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# Cordyceps

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## INTRODUCTION

Cordyceps (sometimes spelled ''cordiceps'') is a rare and exotic medicinal fungus, and it has been a highly regarded cornerstone of Chinese medicine for centuries; one that reportedly has a number of far-reaching medicinal effects.

Most people in the West have only come to know of Cordyceps within the last 20 years, during which time, modern scientific methods have been increasingly applied to the investigation of its seemingly copious range of medicinal applications, in an attempt to validate what Chinese practitioners have noted for centuries.

## NAME AND GENERAL DESCRIPTION

A medicinal fungus of a long and illustrious history, *Cordyceps sinensis* is an Ascomycetes fungus. Although it is not actually a mushroom in the taxonomic sense, it has been regarded as a medicinal mushroom throughout history.

The name Cordyceps comes from the Latin words ''cord'' and ''ceps,'' meaning, ''club'' and ''head,'' respectively. The Latin word-conjunction accurately describes the appearance of this club fungus, whose stoma and fruit body extend from the mummified carcasses of insect larvae, usually that of the Himalayan Bat Moth, *Hepialis armoricanus*.

In historical and general usage, the term ''Cordyceps'' normally refers specifically to the species *C. sinensis*. Also pertinent to the general term ''Cordyceps'' are a number of closely related species, found throughout the world. While *C. sinensis* may be the most well known variety, there are many other species in the genus Cordyceps, in which modern science may have uncovered potentially valuable medicinal properties.

*C. sinensis* has been appreciated for many centuries in traditional Chinese medicine (TCM). In nature, it is found only at high altitudes on the Himalayan Plateau and is thus difficult to harvest. Because of such difficulties, Cordyceps has always been one of the most expensive medicinal ''herbs.'' Its high price had relegated its availability almost exclusively to members of the Emperor's court and others among the Chinese nobility and historically beyond the reach of the average Chinese subject. Despite its cost and rarity, the unprecedented litany of medicinal possibilities for Cordyceps has made it a highly valued staple of the Chinese medical tradition.

The medicinal value of this fungus has been recognized for more than 2000 years in China and the Orient. But knowledge of this reached Western scientific audiences only in 1726, when it was introduced at a scientific meeting in Paris. The first specimens were carried back to France by a Jesuit priest, who chronicled his experiences with the Cordyceps mushroom during his stay at the Chinese Emperor's court.[1] While always a rarity in nature, modern technological advances in cultivation have made the prospect of affordable Cordyceps a reality, and its potential medicinal uses continue to augment conventional therapy and gain recognition as clinical trials proceed to probe the claimed efficacy of the Cordyceps mushroom.

| Mycological Data | |
|---|---|
| **Place and System, Description, and Habitat** | |
| Kingdom | Fungi |
| Phylum | Ascomycota |
| Class | Ascomycetes |
| Order | Hypocreales |
| Family | Clavicipataceae |
| Genus | Cordyceps |
| Species | *C. sinensis* (Berk.) Sacc. |
| Basionym: Sphaeria sinensis Berk. | |
| Anomorphs: *Cephalosporium donqchongxiacao*, *C. sinensis*, *Chrysosporium sinense*, *Hirsutella sinensis*, *Mortierella hepiali*, *Paecilomyces hepiali*, Scytalidium sp., *Scytalidium hepiali*, *Tolypocladium sinensis*, and others | |
| English names: Cordyceps mushroom, caterpillar fungus | |
| Japanese names: Totsu kasu, tochukasu | |
| Chinese names: Hia tsao tong tchong, dongchongxiacao [chongcao], literal translation: ''winter worm,'' ''summer plant'' old Chinese: modern Chinese | |

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### Description

The ascocarp or fruitbody of the *C. sinensis* mushroom originates at its base, on an insect larval host [usually the larva of the Himalayan bat moth, *Thitarodes (Hepialis) armoricanus*, although occasionally other insect hosts are encountered] and ends at the club-like cap, including the stipe and stoma. The fruitbody is dark brown to black; and the ''root'' of the organism, the larval body pervaded by mycelium, appears yellowish to brown.

### Habitat

Cordyceps is a fungus with an annual appearance. The normal harvesting period is between the months of April and August. Fruiting off of moth larvae, Cordyceps thrives only at altitudes above 3800 m above sea level, in cold, grassy, alpine meadows on the mountainous Himalayan Plateau of modern day Tibet, Nepal, and Chinese provinces of Sichuan, Gansu, Hubei, Zhejiang, Shanxi, Guizhon, Qinghai, and Yunnan.

### Edibility

While not usually considered edible, because of its small size and rarity as well as its tough texture, Cordyceps has, however, been consumed traditionally as a medicine with a variety of meats in the form of a medicinal soup, with the type of meat used dependent upon the target medical condition.[12]

## HISTORY AND TRADITIONAL USES

Both resilient and rare, Chinese legends and myths of this revered healing mushroom and its chameleonic characteristics span the course of millennia. The first written record of the Cordyceps mushroom comes from China, in the year A.D. 620, at the time of the Tang Dynasty (A.D. 618–A.D. 907), bringing substance to the once intangible allegorical narrative, which spoke of a creature, whose annual existence alluded to a transformation from animal to plant in summer, and then again from plant to animal in winter. Tibetan scholars wrote of the healing animal/plant through the fifteenth to eighteenth centuries, and, in 1757, the earliest objective and scientifically reliable depiction of the Cordyceps mushroom was written by Wu-Yiluo in *Ben Cao Congxin* (''*New Compilation of Materia Medica*''), during the Qing Dynasty.

A member of the largest subdivision of true fungi, Ascomycotina, Cordyceps finds itself among other well-known fungi such as Penicillium, from which the antibiotic penicillin is derived, the most potent hallucinogen, L.S.D., derived from the plant-parasitic ergot fungus (*Claviceps purpurea*), and the most highly prized and rare fungal delicacies (truffles and morels). To date, hundreds of species of Cordyceps have been identified on six continents, in a variety of habitats, and with equally varied food sources.

The Cordyceps organism was discovered by yak herders in the Himalayas of ancient Tibet and Nepal who, recognizing the ardent behavior of their animals after grazing on Cordyceps at high altitudes in the spring, sought the causal agent. The cap-less mushroom they eventually found has been used in traditional Chinese medicine ever since to treat kidney, lung, and heart ailments, male and female sexual dysfunction, fatigue, cancer, hiccups, and serious injury, to relieve pain, and the symptoms of tuberculosis and hemorrhoids, to restore general health and appetite, and to promote longevity. More potent than Ginseng and worth four times its weight in silver in ancient times, Cordyceps has held, and continues to hold, a highly esteemed position in the vast ranks of Chinese pharmacopeia, which the West has only recently begun to incorporate into medical practices. Although it was once a rather exclusive medicine, modern cultivation techniques have made the mycelium of this caterpillar-borne fungus more readily available, lowering its cost on the world market, and allowing for more in-depth research into its healing potential.

## RELATED SPECIES AND ARTIFICIAL CULTIVATION

There are currently more than 680 documented species of Cordyceps, found on all six inhabited continents and in many climatic zones and habitats, and feeding off a range of hosts, including plants, insects, arachnids, and even other fungi, such as truffles. These figures are subject to rapid change, as what we know of this genus, and the life cycles of its constituents expand. As studies of related species continue, it has become increasingly apparent that the potential medicinal benefits of *C. sinensis* are, in fact, not related to only one species. Of the many different varieties of Cordyceps, those presently being cultivated for medicinal purposes and use in health supplements include *C. sinensis*, *C. militaris*, *C. sobolifera*, *C. subsessilus*, *C. ophioglossoides*, and others.

Because of the rarity and high prices of the wild collected variety, attempts have long been made to cultivate Cordyceps. By the mid-1980s, the majority of Cordyceps available in the world's marketplace were artificially cultivated.[2] Because of the development of modern biotechnology-based cultivation methods, the availability of this previously rare health supplement has greatly increased in the last 20 years.

The demand for Cordyceps has also compounded exponentially, in this same time frame, partly because of the opening of China to trade with the West in the 1970s, exposing many more people around the world to the concepts and practices of TCM. As Cordyceps has always been highly revered in TCM, it is reasonable that, with increased exposure to TCM, the demand for this herb has also increased. Such an increase has lead to overharvesting of the wild stocks and a subsequent shortage of wild collected varieties of Cordyceps.[2–4]

Many companies now produce artificially cultivated Cordyceps products, both from the mycelium and from the fruit body. The increase in supply has given rise to variations in purity and quality, creating a situation in which there are a large number of counterfeit and adulterated products being sold.[4] Recently, new methods for assaying the quality of Cordyceps products have been introduced.[2]

Another issue has been raised regarding the quality of Cordyceps: lead contamination. Incidents of lead poisoning from consumption of Cordyceps by people in China and Taiwan have been reported.[5] A practice of adulteration, long practiced by the collectors of natural Cordyceps, introduces excessive lead into the organism. As found in its natural state, Cordyceps is attached to the mummified body of the caterpillar, from which it arises. It is harvested whole in this form, dried, and supplied into the market. Because Cordyceps is sold by weight, the collectors have historically inserted a small bit of twig into many of the caterpillars, resulting in an increase in weight.[2] Better quality

**Fig. 1** Wire and twigs inserted into Cordyceps to increase weight.

Cordyceps traditionally had fewer inserted sticks; however, the practice has been so widespread for so long that it is virtually impossible to find wild collected Cordyceps without these fillers inserted (Figs. 1 and 2). This is probably a harmless practice, as long as the object inserted is derived from a nontoxic source.

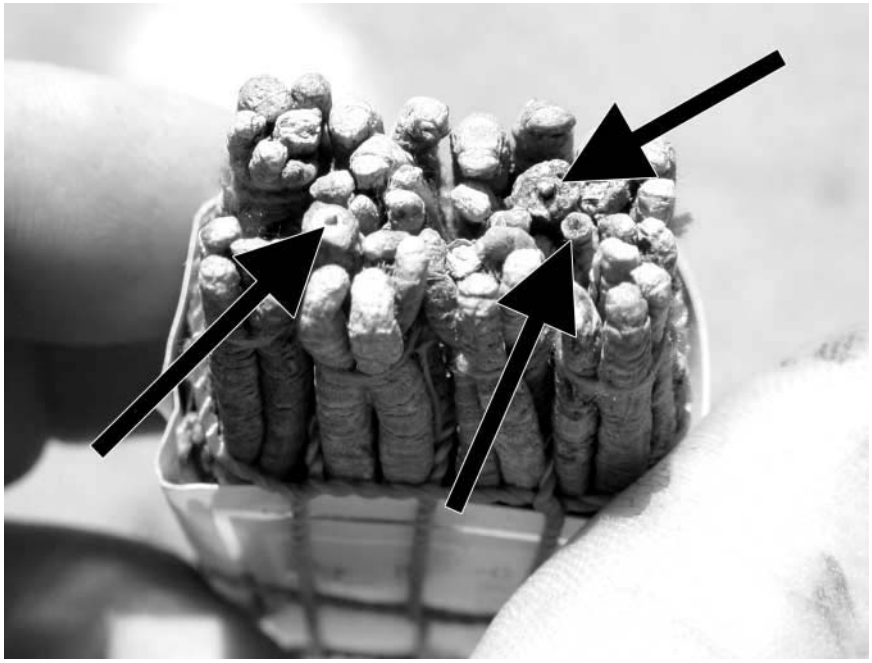

**Fig. 2** Inserted twigs and telltale holes.

But modern collectors have found that more weight can be gained if a bit of wire is inserted into the caterpillar, rather than the traditional twig. As long as the wire is steel, such a practice, as is the case with the aforementioned wood insertion, is probably not too harmful. Unfortunately, the wire of choice is now lead solder. A careful examination of the ends of the caterpillars will often reveal the holes where the sticks or wire have been inserted (Fig. 2), and anyone who chooses to use the wild collected Cordyceps, rather than the cultivated variety, would be well advised to break each one of the caterpillars in half before use, so that any bits of foreign matter can be readily discerned and removed.

Cultivated cordyceps appears to offer far less risk of lead contamination than the wild type. The presence of lead or other substances in the growth medium certainly could be absorbed by any growing organism. We have conducted chemical analysis on many thousands of Cordyceps samples over the years and observed that Cordyceps does not have any more tendency to accumulate lead or other heavy metals than do any other fungi.

## GENERAL NUTRITIONAL COMPONENTS OF CORDYCEPS

### Chemical Constituents

Cordyceps contains a broad range of compounds, which are considered nutritional.[1,2] It contains all of the essential amino acids, vitamins E and K, and the water-soluble vitamins B1, B2, and B12. In addition, it contains many sugars, including mono-, di-, and oligiosaccharides, and many complex polysaccharides, proteins, sterols, nucleosides, and trace elements (K, Na, Ca, Mg, Fe, Cu, Mn, Zn, Pi, Se, Al, Si, Ni, Sr, Ti, Cr, Ga, V, and Zr).

#### Potentially bioactive constituents

Cordycepin [3′-deoxyadenosine] and cordycepic acid [D-mannitol] were the initial bioactive compounds first isolated from *C. militaris*. Chen and Chu[6] announced the characterization of cordycepin and 2′-deoxyadenosine, using nuclear magnetic resonance (NMR) and infrared spectroscopy (IR) in an extract of *C. sinensis*. Other components found included various saccharides and polysaccharides, including cyclofurans, which are cyclic rings of five-carbon sugars, whose function is yet unknown, beta-glucans, beta-mannans, crosslinked beta-mannan polymers, and complex polysaccharides consisting of both five- and six-carbon sugars joined together in branching chains, employing both alpha- and beta-bonds. Many other nucleosides have been found in Cordyceps, including uridine, several distinct structures of deoxyuridines, adenosine, 2′3′-dideoxyadenosine, hydroxyethyladenosine, cordycepin [3′-deoxyadenosine], cordycepin triphosphate, guanidine, deoxyguanidine, and altered and deoxygenated nucleosides, which were not found anywhere else in nature (Fig. 3). Of particular note are various immunosuppressive compounds found in Cordyceps, including cyclosporin, a constituent of the species *C. subsessilis* [anamorph: *Tolypocladium inflatum*].[29] Other immunosuppressant compounds have also been found in *Isaria sinclairii*, a species closely related to Cordyceps.[7]

#### Polysaccharides

In the fungal kingdom, and particularly in Cordyceps, polysaccharides are perhaps the best known and understood of the medicinally active compounds.[8,9] A number of polysaccharides and other sugar derivatives, such as cordycepic acid [D-mannitol], have been identified. Research has shown that these polysaccharides are effective in regulating blood sugar,[10] and have antimetastatic and antitumor effects.[11]

#### Proteins and nitrogenous compounds

Cordyceps contains proteins, peptides, polyamines, and all essential amino acids. In addition, Cordyceps contains some uncommon cyclic dipeptides, including cyclo-[Gly-Pro], cyclo-[Leu-Pro], cyclo-[Val-Pro], cyclo-[Ala-Leu], cyclo-[Ala-Val], and cyclo-[Thr-Leu]. Small amounts of polyamines, such as 1,3-diamino propane, cadaverine, spermidine, spermine, and putrescine, have also been identified.

#### Sterols

A number of sterol type compounds have been found in Cordyceps: ergosterol, Delta-3 ergosterol, ergosterol peroxide, 3-sitosterol, daucosterol, and campeasterol, to name a few.[12]

#### Other constituents

Twenty-eight saturated and unsaturated fatty acids and their derivatives have been isolated from *C. sinensis*. Polar compounds of Cordyceps extracts include many compounds of alcohols and aldehydes.[12] Particularly interesting are the range of polycyclic aromatic hydrocarbons produced by *C. sinensis* as secondary metabolites. These PAH compounds react with the polypropylene used in common mushroom culture bags, resulting in the production of byproducts toxic to Cordyceps that stunt its growth as time progresses. Eventually, these polypropylene/PAH byproducts will kill the organism. For extended periods of growth,

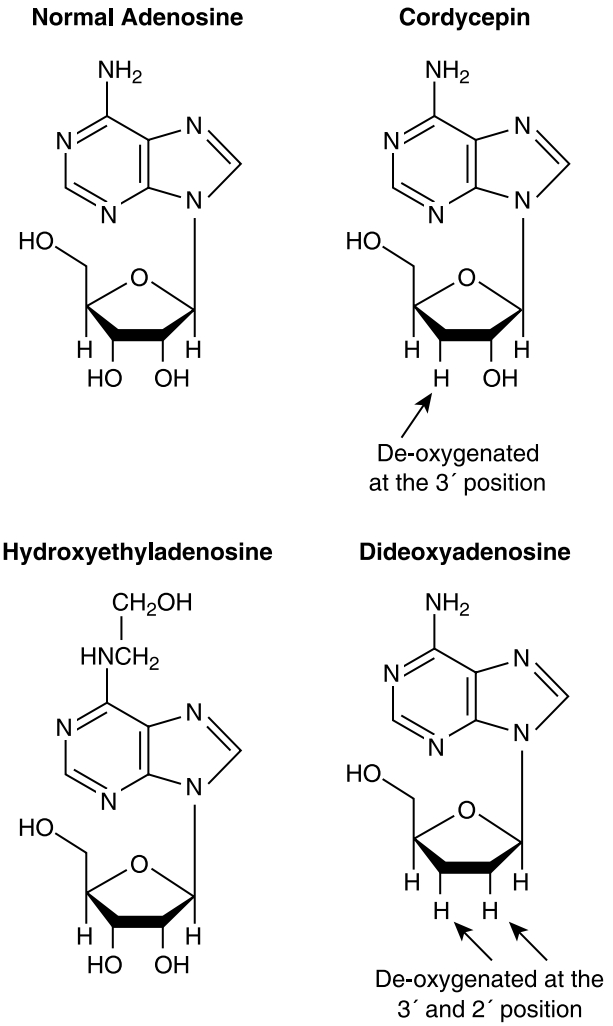


**Fig. 3** Some of the unique nucleosides found in Cordyceps.

*C. sinensis* must be grown in glass or metal containers.[2] The PAH compounds are present in the living culture, but are volatile compounds and are lost upon drying.

## THERAPEUTIC APPLICATIONS, INDICATIONS, AND USAGE

The range of therapeutic uses claimed for Cordyceps species is far reaching; and most of them have yet to be sufficiently investigated. In TCM, Cordyceps has been used to treat conditions including respiration and pulmonary diseases, renal, liver, and cardiovascular diseases, hypo sexuality, and hyperlipidemia. It is also used in the treatment of immune disorders and as an adjunct to modern cancer therapies (chemotherapy, radiation treatment, etc.).[12] Cordyceps is believed by many, particularly in and around Tibet, which is its place of origin, to be a remedy for weakness and fatigue, and it is often used as an overall rejuvenator for increased energy while recovering from a serious illness. Many also believe it to be a medicine for the treatment for impotence, acting as an aphrodisiac in both men and women. Cordyceps is often prescribed for the elderly to ease general aches and pains. Practitioners of TCM also recommend the regular use of Cordyceps to strengthen the body's resistance to infections, such as colds and flus, and to generally improve the homeostasis of the patient. Cordyceps is traditionally most often used in the treatment of health issues related to or stemming from the kidneys and the lungs. For example, it is used to ease a range of respiratory ailments: cough and phlegm, shortness of breath, bronchial discomfort, chronic obstructive pulmonary disease (COPD), and asthma. Modern science is attempting to confirm the efficacy of Cordyceps for most of its traditional uses; however, most medical studies regarding its efficacy remain incomplete.

Today in the West, Cordyceps is most widely used by two groups of people: athletes and the elderly. The use of Cordyceps by athletes stems from the publicity surrounding the performance exhibited by the Chinese women's track and field team at the Chinese National Games in 1993. In this competition, nine world records were broken by substantial margins. At first, governing sports authorities suspected that a performance-enhancing drug had been used, but the team's coach attributed their success to Cordyceps.[50]

An increase in cellular ATP[13,46] results in an increase in useful energy, in contrast to the perceived increase in energy, which occurs from the use of CNS stimulants, such as caffeine, ephedrine, and amphetamines, ultimately resulting in an energy deficiency. However, it should be noted that in a recent study with highly trained professional athletes, *C. sinensis* was shown to have no appreciable effect in enhancing the performance in this group of people.[15] We are not aware of any test that has been conducted showing a difference in the energy increase potential between highly trained athletes and normal healthy adults using Cordyceps.

## FATIGUE

Inhabitants in the high mountains of Tibet and Nepal consume Cordyceps, claiming that it gives them energy and offsets the symptoms of altitude sickness. The proposed reason for the alleged increase in energy is an increase in cellular ATP, as previously mentioned; likewise, increased oxygen availability has been posited as the primary agent in combating the effects of altitude sickness.

In a placebo-controlled clinical study of elderly patients with chronic fatigue, results indicated that

most of the subjects treated with *C. sinensis* reported a significant clinical improvement in the areas of fatigue, cold intolerance, dizziness, frequent nocturia, tinnitus, hypo sexuality, and amnesia, while no improvement was reported in the placebo group.[1,7,16–18] Another study involving healthy elderly volunteers, with an average age of 65, tested the output performance and oxygen capacity of subjects while exercising on stationary bicycles. A portion of the volunteers consumed *C. sinensis* for six weeks, while others consumed a placebo. The results demonstrated that the group that consumed Cordyceps had a significant increase in energy output and oxygen capacity over the other group after six weeks.[47]

Among the simplest and most reliable tests used to determine a compound's ability to increase the energy output of a subject or decrease fatigue is the mouse swim test. In this test, two groups of mice (or other animals) are used. One group receives a standard diet, while the other receives the same diet with the addition of the test compound. In this case, the test compound is Cordyceps. After a period of time, the two groups are put into a steep-sided container filled with water, from which escape is not possible. In this way, the animals are forced to swim. The time-to-exhaustion is measured for each group, which was compared and contrasted with that of the other. If the group receiving the test compound swims longer than the group on the standard diet without the test compound, then it has been determined that they had increased energy output/decreased fatigue when compared with the control group. Trials of this nature have been conducted using Cordyceps as the test compound and have invariably shown that the use of Cordyceps significantly increases the time-to-exhaustion in laboratory animals when compared with the control groups.[7]

## PRECLINICAL AND CLINICAL DATA

Therapeutic applications of Cordyceps and its extracts are hypothesized to be centered primarily on the key effects of increased oxygen utilization, increased ATP production, and the stabilization of blood sugar metabolism.[12] The presence of Adenosine, Cordycepin, and Cordycepic acid [D-Mannitol] (Chen and Chu[6]), polysaccharides, vitamins, and trace elements may be, at least partially, the cause for such effects. Because of the historically high cost of the fungus and the only recently developed methods for artificial cultivation, preclinical and clinical trials of Cordyceps and its extracts are still relatively new endeavors. Earlier trials, although few in number, have set the precedent from which modern trials are building, expanding, and cementing our understanding of Cordyceps.

## CANCER

A possibly valuable therapeutic application of Cordyceps is in the treatment for cancer, as an adjunct to chemotherapy, radiation, and other conventional and traditional cancer treatments.

### Animal Studies

The survival time of mice inoculated with murine B16 melanoma cells and treated with a combination of water extracts from *C. sinensis* and the conventional agent, methotrexate, has been shown to be significantly longer than that of either the untreated control group or those treated with methotrexate alone, indicating that some water extracts of *C. sinensis* may be beneficial in the prevention of tumor metastasis.[19]

Antitumor and immuno-stimulating activities were observed in the treatment of mice inoculated with Sarcoma 180 tumor cells, when treated with an ethanol extract of *C. sinensis*[20] (the reference refers to *Paecilomyces japonica*, which is believed to be an anamorph of *C. sinensis*), while a study using murine models verified that oral administration of a hot water extract of *C. sinensis* consequently resulted in the activation of macrophages, thereby increasing the production of GM-CSF and IL-6, which act on the systemic immune system.[21] In a study of mice subcutaneously implanted with lymphoma cells, oral administration of an extract of *C. sinensis* led to a decrease in tumor size and a prolonged survival time.[30] Furthermore, mice treated with cyclophosphamide, which suppresses immune function, also treated with the same hot water extract saw their immune function return to normal, as measured by the IgM and IgG response and macrophage activity.[30] Further evidence of the immunoenhancing action of *C. sinensis* was provided by another study treating mice inoculated with Erhlich ascites carcinoma (EAC) cells with a warm water extract of Cordyceps. The median survival time of the treated mice compared to untreated controls was over 300%, and the lack of activity of the extract against EAC cells grown in vitro indicated that the antitumor effect in the mice may be mediated through immunoenhancing activity, rather than directly.[31]

Oral administration of polysaccharide fractions CI-P and CI-A, derived from *C. sinensis*, in doses of 1–10 mg/kg/day, demonstrated antitumor activities in mice inoculated with Sarcoma 180. Similar results were observed with an alkali soluble polysaccharide (CI-6P), derived from the species *C. sobolifera*, when administered in doses of 10 mg/kg/day.[7] In a related study, B-(1-3)-D-glucan, fraction CO-1 and the galactosaminoglycan fraction CO-N, derived from *C. ophioglossoides*, inhibited the growth of ascitic Sarcoma 180.

Increased immune function was noted as well, quantified by an increase in carbon clearance activity.[22,23]

It is well established that numerous fungal derived simple- and protein-bound polysaccharides exert a significant potentiation of immune function.[9] This is thought to be one of the major mechanisms of antitumor activity in Cordyceps. Among the multiple polysaccharides produced by *C. sinensis*, beta-d-glucans are one class of polymers that have been shown to increase both innate and cell-mediated immune response. These polysaccharides increase the production of such cytokines as TNF-α, interleukins, interferons, NO, and antibodies by the activated immune cells. This activation of immune response may be triggered by polysaccharide binding to specific receptors on the surface of the immune systems cells, called the CR3 receptor.[24] They are also thought to be involved in cell-to-cell communications, perhaps acting as messenger molecules.

There is evidence of another mechanism at play in the antitumor response of Cordyceps, as well, pertaining to the structure of at least one, and possibly more, of the altered nucleosides found in some species of Cordyceps and exemplified by the compound cordycepin [3′-deoxyadenosine] (Fig. 1). These deoxynucleosides interfere with DNA replication in tumor cells. Such interference is reduced in normal healthy cells by the operation of a DNA repair mechanism, which is absent in tumor cells, and by the fact that tumor cells generally multiply at a rate well in excess of that of normal cells.

## Clinical Trials

Clinical studies have been conducted in China and Japan involving cancer patients,[25] yielding positive results. In one study of 50 patients with lung cancer who were administered *C. sinensis* at 6 g/day in conjunction with chemotherapy, tumors were reduced in size in 23 patients. A trial involving cancer patients with several different types of tumors found that *C. sinensis*, taken over a two-month period at 6 g/day, day, improved subjective symptoms in the majority of patients. White blood cell counts were kept at $3000/mm^3$ or higher; even with radiation or chemotherapy, other immunological parameters showed no significant change, while tumor size was significantly reduced in approximately half of the patients observed, indicating an improved tolerance for radiation and/or chemotherapy.[12]

A serious side effect of the use of conventional cancer chemotherapy and radiation therapy is the suppression of the patient's immune system. The use of *C. sinensis* in combination with conventional chemotherapy appears to have an immuno-stimulatory effect, which enhances the effectiveness of conventional chemotherapy by balancing its side effects.

The belief in the efficacy of *C. sinensis* against cancer is widespread in the Orient, and many cancer patients in Japan, Korea, and China are taking Cordyceps or some other mushroom-derived immunomodulator (such as PSK, PSP, Lentinan, AHCC, and Arabinoxylane [MGN3$^{TM}$]) while undergoing conventional treatment.[12,25,26]

## Immunomodulating Effects

Immuno-enhancing effects of *C. sinensis* have already been described. It is of interest to note that the fungus which produces the immuno-suppressive drug, cyclosporin, *Tolypocladium inflatum*, was discovered in 1996 to be the asexual stage of yet another Cordyceps species, *C. subsessilus*.[29] Thus, the same genus of fungus, having been used for centuries to provide immune stimulation, was now known to provide an immune suppressant valuable in organ transplantation surgery. Other such experiments demonstrating both inhibiting and potentiating effects of Cordyceps are controversial; and the effects observed are possibly the result of differing experimental conditions and variables. However, with such evidence of a possibly bidirectional immunomodulating effect,[28] further research is in order.

While the drug cyclosporin has allowed some advances in medicine, facilitating the transplant of organs, there has been a drawback to its use. The high toxicity of cyclosporin has caused many patients suffer from serious kidney damage, related to the use of the drug. In 1995, a study was undertaken in China in which 69 kidney-transplant patients were given either cyclosporin alone or in conjunction with *C. sinensis*, at 3 g/day. After 15 days it was clearly evident that the group receiving *C. sinensis* in addition to cyclosporin had a much lower incidence of kidney damage than the group receiving only cyclosporin, as measured by the levels of urinary NAG, serum creatinine, and blood urea nitrate.[27]

## KIDNEY AILMENTS

Traditional views of the Cordyceps mushroom held that its consumption strengthened the kidneys. Studies have shown that much of Cordyceps' kidney-enhancing potential stems from its ability to increase 17-hydroxy-corticosteroid and 17-ketosteroid levels in the body.[12]

Chronic renal failure is a serious disease, one often affecting the elderly. In a study among 51 patients suffering from chronic renal failure, it was found that the administration of 3–5 g/day of *C. sinensis* significantly improved both the kidney function and overall

immune function of treated patients, compared to the untreated control group.[32]

Patients with chronic renal failure or reduced kidney function often suffer from hypertension, proteinuria, and anemia. In a study with such patients, it was found that after one month on *C. sinensis*, a 15% reduction in blood pressure was observed. Urinary protein was also reduced. Additionally, increases in superoxide dismutase (SOD) were seen. The increase in SOD, coupled with an observed decrease in serum lipoperoxide, suggests an increase in the oxygen free radical scavenging capacity, resulting in reduced oxidative cellular damage.[33]

In another human clinical study, 57 patients with gentamicin-induced kidney damage were either treated with 4.5 g of Cordyceps per day or by other, more conventional methods. After six days, the group that received Cordyceps had recovered 89% of their normal kidney function, while the control group had recovered only 45% of normal kidney function. The time-to-recovery was also significantly shorter in the Cordyceps group when compared with that of the control group.[12]

## HYPOGLYCEMIC EFFECT

Another area of particular interest is the effect of Cordyceps on the blood glucose metabolism system. Cordyceps has been tested on animals and humans to investigate its potential as an agent in blood sugar regulation. In one randomized trial, 95% of patients treated with 3 g/day of *C. sinensis* saw improvement in their blood sugar profiles, while the control group showed only 54% improving with treatment by other methods.[34]

In animal studies, isolated polysaccharides have been shown to improve blood glucose metabolism and increase insulin sensitivity in normal animals,[35] to lower blood sugar levels in genetically diabetic animals,[36] and to positively affect blood sugar metabolism in animals with chemically induced diabetes.[37] The common thread throughout all these trials is the increase in insulin sensitivity and hepatic glucose-regulating enzymes, glucokinase and hexokinase.

In one unpublished trial conducted by us on nondiabetic patients treated with 3 g/day of Cordyceps, it was found that blood sugar levels vary throughout the day; the increase in blood glucose levels after eating and the dropping of glucose levels between meals were significantly dampened in the Cordyceps group. This indicates an increase in the efficiency of the blood sugar regulation mechanism. Furthermore, it was found that the subjects who happened to be alcoholic tended to lose their desire for alcohol within 48 hr after the commencement of this study. Subsequent unpublished and ongoing studies by us have confirmed this effect of reduction in alcohol craving. Further research into this area is clearly needed.

## LUNG AILMENTS

Chinese medicine has characterized *C. sinensis* as a guardian of respiratory health for more than a thousand years. There have been trials on humans, using Cordyceps to treat many respiratory illnesses, including asthma, COPD, and bronchitis, either alone or as an adjunct to standard antibiotic therapy, and in many studies that have been conducted, it appears to be useful for all of these conditions.[14,48,49,51–55]

Much of its reputation for protecting the lungs, again, is believed to stem from its ability to promote enhanced oxygen utilization efficacy. In environments lacking sufficient oxygen, mice treated with Cordyceps were able to survive up to three times longer than those left untreated, demonstrating a more efficient utilization of the available oxygen. This provides support for Cordyceps' long history of use in preventing and treating altitude sickness.[14] Such efficacy alludes to the use of Cordyceps as an effective treatment for bronchitis, asthma, and COPD. Extracts of *C. sinensis* have been shown to inhibit tracheal contractions, especially important in asthma patients, as it allows for increased airflow to the lungs. In addition, its anti-inflammatory properties may prove to bring further relief to asthma patients, whose airways become obstructed, because of an allergic reaction resulting in the swelling of the bronchial pathways.[1,12,38] In an unpublished clinical trial conducted at the Beijing Medical University involving 50 asthma patients, symptoms among the group treated with Cordyceps were reduced by 81.3%, within an average of five days; while among those treated with conventional antihistamines, the symptom reduction averaged only 61.1%, and took an average of nine days for symptoms to subside.[48,38]

## HEART AILMENTS

Cordyceps is also a medication used in stabilizing the heartbeat and correcting heart arrhythmias in China. While the exact mechanism responsible for Cordyceps' reputation with regard to controlling arrhythmias is not completely understood, it is thought to be at least partially because of the presence of adenosine,[39] of which Cordyceps often has a significant quantity, along with deoxyadenosine, related adenosine-type nucleotides, and nucleosides. It has been shown that these compounds have an effect on coronary and cerebral circulation.[40,41] While no single drug or herb is equally effective in all patients, it appears rare for a

patient's arrhythmia to remain unaffected by the addition of Cordyceps to the treatment regimen. Cordyceps has been used traditionally to treat patients with heart disease and those recovering from stroke.[1]

In studies of patients suffering from chronic heart failure, the long-term administration of Cordyceps, in conjunction with conventional treatments—digoxin, hydrochlorothiaside, dopamine, and dobutamine—promoted an increase in the overall quality of life. This included general physical condition, mental health, sexual drive, and cardiac function, compared to the control group.[18]

## LIVER AILMENTS

Another area of considerable research interest is the relation of Cordyceps and liver function. Cordyceps has been shown in nearly all such studies to enhance the efficient functioning of the liver. For example, in the Orient today, Cordyceps is commonly used as an adjunct in the treatment of chronic hepatitis B and C. In one study, Cordyceps extract was used in combination with several other medicinal mushroom extracts as an adjunct to lamivudine for the treatment of hepatitis B. Lamivudine is a common antiviral drug used in the treatment of hepatitis. In this study, the group receiving Cordyceps along with other medicinal mushroom extracts had much better results in a shorter period of time than the control group who received only lamivudine.[42]

In another study using 22 patients who were diagnosed with posthepatic cirrhosis,[43] after three months of consuming 6–9 g of Cordyceps per day, each patient showed improvement in liver function tests.

## HYPERCHOLESTEROLEMIA

While hypercholesterolemia is not typically considered a disease, it is a clear indicator of metabolism dysfunction and an indicator of increased cardiovascular risk. In both human and animal studies, administration of Cordyceps has been associated with cholesterol and triglyceride reduction and an increase in the ratio of HDL to LDL cholesterol.[1,12,13] Whether the causative mechanism for this lipid-balancing effect is through blood sugar stabilization, from enhancing liver function, or because of some other as yet unknown cause remains to be seen.

## USES AGAINST MALE/FEMALE SEXUAL DYSFUNCTION

Cordyceps has been used for centuries in traditional Chinese medicine to treat male and female sexual dysfunction, such as hypolibidinism and impotence. Preclinical data on the effects of *C. sinensis* on mice showed sex-steroid-like effects.[1,7] Human clinical trials have demonstrated similarly the effectiveness of Cordyceps in combating decreased sex-drive and virility.[14,44]

## OTHER USES

Many species of Cordyceps and other entomopathogenic fungi have been mentioned in scientific discourse in relation to their potential as biological control agents.[57]

## DOSAGE

Because clinical data on Cordyceps is relatively new, and even more so in Western countries, recommended dosage requirements may vary, depending on the source. In general, clinical trials have been conducted using 3–4.5 g of *C. sinensis* per day, except in cases of severe liver disease, where the dosage has usually been higher, in the range of 6–9 g/day.[1,7] There are some practitioners known to us, who keep their cancer patients on 30–50 g of Cordyceps per day. While this may seem excessive, the clinical results seen with this treatment regimen are promising, and Cordyceps-related toxicity has never been reported.

It has been traditionally taken in tea or eaten as whole, either by itself or cooked with a variety of meats. Today, in addition to the established traditional means of consumption, powdered mycelium and mycelial extracts are also available in capsulated and noncapsulated forms. At present, there are no reliable standards by which to compare different brands, but in general, the quality of Cordyceps is improving, as methods of more efficient cultivation are investigated; and as more clinical trials are conducted, a clearer picture of recommended dosages for a particular condition will become more standardized. Considering the quality of cultivated Cordyceps on the market today and the risk of lead exposure as well as the cost of the wild Cordyceps, use of natural Cordyceps over the artificially cultivated variety is not recommended. Obtaining Cordyceps from a reliable source, with complete analytical data provided, is the safest way to purchase Cordyceps.

### Safety Profile

Contraindications: none known.

### Drug Interactions

We have observational evidence that the alteration of the body's blood glucose metabolism, in patients consuming Cordyceps, often results in the reduction of oral or injected antidiabetic medications. It is also posited that the naturally occurring antiretroviral compounds found in Cordyceps (2′3′-dideoxyadenosine for example, which is found in *C. sinensis*, and which is marketed as a major anti-HIV drug under the name Videx™ and Didanosine™, as well as 3′-deoxyadenosine which has the same or at least similar activity) could increase the effectiveness or decrease the dosage requirements for patients undergoing concurrent therapy with other antiretroviral drugs. Caution should be exercised in these patients, especially considering the newer, more potent hybrid strains of Cordyceps being developed, and the targeted medicinal compounds being selectively cultivated. Many antiretroviral drugs currently on the market have quite considerable toxicity, and it is hoped that the incorporation of Cordyceps into the treatment regimen of those patients undergoing such therapy might result in a reduction of the toxic effects of some of these more toxic synthetic drugs, while sacrificing none of their efficacy. While no detrimental drug interactions have yet been noted in the scientific literature, caution is advised, as both the fields of pharmaceutical discovery and Cordyceps cultivation are rapidly expanding. As with any substance of considerable bioactivity, some drug interaction is always a possibility.

## SIDE EFFECTS

Very few toxic side effects have been demonstrated with Cordyceps use, although a very small number of people may experience dry mouth, nausea, or diarrhea.[12] One study reported that a patient had developed a systemic allergic reaction after taking Cs-4;[56] however this type of reaction is not common. There are little published data on the use of Cordyceps in pregnant or lactating women, or in very young children, but appropriate precautions should be taken with these types of patients.

## TOXICITY

Cordyceps has proven to be a nontoxic fungal substance with wide-ranging physical and chemical effects on the body. No human toxicity has been reported, and animal models failed to find an LD50 (median lethal dose) injected i.p. in mice at up to 80 g/kg per day, with no fatalities after seven days (Wang and Zhao, unpublished report; Xu, unpublished report). Given by mouth to rabbits for three months, at 10 g/kg per day ($n = 6$) no abnormalities were seen from blood tests or in kidney or liver function.[45]

## REGULATORY STATUS

Still relatively new to the scrutiny of modern science, Cordyceps remains, in many nations throughout the world, an unrecognized substance. Other than import/export taxes and restrictions, which vary from country to country (many of which ban the import of any such substance), most governments do not require a prescription to purchase or use Cordyceps. There are a few countries that do require a doctor's prescription: Portugal, Romania, and Austria, to name a few. Many governments require that vendors obtain a special license to distribute any product relating to human health.

In the U.S.A., Cordyceps is marketed privately and considered by the FDA as a dietary supplement. Generally Recognized As Safe (GRAS) applications referring to Cordyceps' status as a food additive are unavailable; however, a premarket notification to the FDA regarding Cordyceps, containing in-depth information relating to preclinical trials and toxicology studies has been available to the public on the FDA website, since 1999 at http://www.fda.gov/ohrms/dockets/dockets/95s0316/rpt0039.pdf.

## CONCLUSIONS

*Cordyceps* is a medicinal substance of long history and promising potential. Once so rare that only the emperor of China could afford to use it, modern biotechnology techniques have brought it within the reach of the common man. Western medicine is finally starting to realize some of the value of the Eastern system of medicine. This Oriental medicine, so perfectly typified by TCM, is really the result of thousands of years of human observation. And people are good observers. They are especially good observers about important issues such as health. Generations untold have been observing what happens when you eat this or that herb, and passing that information along from one generation to the next. Today, we have become so jaded that we think observations are not valid unless someone ''proves'' it in a lab. And in the last few years, our potential to prove has become incredible. We have developed ways to prove statistically if, how and why medicines work. *Cordyceps* is one of those ancient observational wonders that have passed the litmus test of long periods of observation and is now gaining scientific proof. It is clear from our studies, that we know only a little of the wonders of these strange

*Cordyceps* creatures. *Cordyceps* yet has many secrets in store for us.

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