

INTRODUCTION





- *Cordyceps militaris* is a species of <u>fungus</u> in the family <u>Clavicipitaceae</u>, and the <u>type species</u> of the genus <u>Cordyceps</u>.
- The name Cordyceps has been derived from two Latin words, i.e., cord and ceps meaning club and head, respectively. Cordyceps militaris belongs to the phylum Ascomycota classified in the order hypocreales, as spores are produced internally inside a sac, called ascus (Wang et al. 2008).
- Main constituent of the extract derived from this fungus comprises a novel biometabolite called as Cordycepin (3'deoxyadenosine) which has a very potent anti-cancer, anti-oxidant and anti-inflammatory activities.
- The current review discusses about the broad spectrum potential of Cordycepin including biological and pharmacological actions in immunological, hepatic, renal, cardiovascular systems as well as an anti-cancer agent. The article also reviews the current efforts to delineate the mechanism of action of Cordycepin in various bio- molecular processes.
- The study will certainly draw the attention of scientific community to improve the bioactivity and production of Cordycepin for its commercial use in pharmacological and medical field.





- The constituents of medicinal mushroom *Cordyceps militaris*, especially the anti-cancer agent cordycepin (3'-deoxyadenosine), are expected to play evolutionary roles in the pharmacognosy sector in future.
- Over two-third of cancer-related deaths could be prevented or reduced by modifying our diet with mushrooms, as they contain anti-oxidants (Borchers et al. 2004; Zaidman et al. 2005). Cordyceps have a history of medicinal use spanning millennia in parts of Asia (Gu et al. 2007).
- It is an entomopathogenic fungus having an annual appearance which often grows parasitically on lepidopteron larvae and pupae of insects and spiders. It normally inhabits on the surface of insects pupae in winters and leading to the formation of fruiting body in summers justifying its name as "winter-worm summer-grass".
- An entomopathogenic fungus, Cordyceps sp. has been known to have numerous pharmacological and therapeutic implications, especially, in terms of human health making it a suitable candidate for ethnopharmacological use.



HISTORY





- Cordyceps has been found mainly in North America, Europe and Asia (Mains 1958; Winkler 2010; Panda and Swain 2011).
- In India, it is prominently found in subalpine regions of grassy lands of Himalayas commonly known as "Keera Ghas". Recently it has been reported from Sutol and Kanol villages of Chamoli district of Uttarakhand (Singh et al. 2010).
- The ethnopharmacological use of Cordyceps sinensis has been reported from western Nepal for the cure of different diseases like diarrhea, headache, cough, rheumatism, liver disease, etc. This herb is also referred as "Himalayan Viagra" or "Himalayan Gold" due to its broad clinical and commercial value (Devkota 2006).
- Cordyceps requires specific set of conditions for its growth and has small size; therefore, the large-scale collection of this mushroom is a daunting task.
- The species has been used as medicine in the East for decades, but has only been cultivated since the 1980s in asia.

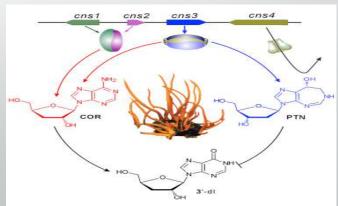
MEDICINAL VALUES



- There have been a variety of pharmacologically active compounds (e.g., Cordycepin) reported from Cordyceps sp. Cordycepin has received much attention due to its broad-spectrum biological activity. It is known to interfere with various biochemical and molecular processes including purine biosynthesis, DNA/RNA synthesis and mTOR (mammalian target of rapamycin) signaling transduction.
- Cordyceps has been included as one of the growing numbers of fungal traditional Chinese medicine (FTCM) used as cures for modern diseases with many products available commercially.
- Cordyceps and its product have remarkable clinical health effects including action on hepatic, renal, cardiovascular, respiratory, nervous, sexual, immunological systems, besides having anti-cancer, anti-oxidant, anti-inflammatory and anti-microbial activities.

PROCESS OF CORDYCEPIN BIOSYNTHESIS







- In Cordyceps, there occurs a wide range of nutritionally important components including various types of essential amino acids, vitamins like B1, B2, B12 and K, different kinds of carbohydrates such as monosaccharide, oligosaccharides and various medicinally important polysaccharides, proteins, sterols, nucleosides, and other trace elements.
- In the fruiting body and in the corpus of C. militaris, the reported total free amino acid content is 69.32 and 14.03 mg/g, respectively. The fruiting body harbors many abundant amino acids such as **lysine**, **glutamic acid**, **proline and threonine** as well.
- The fruiting body is also rich in unsaturated fatty acids (e.g., **linoleic acid**), which comprises of about 70 % of the total fatty acids. There are differences in **adenosine** (0.18 and 0.06 %) and **Cordycepin** (0.97 and 0.36 %) contents between the fruiting body and the corpus, respectively.

$$H_2N$$
 OH H_3C OH H_3C

LYSINE

GLUTAMIC ACID

PROLINE

THREONINE

BIO-METABOLITES ISOLATED FROM CORDYCEP



- Cordyceps, especially its extract has been known to contain many biologically active compounds like Cordycepin, cordycepic acid, adenosine, exo-polysaccharides, vitamins, enzymes etc.
- Out of these, Cordycepin, i.e.,3'-deoxyadenosine isolated from ascomycetes fungus C. militaris, is the main active constituent which is most widely studied for its medicinal value having a broad spectrum biological activity (Cunningham et al. 1950).

BIOACTIVE COMPOUND ISOLATED FROM CORDYCEPS MITITARIS





S. no	Bioactive compounds	References
1	Cordycepin	Cunningham et al. (1950)
2	Cordycepic acid	Chatterjee et al. (1957)
3	N-acetylgalactosamine	Kawaguchi et al. (1986)
4	Adenosine	Guo et al. (1998)
5	Ergosterol and ergosteryl esters	Yuan et al. (2007)
6	Bioxanthracenes	Isaka et al. (2001)
7	Hypoxanthine	Huang et al. (2003)
8	Acid deoxyribonuclease	Ye et al. (2004)
9	Polysaccharide and exopolysaccharide	Yu et al. (2007, 2009), Xiao et al. (2010), Yan et al. (2010)
10	Chitinase	Lee and Min (2003)
11	Macrolides $(C_{10}H_{14}O_4)$	Rukachaisirikul et al. (2004)
12	Cicadapeptins and myriocin	Krasnoff et al. (2005)
13	Superoxide dismutase	Wanga et al. (2005)
14	Protease	Hattori et al. (2005)
15	Naphthaquinone	Unagul et al. (2005)
16	Cordyheptapeptide	Rukachaisirikul et al. (2006)
17	Dipicolinic acid	Watanabe et al. (2006)
18	Fibrynolytical enzyme	Kim et al. (2006)
19	Lectin	Jung et al. (2007)
20	Cordymin	Wonga et al. (2011)

HEALTH BENEFITS OF CORDYCEPS MILITARIS





Boost energy level and immune system



Prevents respiratory distress and weakness



• Aids in prevention of cancer



Provides relief from sexual dysfunction



Helps to rejuvenate skin and reduces age spots



Helps to prevent arrhythmia and heart disorders



Helps to detoxify body and improve kidney health



Beneficial in regulating cholesterol levels in body

BENEFITS



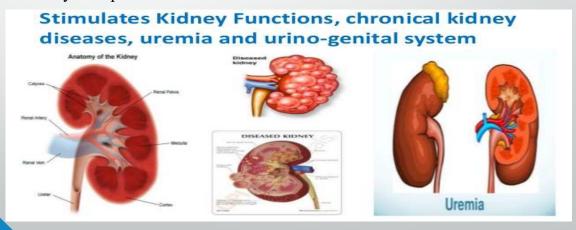
- Athletic performance Several studies have shown that taking cordyceps or a combination of cordyceps and roseroot improve endurance in trained male cyclists.
- Kidney injury caused by certain antibiotics (aminoglycoside nephrotoxicity) Early research shows that using cordyceps with the drug amikacin might reduce kidney damage caused by the drug in older people.
- **Asthma** Early research suggests that taking cordyceps alone can reduce asthma symptoms in adults.
- Long-term kidney disease (chronic kidney disease or CKD). Early research shows that taking cordyceps along with standard therapy for chronic kidney disease may improve kidney function.
 - Kidney damage caused by contrast dyes (contrast induced nephropathy).

Some early research shows that taking cordyceps while undergoing an exam using contrast dye reduces the chance of kidney damage caused by the dye.

• Kidney damage caused by the drug cyclosporine There is early evidence that taking cordyceps with cyclosporine can reduce kidney damage caused by cyclosporine in people with kidney transplants.



- Swelling (inflammation) of the liver caused by the hepatitis B virus (hepatitis B). Early evidence shows that taking cordyceps by mouth might improve liver function in people with hepatitis B.
- **Kidney transplant.** Early research shows that taking cordyceps with low-dose cyclosporine can improve 1-year survival, prevent transplant rejection, and reduce the risk of infection similar to taking standard dose cyclosporine in people who received a kidney transplant. Also, cordyceps seems to improve kidney transplant survival, kidney transplant rejection, and infection similar to azathioprine when taken with medications to prevent organ rejection. It might also reduce the risk of long-term impaired kidney function called chronic allograft nephropathy, which is the leading cause of kidney transplant failure.





Sexual problems that prevent satisfaction during sexual activity. Early research shows that taking a specific cordyceps product daily for 40 days might improve sex drive in people with low sex drive.

- Anemia.
- Antifungal
- Breathing disorders.
- Anti-Inflammatory Properties Inhibition of cell proliferation
- Lung infections (Bronchitis). Frequent urination at night
- Anti-tumor
- Cough
- Anti-metastatic
- Decreasing fatigue.

- Neuroprotective and therapeutic Liver disorders
 - effect
- Dizziness

- Fertility enhancer
- Heart arrhythmias
- Anti cholesterol agent
- High cholesterol.

- Promoting longevity.
- Ringing in the ears
- Weakness.

MAJOR PHARMACOLOGICAL FUNCTIONS OF CORDYCEPS



Hepatic function

Stimulation of energy metabolism

Activation of Kupffer cell function: water-soluble fraction

Reduction of post-hepatitic cirrhosis: unknown

Renal function

Reduction in aminoglycoside antibiotic induced nephrotoxicity

Reduction in hematuria and proteinuria in experimental IgA nephropathy (IgA N): low MW sterols (CS-HI-A)

Endocrine and steroid system

Stimulation of corticosteroid production in animals: unknown

Stimulation of corticosterone production by cultured rat adrenal cells: water-soluble fraction

Cardiovascular function

Inhibition of platelet aggregation: adenosine and other related nucleosides

Reduction in aconitine, BaCl., and ouabain-induced arrhythmia: low MW metabolites

Anticancer activities

Sterols and their glucosides

Low MW metabolites other than cordycepin

Modified nucleosides

Antitumor function via immunopotentiation and cytokine production: polysaccharides

Immunomodulation

Immunopotentiation: polysaccharides

Immunosuppression: cyclosporine-like metabolites and others hypoglycemic activity in STZ- induced diabetes polysaccharides

Erythropoiesis and hemopoiesis

Proliferation of fibroblast observed in vivo and in vitro

Platelet hemopoiesis

Ref:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121254/

IMMUNE SYSTEM





- The **immune system** is a host defense system comprising many biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic_worms and distinguish them from the organism's own healthy tissue.
- Cordyceps is a traditional Chinese herb that produces various biopharmaceutical effects, including immune-enhancing effects. Cordyceps extract confirm its efficacy in enhancing the immune system and to evaluate its safety in healthy adults.
- Cordycepin including biological and pharmacological actions in immunological, hepatic, renal, cardiovascular systems as well as an anti-cancer agent.



ANTICANCER ACTIVITY



- Cancer is the second leading cause of disease-related mortality throughout the world (<u>Xiao and Zhong 2007</u>). However, related therapy strategies are still limited to surgery, radiotherapy, and chemotherapy. Due to the limitations of surgery and radiotherapy and the side effects of chemotherapy, there is increasing interest in developing antitumor drugs from natural products. Studies have shown that cordyceps has antitumor activity in various cancers through several pathways. Both natural and cultured cordyceps have demonstrated antitumor effects (<u>Feng. Yang.</u>, and <u>Li 2008</u>; <u>Zhou et al. 2009a</u>).
- Cordycepin is an anticancer compound and has potential for development as a therapeutic agent and functional food.
- Cordyceps militaris is a well-known medicinal mushroom. It is non-toxic and has clinical health benefits including cancer inhibition.
- The *C. militaris* concentrate and cordycepin exhibited significant anticancer effects through their ability to induce apoptosis in breast cancer cells.
- Cordyceps effectively and specifically inhibited cell proliferation in breast cancer cells , leukemia cells, and gastric cancer cells



Cordyceps and Cancer

🛅 January 9th, 2011 🧸 admin



Researchers from the University of Nottingham have found that a rare, wild mushroom called cordyceps is an effective treatment for cancer. Commonly used in Chinese medicine, the cordyceps fungi inhibits the growth, division, and proliferation of cancer cells in the body.

Cordyceps was originally formulated into a cancer drug called cordycepin back in the 1950s. Though the drug version was ultimately found to be ineffective because of rapid degradation inside the body once it was administered, the active components from the mushroom continue to be effective cancer fighters.

Depending upon dosage levels, cordyceps mushroom extracts directly impact the process of cell protein development, impeding the production of the mRNA molecules that create them. At high doses, cordyceps inhibits

protein development directly, essentially eliminating the ability of cancer cells to function and survive.

Since the study focused on the pharmaceutical drug formulation derived from cordyceps, called cordycepin, lead scientist Dr. Cornelia de Moor and her team specifically sought ways to improve the effectiveness of that particular drug. Their only solution was to suggest giving another drug alongside cordycepin in order to prevent it from degrading in the body. The team warned that the other drug causes serious side effects which may discourage its use.

Though the research focused primarily on cordycepin, it ultimately revealed the powerful effects of cordyceps in preventing and treating cancer. The study is set to be published in the Journal of Biological Chemistry and its authors hope that the findings will spark further research into the potential uses for cordyceps as a cancer treatment.

by Mike Adams, the Health Ranger

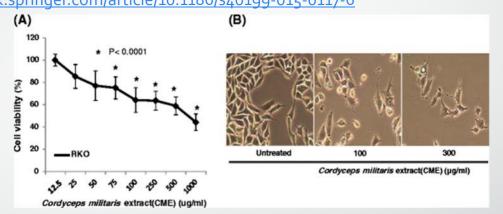
• http://www.vitalitymushrooms.com/2 011/01/09/cordyceps-and-cancer/



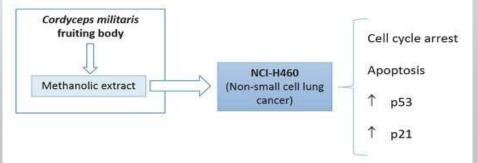
- The fungus *Cordyceps militaris* has been used as a herbal tonic in traditional Chinese medicine for > 300 years. Numerous studies have recently reported that the anticancer activity of *Cordyceps*, including the inhibition of B16 melanoma, leukemia, thyroid carcinoma, hepatocellular carcinoma, and renal cancer cells, is due to cordycepin, a crucial bioactive compound produced by *C. militaris*.
- However, Tumor inhibition by cordycepin is attenuated by adenosine deaminase catalysis in vivo.
- *C. militaris* might be able to inhibit cancer growth through regulation of p85/AKT-dependent or GSK3 β -related caspase-3-dependent apoptosis. https://www.hindawi.com/journals/ecam/2017/8474703/.
- Anti-cancer effect of Cordyceps militaris in human colorectal carcinoma RKO cells via cell cycle arrest and mitochondrial apoptosishttps://www.researchgate.net/publication/280030218 Anti-cancer effect of Cordyceps militaris in human colorectal carcinoma RKO cells via cell cycle arrest and mitochondrial apoptosis



Anti-cancer effect of *Cordyceps militaris* in human colorectal carcinoma RKO cells via cell cycle arrest and mitochondrial apoptosis. https://link.springer.com/article/10.1186/s40199-015-0117-6



• Cordyceps militaris (L.) Link Fruiting Body Reduces the Growth of a Non-Small Cell Lung Cancer Cell Line by Increasing Cellular Levels of p53 and p21.https://www.mdpi.com/1420-3049/20/8/13927







- Human immunodeficiency virus (HIV) is the virus that causes AIDS. When a person becomes infected with HIV, the virus attacks and weakens the immune system.
- Cordycepin analogues of 2',5'-oligoadenylate inhibit human immunodeficiency virus infection via inhibition of reverse transcriptase.
- In Vitro Anti-HIV-1 Activity of Cordyceps Extracts.

https://www.ncbi.nlm.nih.gov/pubmed/29979545

- HIV is a retroviral disease of the immune system that leads to decreased immunity via reduced CD4+ T-helper cells (CD4 cells) and increased susceptibility to infections, and ultimately AIDS. Currently it is an epidemic in parts of Asia such as southern Yunnan, China and regions of southern Africa.
- In these countries herbal medicines are often used for primary care and treatment of opportunistic infections, whereas in developed countries they are used along with conventional modern medicine as 'complementary medicines.
- Herbal medicines are also commonly used in HIV-AIDS treatment, in line with growing evidence suggesting the utility of herbal medicines to be beneficial for immune support, anti-oxidant status and anti-retroviral activity.



CORDYCEPS TREATS ASTHMA





- Several studies over the past decade have shown that Cordyceps helps the lungs and improves airway health. A 2016 study has now found that C. sinesis can indeed be used to treat asthma.
- Researchers from the Department of Respiratory Medicine at the Beijing University of Chinese Medicine studied 120 people with moderate to severe cases of chronic asthma. The study excluded smokers, those with other lung conditions, pregnancy, or recent hospitalization.
- The researchers randomly divided the patients into two groups of 60 people each. The control group was treated with standard prescriptions of corticosteroid inhalers and Beta2-adrenergic agonists. The other 60 people were given 1.2 grams of C. sinesis three times a day for three months. The Cordyceps group was also given the ability to use the same inhalers and B2-adrenergic agonists as needed.
- Before and after the three months of treatment, the patients received a battery of tests. These included lung function testing using the spirometer. The researchers tested the patients for forced expiratory volume one second (FEV1), forced vital capacity (FVC) and mean peak expiratory flow (PEF).
- The researchers also found the Cordyceps group had improved scores in asthma symptoms, activity limitations and emotional function categories. Their asthma symptom improvements compared to the control group continued.

CORDYCEPS TREATMENTS PROVEN IN RESEARCH



Kidney disease

Six clinical research studies found that Cordyceps improved outcomes for <u>kidney</u> <u>disease</u> patients. Among those who received kidney transplants, Cordyceps improved survival and reduced rejection rates.

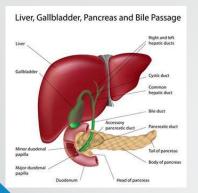
A study of 120 patients with type-2 diabetes found that 2 grams of Cordyceps three times per day helped protect patients from kidney injury and renal insufficiency.

An analysis of 22 studies that included 1,746 people with chronic kidney disease found that Cordyceps significantly:

- Reduced serum creatinine
- Increased creatinine clearance
- Reduced proteinuria
- Reduced kidney disease complications

A study from Peking University Hospital studied 231 people with chronic kidney disease. Among the group treated with Cordyceps, renal function improved in 72 cases, stabilized in 38 cases and worsened in only 12 cases. Among the control group, renal function improved in only 14 cases.





Liver disease

A study from Japan's Tosashimizu Hospital tested 101 patients with liver cancer. Most also had cirrhosis, hepatitis-C virus (HCV) or hepatitis-B virus (HBV). The researchers found that included Cordyceps in their treatment resulted in significantly better survival rates and reduced symptoms of the other liver issues.

Pain

A study from South Korea's Duksung Women's University found that Cordyceps contains compounds that inhibit <u>COX-2 enzymes</u>. This means it reduces pain.

Metabolic issues and athletic performance

Researchers from UCLA tested 20 healthy people between 50 and 75 years old. They gave the subjects either a Cordyceps supplement (1,000 milligrams per day) or a placebo for 12 weeks. The researchers found that the Cordyceps increased metabolic threshold and ventilation threshold. The placebo group did not experience any increases.



Cancer

Cordyceps and one of its constituents, cordycepin, has been studied extensively against a number of types of <u>cancer</u>. In several studies, cordycepin has been found to kill breast cancer cells. Research has also found Cordyceps inhibited colorectal cancer cells, lung cancer cells and oral cancer cells.

Oxidative stress

Consistent with this point: Cordyceps and cordycepin has also been found in the research to inhibit oxidative stress. Researchers found cordycepin blocked osteogenesis in the bone marrow among mice in one study.

Inflammation

Illustrating nature's intelligence, researchers from Taiwan's National Cheng Kung University studied Cordyceps and identified 50 medicinal compounds. These included a number of compounds that exhibited anti-inflammatory activity.

https://plantmedicines.org/cordyceps-treats-asthma/

TYPE 2 DIABETES



- Diabetes is a disease in which the body either does not produce or respond to the hormone <u>insulin</u>, which normally transports the sugar glucose into your cells for energy.
- When your body does not produce enough insulin or respond well to it, glucose cannot enter the cells, so it stays in the blood. Over time, having too much glucose in the blood can cause serious health problems.
- Therefore, it's important for people with diabetes to make sure their blood sugar levels are well controlled.
- Interestingly, *Cordyceps* may keep blood sugar levels within a healthy range by mimicking the action of insulin. *Cordyceps* contain a special type of sugar that may help treat diabetes.
- In several studies in diabetic mice, *Cordyceps* have been shown to decrease blood sugar levelshttps://www.ncbi.nlm.nih.gov/pubmed/15050427
 https://www.ncbi.nlm.nih.gov/pubmed/15050427
- Some evidence suggests that they may also protect against kidney disease, a common complication of diabetes.
- Chronically elevated blood sugar levels are common in people with uncontrolled diabetes and can have serious health effects. Research in animals suggests *Cordyceps* may have potential as a diabetes treatment.

ACCORDING TO PM NARENDRA MODI



 Prime Minister Narendra Modi addressed the nation on 14 April and directed citizens to strengthen their immune systems to fight the novel coronavirus.



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THANK YOU