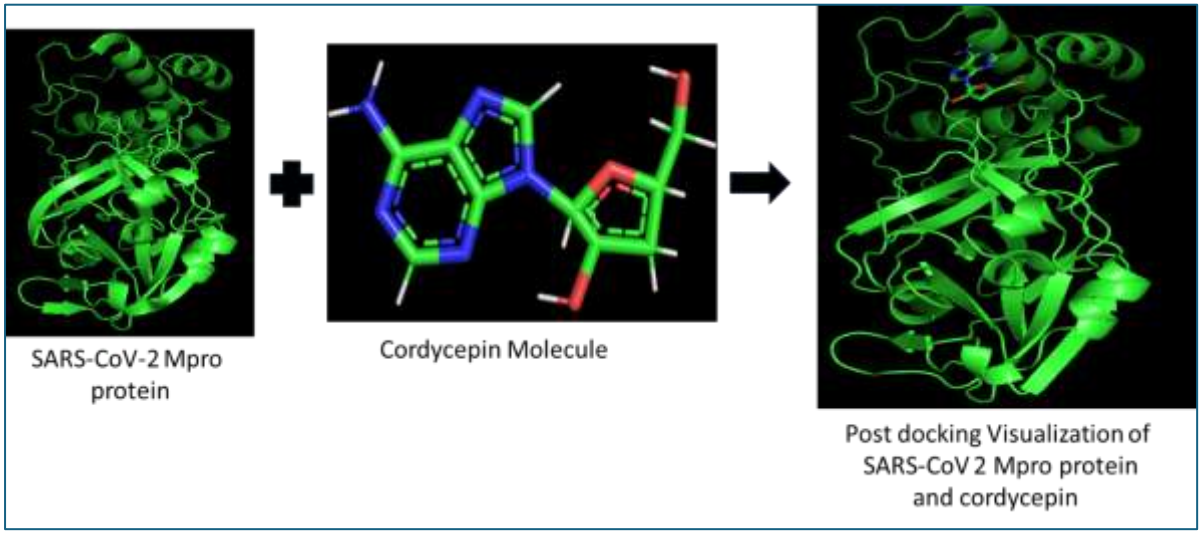


**Figure 1.** Molecular docking of cordycepin with SARS-CoV-2 main protease (Mpro). The receptor protein (left, green ribbon) and the ligand cordycepin (center, stick representation: carbon = green, nitrogen = blue, oxygen = red) were docked to predict binding interactions. The docked complex (right) shows cordycepin positioned within the active site of Mpro.

### ADMET and Drug-Likeness Evaluation

To assess the pharmacokinetic behavior and drug-likeness of cordycepin, an in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile was generated using SwissADME software. The computational predictions indicate favorable characteristics for oral drug development.

- **Physicochemical Properties**

Cordycepin ($C_{10}H_{13}N_5O_3$) possesses a molecular weight of 251.24 g/mol and a topological polar surface area (TPSA) of 119.31 Å$^2$. The compound contains 6 hydrogen bond acceptors and 3 hydrogen bond donors, with only 2 rotatable bonds, suggesting low conformational flexibility. The fraction of $sp^3$-hybridized carbons is 0.50, indicating a balanced mix of aromatic and aliphatic character. These parameters are within the acceptable range for drug-like molecules.

- **Lipophilicity and Solubility**

The consensus Log P value was calculated as −0.85, with individual models (iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT) yielding values ranging from 1.07 to −1.94. These values indicate low lipophilicity, consistent with high aqueous solubility. Water solubility predictions further support this, with Log S values of −1.25 (ESOL), −1.42 (Ali), and −0.40 (SILICOS-IT), corresponding to classifications of "very soluble" to "soluble."

- **Pharmacokinetics**

Cordycepin demonstrated high gastrointestinal (GI) absorption, which is favorable for oral administration. It is predicted not to cross the blood-brain barrier (BBB) and is not a substrate for P-glycoprotein (P-gp), reducing the likelihood of efflux-related bioavailability issues. Additionally, cordycepin is not predicted to inhibit any of the major cytochrome P450 isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), suggesting a low potential for metabolic drug-drug interactions. The predicted skin permeability (Log Kp = −8.27 cm/s) is low, which is consistent with the compound's hydrophilic nature.

- **Drug-Likeness Analysis**

Cordycepin satisfies Lipinski's Rule of Five with no violations, indicating favorable oral bioavailability potential. It also complies with Veber, Egan, and Muegge rules. However, it slightly violates the Ghose filter due to a WLOGP value below −0.4. The bioavailability score is calculated at 0.55, indicating moderate oral bioavailability. Cordycepin received zero alerts for PAINS and Brenk filters, confirming the absence of reactive or problematic substructures. The synthetic accessibility score of 3.67 further suggests that the compound is feasible to synthesize.


**Figure 2.** *In silico ADMET and drug-likeness profile of cordycepin.*

The figure summarizes the physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug-likeness, and medicinal chemistry characteristics of cordycepin. Key physicochemical descriptors include a molecular weight of 251.24 g/mol, TPSA of 119.31 Å², and 3 hydrogen bond donors with 6 acceptors. Cordycepin exhibits high water solubility across ESOL, Ali, and SILICOS-IT models, and displays favorable lipophilicity (consensus Log P = –0.85). Predicted pharmacokinetic parameters suggest high gastrointestinal (GI) absorption, no blood-brain barrier (BBB) permeation, and no inhibition of major cytochrome P450 enzymes. Drug-likeness filters (Lipinski, Veber, Egan, Muegge) are satisfied, with no PAINS or Brenk alerts. The compound is considered synthetically accessible (score = 3.67) and bioavailable (score = 0.55), supporting its potential as an orally active therapeutic agent.

## CONCLUSION

The present study provides in silico evidence supporting the therapeutic potential of cordycepin against SARS-CoV-2 through inhibition of the viral main protease (Mpro), a pivotal enzyme in viral replication. Molecular docking revealed that cordycepin binds stably within the active site of Mpro with a binding affinity of −6.3 kcal/mol, suggesting a moderate but biologically relevant interaction that may enable competitive inhibition of the protease. These findings align with the hypothesis that natural nucleoside analogues can interfere with viral enzymatic activity, thereby impairing replication efficiency.

Complementary ADMET and drug-likeness analyses further strengthen the drug development prospects of cordycepin. The compound demonstrated favorable physicochemical properties, including an optimal molecular weight, balanced hydrogen bonding profile, and low conformational flexibility. Predictions of low lipophilicity alongside high aqueous solubility indicate that cordycepin possesses suitable absorption characteristics. Its pharmacokinetic profile revealed high gastrointestinal absorption, absence of P-gp substrate liability, and non-inhibitory behavior toward major cytochrome P450 isoforms, collectively suggesting a low risk of efflux- or metabolism-mediated drug–drug interactions. Importantly, cordycepin complied with multiple drug-likeness filters, exhibited no structural alerts for toxicity, and displayed a moderate bioavailability score with reasonable synthetic accessibility.

Taken together, these computational results indicate that cordycepin is a promising candidate for further evaluation as an antiviral agent against SARS-CoV-2. While the predicted binding affinity and favorable pharmacokinetic parameters highlight its potential, experimental validation through in vitro enzymatic inhibition assays and subsequent in vivo studies will be essential to confirm its efficacy and pharmacological safety. This study thus lays a rational groundwork for advancing cordycepin into preclinical investigations as a natural lead compound in the development of novel anti-SARS-CoV-2 therapeutics.

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