

Pharmacology, phytochemistry and traditional uses of *Cordyceps sinensis* (Berk.) Sacc: A recent update for future prospects

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Received 06.05.13, revised 12.11.13

This review highlights the pharmacology, biological properties and traditional uses of a very important folklore medicine, known as '*Keeda jadi*'. In nature, it is found at high altitudes of 3500-5000 m on the high Himalayan mountains in India, Nepal and Tibet. It is an entomo-fungal combination of a larva of small moth, *Hepialus armoricanus* and a parasite fungus *Cordyceps sinensis*. *Cordyceps* is best known medicine for increasing physical stamina and sexual functions. It has been traditionally used to treat patients with heart disease and also shown to increase liver, kidney and lung functions. *C. sinensis* is unique and valuable for its medicinal properties. Many studies support that it has diverse biological activities and pharmacological potential, while it is not extracted sustainably in planned way. So, awareness and scientific knowledge is very necessary for the future prospects of *Cordyceps* such as conservation, sustainable harvesting, cultivation practices and trade.

Keywords: *Cordyceps sinensis*, Pharmacology, Traditional uses, Cordycepin

IPC Int. Cl.⁸: AO1G 1/04, AO1H 15/00, DO5B 91/08, A01D 14/01, A01D 7/31, A01D 20/00

Indian Himalaya region is known as the veritable emporium of herbal wealth due to its various bio-diversity wealth. In this region, important medicinal and aromatic plants grow in abundance and these have various folklore uses. In alpine regions of Indian Himalaya, mainly in Arunachal Pradesh and Uttarakhand, generally at the altitudes of 3500-5000 m a very important folklore medicine is prominently found which is known as *Keeda jadi*, *Keeda ghaas*, *Yarsa gumba*, *Yarsa gunbu*, etc.¹⁻³. It is an entomo-fungal combination of a larva of small moth, *Hepialus armoricanus* (Lepidoptera; caterpillar host) and a parasite fungus *Cordyceps sinensis*. The mycelium of the fungus grows in the soil and colonizes the buried larvae of this moth. The caterpillar becomes mummified by the growth of the mycelium. When alpine grasses start sprouting during summer, the mycelium of the fungus forms a fruiting body which emerges from the head of the larva² (Fig. 1).

Cordyceps sinensis (Berk.) Sacc. is a fungus belongs to subphylum Ascomycotina, class Pyrenomycetes,

order Clavicipitales and family Clavicipitaceae. Many researchers have earlier investigated about *C. sinensis* from Indian Himalaya on different aspects such as medicinal value, trade, market value, conservation strategies, collection process and history, etc.^{1,2,4-7}.

C. sinensis is used as a traditional medicine since ancient times due to its incredible medicinal properties. Researchers reported that it is used to relieve the mental stress as well as for the preparation of energetic and revitalizing formulations, asthma, renal injuries, bronchitis, cough, resistance of respiratory tract, blood pressure, weakness, immunity strengthening, malfunction of lungs and irregular menstruation^{5,8}.

There are some other closely related species of *Cordyceps* found, but in historical usage, the term *Cordyceps* normally refers to the species *C. sinensis* only, which has been valued for many centuries in Traditional Chinese Medicine. In nature, *Cordyceps* is found only at the high altitudes of the Himalaya and therefore very difficult to collect. Because of such difficulties, it has always been one of the most expensive medicinal fungi known⁹.

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Pharmacology

Cordyceps species, especially *C. sinensis* is extraordinary nutritional supplement and medicinal mushroom and an important source of material in Traditional Chinese Medicine. One of the highlight of modern research has been the discovery of new antibiotics in this mushroom. One of these, cordycepin is very effective against various types of bacteria that have showed resistance to other more common antibiotics. *Cordyceps* controls low blood pressure and strengthens the heart beat and use in the treatment of kidney, immune disorder, chronic obstructive pulmonary diseases and asthma. It is used in treatment for impotence, as an aphrodisiac in both men and women. Some additional health benefits of *Cordyceps* are given below:

- **Enhances physical stamina**

Cordyceps is best known medicine for increasing physical stamina. Clinical research has shown that *Cordyceps* increased cellular bio-energy ATP¹⁰. An increase in cellular ATP results in an increase in useful energy and improves internal balance mechanism, thus making the utilization of oxygen more efficient. The presence of adenosine, cordycepin, cordycepin acid, d-mannitol, polysaccharides, vitamin and trace elements may be the cause for such effects. These properties cause physical enhancement, the extra endurance and the anti-fatigue that are seen in human using *Cordyceps*.

- **Effects on heart**

C. sinensis has been traditionally used to treat patients with heart disease and those recovering from stroke. *C. sinensis* has many effects on the cardiovascular system, reducing myocardial oxygen consumption, improving myocardial ischemia and anti-platelet aggregation, etc. *C. sinensis* has an inhibitory effect on arrhythmia induced by aconitine, barium chloride and adrenaline and can increase nutritional myocardial blood flow, thereby improving myocardial ischaemia¹¹. It has promoted an increase in the overall quality of life in the patients suffering from chronic heart failure and has curative role in renal hypertension¹²⁻¹³.

- **Maintains liver function**

C. sinensis has been shown to increase the efficient functioning of liver. Efforts have made for preventing liver disease using Traditional Chinese Medicine and *Cordyceps* is one of the key materials of Traditional Chinese Medicine. *Cordyceps* is very much effective against the liver patients, including those with viral



Fig. 1—*Cordyceps sinensis*

hepatitis A, chronic hepatitis B, chronic hepatitis C, hepatitis fibrosis, etc. It enhance organic cell, immunological function, improve liver function, and inhibits hepatic fibrosis¹⁴. Bioactive compound of *Cordyceps* for liver protection is mostly *Cordyceps* polysaccharides and its efficacy varies with the species. *C. sinensis* can considerably relieve the liver fibrosis and promote the degradation of the collagens. Polysaccharide of *C. sinensis* action on liver fibrosis and inhibit stellate cell activation and TGF β 1 expression¹⁵.

- **Maintains kidney function**

C. sinensis have potential of kidney enhancing ability by increasing 17-hydroxy-corticosteroid and 17-ketosteroid level in the blood³. Studies have shown that *C. sinensis* extract is used as therapeutic drug for chronic kidney diseases and also improves kidney diseases like glomerular sclerosis¹⁶. Drug cyclosporin is used during kidney transplant and is high toxicity and cause many patient to suffer from serious kidney damage by use of related drug. Study revealed that patient receiving *C. sinensis* in addition with cyclosporin showed much lower incidence of kidney damage than group receiving only cyclosporin¹⁷.

- **Maintains lung function**

C. sinensis has a significant relaxant role in the bronchi, markedly increase adrenaline secretion from the adrenal glands and also has a role in tracheal contraction caused by histamine. It also an antitussive, expectorant and anti-asthmatic action and prevent pulmonary emphysema¹⁸. In many studies it has been shown that *C. sinensis* is used in treatment of many respiratory illnesses, including asthma, chronic obstructive pulmonary diseases and bronchitis¹⁹⁻²¹.

C. sinensis extract has been shown to inhibit tracheal contractions, which is important in asthma patients because it allow for increased airflow to the lungs.

Improves sexual function

C. sinensis has been used for centuries in Traditional Chinese Medicine to treat male and female sexual troubles, such as hypolibidinism and impotence. It has been shown to improve libido and quality of life in men and women, check infertility and increase sperm count and survival. Human clinical trials have similarity demonstrated the effectiveness of *C. sinensis* in combating decreased sex drive and virility²². *C. sinensis* also showed sex-steroids like effects on mice²³.

- **Antibacterial properties**

C. sinensis possessed antibacterial activities. An antibacterial protein CSAP isolated from cultured mycelia of *C. sinensis* inhibited the growth of Gram-positive and Gram-negative bacteria but had no significant inhibition activity against fungi and yeast²⁴. Fermentation broth of *C. sinensis* showed antibacterial activity on *Staphylococcus aureus*, *E. coli*, *Bacillus subtilis*, *Bacillus thuringiensis* especially has stronger effect on *Staphylococcus aureus* and *E. coli*²⁵.

- **Antioxidant properties**

C. sinensis has anti-oxidant activity. Water extracts of various sources of natural *C. sinensis* and cultured *Cordyceps* mycelia were analyzed for their anti-oxidant activity by using three different assay methods, the xanthine oxidase assay, the induction of hemolysis assay and the lipid peroxidase assay. The result showed that *Cordyceps* possess a strong anti-oxidant activity in all assays²⁶. Water soluble polysaccharide CPSI, a glucomannogalactan with the monosaccharide composition of glucose, mannose and galactose, isolated from *C. sinensis* has shown antioxidant activity in vitro, including scavenging effect of the hydroxyl radicals, the reducing power and Fe²⁺ chelating activity²⁶.

- **Antitumor activities**

C. sinensis has the ability to inhibit the growth of tumour and their extract have been recognized as a traditional remedy, used in Traditional Chinese Medicine for the prevention and treatment of cancer and several other disease²⁷. Polysaccharides, sterols and adenosine are mainly bioactive component in *Cordyceps* that have antitumour activity. The antitumour action of *Cordyceps* polysaccharides has

been proved extensively²⁸ new antitumour compounds have been continually isolated and the effects of *Cordyceps* extract have been evaluated²⁹. Different extracts of *Cordyceps* also showed stronger cytotoxicity on the B16 cell line and the ethyl acetate extract had the most potent activity. Ergosterol and adenosine were potential compounds isolated from the extract³⁰.

- **Immuno modulating effects**

C. sinensis extracts and isolated components both have immune-suppressive and immune-stimulating functions. Immunomodulators can be effective agents for treating and preventing diseases and illnesses caused by certain immune deficiencies³¹. Active substance isolated from *Cordyceps* has major immunomodulating effect which includes mitogenicity and activation of immune cells, such as lymph proliferation response, natural killer cell activity and phytohaemagglutinin stimulated interleukin-2 and tumour necrosis factor- α production on human mononuclear cells³². Therapeutic effect of mushrooms, such as suppression of immune diseases and allergy, is associated with their immunomodulating effects³³⁻³⁴. A study showed that different components of *Cordyceps* polysaccharides enhanced the immune response, spleen index, thymus index, phagocytic function of monocyte-macrophage³⁵, cellular immune function in chronic renal failure and also improved renal functions³⁶.

- **Side effects of *C. sinensis***

No death or serious injury has been known to have occurred with the consumption of *C. sinensis*, though nausea, diarrhea and dry mouth³ diseases have been noticed in a small number of people. One study reported that a patient had developed a systematic allergic reaction after taking a strain of *Cordyceps* called Cs-4³⁷. One of the main and most dangerous *Cordyceps* side effects could be lead poisoning. To increase the weight, the harvesters add lead which is easily apparent in the mass of the small elongated *Cordyceps* and caterpillars. Lead poisoning can cause damage to kidneys, increase blood pressure and reduce fertility in men and women. Miscarriage and premature births have also been seen in women affected by lead poisoning. It also affects motor nerve and cause severe joint pain. *Cordyceps* improves fertility, cardiovascular function, renal function etc. but its contamination with lead has adverse effects on the patient's health. *Cordyceps* are formed by parasiting on insects, if they had

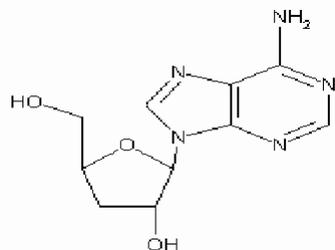
been afflicted with some disease that could also pass on to the *Cordyceps* and hence it becomes contaminated and unsafe.

Phytochemical constituents

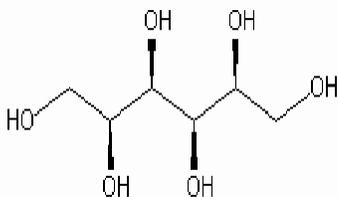
Cordyceps contain a wide range of compounds that are nutritional. It contains crude fats, proteins, fibers, carbohydrates, cordycepin, cordycepin acid, polysaccharides and vitamins etc. It contains many sugars, including mono, di and oligosaccharides, sterols, nucleosides and macro and microelements.

- **Cordycepin and Cordycepin acid**

Cordycepin and Cordycepin acid have been isolated and proposed as important constituents of *C. sinensis*³. Cordycepin was first isolated from *C. militaris* and its structural formula was confirmed as 3'-deoxyadenosine³⁸. Cordycepic acid, an isomer of quinic acid, is one of the main active medicinal components and its structure was concluded to be 1,3,4-trihydroxycyclohexane³⁹. The content of Cordycepin acid in *C. sinensis* is 7-29%, differing in the various growing stage of the body⁴⁰. It is used in injection as well as supplement in other medicine⁴¹.



Cordycepin



Cordycepin acid

- **Polysaccharides**

Polysaccharides, the medicinally active compound, found in large amount which ranged from 3-8% of the total weight in *Cordyceps*^{25,42}. These are effective in regulating blood sugar and have antimetastatic, antitumour and immunomodulating effects^{28-29,32,43-44}. Topography of *Cordyceps* polysaccharides was studied by using an atomic force microscope (AFM)⁴⁵

and showed that *Cordyceps* polysaccharides as a multi-branched galactomannan structure. Galactomannan was isolated from sodium carbonate extract of *Cordyceps* which contain water soluble protein and its molecular weight was estimated by gel filtration to be 23kDa. The compound isolated is composed of D-mannose and D-galactose in a molar ratio of 3:5 and small portion of protein⁴⁶. Pharmacological activity of polysaccharides is correlated with the molecular weight. Higher molecular weight of polygucans tends to have greater water solubility and have more effective anti-tumour activity.

- **Nucleotides**

Cordyceps contain effective nucleotides components including adenosine, uridine and guanosine. In natural and artificial *Cordyceps*, guanosine has the highest content out of all nucleotides⁴⁷ beside this nucleotides content in artificial *Cordyceps* is higher than that natural *Cordyceps*.

- **Sterols**

Cordyceps contain number of sterol-type compounds ergosterol, δ -3ergosterol, ergosterol peroxide, 3-sitosterol, daucosterol and campesterol. Ergosterol has important medicinal value and is an important precursor to Vitamin D₂. The content of free ergosterol varies significantly in natural *Cordyceps* but evidently found higher in the mycelia of *Cordyceps*.

- **Protein and amino acids**

Cordyceps contain crude protein in the range of 29-33%⁴⁸. The protein is made of 18 amino acids and after hydrolysis of amino acid its content is mostly reported as 20-25%. Arginine, glutamate, tryptophan and tyrosine are the major pharmacological components, among these glutamate, arginine and aspartic acid have highest content⁴⁹. Amino acid contents are higher in the commercial preparation of *Cordyceps* than in the mycelia of *C. sinensis*, which is similar to the content in the fruiting body of *C. sinensis*.

- **Fatty acids and metals**

Cordyceps contain both unsaturated and saturated fatty acids. Unsaturated fatty acids contents reach 57.84%. The linoleic acid content is the highest at 38.44%, followed by oleic acid, which is 17.9%. Saturated fatty acids content is 42.16%. The palmitic acid and the octadecanoic acid contents are the highest and are 21.86% and 15.78%. Unsaturated fatty acid has the unique function of decreasing blood lipid and protecting against cardiovascular diseases.

Many metals are found in *Cordyceps* and its content depends on different species and metal elements²⁵. High content of Zn, Mg and Mn play an important role in warming the kidney and aiding kidney recovery⁵⁰.

Market potential

In traditional medicinal practices, wild harvested and naturally occurring plants are considered to have higher therapeutic benefits; thus they command higher prices. *Cordyceps* has been highly prized for its medicinal properties for centuries, and the same tradition still continues. Traditionally, the fungus is traded in China for its weight in silver or gold. *Cordyceps* still hold high value in the markets of China and sold 1 kg of the fungus at Rs. 1,00,000⁷. In local areas of fungus availability, the price may vary between NR (Nepali Rupees) 30,000 and 60,000 for a kilogram in Nepal, while in India, Uttarakhand is the highest producer of *Cordyceps* with the unofficial average rates of Rs. 2,50,000 to 3,00,000 for a kilogram^{5,7}. The collection of *Cordyceps* is being done mainly by the villagers of districts Chamoli and Pithoragarh. As a result, drastic changes in the economy and livelihood of villagers have been occurred due to collection of *Cordyceps*. For the sustainable collection of *Cordyceps*, policies and guidelines have been made by Government of Uttarakhand and government has given the responsibilities to 'Van Panchayats'⁷.

Traditional significance of the study

C. sinensis is unique and valuable for its various medicinal properties. Owing to the availability, it is collected by the local inhabitants in different parts of Himalayan region for betterment of their livelihood, but the local inhabitants are not much aware about collection techniques and conservation strategies. The collection for *C. sinensis* is often perceived to pose a threat for the Himalayan environment where it grows. Keeping in view the importance of *Cordyceps*, scientific knowledge needs to be given to the villagers and local inhabitants and also trained for conservation salvages and sustainable harvesting in planned way.

Conclusion

Many studies support that it has diverse biological activities and pharmacological potential, while it is not extracted sustainable in planned way. Our challenges in the modern era are to scientifically unravel the many claims and conflicts. With *Cordyceps*, these challenges have been greater than

many other herbs due to the enormous cost and scarcity of the material. The one field that needs the attention is the mycelium culture in the laboratory, standardization, formulation of appropriate dosage forms and conducting accelerated stability studies of the same. So, awareness and scientific knowledge is very necessary for the future prospects of *Cordyceps* such as conservation, sustainable harvesting, cultivation practices and trade.

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