

Insight into novel caterpillar fungus, *Cordyceps sinensis*

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Abstract

Indian Himalayan region, known for its wide herbal heritage is rich in different medicinal mushrooms. Among these, *Cordyceps sinensis* is considered to be important and is also known as Keeda jadi, Keeda ghaas, Yarsa gumba, Yarsa gunbu etc. It is an entomo-fungal combination of a larva of small moth, *Hepialus armoricanus* (Lepidoptera; caterpillar host) and a parasite fungus *Cordyceps sinensis*. *Cordyceps* have a history of medicinal use spanning millennia in parts of Asia. Recently, a new kind of chemotherapy derived from a molecule i.e., NUC-7738 synthesized at the University of Oxford in partnership with UK-based biopharmaceutical company NuCana, is under research trial and can be considered as a potential anti-cancer agent and its further medicinal potential can be exploited.

Keywords: *Cordyceps sinensis*, chemotherapy, entomo-fungal combination, NUC-7738

Introduction

Due to its wide bio-diversity, the Indo- Himalayan region is renowned as a real hub of herbal treasure. Important medicinal and aromatic plants grow in abundance in this area, and these have a variety of folkloric purposes. For thousands of years, medicinal mushrooms have been known to produce biometabolites that are used or studied as potential treatments for ailments. *Cordyceps* has been found mainly in North America, Europe and Asia (Kang et al., 2017). 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. It is an entomo-fungal combination of a larva of small moth, *Hepialus*

armoricanus (Lepidoptera; caterpillar host of family Hepialidae) and a parasite fungus *Cordyceps sinensis*. *Cordyceps* have a history of medicinal use spanning millennia in parts of Asia (Hur, 2008). The name *Cordyceps* has been derived from two Latin words, i.e., cord and ceps meaning club and head, respectively. 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 larva (Kang et al., 2017). The ethno-pharmacological use of *Cordyceps sinensis* has been reported from western Nepal for the cure of different diseases like diarrhoea, 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).

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 (Kang et al., 2017), DNA/RNA synthesis (Kang et al., 2017) and mTOR (mammalian Target Of Rapamycin) signalling transduction (Seth et al., 2014). *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. Due to recent advancements in pharmaceutical biotechniques, it is possible to isolate bioactive compounds from *Cordyceps* and make it available in powder as well as in capsular form (e.g., Didanosine). *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 (Seth et al., 2014). Over two-third of cancer-related deaths could be prevented or reduced by modifying our diet with mushrooms, as they contain anti-oxidants (Seth et al., 2014).

Mode of action of caterpillar fungus and *Cordyceps*- derived molecules

Cordycepin, cordycepic acid, adenosine, exo-olysaccharides, vitamins, enzymes, and other biologically active substances have been identified from *Cordyceps* bio-metabolites, particularly its extract. Out of these, Cordycepin, i.e., 30-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 (Seth et al., 2014).

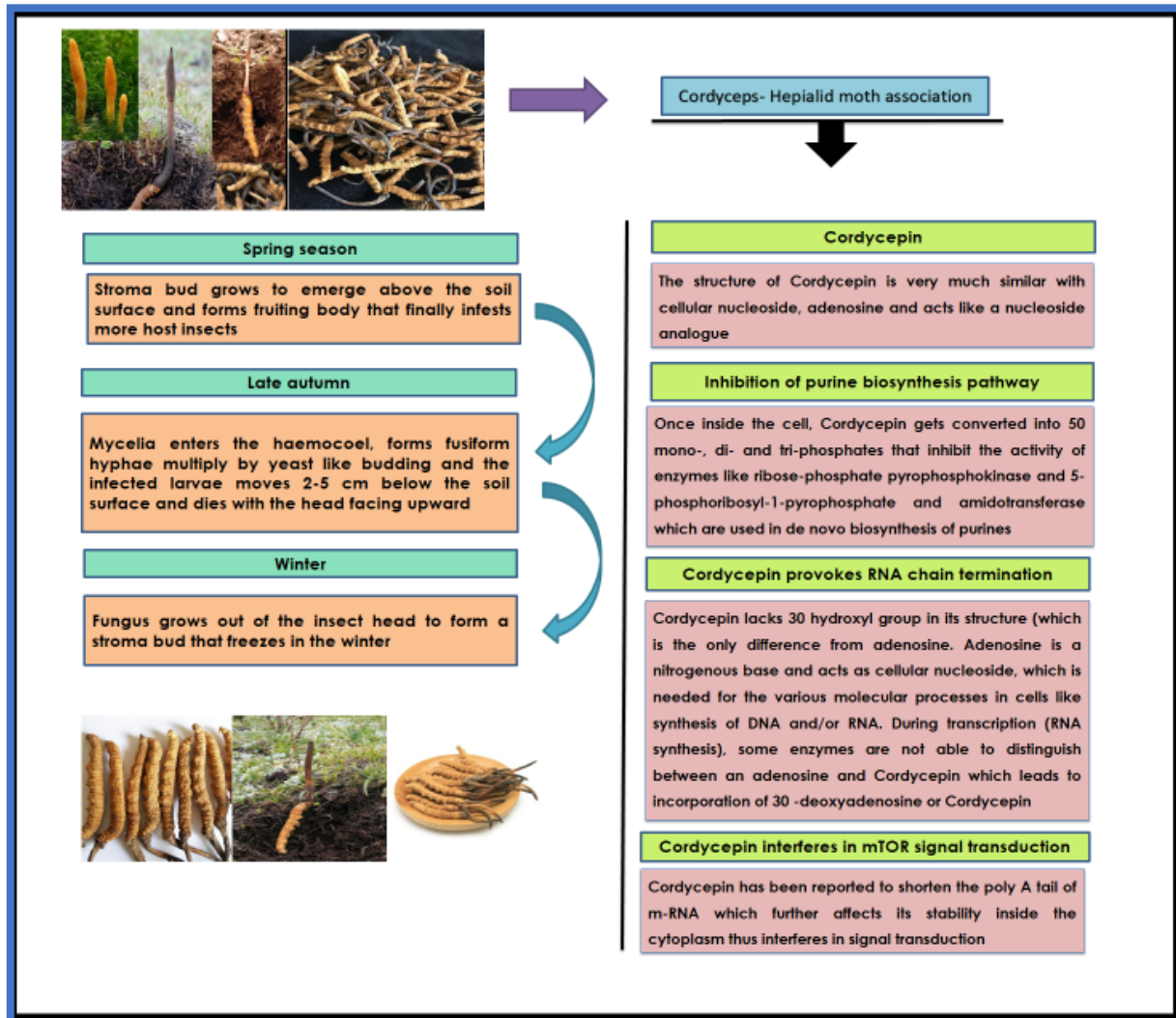


Figure 1. Diverse mode of action of cordycepin

Recent development

Recently, a new kind of chemotherapy derived from a molecule found in a Himalayan fungus i.e., NUC-7738 (Reported first by Science Alert) synthesized at the University of Oxford in partnership with UK-based biopharmaceutical company NuCana, is under research trial. Yet, clinical trials have proven this as a potential anti-cancer agent. The active ingredient in NUC-7738 is called Cordycepin, or 3'-deoxyadenosine (or 3'-dA), is a naturally occurring nucleoside analogue, already been reported to have range of anti-cancer, anti-oxidant, and anti-inflammatory effects, so this fungus is effectively

called the world's most valuable parasite (Dockrill, 2021). The naturally occurring cordycepin (as described in the figure 1.) extracted from *O. sinensis* does have its drawbacks, such as:

- ✓ It is broken down quickly in the bloodstream having a half-life of 1.6 minutes in plasma by the enzyme adenosine deaminase, or ADA (Khanna, 2021).
- ✓ It also shows poor uptake into cells, meaning the molecule's actual potency against tumor cells in the body is greatly diminished.
- ✓ Cordycepin enters cell through nucleoside transporters, such as Human Equilibrative Nucleoside Transporter 1 (hENT1) (Yong, 2018).

Unlike naturally occurring cordycepin, NUC-7738 doesn't rely on hENT1 to gain access to cells, and it is already pre-activated (bypassing the need for the enzyme adenosine kinase), and already self-protected and is also resistant to breaking down in the bloodstream, with built-in protection against ADA. Furthermore, studies also suggested that NUC-7738, has anti-cancer properties up to 40 times more potent than cordycepin when tested against a range of human cancer cell lines. Moreover, early results from the first in-human clinical trial of NUC-7738 appear to be positive so far too. The Phase 1 trial provide evidences that NUC-7738 overcomes the cancer resistance mechanisms and support the further clinical evaluation of NUC-7738 as a novel cancer treatment.

Conclusion

In the lap of nature, mankind finds itself as the most potent and brainy creature in utilizing the natural resources for its benefits. In the due course of time, cancer has been discovered as the most threatening disease for mankind and prominent-effective treatment is yet to be a dream for it. Many scientists work on various possibilities in order to find a permanent solution to cancer ailment. In search of a possibility, cordyceps fungus is found to be a ray of hope in cancer treatment. Its broad-spectrum adaptability along with effectiveness make it a double-sided sword against cancer, yet needs to be explored more in this sector. Nevertheless, it has been a win for mankind, the side-effects of the fungus and growth pattern need to be thoroughly studied in order to invent its hidden treasure. The sustainable exploitation of the fungus along with biological conservation of its habitat are other areas that need to be focused on.

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