ISSN:2394-2371
CODEN (USA):IJPTIL

REVIEW PAPER

Bioactive Metabolites of *Cordyceps militaris* with Therapeutic Potential against Covid-19: Review

YashideepThapa*, Sudarshan Singh Lakhawat, Sunil Kumar, Vikram Kumar
Amity Institute of Biotechnology, Amity University Rajasthan, Jaipur-303002, Rajasthan, India
*Corresponding Author: **YashideepThapa**

ABSTRACT

The entomopathogenic fungus Cordyceps militaris is famous in traditional Chinese medicine for its medicinal properties, which are used to fight inflammation, immunomodulatory, cellular, and organ repair, antiviral activities, and other restorative purposes. Advanced research of C. militaris has proven that several compounds from this fungus have active anti-Coronavirus activity and recovery from its effects. Cordyceps has a long history of use as a tonic for the lungs and kidneys, as well as for the treatment of chronic bronchitis, asthma, tuberculosis, and other diseases of the respiratory system. The antiviral activities of cordyceps against Influenza Virus, HIV, Murine leukemia, plant viruses, Epstein-Barr Virus, etc., and anti-tumor activity against gastric carcinoma and EBV have been confirmed in previous studies. Cordycepin, a bioactive compound from cordyceps, is under clinical trials (NCT00709215) and has similar properties to adenosine except that, it does not have a 3 ′ hydroxyl group in ribose moiety and acts as a poly (A) polymerase inhibitor and disconnect prematurely. protein synthesis. Additionally, it is known that the active RARS of the SARS-CoV-2 genome are highly 3'-polyadenylated and lead to the formation of all viral proteins and when cordycepin is unable to activate SARS-CoV-2 RNAs by inhibiting the polyadenylation. proceed further by preventing viral repetition and host duplication. In addition, cordycepin showed strong binding affinity with SARS-CoV-2 spike protein (-145.3) and larger proteases (-180.5) further strengthening the therapeutic potential against COVID-19. Spike proteins and SARS-CoV-2 primary proteases have been identified as potential therapeutic targets and their inhibition may result in delayed viral entry and repetition in the host body. This study aims to discuss how metabolites of C.militaris provide a promising therapeutic potential for COVID-19 treatment given previous studies.

Keywords: - *Cordycepsmilitaris, Coronavirus, spike protein, SARS-CoV-2*

1. INTRODUCTION

The outbreak of highly contagious, mutagenic, novel coronavirus, the causative agent of Severe Acute Respiratory Syndrome has created the SARS-COV-2 epidemic and social and economic disruption worldwide. The WHO reported more than 215,524,007 cases of infection, with 4,489,162 deaths. Covid19 is a potentially fatal disease with mild to severe symptoms ranging from general weakness, headache, dizziness, fever, cough, and dyspnea to severe hypoxia and acute

***CORRESPONDING AUTHOR**
YashideepThapa
B.Tech Bioinformatics Scholar, Amity Institute of Biotechnology, Amity University Rajasthan, Jaipur-303002, Rajasthan, India
E.Mail: yashideep16@gmail.com
Article Published: July-Sept. 2022
CITE THIS ARTICLE AS
Yashideep Thapa, Sudarshan Singh Lakhawat, Sunil Kumar, Vikram Kumar. Bioactive Metabolites of Cordyceps militaris with Therapeutic Potential against Covid-19: Review. Int J Pharm Technol Biotechnol. 2022; 9(3):01-13.

breathing distress syndrome as well as multiple organ failure and long-term side effects. It has raised concerns about health worldwide. Although epidemics of the previous coronavirus SARS-CoV and MERS-CoV have raised awareness of the need for clinical or preventive interventions, to date, no proven effective treatment is available. The ambiguity and the highly mutagenic nature of the virus, make it very difficult to treat for doctors. [1,2]

Cordyceps militaris

Cordyceps militaris naturally grows in more than 3,500 feet [3,500 m] in the Himalayan region of Nepal, Bhutan, India, and Tibet. It can be grown artificially in an environment that provides the conditions for it to yield better and be more productive.

Active Ingredients in Cordyceps Militaris

Cordyceps Polysaccharides[exist only in C. militaris]-

A galactomannan structure with many branches with various connections between nearby monosaccharides [small rings and helical structures] [12].

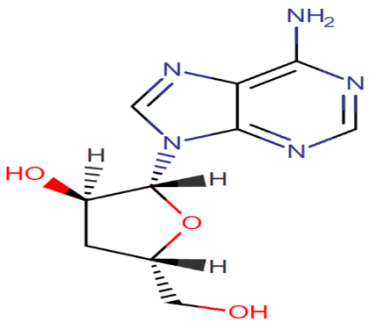
Cordyceps polysaccharides contains a wide variety of organisms that include: Immunomodulation, Anti-oxidant, Anti-tumor, Eliminate inflammation, Hypoglycemic effects, Hypocholesterolemic effects A large amount of experimental evidence has proved that Anticancer effects of cordyceps polysaccharides have been widely used in medical practice. It arises from the development of antibodies and metastasis rather than cytocidal effects. Cordyceps polysaccharides improve the immune system by activating immune and cellular immune systems and promoting cytokine production. [16]. Cordyceps polysaccharides can help diabetic patients by reducing their symptoms and complications. It can stimulate islet cells to release insulin, protect and repair islet cells, increase insulin levels in blood serum and speed up hepatic glucose metabolism (improves glucose oxidation) to directly lower blood sugar levels. [10] [31] Several studies in mice have shown that Cordyceps polysaccharides can improve immune response, mammary gland, thymus index, and phagocytic activity of monocyte-macrophages and lower blood sugar. [31]

Cordycepin(3'-Deoxyadenosine) [exist only in Cordyceps militaris]

It is Nucleoside, Water-insoluble organic compound and structural analog of the nucleoside adenosine Cordycepin was first isolated from C. militaris in 1950. Based on in vitro and in vivo studies conducted to date, this combination has been confirmed to exhibit the following functions: immunostimulating, anti-inflammatory, antiviral, antitumor, ergogenic, hypolipidemic, hypoglycemic and steroidogenesis, spermatogenesis, and antioxidant activity has been described in scientific studies based on the biological mechanisms of polysaccharide compounds contained in C-fruit bodies.

Studies have shown that low concentration of cordycepin can effectively block the oxidation reaction of free radicals. Studies in mice have shown that the immunostimulatory activity of cordycepin results

in its ability to induce immune responses to cellular and humoral infections. The study revealed an increase in the concentration of interleukins IL-4, IL-10, and IL-12, as well as Th1 and Th2 cytokines, decreased IL-2 concentration, and altered β (TGF-β) growth, and increased of T. lymphocyte levels (CD4 and CD8).



It is one of the most important types of active biological metabolites.

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Cordycepin is also a 2/3 phase third-line treatment for patients with refractory acute lymphoblastic leukemia [ALL] expressing enzyme terminal deoxynucleotidyltransferase [TDT] (http://www.ClinicalTrials.gov certified by OncoVista, OncoVista. Inc., 2009).

It has various advantages:

• Having antimicrobial, anticancer, antimetastatic, insecticidal, and immunomodulatory properties;

• Prevent cell proliferation;

• Stimulation of cellular apoptosis;

• Reducing platelet aggregation;

• Reducing invasion / cell migration;

• Prevention of inflammation;

• Reducing polyadenylation of mRNA;

• Reducing plant growth and development;

• Antiretroviral activities against Influenza Virus, HIV, Murine leukemia, plant viruses, Epstein-Barr Virus [10]

• Like cordyceps polysaccharides, cordycepin also has anti-tumor but interacts directly with Tumor DNA and RNA and has a positive effect on tumor inhibition.

• In experimental tuberculosis studies, Cordycepin has been shown to inhibit the growth of many types of human cancer cells, including lung, colon, skin, and liver cancers.

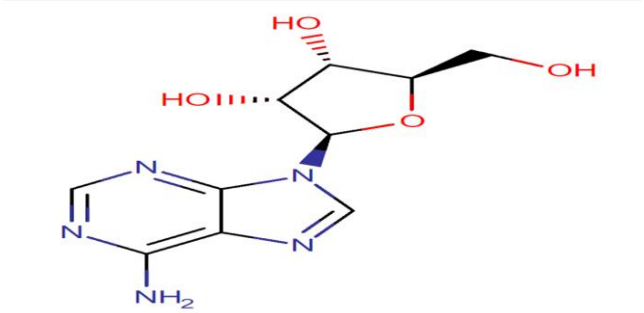
Cordycepin may also reverse the side effects associated with multiple cancer treatments.

Ex: Leukopenia [decreased WBC, decreased immune response leading to increased risk of infection]

Interestingly, Cordycepin reversed leukopenia and helped alleviate some of the problems associated with certain cancer treatments [17]. In addition, it has shown cytotoxicity against leukemic cell lines in vitro, promotes cell division, promotes lymphocyte transformation, and enhances the phagocytic function of the body's macrophage system thereby enhancing the immune response. [1] [6] [11] [12]

Adenosine

The adenosine contained in the Cordycepsmilitaris combines with phosphates to produce energy-producing molecules, such as AMP [ADENOSINE MONOPHOSPHATE] and ATP [ADENOSINE TRIPHOSPHATE]. [9]



Adenosine is produced from damaged lung tissue and plays a key role in regulating inflammation and regeneration of tissues. It acts as an anti-inflammatory molecule by suppressing the production of cytokine storms, preventing damage to the organ, and repairing damaged tissue in serious lung diseases such as pneumonia. [18]

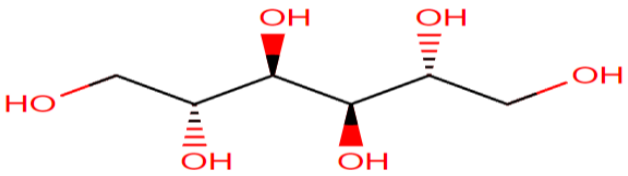
The American clinic and doctors use adenosine and its derivatives for a variety of medical purposes. Taken under the tongue, swallowed, or injected, other therapeutic uses of AMP and ATP include treatment:

• Herpes zoster infection (shingles); High pulmonary hypertension; Multiple organ failure; Cystic fibrosis; Lung and / or skin cancer; Cachexia and cancer-related weight loss; Arrhythmia; Nervous pain; Varicose veins; Multiple sclerosis; Tendonitis; Cold sores and genital herpes; Poor Circulation etc.

D-Mannitol / Cordycepic Acid

- Carbohydrate
- Classified as polyhydric alcohol (polyol).
- D-Mannitol from C. militaris is commonly referred to as cordycepic acid.

It is used by C. militaris as a carbohydrate reserve and as a transporter of other compounds in several processes like osmoregulation and control of metabolic pathways. Due to the osmotic activity of D-Mannitol, it can be used in clinical practice as a diuretic and anti-edematous drug.



D-Mannitol is an osmotic diuretic compound that makes metabolically inert to people and occurs evidently in sugar or sugary alcohol from fruits and vegetables. Mannitol increases the blood plasma osmolality, main to improved fluid float from the tissues, which includes the mind and cerebrospinal fluid, into the valuable fluid and plasma. As a result, cerebral edema, high intracranial stress, and cerebrospinal fluid quantity and pressure may be decreased. Mannitol can be used to improve diuresis earlier than it is recognized with irreversible renal failure; merchandising of urine excretion; as an Antiglaucoma agent; and as aresource in diagnosing kidney function.

On October 30, 2020, mannitol become permitted through the FDA as an extra dietary treatment to manipulate lung symptoms related to cystic fibrosis in adult patients and is currently advertised as a emblem under BRONCHITOL® via ChiesiAmericaInc.eight

Mannitol, as a purposeful polyol with fantastic houses, has been broadly used within the pharmaceutical and food industries.

Researchers have discovered that it does have effects on:

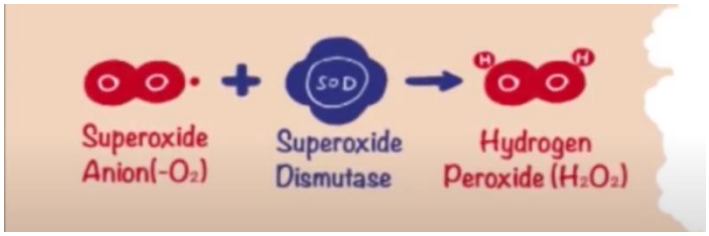
- Diuretic, enhancing plasma osmotic pressure, Anti-loose radical, lowerldl cholesterol and triglyceride ranges and prevent thrombosis (indicated by way of reduced Ca + concentration) [1] [3].

SOD [Superoxide Dimutase]

It eliminates superoxide-free radicals in the body. It has the function of:

- o Fatigue resistance
- o Anti-aging
- o Beauty maintenance
- o Immunity enhancement
- o Digestive and nerve system improvement

Furthermore, it has been experimentally proven that Cordyceps itself can improve the absorption of the SOD and strengthen the effect of SOD.



According to chemical analysis, Cordyceps also contains Crude fats, Proteins, Fiber, Carbohydrates and series of vitamins. Animal research and scientific research statistics show that Cordyceps has a protecting impact on liver patients. Improves organic cell immunological characteristic, restores HBeAg-superb to HBeAg-poor, improves liver function, prevents hepatic fibrosis. The effects on the kidneys, coronary heart, and respiration device were shown to be widespread. Numerous studies have found that Cordyceps will increase antioxidants in older mice, assisting to improve reminiscence and patience. One study discovered that rats given cordyceps lived some months longer than placebo-handled mice. One look at found that cordyceps prolongs the lifestyles of flies, in addition supporting the notion that they've anti-growing older advantages. Cordyceps will increase ATP production. this will enhance the body's oxygen intake. Recent studies shows that cordyceps has an anti-rejection impact in an experimental observe of organ transplants.

Ergosterol

The antitumor compound became purified from the extraction of n-hexane by synthetic produced organism C. militaris became also recognized as ergosterol peroxide

(fiveα, 8α −epidioxy− 24 (R) −methylcholesta− 6,22 −dien− threeβ− o1, C28H44O3) (5α, 8α−epidioxy− 24 (R) thmethylcholesta− threeβ− 1β− 6,22, C28H44O) specifically in Spectroscopic approach of 1Hand13C − NMR1Hand13C − NMR. Ergosterol comes in two forms, free ergosterol,

and esterified ergosterol, which have extraordinary frame capabilities. Simultaneous management of loose and esterified ergosterol with a gradient reversed-phase high-performance liquid chromatography (HPLC) approach. Checks for cell function and inhibition of nitric oxide (NO) production of Lipopolysaccharide (LPS) initiated BV2 microglial cells, which had been extracted from the solvent of Cordycepsmilitarisstroma powder. [15]

Chemical evaluation of the ethyl acetate fraction has resulted in ergosterol concentrations beneath the fraction of CE3. BV2 cells confirmed no cytotoxic consequences when dealt with with a fraction of ethyl acetate and a small fraction of CE3 at a attention of 0.1 µg / ml-a hundred µg / ml in comparison to controls. At 10 µg / ml, element ethyl acetate and a small fraction of CE3 had a high reduction of forty eight.zero% and forty four.7% of nitric oxide manufacturing, respectively. the main compound in subfraction CE3 was ergosterol, diagnosed by means of the GCMS and purity tested by way of HPLC. The reduction in nitric oxide in LPS brought on by BV2 cells become nearly threefold in comparison with commercially to be had ergosterol. [14] [15]

Whilst the antitumor pastime of ergosterol peroxide was measured against tumor cellular 3 traces from Korean cancer sufferers, it showed the maximum strong interest in opposition to SNU-l belly most cancers cellular line three days after remedy. 50% inhibitory concentrations (IC50) (IC50) of ergosterol peroxide 6 days after treatment had been 75.eightµg / ml75.8µg / ml of human gastrointestinal line of SNU-1, 39.7µg / ml39. 7µg / ml in human SNU-ml colorectal C4 tumor cellular line and 32.7µg / ml32.7µg / ml hepatoma cellular line SNU-354. [7]

RESULT and DISCUSSION

Cordycepin can selectively inhibit the formation of messenger RNA polynucleotide A chains

Cordycepin can be phosphorylated to generate 3’- deoxytriphosphateadenosine, this can interact with RNA polymerase to stop the synthesis of polyadenylated RNA strands, which is vital practice for constraining RNA viruses. The coronavirus is a positive, single-stranded RNA virus with a polyadenylic acid tail, which is similar to poliovirus. Experiments have revealed that its reproduction can be inhibited by cordycepin. Cordycepin inhibits virus replication and synthesis.

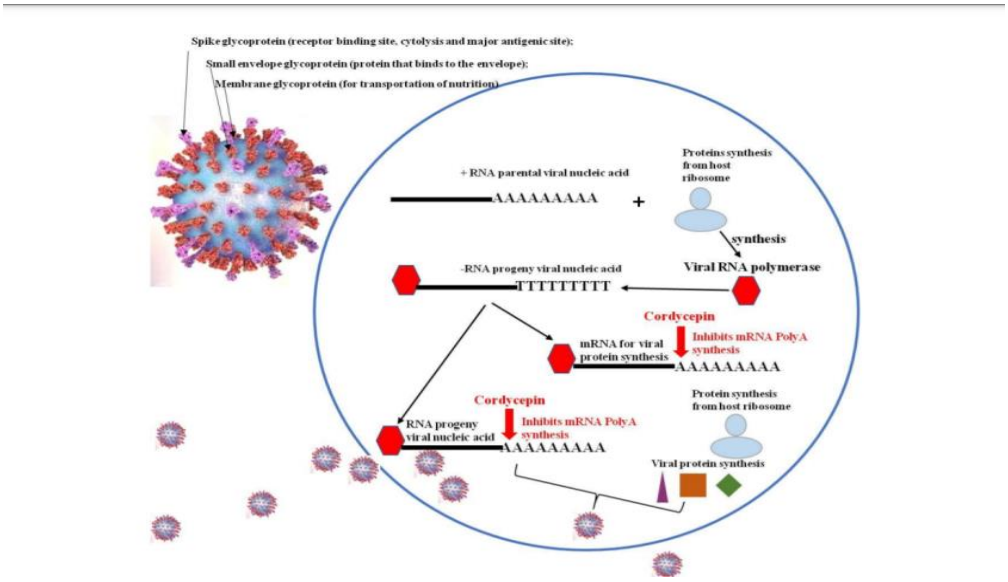


Figure1. "Coronavirus Covid-19 reproduction and how cordycepin may inhibit the poly-A tail formation as a mechanism to block Covid-19 virus synthesis." [5]

Cordycepsmilitaris enriches the immune cell function of lymphocytes and monocytes

Studies have shown that cordyceps can promote the proliferation and production of lymphocytes T and B. Cordycepin accelerates T lymphocytes activity, regulates T cell activity, and boosts the release of active body lymphokines: interleukins, interferon, and others. Cordycepin directly stimulates the proliferative response in B lymphocytes or increases and regulates the response of B lymphocytes. It also stimulates the production of fer interferon (IFN-γ), which is highly effective as an antiviral with broad-spectrum antibodies, the development and proliferation of B-lymphocytes, and the strengthening of resistance to bacteria, viruses, and other viruses. [5]

Cordycepin improves respiratory tract inflammation, as an adenosine receptor agonist

As an A3 adenosine receptor agonist, Cordycepin attains its anti-inflammatory effects by restricting the production of pro-inflammatory cytokines. "Studies have revealed that cordycepin inhibits the production of NO and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) produced by LPS in macrophages from animals. Cordycepin increased the expression of the anti-inflammatory interleukin-10 (IL-10) in human mononuclear cells, which plays a role in regulating inflammation. Cordycepin inhibited NF-κB activation, thereby reducing tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-12, and macrophage inflammatory protein -1α (MIP-1α). "Cordycepinenhanced the expression of MIP-2, suggesting the impression of preventing autoimmune inflammation." [5]

Cordyceps prevents viral entry into the host

Molecular interaction simulations between potent antiviral compounds, cordycepin, and SARS-CoV-2 target proteins were studied by using MD 2010.4.0 software for Windows (Bitencourt-Ferreira & De

Azevedo, 2019; Kusumaningrum et al., 2014). The post docking protein-ligand complex along with chemical interaction was further analyzed and visualized by Chimera software. [19] [20]

SARS-CoV-2 utilizes a spike glycoprotein trimer for recognition and binding to the host cell surface receptor angiotensin-converting enzyme 2 (ACE2) glycoprotein and facilitates targeting and entry into the host cell. Spike proteins on Coronavirus surface are often targeted as immunogens for vaccines to generate neutralizing antibodies and are frequently targeted for inhibition by small molecules that might block host receptor binding and/or membrane fusion.[28] The molecular interaction study exposed that cordycepinvigorously bonds with the SARS-CoV-2 and has a high binding affinity (-145.3). RBD domain of spike protein. Cordycepin has shown chemical interactions (H-bond) in RBD domain-human ACE2 interface with Asn33, His34, and Lys353.[29] It is worth mentioning that all these amino acids are localized in the interface region of spike glycoprotein and host receptors that ultimately facilitate receptor-mediated endocytosis during primary infection. In a recent study, it has been reported that pan-coronavirus fusion inhibitor (EK1C4), targeting spike protein successfully restricted viral entry into the host body in many coronaviruses such as SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43, and SARS-CoV. [24]

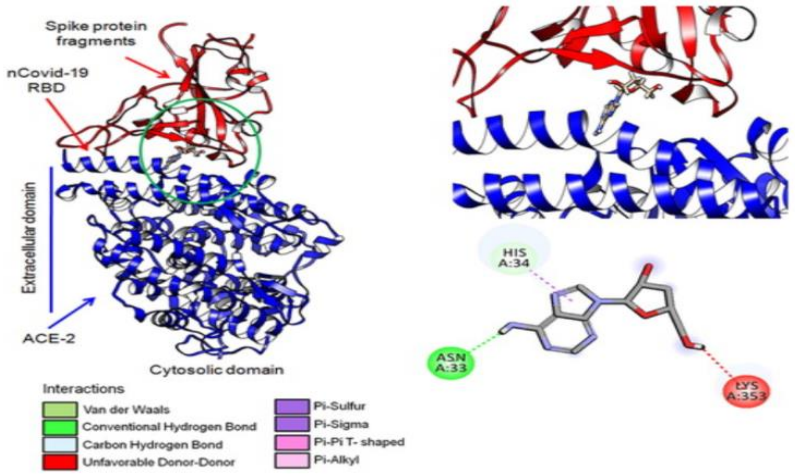


Figure2. “Docking structure and chemical interactions of cordycepin along with ligand atoms and interacting amino acids in the binding sites of the SARS-CoV-2 spike protein RBD.” [21]

Cordyceps in cleavage of the functional viral polyproteins

Cordyceps in cleavage of the functional viral polyproteins an interesting and additional drug target in coronavirus species is the ~306 amino acid long main protease (Mpro, 3CLpro).[23] Mpro is essential for processing the polyproteins that led to the proteolytic activation of the viral functional proteins in SARS-CoV-2. An in silico analysis exposed that the cordycepin bind robustly (interaction score: −180.5) with Mpro. The Mpro active site amino acids such as Thr26, Gly143, Cys145, Ser144,

Leu141, His172, Phe140, Glu166, His163, and His164 play a major role during chemical interactions with cordycepin, thus can be used to restraint the spread of disease. [1][23]

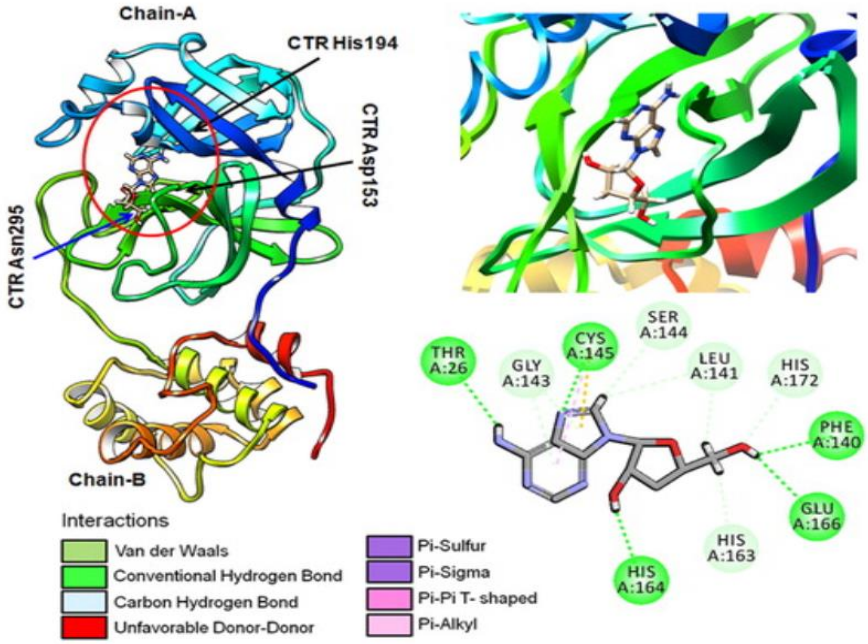


Figure3: "Docking structure and chemical interactions of cordycepin along with ligand atoms and interacting amino acids in the binding sites of Mpro" [1][21]

Cordycepin mediated biological response for SARS-CoV-2 RNA degradation

Polyadenylation is a crucial process mutual among all viruses for increasing the half-life of the polyadenylated transcripts by protecting the RNA from degradation by the exonucleases. Polyadenylation at the 3′ end in COVID-19 plays a major role in pathogenesis and viral multiplication.[22] Cordycepin possesses structural similarity with adenosine except that; it lacks a 3′ hydroxyl group in its ribose moiety, due to this some enzymes fail to discriminate between the two. This asserts that it can participate in certain biochemical reactions including poly(A) polymerase inhibition, shortening of poly(A) tails, destabilization of mRNAs, purine biosynthesis inhibition, and also resulting in premature termination of protein synthesis.[23]

Several researchers have reported that cordycepin possesses antiviral activity against several viruses including influenza virus, human immunodeficiency virus, murine leukemia virus, plant viruses, and Epstein-Barr virus. Cordyceps militaris has been used for making lung and kidney tonic, and for the treatment of continual bronchitis, bronchial asthma, tuberculosis, and other illnesses and disorders of the respiratory system in ancient medicine.

The non-structural protein 13 (nsp13) helicase is a promising target for drug development against COVID-19.

A unique collection of nucleoside analogs was screened as anti SARS-CoV-2 helicase protein. [32] A molecular docking experiment was conducted between Cordycepin and Pritelivir (ligand- SARS-COV-2 helicase protein) to depict binding affinity, protein's binding site's conformational stability, flexibility, and interaction with the ligands. Based on docking scores, Significant nucleoside ligands were selected for pharmacokinetic analysis. [33] Nominated ligands (cordycepin and pritelivir) expressed exceptional pharmacokinetics and were well stabilized at the proteins' binding site all through the MD simulation.

A similar binding free strength analysis was finished for determination of the binding characteristics of ligands with Nsp13 the usage of MM-PBSA and MM-GBSA. Free energy calculation through MM-PBSA and MM-GBSA evaluation suggests that pritelivir can work as feasible therapeutics for effective drug advancement towards SARS-CoV-2 Nsp13 helicase, doubtlessly arresting the SARS-CoV-2 replication.[30]

CONCLUSION

Thus, based on strong molecular interactions, binding affinity, and pharmacokinetic analysis between compounds of Cordyceps militaris and ligands of SARS-CoV-2 spike proteins, proteases; suggesting a higher potential of cordyceps to exhibit therapeutic effects against Covid-19 as it participates in the process of inhibition of viral entry, replication and synthesis; in addition to reported polyadenylation inhibition. Moreover, the remarkable clinical benefits from Cordycepsmilitaris include protective action on hepatic, renal, cardiovascular, respiratory, nervous, digestive, immunological systems, besides having anti-cancer, anti-oxidant, anti-inflammatory, and anti-microbial activities also support the study most times these tissues are affected during the late phase of infection.

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