**Cordyceps sinensis**
—a Traditional Chinese Medicine Known as Winter-worm Summer-grass

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**Introduction**

Cordyceps sinensis is the complex of fungus *Cordyceps sinensis* (Berk.) Sacc. (Clavicipitaceae) growing on the larva of *Hepialus armoricanus* Oberthür (caterpillar) that lives a few inches underground. It is also commonly known as Cordyceps, or “Dong Chong Xia Cao” (winter-worm and summer-grass) in Chinese, because of its appearance during different seasons. *Cordyceps* has been used in China as a medication for over a few hundred years. In Chinese medicinal theory, *Cordyceps* processes both “Yin-nourishing” and “Yang-invigorating” activities. Indeed, numerous reports have shown the pharmacological properties of *Cordyceps*. Different therapeutic effects of *Cordyceps* have been reported: stimulating immune response; inhibiting cancer growth; protecting the kidney and liver; stimulate cardiovascular circulation; lowering blood glucose; and acting against free-radical formation. Today, *Cordyceps* is commonly used in many hospitals in China and as a household remedy. However, more than 100 different types of *Cordyceps* or its substitutes have been found worldwide today. The authentication of *Cordyceps* is a serious problem on the market.

Many *Cordyceps*-related species could be found which are based on different fungi growing on different insect hosts; however, most of them are not considered as *Cordyceps*, except *C. sinensis* that is listed officially in the Chinese Pharmacopoeia. China is a major producer of *Cordyceps*. The *C. sinensis* is grown in a very restricted habitat, and the yield is decreasing every year. In China, the parasitic complex is found in the soil of a prairie at an elevation of 3500 to 5000 meters, mainly in the provinces of Qinghai, Tibet, Sichuan, Yunnan and Gansu (Fig. 1). In 2001, a total of a few thousands kilograms of *Cordyceps* were collected in China; this represents a decrease of over 70% as compared with 1978. Owing to the environmental concerns, Ordinance of Resources Protection on Wild Herbal Medicine was issued in 1987 by the Chinese government, and therefore the collection of *Cordyceps* is being restricted. The price of *Cordyceps* is US$5000 per kg in 2005, about 100 folds greater than that in the 1980s.

Scientists in Asia have developed substitutes extensively by using mycelial fermentation that is derived
from natural *Cordyceps*. Up to date, more than 9 genera including 31 species have been isolated from natural *C. sinensis*. Mycelia, or fruiting bodies, of 16 species have been produced in large quantities by culture. More than 20 fermented products are commonly sold as health food products in China; the annual production value is more than US$100 million.

Amongst all the fermented *Cordyceps* CS-4 is the most common and reportedly to be isolated from *C. sinensis*; CS-4 is known to be *Paecilomyces hepialid*. The fermentation methodology, chemical composition, therapeutic function, basic biology and toxicity of CS-4 have been investigated extensively. Jin Shui Bao capsule, the commercial product that is derived from CS-4, have also been sold and used in clinics throughout China. This product generates over several million US dollars of sales per year. Besides CS-4, several mycelial strains of *Cordyceps* have been isolated and manufactured on a large scale by fermentation. In 2000, our laboratory in Hong Kong isolated a strain of *C. sinensis* from Qinghai’s *Cordyceps*, which shows close resemblance to natural *Cordyceps* both chemically and genetically (Fig. 2). In addition, *Cordyceps militaris* is often used as a substitute for *C. sinensis* as a health food market in Asia, being also known as *Cordyceps* from the north (Bei Chong Cao). Thus, the cultivated products of *Cordyceps* as health food products are very popular and they can be priced extremely high. However, it is still doubtful how authentic these products are, on the other hand adulterated *Cordyceps* are commonly found on the market.

**Quality control of *Cordyceps***

Currently, different types of cultured *Cordyceps* are being sold on the markets, and their prices are markedly lower than that of the natural *Cordyceps*. The market price of *Cordyceps* varies greatly depending on their sources. Unfortunately, there is no absolute chemical marker to ensure better quality nor are there markers to assess the authenticity of *Cordyceps*. At present, the quality of these products is an issue of concern to consumers. On the average, natural *Cordyceps* contains 25% protein, 8.4% fat, 18.5% fiber, 29% carbohydrate and 4.1% ash. In addition, *Cordyceps* contains uracil, adenine, adenosine, trehalose, mannitol, ergosterol and stearic acid (Table 1). Historically, adenosine has been used as a marker for quality control of natural *Cordyceps* and cultured *Cordyceps* mycelia. Nucleoside is believed to be the active component in *Cordyceps*. Indeed, *Cordyceps* contains a high concentration of adenosine, guanosine and uridine.

![Fig. 2.](image-url)
Amongst the nucleosides, adenosine is deemed to play a key role in many pharmacological effects of *Cordyceps*, which include the widespread effects on coronary and cerebral circulation; prevention of cardiac arrhythmias, and effects on functions in nervous system e.g. the inhibition of neurotransmitter release and the modulation of adenylate cyclase activity. Fresh natural *Cordyceps* contains very little nucleoside, as compared with dry and processed *Cordyceps*, and more interestingly cultured *Cordyceps* mycelium contains high levels of nucleosides. Furthermore, humidity and heat significantly increase the amount of nucleoside in natural *Cordyceps*. If *Cordyceps* is stored at 75% relative humidity and 40°C for 10 days, the nucleoside content in natural *Cordyceps* will be markedly increased by about 4 folds. Therefore, it is believed that nucleosides in natural *Cordyceps* may be derived from the degradation of nucleic acids. In addition, recent studies indicated that the content of adenosine in *Cordyceps* has no obvious relationship to its biological activity. Therefore, having adenosine as a marker for good quality of *Cordyceps* may not be indicative.

In 1964, 3’-deoxyadenosine, viz cordycepin, was isolated from *C. militaris*, a related species of *C. sinensis* commonly used as a substitute for *Cordyceps*; however, the existence of cordycepin in *C. sinensis* is controversial. Up to date, cordycepin has never been identified from *C. sinensis*. In 1957, cordycepic acid, which was subsequently identified as D-mannitol, was isolated from *C. sinensis*, and which therefore has been used as a quality control marker for *Cordyceps* for a number of years. Mannitol is a major component of carbohydrate in natural *Cordyceps*, and which contributes to over 3.4% of the total dry weight. Mannitol is being used to treat many diseases, and therefore has been used as a marker for *Cordyceps*. The content of mannitol in natural *Cordyceps* was higher than that in the cultured one.

### Table 1: The contents of ergosterol, nucleosides and their bases in *Cordyceps*.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Natural C. sinensis</th>
<th>Cultured C. sinensis</th>
<th>Cultured C. militaris</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Qinghai 1</td>
<td>Tibet 1</td>
<td>Tibet 2</td>
</tr>
<tr>
<td>Ergosterol</td>
<td>1.43 a</td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>Adenosine (+Adenine)</td>
<td>0.45</td>
<td>0.42</td>
<td>0.36</td>
</tr>
<tr>
<td>Cytosine</td>
<td>-b</td>
<td>+c</td>
<td>+</td>
</tr>
<tr>
<td>Cytidine</td>
<td>0.29</td>
<td>0.19</td>
<td>0.32</td>
</tr>
<tr>
<td>Cordycepin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Guanosine</td>
<td>0.20</td>
<td>0.18</td>
<td>0.32</td>
</tr>
<tr>
<td>Thymine</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Thymidine</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Uric acid</td>
<td>+</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Uridine</td>
<td>0.66</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>2’-deoxyuridine</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>0.03</td>
<td>0.06</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* The amount of marker is in mg/g of dry weight. The mean values of five determinations are presented. The SEM is less than 5% of the mean, which is not shown for clarity.

b Undetectable.

c Beyond lower limit of linear range of detection.
Ergosterol is an unique component in fungi, and it is required for vitamin D2 synthesis. Ergosterol, therefore, could be another choice of quality control marker of choice for Cordyceps. Sterols and their derivatives have been isolated from natural and cultured Cordyceps. Ergosterol exists as free and or in combined forms in Cordyceps. The content of ergosterol is higher in cultured Cordyceps mycelia than in natural Cordyceps, and indeed the level of ergosterol reflects the amount of Cordyceps mycelia. During the fermentation of Cordyceps, the level of ergosterol changed according to the time of culture; a steady level of ergosterol was revealed when the maturation of Cordyceps mycelia was reached. Pharmacological study showed that ergosterol possessed anti-arrhythmia effect. In addition, the ergosterol derivatives also have multiple pharmacological activities, such as cytotoxic activity and anti-viral activity; these activities vary in accordance with the quality of Cordyceps for both natural or cultured products.

Cordyceps contains a large amount of polysaccharide, which could range from 3 to 8% of the total dry weight. In cultured Cordyceps, functional polysaccharides are known to be secreted by the mycelium. Cordyceps polysaccharide was found to have different biological activities, which include anti-oxidation, immuno-modulation and tumor-inhibition. Until now, the pharmacological profile of Cordyceps correlates very well with the amount of polysaccharide in the herb. Based on the activity-guided fractionation, several polysaccharides have been isolated from cultured Cordyceps; these Cordyceps polysaccharides could stimulate our immune system and prevent free radical formation; however, the existence of these polysaccharides in natural Cordyceps has not been revealed. Moreover, the detailed structure of these polysaccharides is still unclear. These problems hinder the usage of polysaccharide in qualifying Cordyceps.

**Future prospectus**

Because of the decreasing supply of natural Cordyceps, the isolation of mycelial strain from Cordyceps is a trend of the current herbal market. Indeed, the health food market is full of fermented products of Cordyceps; however, many of them are adulterated. The methodology for authentication of these products has to be well defined, and chemical markers are needed for quality control. Although many so called active constituents have been identified, the exact roles of these chemicals for the functions of Cordyceps are still not known. At present, multiple markers such as ergosterol, nucleoside, mannitol and polysaccharide are being used for quality control of Cordyceps’ products. Unfortunately, these markers are far from optimal and extensive works are needed to define the pharmacological efficiency of these chemical markers.

Another approach in quality control of the herb is using chemical profiling instead of a single compound. By capillary electrophoresis, distinct fingerprints could be revealed in water-soluble constituents derived from different sources of Cordyceps. The result shows that samples of natural Cordyceps resemble to each other in the fingerprinting, as compared with the cultured products. This method does not depend on the identities of any chemicals. Thus, the profiles generated from capillary electrophoresis could serve as fingerprints for the quality control of Cordyceps. To meet the needs of the health food market, fingerprinting using multi-markers, that represent different Cordyceps fractions, should be used for quality control of Cordyceps.
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