On the Trail of The Yak

Ancient Cordyceps in the Modern World

John Holliday

Matt Cleaver

June 2004

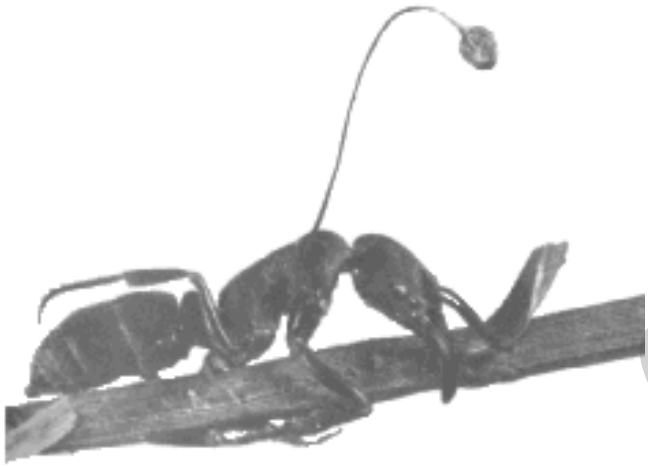


Illustration on the cover – *Cordyceps caustrali* growing out of an ant

Introduction

Cordyceps is a rare and exotic medicinal mushroom, known in China for centuries. One that reportedly has a number of far reaching medicinal effects. Most people in the West have come to know this rare herbal medicine in only the last twenty years or so. During that time, modern scientific investigation into its seemingly miraculous range of healing powers has proven what Chinese practitioners have noted for centuries: That it works well in combating a myriad of medicals problems. This chapter is an overview of the description and uses for this once rare medicinal treasure.

Name and general description

A medicinal herb of long and illustrious history, *Cordyceps sinensis* is an Ascomycetes fungus closely related to the mushrooms. While not actually a mushroom in the taxonomic sense, it has been regarded as, and called, a medicinal mushroom throughout history. We will continue that tradition in this paper – referring to it as a mushroom. Please excuse such literary license.

The name *Cordyceps* comes from the Latin words: *cord* and *ceps*, meaning "club" and "head", respectively. The Latin conjugation accurately describes the appearance of the club fungus, *Cordyceps sinensis*, whose stroma or fruitbody extend from the mummified carcasses of insect larvae, usually caterpillar larva of the Himalayan Bat Moth, *Hepialis armoricanus*.

In historical and general usage the term "*Cordyceps*" usually refers specifically to the specific species *Cordyceps sinensis,* but there are also many other closely related species that come under the general term of *Cordyceps*. While *Cordyceps sinensis* may be the species of *Cordyceps* that is most well known throughout the world, there are many other species in the genus *Cordyceps* in which modern science has found valuable medicinal properties in as well. In this paper we will generally use the term *Cordyceps* without the species designator, as many of the different species of *Cordyceps* fit the description and uses revealed herein. Where a specific species designation is important, that species name will be given as well.

Cordyceps sinensis

Cordyceps sinensis has been known and used 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 find and harvest. Because of the difficulties involved in harvesting this exotic medicinal, *Cordyceps* has always been one of the most expensive medicines known. This high price relegated it almost exclusively to members of the Emperor's court and other of the Chinese nobility, and it was historically beyond the reach of the average Chinese subject. Despite its cost and rarity, the unprecedented litany of medicinal uses for *Cordyceps* has made it a highly valued staple of the Chinese medical tradition.

A recognized wonder of the natural world for upwards of 2000 years in China and the surrounding Orient, knowledge of this incredible phenomenon only reached Western scientific audiences in 1726, when it was introduced at a scientific meeting in Paris. A Jesuit priest, who chronicled his experiences with the Cordyceps mushroom during his stay at the Chinese Emperor’s court, carried the first specimens back to

France. (Pereira, 1843) While always a rarity in nature, modern technological advancements in cultivation have made the prospect of affordable *Cordyceps* a reality, and its assembly of potential medicinal uses continues to augment therapy and gain audience as clinical trials proceed to scientifically prove what TCM practitioners have recognized for centuries, the legendary efficacy of the *Cordyceps* mushroom.

Mycological Data:

Kingdom- Fungi

Phylum- Ascomycota

Class- Ascomycetes

Order- Hypocreales

Family- Clavicipataceae

Genus- Cordyceps

Species- *Cordyceps Sinensis*

Basionym: *Sphaeria sinensis*

Synonyms: *Metarhyzium,Buevaria, Isaria*

Anomorphs: *Cephalosporium donqchongxiacao, Cephalosporium sinensis, Chrysosporium sinense, Hirsutella sinensis, Mortierella hepiali, Paecilomyces hepiali, Scytalidium sp., Scytalidium hepiali, Tolypocladium sinensis*

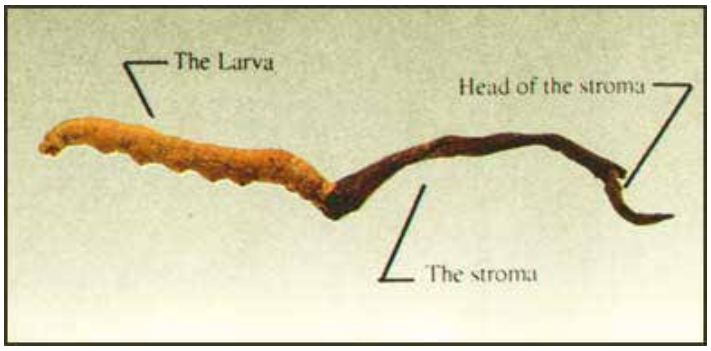
English names: Cordyceps mushroom, Caterpillar Fungus

Japanese names: Totsu kasu, Tochukasu

Chinese names: Hia tsao tong tchong, dongchongxiacao [chongcao], (Literal translation: "winter worm, summer plant" old Chinese; modern Chinese)

Description: The ascocarp or fruitbody of the *Cordyceps sinensis* mushroom originates at its base on an insect larval host (usually the larva of the Himalayan bat moth, *Hepialis armoricanus,* although occasionally other insect hosts besides the bat moth are encountered.) and ends at the club-like cap,

including the stipe and stroma. The fruitbody is dark brown to black; and the 'root' of the organism, the larval body pervaded by the mushroom's mycelium, appears yellowish to brown in color. The immature larvae, which forms the host upon which the *Cordyceps* grows, usually lives about 6 inches below ground, is ca. 10-15 mm long and has a weight of ca. 0.05 g. The infesting spores of the Cordyceps, which are thought by some mycologists to be the infectious agent for the insect, are ca. 5-10 um long. As the fungus approaches maturity, it will have consumed greater than 99 % of the infested organism, effectively mummifying the host. As the stroma matures, it will swell and develop perihelia. The average weight of an individual stroma is only ca. 0.06 g. Optimal conditions permitting; the spores are eventually discharged and taken by the wind or fall within a few centimeters of their origin.



Habitat: *Cordyceps* is a fungus with an annual appearance. The normal harvesting period is between the months of April and August. Fruiting off the larvae of the moths, *Cordyceps* thrives only at altitudes above 3,800 meters above sea level, in the cold, grassy, alpine meadows on the mountainous Himalayan Plateau of modern day Tibet, Nepal, and the modern Chinese provinces of: Sichuan, Gansu, Hubei, Zhejiang, Shanxi, Guizhon, Qinghai, and Yunnan. The caterpillar shows signs of the fungal infection underground in the spring, at which time the mycelium begins to decompose the host until fruiting is stimulated. This is after the food source (the caterpillar) has been depleted and winter gives way to the spring and summer months, when the thawing of snow at lower altitudes allows foragers to more easily find the mushroom. Whether it also fruits under the snow in the more severe months, while seeming unlikely, is at present unknown.

Cordyceps: Parasite or Symbiont?

Although the spore is possibly an "infectious" agent that attacks the moth larvae as some authors have advanced, it is worth noting that the entomopathogency of the C*ordyceps* mushroom is disputed. A growing body of logical and empirical data is suggesting to many prominent researchers that *Cordyceps sinensis* actually has a symbiotic relationship with the host; that the connection is mutually beneficial, rather than pathogenic. This stands to logical reason, considering the remote and inhospitable environment in which the moth/*Cordyceps* pairing occurs. Nature tends to select against a parasite, in that a parasite usually results in the death of the host. A more logical explanation for the unique pairing between an insect and this fungus would be that it is a mutually beneficial symbiosis, whereby the moth perhaps gains an energy boost from the Cordyceps living in it's body, as is known to occur when other animals consume *Cordyceps* (Jia et al 2004). In cultivation, *Cordyceps* often exhibits a single celled, yeast-like anamorph growth stage. Similar yeast-like symbionts of the genus *Cordyceps* have been found in other insects, most logically existing to some benefit of the host insect. (Suh et al 2001) If this is the case with the *Cordyceps*/moth pairing, then it may be the death of the insect host that is the stressor triggering the *Cordyceps* to produce its fruitbody. Once the host insect dies, the *Cordyceps* would have to go into a reproduce-or-die mode. In most fungi, the mycelium is the stable-state life form, rather than the more usually seen fruitbody. It is most common in the fungal kingdom that fruitbody formation does not happen unless and until some severe stressor occurs, forcing this defensive reproductive-phase response. In nature, these stressors are usually heat and cold, fire and flood, or the complete consumption of the food source and the resulting nutrient deficiency. In the laboratory it is very difficult to trigger *Cordyceps* to fruit, but when fruiting does occur, it is always in connection with one or more of these types of stressors.

Edibility: Not usually considered an edible mushroom due to its small size and rarity as well as its tough texture. Traditionally, *Cordyceps* has been consumed with a variety of meats in the form of a medicinal soup, with the type of meat used based upon the target medical condition. (Zhou et al 1998) In the medical usage of today *Cordyceps* is often taken with some form of vitamin C, which has been found to aid the body in its digestion and absorption of the medicinal components of the mushroom.

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 AD 620, at the time of the Tang Dynasty (AD 618-AD 907), bringing substance to the once intangible allegorical narrative, which spoke of a magical creature, who's annual existence alluded to a miraculous transformation from animal to plant, in summer, and then again from plant to animal, in winter. Published works on the subject continued; Tibetan scholars wrote of the mysterious 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 the author Wu-Yiluo in the Ben Cao Congxin ("New Compilation of Materia Medica"), during the Qing Dynasty.

A member of the largest subdivision of true fungi: Ascomycotina, C*ordyceps* finds itself amongst the most famous medicinals of the modern age; *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.

Discovered by yak herders in the Himalayas of ancient Tibet and Nepal, nature's disclosure of the *Cordyceps* organism was secondhand. Recognizing the ardent behavior of their animals after grazing on *Cordyceps* at high altitudes in the spring, these herdsmen 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. Due to its rarity, legend, and efficacy against a variety of health-related conditions, *Cordyceps* has held, and continues to hold, a highly esteemed position in the vast ranks of Chinese herbal remedies, which the

West has only recently begun to incorporate into officially accepted medical practices. Western descriptions of the health benefits of the *Cordyceps* mushroom came as early as the eighteenth century. The first such publication came from a French Jesuit priest named Perennin Jean Baptiste du Halde, who recounted his experiences with the mythical healing agent while a guest at the Emperor's court in China. Shortly after its introduction to the French scientific community, “hia tsao tong tchong” as it was then known, began to intrigue men of science and medicine. Perennin's illustration of the never-before seen association between a mushroom and an insect sparked the first Western concept of and interest in biological pest control. However, it wasn't until 1843, that the Reverend Dr. M.J. Berkeley, having published his findings in the New York Journal of Medicine, officially defined the “root” of the *Cordyceps* organism, which at that time, had been taxonomized as *Sphaeria sinensis*. Berkley described this “root” as he called it, as that of a caterpillar, which "had been taken over almost entirely by the mushroom's mycelium". *Sphaeria sinensis* was not moved into the *Cordyceps* genus until 1878, by Pier Andrea Saccardo, who was at that time the Professor of Natural History at the University of Padua, Illinois.

The evidence of its use as a medicinal by the Chinese-American community dates as far back as the early to mid-nineteenth century, when the Lloyd Brothers of Cincinnati, Ohio first marketed the mushroom in the United States. By the turn of the twentieth century, the Lloyd Bro’s company had become the largest producer of herbal remedies in the United States. Once a rather exclusive medicine, modern cultivation techniques have now made the mycelium of this caterpillar-borne fungus more readily available, lowering its cost on the world market and have allowed for more in-depth research into its healing potential.

Native Himalayan Habitat of *Cordyceps sinensis.* Elevation approx 5000 meters

Related Species And Artificial Cultivation

There are currently more than 680 documented species of *Cordyceps*. This number is subject to rapid change, as what we know of this genus and the life cycles of its constituents treads into unfamiliar territory. To date, species of the *Cordyceps* genus have been found on all six inhabited continents and in many climatic zones and habitats, and feeding off of a range of hosts, which include plants, insects and arachnids, and even other fungi (such as truffles). As studies of related species continues, it becomes increasingly obvious that the medicinal benefits of *Cordyceps* are not relegated to one species. Of these many different varieties of *Cordyceps*, those presently being cultivated for medicinal purposes and use in health supplements and pharmaceutical drugs worldwide include: *Cordyceps sinensis*, *Cordyceps militaris*, *Cordyceps sobolifera*, *Cordyceps subsessilus*, *Cordyceps ophioglossoides* and others. Cultivation methods of the *Cordyceps* genus are varied. Its mycelium is grown on a multitude of mediums, commercially most notable being spent insect larvae (silkworm residue) and various cereal grains. This fungus has, after some initial difficulty, been fruited from both insect larvae and grain based substrates. For medicinal purposes this is less important than one may think, as the analytical profile of the mycelium is very similar to the wild fruitbody, so that fruiting is not necessary in order to achieve a quality medicinal product. (Holliday et al 2004)

Due to the rarity and high prices of the wild collected variety, attempts have long been made to cultivate *Cordyceps.* After much early frustration in attempted cultivation, commercially viable methods were finally achieved in the late 1970's. By the mid 1980's, the majority of *Cordyceps* available in the world's marketplace was artificially cultivated. Because of the development of these modern biotechnology-based cultivation methods, the availability of this previously rare health supplement has greatly increased in the last twenty years. The demand for Cordyceps has also compounded exponentially in this same time frame, partly due to the fact that the opening of China with trade to the west in the 1970's exposed many more people around the world to the concepts and practices of Traditional Chinese Medicine (TCM). As Cordyceps has always been highly revered in TCM, it is natural that with increased exposure to TCM, the demand for this herb has also increased. This has lead to over-harvesting of the wild stocks and a subsequent shortage of wild collected varieties of *Cordyceps*. (Chen et al, 2000)

Due in part to this ever-increasing demand and the resulting endangerment of the wild stocks, the price of *Cordyceps* is ever compounding, which has lead to many companies now in the business of producing artificially cultivated *Cordyceps*. This increase in supply has lead to wide variations in the purity and quality of the different *Cordyceps* products available. This has also created a situation where there are an unacceptably large number of counterfeit and adulterated products being sold under the name *"Cordyceps*" by some less-than-ethical companies. (Hsu et al 2002) This is quite unfortunate as it undermines the public's trust and acceptance of what could be perhaps one of the most profoundly acting natural medicines ever known.

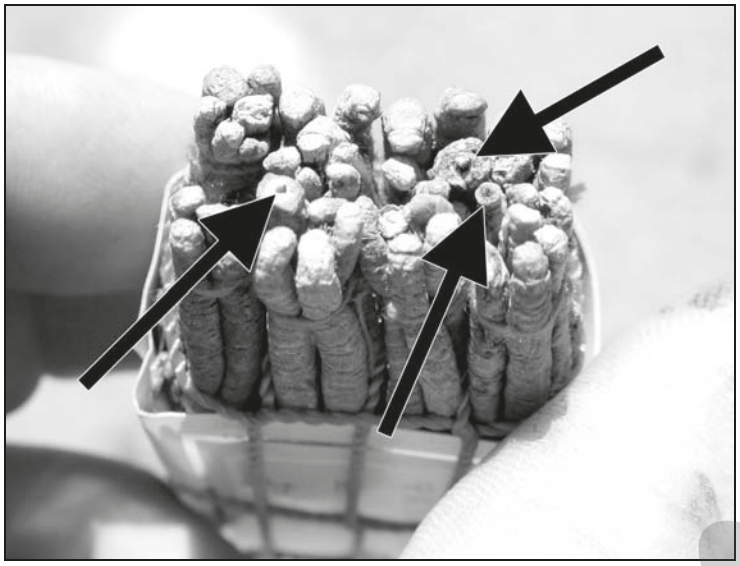
One of the main reason for this situation of adulterated and counterfeit *Cordyceps* products making their way into the market is that there are few standardized and accepted methods for assaying the purity or quality of *Cordyceps*. Not many of the end-users of *Cordyceps* know what it should taste, smell or look like, or perhaps it is compounded into some other product such as a functional food breakfast cereal, so how is the consumer to know what to expect? After using what has been represented to them as *Cordyceps*, and not achieving the desired health benefits, the consumer is unlikely to try the product again.

That situation is changing as more critical analytical methods become available (Holliday et al 2004). These modern computer-based analytical methods clearly define not only what is true *Cordyceps*, but also give a relative potency value, where different types and grades of *Cordyceps* from different sources can be fairly and consistently evaluated. The quality of the *Cordyceps* available is therefore increasing, and will continue to increase, as more of the commercial buyers demand analytical profiles of the *Cordyceps* to be provided from the manufacturer, before it is used in their products.

Another issue that has been raised regarding the quality of *Cordyceps* is the possibility of lead contamination. This is from reports that have arisen from cases of Lead Poisoning caused by consuming wild collected *Cordyceps* in China and Taiwan. (Wu et al 1996). This does not actually have to do with the *Cordyceps*, but rather with another practice of adulteration long practiced by the collectors of the natural *Cordyceps*. The *Cordyceps* as found in the natural state is attached to the mummified body of the caterpillar from which it arose. It is harvested whole in this way; dried and supplied into the market complete – caterpillar and fruitbody connected. Because the *Cordyceps* is sold by weight, the collectors have historically inserted a small bit of twig into many of the caterpillars. This results in an increase in weight, and a bit more money for the collectors when taken to market. Better quality *Cordyceps* traditionally had fewer inserted sticks, but the practice has been so widespread for so long that it is virtually impossible to find any wild collected *Cordyceps* without some of these fillers inserted. (see Illustration on the next page). While this is not an entirely ethical practice, it is probably a harmless one. As long as the type of twig inserted is from some non-toxic species of plant. But that is where the problem comes in. In our modern age, the collectors have found that they can gain much more weight if they insert a bit of wire into the caterpillar rather than the traditional twig. As long as the wire is steel, again this is probably not too harmful of a practice. But unfortunately, the wire of choice is lead solder due to its greater weight. The local tribes people that collect these wild Cordyceps for a living are generally not well educated, and few of them realize the dangers they are introducing into the product. They are merely trying to gain an economic advantage in the best way they know how.

Wire and Twigs inserted into Cordyceps to increase weight

A careful examination of the ends of the caterpillars will often reveal the holes where the sticks or wire has been inserted. This is shown in the illustration below.



Inserted Twigs and telltale holes

Consumption of these bits of lead wire, especially over long periods of time, can create a serious lead poisoning issue. Compounding this problem is the groups of patients most likely to be consuming *Cordyceps* over long periods of time are the ones most at risk: the elderly and infirm. Anyone who wishes to use the wild collected *Cordyceps* rather than the cultivated variety would be well advised to break each of the caterpillars in half before use, so that any bits of foreign matter can be readily discerned.

Cordyceps does not accumulate lead or other heavy metals any more so than other fungi. The problem is not, and has never been in the *Cordyceps* itself. It is in the lead wire. In that way, the artificially cultivated *Cordyceps* is much safer. There is no lead used in cultivating *Cordyceps*, and the adulteration of a dry powdered product with lead is neither practical nor really even possible, so there is no risk of lead poisoning with the use of cultivated *Cordyceps*.

***Cordyceps* growing on a dragonfly**

Therapeutic Applications

The range of therapeutic uses claimed for *Cordyceps* species is large indeed. In TCM, *Cordyceps* has been used to treat a wide range of conditions, including respiration, pulmonary diseases, renal, liver, cardiovascular diseases, hyposexuality, and hperlipidemia . It is also regularly used in all types of immune disorders, and as an adjunct in cancer therapy. (Zhou et al 1998) *Cordyceps* is thought to be a remedy for weakness and fatigue and is often used as an overall rejuvenator for increased energy while recovering from serious illness. It has a large following that believe it to be a cure for impotence or act as an aphrodisiac in both men and women. *Cordyceps* is often prescribed for the elderly to ease general aches

and pains. TCM practitioners also recommend regular use of *Cordyceps* to strengthen resistance to infections, treat colds and flues and generally improve the homeostasis of the patient. *Cordyceps* has traditionally been, and is still most often used for kidney and lung problems, or health issues thought to stem from the lung or kidney meridian. For example, it is used to ease a wide range of respiratory ailments such as to reduce cough and phlegm, shortness of breath, bronchial discomfort, COPD, and asthma. Modern science has confirmed the efficacy of *Cordyceps* for most, if not all, of the traditional uses.

Today in the West *Cordyceps* is most widely used by two groups of people: Athletes and the elderly. The use of *Cordyceps* by athletes stem from the publicity surrounding the remarkable performance exhibited by the Chinese Women's Track and Field team at the Chinese National games in 1993. In that competition, 9 worlds records were broken, and not just by a little bit, but by startling amounts! At first the governing sports authorities suspected that some performance-enhancing drug had been used. But it was freely admitted by the team's coach that the secret to their success was in the *Cordyceps* he had been giving the team! Recent research has confirmed that *Cordyceps* usage increase both the cellular ATP level (Guowei, 2001) and the oxygen utilization (Jia-Shi Zhu, 2004). ATP (adenosine tri-phosphate) is the molecule that actually releases energy in the cell. We talk about consuming fats, and proteins and starches to gain energy, but what it all boils down to at the cellular level is ATP. ATP releases energy in the cell by losing a phosphate and converting from a three-phosphate form of adenosine to a two-phosphate form, called ADP (adenosine di-phosphate). When the ATP loses a phosphate, the breaking of that bond releases energy that is then available for the cell to use. An increase in cellular ATP means a real increase in actual energy, energy that is available for use. This contrasts to the perceived increase in energy such as that which occurs from the use of CNS stimulants such as caffeine, ephedrine and the amphetamines. While some drugs such as amphetamines may make the patient feel like they have more energy, they actually don't. That is a CNS effect rather than a cellular effect, and it results ultimately in an energy deficiency. That is why amphetamines lead to weight loss. The brain thinks there is plenty of energy to burn and keeps going. But of course with no actual extra energy available for the moment-by-moment needs of the cell, the body is forced to draw on its reserves, the fat stores. With *Cordyceps* use, the double

effect of increased ATP and better oxygen utilization go hand-in-hand; more fuel to burn and more oxygen to burn it with. This is why athletes gain extra energy with *Cordyceps* and soldiers use it for the lessening of fatigue. It has also found favor with the elderly for much the same thing; extra energy and easier breathing.

An interesting note is that the energy and performance increases seen with *Cordyceps* may be more profound in people that are less than optimally fit verses the highly trained athlete. In one recent study, *Cordyceps* was tested in highly trained professional athletes and, contrary to most of the other studies that have been done on the performance of non-professional athletes, it was shown to have no appreciable effect in increasing performance. Perhaps these subjects were already optimally fit, and an increase in available ATP or oxygen utilization was of no significant physiological value to them. (Parcell et al 2004) For the rest of us though, it seems that *Cordyceps* could supply that bit of extra energy we need to get through our day-to-day hectic lifestyle. Perhaps we should consider *Cordyceps* to be the ancient herbal treatment for the stresses of modern life.

***Cordyceps tuberculata* growing out of the head of a moth**

Fatigue

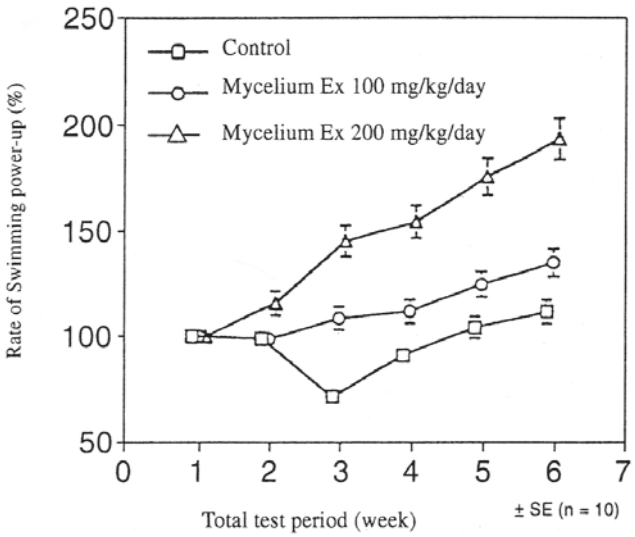
Of all the effects that *Cordyceps* is noted for, perhaps the one that is best known is the relief of fatigue. There is an ancient legend told in the Himalayas, relating the way *Cordyceps* was originally found; it was from a time long ago, when the tribes people of Tibet and Nepal took their animals into the high mountain pastures for springtime grazing. There they would see goats and yaks grazing on some sort of a small, brown grass-like mushroom, growing from the head of a caterpillar. After eating this strange looking creature, the animals would become frisky and start chasing the other goats and yaks around with lustful intent. I guess this added vigor must have looked like a pretty good thing to those tribes' people, so they started collecting these small mushrooms and eating them as well. They got frisky as well, and even a bit lustful, or so the story goes…

Today, those people that live in the high mountains consume *Cordyceps* on a regular basis. It gives them energy, and offsets the symptoms of altitude sickness. With *Cordyceps* at their disposal, they are able to trek higher into the mountains and stay there for longer periods of time. We now know the reason for this energy boosting effect to be this increase of cellular ATP as mentioned earlier. In addition, the increased oxygen availability facilitated from taking *Cordyceps* would also assist in these high altitude jaunts. *Cordyceps* is in regular used today by most high altitude mountain climbers, and it is doubtful if Mount Everest would get nearly so many visitors if it were not for the remarkable fatigue reducing effectiveness of *Cordyceps*.

In a placebo-controlled clinical study of elderly patients with chronic fatigue, results showed that most treated with C*ordyceps sinensis* reported significant clinical improvement in the areas of fatigue, cold intolerance, dizziness, frequent nocturia, tinnitus, hyposexuality, and amnesia, while no improvement was reported in the placebo group. (Cao and Wen, 1993; Zhang et al., 1995). This is a pretty clear indication that *Cordyceps* works in addressing some of the issues affecting the elderly. Another study with healthy elderly volunteers, average age of 65, tested the output performance and the oxygen capacity of the subjects, while exercising on stationary bicycles, either taking *Cordyceps* for 6 weeks or while taking a

placebo. The results showed that the Cordyceps group had a significant increase in energy output and oxygen capacity over the placebo group after 6 week on *Cordyceps*.

One of the simplest and most reliable tests used to determine whether a compound can increase energy output or decrease fatigue is the mouse swim test. In this test, two groups of mice (or rats, or dogs, or other animals) are used. One group gets the normal diet and the other group a normal diet with the addition of the test substance, *Cordyceps* in this case. After a period of time on the test substance, the two groups of animals are put into a steep-sided container full of water from which they cannot escape, a five-gallon bucket for example. That way they are forced to swim. The time-to-exhaustion is measured for the two groups and compared. If the group receiving the test compound swims longer than the group on the normal diet, then it has been determined that they had increased energy output and/or decreased fatigue than the other group. Many trials of this nature have been conducted using *Cordyceps* and invariably they show that the use of *Cordyceps* significantly increases the time to exhaustion in the test animals. An example of this test is seen in this illustration from the article by Mizuno, 1999.



Mouse Swim Test w/ Cordyceps

Preclinical And Clinical Data

The therapeutic applications of *Cordyceps* and its extracts are hypothesized to be centered primarily around the key effects of increased oxygen utilization, increased ATP production, and the stabilization of blood sugar metabolism. The presence of Adenosine, Cordycepin, Cordycepic acid, the Polysaccharides and vitamins and trace elements may be at least partially the cause of these well-known effects. Due to 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 have been rather recent endeavors. Earlier trials, although relatively few in number, have set the precedent from which modern trials are building, expanding, and cementing our understanding of *Cordyceps*.

Cancer

One of the most exciting benefits of *Cordyceps* is its potential as a source of new anti-cancer drugs. *Cordyceps* is currently being recommended and used by a growing number of doctors worldwide as an adjunct to chemotherapy, radiation and other conventional and traditional cancer treatments. It has shown remarkable prowess in not only inhibiting the growth of, and in some cases even dissolving certain types of tumors, but also as a means by which the immune system and indeed the body in general may be kept strong and vital as it is being devastated by the effects of chemotherapy and radiation treatment. (Nakamura et al 2003) Its secondary effects on immune function help the body to more efficiently manage its immune resources while undergoing the stresses of the attack by cancer, (Shin et al 2003) allowing it to recognize, eradicate, and prevent abnormalities and disease, both at the local and the systemic level. (Koh et al 2002).

Antitumor Effect

Administration of polysaccharides fractions CI-P and CI-A derived from *Cordyceps* in doses of one to ten mg/kg per day, demonstrated substantial antitumor activities in mice with sarcoma 180. An alkali soluble polysaccharide, named CI-6P, derived from the species *Cordyceps sobolifera*, yielded remarkable results against murine sarcoma 180 when administered in doses of 10 mg/kg/day. (Mizuno 1999) In a related study, B-(1- 3)-D-glucan, fraction CO-1 and the galactosaminoglycan fraction CO-N, derived from *Cordyceps ophioglossoides*, inhibited the growth of ascitic Sarcoma 180. Increased immune function was detected as well, quantified by an increase in carbon clearance activity. (Ohmori 1998, 1999) In one study, the CO-N fraction of *Cordyceps ophioglossoides* showed a remarkable effectiveness against the sarcoma 180 cell line, which is a reference solid tumor used for laboratory assays of anti-tumor effectiveness. A single dose of only 0.5 mg/kg-injected i.p into mice inhibited tumor growth by an

astounding 98.7%! (Ohmori et al 1986). This nearly complete tumor inhibition certainly heralds some positive potential in the development of new anticancer drugs and treatment modalities.

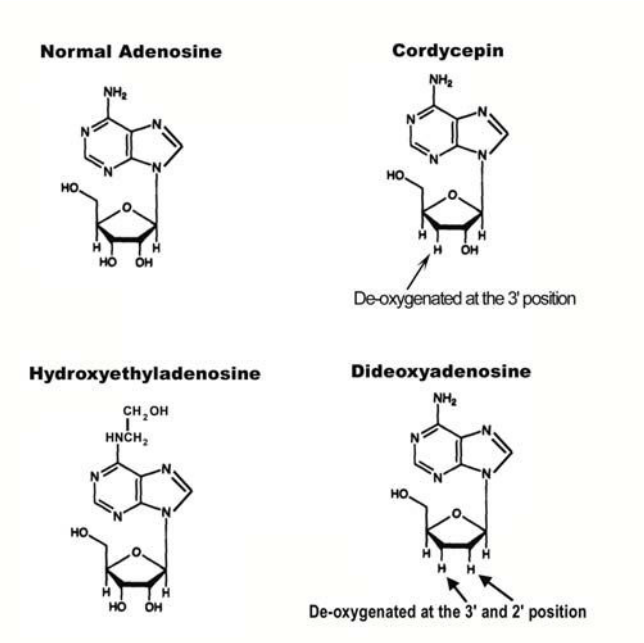
It is well established that numerous fungal derived simple- and protein-bound polysaccharides exert a significant potentiation of immune function. (Wasser, 2002) This is thought to be one of the major mechanisms of antitumor action by *Cordyceps*. Among the multiple polysaccharides produced by *Cordyceps*, beta-d-glucans are one class of these polymers that have been shown to increase both innate and cell-mediated immune response. These polysaccharides increase the production of such cytokines as TNF-a, interleukins, and 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. (Smith et al 2002). They are also thought to be involved in cell-to-cell communications, perhaps by acting as messenger molecules.

Many clinical studies, conducted in China and Japan with cancer patients (Wang et al 2001) with whom *Cordyceps* was used, have yielded positive results. In one study of fifty patients with lung cancer who were administered *Cordyceps* At 6 grams per day in conjunction with chemotherapy, tumors were reduced in size in 46% of patients studied. A trial involving cancer patients with several different types of tumors found that *Cordyceps* taken over a two month period at 6 g per day, improved subjective symptoms in the majority of patients. White blood cell counts were kept high while tumor size was significantly reduced in approximately half of the patients. (Zhou et al (1998)

***Cordyceps ophioglossoides* growing from a truffle**

Mechanism Of Action For Cordycepin (see illustrations on following 3 pages to follow steps)

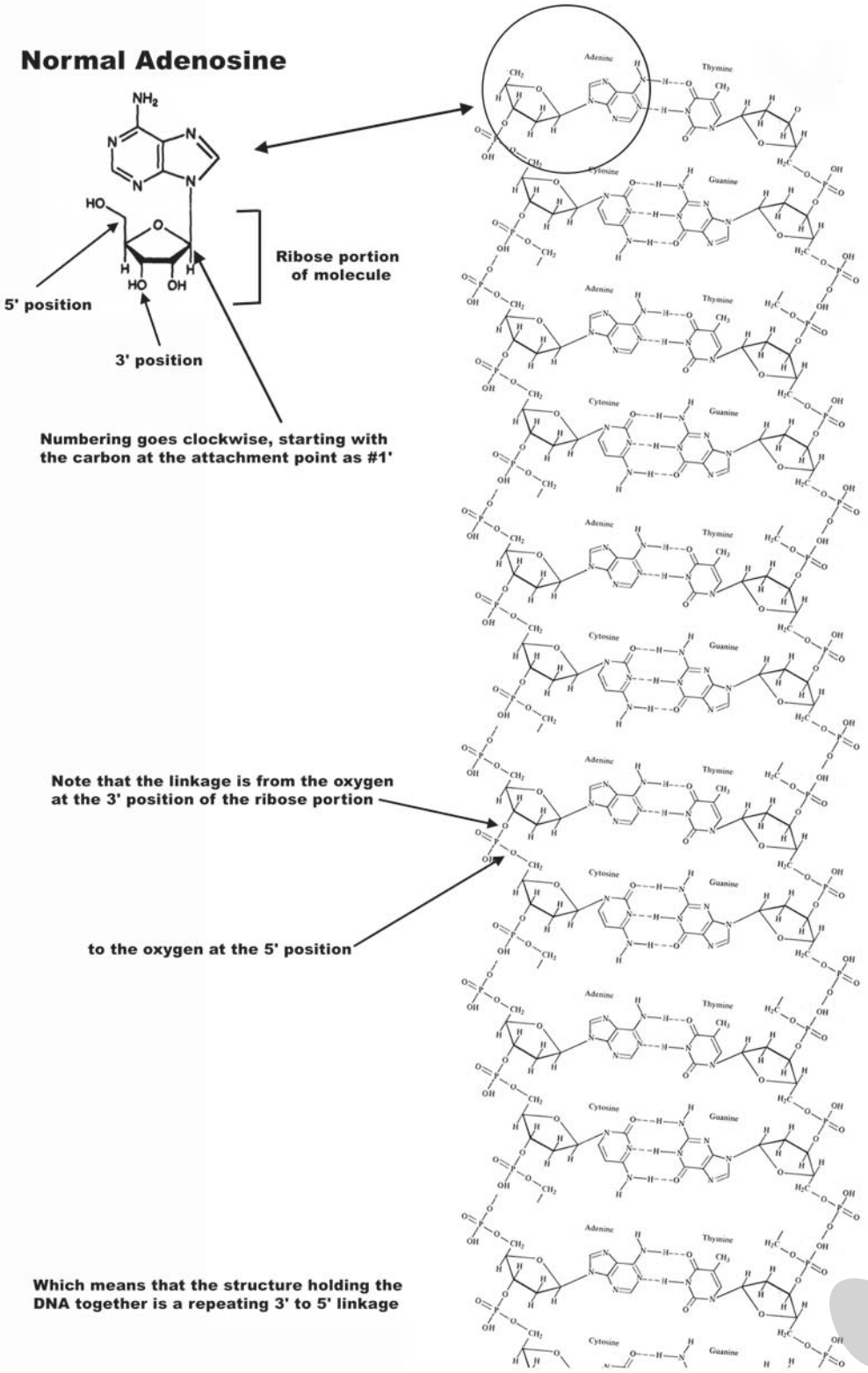
There is evidence of another mechanism at play in the *Cordyceps* antitumor response besides the well-known immune modulation triggered by the polysaccharide compounds. This other mechanism has to do with the structure of at least some of the altered nucleosides found in *Cordyceps*, exemplified by the compound cordycepin [3'deoxyadenosine]. This is a molecule almost identical to normal adenosine, with the exception that it is lacking an oxygen atom on the ribose portion of the molecule at the 3' position. The same lack of this 3' oxygen can be seen in other *Cordyceps* compounds as well, such as Dideoxyadenosine, (Didanosine™, Videx™). The lack of oxygen at this particular position is thought to be important in a very specific way. The structure of DNA depends on this oxygen to create the bond between adjacent nucleosides. This bond is between the 3' and the 5' positions on the ribose portions of the nucleosides, effectively forming the 'ladder structure' that holds the DNA together. In the replication of any cell, the first step is the separation of the DNA molecule down the middle, like unzipping, between the pairs of complimentary nucleosides. The next step is the insertion, one at a time, of new compliment nucleosides. These form hydrogen bonds between the complement pairs, and form phosphate-sugar bonds between the 3' and 5' position at the outside edge of the molecule, which is the ribose portion. This, in essence, is the structure that holds the DNA together. The synthesis of the new DNA molecules proceeds apace, with the sequential insertion of new compliment nucleosides one at a time into the newly forming DNA molecule, until the original strand of DNA is replicated twice, each of these strands being exact copies of the original and forming the genetic code for a new generation of cells. That is, this synthesis continues to proceed with the insertion of each new nucleoside, unless a 3' deoxyadenosine (cordycepin) molecule is pulled in. When this happens, there is no oxygen present at that vital position to form the 3'-5' bond, and the replication of the new DNA molecule stops. Once the DNA synthesis stops, the cell cannot continue to divide and no new cell is formed. In normal mammalian cells, this insertion of the deoxygenated adenosine is of little importance, as healthy cells have an inherent DNA repair mechanism. When this sort of error occurs, the altered nucleoside (the cordycepin) is removed from the string of nucleosides, and a new segment of adenosine is inserted. However, by their very nature, cancer cells have lost this DNA repair mechanism. (If they could correct their DNA errors, they would not be cancer cells).



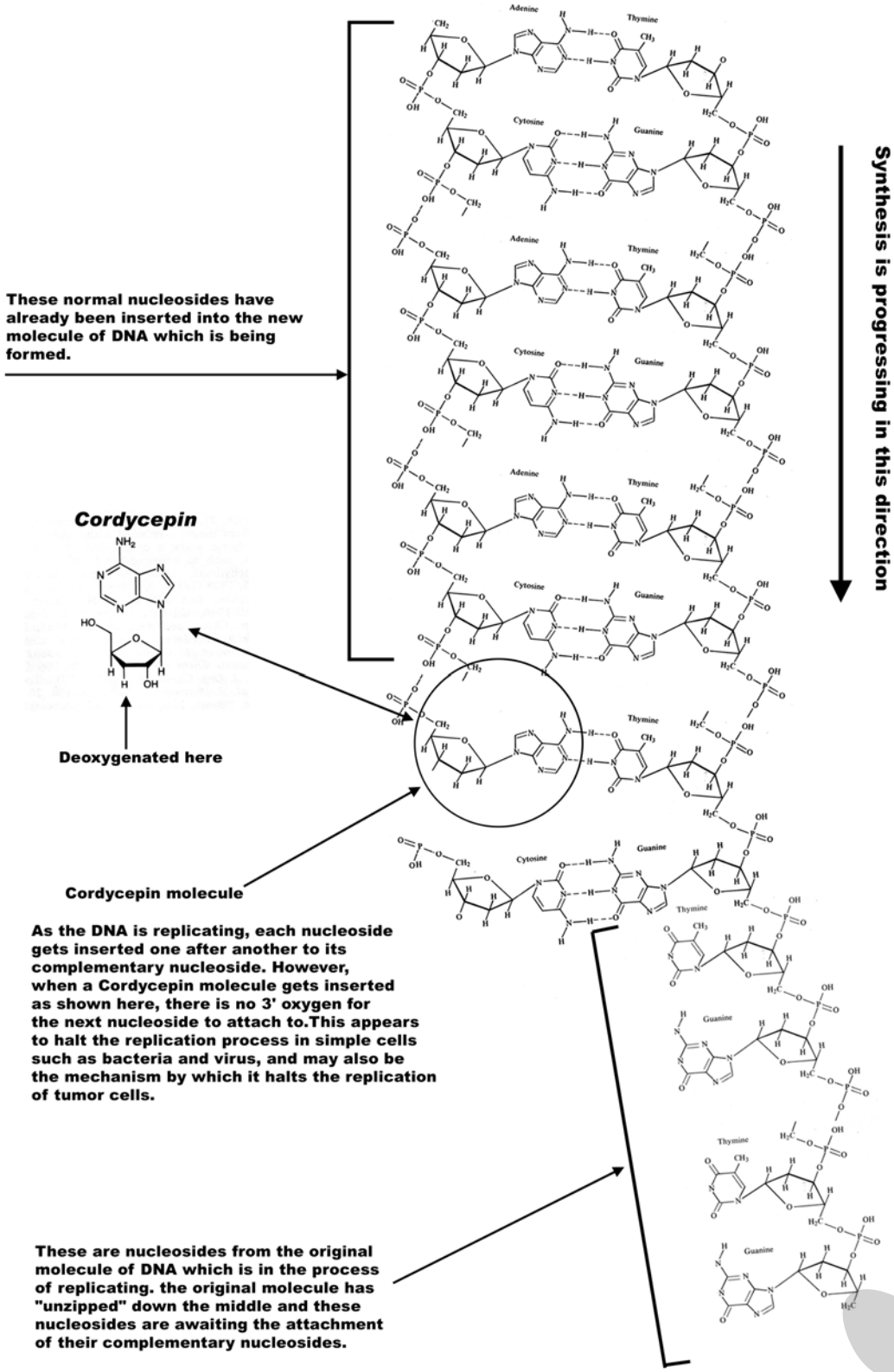
Some of the unique nucleosides found in *Cordyceps*

Most bacteria and all viruses (including the HIV virus) lack this DNA repair mechanism. When we look at the rate at which cancer cells replicate, it is clear how this mechanism could exert a significant antitumor response. For example, normal healthy breast tissue cells have an average life span of about 10 days, after which the reproduce and a new cell is formed. But breast cancer cells multiply much quicker than healthy cells. They reproduce themselves on average every 20 minutes. This means that the breast cancer cells are replicating about 750 times faster than the surrounding healthy tissue. If the cordycepin were equally toxic to both types of cells, it would be killing off the cancer cells 750 times faster than the healthy cells. But because of that DNA repair mechanism in the healthy cells, cordycepin appears not to interfere with the healthy cell replication, and the tumor-cell kill rate is actually much higher than the 750-to-1 ratio. The same sort of DNA interruption mechanism is responsible for the antitumor effects of some other chemotherapy agents as well. This same mechanism of DNA synthesis inhibition is probably the responsible mechanism for the anti-viral effects seen with cordycepin as well. See the following illustrations for a structural analysis of this mechanism. (Holliday 2004b) (Liu and Zheng, 1993 and others by inference)

(1) Structural Arrangement of DNA



(2) Cordycepin Halts DNA Replication



Chemo- and Radio-Preventive Effects

The normal type of clinical trial conducted in America is the placebo-controlled trial, where only half of the patients get the test compound and the other half get a placebo, which is an inactive sugar pill. Because of the seriousness of cancer, it is very uncommon to see placebo-controlled clinical trials with human patients performed in the Orient where most *Cordyceps* research is done. Rather in most of the world, ethical considerations dictate that the very best standard of care is given to a sick patient, with the addition of the promising new drug or herbal medicine added to this treatment regimen. The results are then compared against patients receiving the same types of treatments without the additional drug or herb. There have been many trials of this nature done with *Cordyceps*. In fact, the knowledge of *Cordyceps'* efficacy against cancer is so widespread in the Orient that by far the vast majority of cancer patients in Japan, Korea and China are already taking *Cordyceps* or some other mushroom derived immune modulator while undergoing conventional treatment. Because of this widespread usage, it is a well known fact that *Cordyceps* and other fungal derived polysaccharide immunomodulators (such as PSK, PSP, Lentinan, AHCC and arabinoxilanes [MGN3™]) will reduce the severity and duration of side effects associated with Chemo and Radiation therapy. (Wang et al 2001)(Xu et al 1988)

Chemotherapy's Limitation And How *Cordyceps* Can Help

The single most limiting factor in the effectiveness of chemotherapy treatment for cancer is the toxic destruction of the patient's immune system by the chemotherapy agents themselves. It is a little known fact outside the medical profession that many more patients die of opportunistic infections during chemotherapy than ever die of the cancer itself. The white blood cell count of the cancer patient is carefully monitored during chemotherapy and the dosage and/or the schedule of treatments is adjusted to maintain an adequate immune system. In fact, the pause between chemotherapy treatments is exactly for this reason, to let the immune system recover sufficiently so that the patient can withstand another dose of the toxic medication. The idea is to introduce a toxic compound into the body (the chemotherapy) and hopefully it will kill off the tumor cells quicker than it kills off the healthy cells. Unfortunately the white blood cells are rather sensitive to the chemotherapy compounds used. They tend to die off much quicker than other healthy tissue cells when under this chemotherapy barrage. This leaves the body in an immune-

deficient state. Anything that can bolster the patient's immune response means that the dosage of the chemotherapy can be increased, or the delay before which the follow-up treatments can be given is shortened, both of which will increase the effectiveness of the chemotherapy. This is one of the main mechanisms by which *Cordyceps* appears to increase the effectiveness of conventional cancer treatment. The reduction in chemotherapy and radiation side effects is most likely due to the maintenance of a stronger innate immune function when compared to patients who are receiving the same chemo- or radiation treatments without the addition of *Cordyceps*. Many other mushroom-derived polysaccharides appear to exert this same function in the body.

Immunomodulating Effects

There is an extensive body of research looking at the immune enhancement and immune suppression properties of various species of *Cordyceps*. This bi-directional regulation of immune function, which can be either up-regulated or down-regulated, is termed immunomodulation, and seems to come from the same mechanism in the body. When *Cordyceps* is given to a patient in an immune-deficient state, such as cancer, hepatitis or HIV infection, the number and activity of the white blood cells increase. Conversely, if the same *Cordyceps* is given to someone in a hyper-immune state such as is found in Lupus, Lymphoma or Rheumatoid arthritis, the number and activity of the white blood cells drop, while the red blood cells often increase in number. How can the same compound be both an immune stimulant in some patients and yet act in other patients as an immune depressant? The mechanism appears to be in the differentiation phase of blood cell production. The blood cells are all produced in the bone marrow, primarily in the long bones of the legs. They leave the bone marrow as immature cells, and travel to other organs where they mature into specific types of blood cells such as red blood cells, T-cells, natural killer cells and others. It would appear that *Cordyceps* exerts some influence over the differentiation mechanism that signals the body where to direct these immature cells for maturation. This mechanism is clearly shown in studies looking at the way *Cordyceps* effects leukemia cells maturing. (Chen et al 1997) This immunomodulation-at-the-differentiation level is like nature's smart bomb against disease. The body gets the signal it needs to mount an effective response to a disease state, whether the problem is too great an immune response or not enough.

Cordyceps And Human Organ Transplants

In 1976 the soil of Norway yielded up an interesting filamentous fungi. It was noted that like many filamentous fungi living in the soil, this one, named *Tolypocladium inflatum*, produced some metabolic compounds with potent anti-fungal properties. In the research with this fungus to develop new anti-fungal drugs, it was found that the unique compounds produced by *Tolypocladium* had an even greater potential: Anti rejection drugs. In the transplantation of human organs, the problem has always been the tendency for the recipient body's immune system to see the new tissue as a foreign invader and mount an aggressive immune response against it. That would nearly always mean the organ was rejected, resulting in a near certainty of the patient's death. In trying the anti-fungal drug developed from *Tolypocladium* called Cyclosporin on transplant patients, it was quickly realized that when this drug was used, the patients did not have as much of a tendency to reject their new organs. This appears to be a down-regulation of the immune system, or perhaps the cyclosporin is acting somehow as an anti-recognition factor. This is virtually the only use of cyclosporin today, as an anti-rejection drug for transplant patients. It was not until 1996, that it was discovered *Tolypocladium inflatum* was the asexual stage of another *Cordyceps: Cordyceps subsessilus*. (Segelken 2002) The same genus of fungus that has been used for centuries in providing immune stimulation to sick patients is now known to also provide an immune dampening for other sick patients. *Cordyceps* is the sole medicine that has made human organ transplants possible.

***Cordyceps subsessilus* growing out of an insect buried in a log**

While the drug Cyclosporin has allowed some miraculous advances in medicine in that it makes it possible to transplant organs, there has been a drawback in its use. The toxicity of Cyclosporin is high and many patients suffer from serious kidney damage related to the use of Cyclosporin. In 1995, a study was undertaken in China, where 69 kidney transplant patients were given either Cyclosporin alone, or in conjunction with *Cordyceps sinensis* at 3 grams per day. After 15 days it was clearly evident that the group receiving *Cordyceps sinensis* in addition to the Cyclosporin had a much lower incidence of kidney damage then the group receiving only the Cyclosporin, as measure by the levels of urinary NAG, serum creatinine and blood urea nitrate. (Xu et al 1995)

But *Cordyceps* is not by any means only an immune suppressant. It has also has been shown in many studies to increase immune function as well as suppress it. A study was conducted using mice as models, to determine if *Cordyceps* would increase the activation of macrophages and the intestinal immune system. This is a very important study since the intestinal immune response constitutes approximately 70% of our overall immune protective response. The intestines are bombarded daily with all sorts of foreign invaders which would live in us and use us as a food source if they could. It is the intestinal immune system that is the first line of defense against such an invasion. In the mouse study, it was found that when the mice were given a hot water extract of *Cordyceps sinensis* the activation of macrophages was roughly doubled. Furthermore, the production of certain cytokines, such as GM-CSF and IL-6 also more than doubled. These cytokines are known to act on the systemic immune system, so it can be assumed that from these results that an overall intensification of the systemic immune system would also occur from the consumption of such a hot water extract of the *Cordyceps*. (Koh et al 2002)

Many drugs used in the prevention or treatment of diseases and the amelioration of symptoms can suppress the immune system to a considerable extent. Some examples of these are the steroid drugs such as Prednisone, and many (if not all) of the chemotherapy agents used in combating cancer, such as Cyclophosphamide and 5-FU. In a study of *Cordyceps* on lymphomic mice to see if it would increase their life span, it was shown that the mice lived significantly longer with the addition of 50 mg/kg/day orally of a hot water extract of *Cordyceps sinensis.* Furthermore, a group of mice in this test were being

treated with cyclophosphamide, which drastically suppressed their immune function. The group of mice receiving the *Cordyceps* along with the cyclophosphamide had no significant reduction in immune function, but rather their immune function return to normal as measured by the IgM and IgG response as well as macrophage activity. (Yamaguchi et al 1990)

Cordyceps sinensis has been shown to be highly effective in treating mice with implanted Ehrlich ascites carcinoma, with a survival rate of 80% at 60 days following the tumor cell implantation. This is quite an amazing survival rate for such an aggressive form of cancer, yet when the same *Cordyceps sinensis* extract was tested in vitro against the Ehrlich ascites carcinoma cells, no antitumor effect whatsoever was found. This would seem to indicate that the mechanism of action is not a direct cytotoxicity against the cancer cells, but rather it is some type of host-mediated immune response that allows the host's immune system to effectively fight off the cancer's invasion. (Yoshida et al 1989)

Kidney

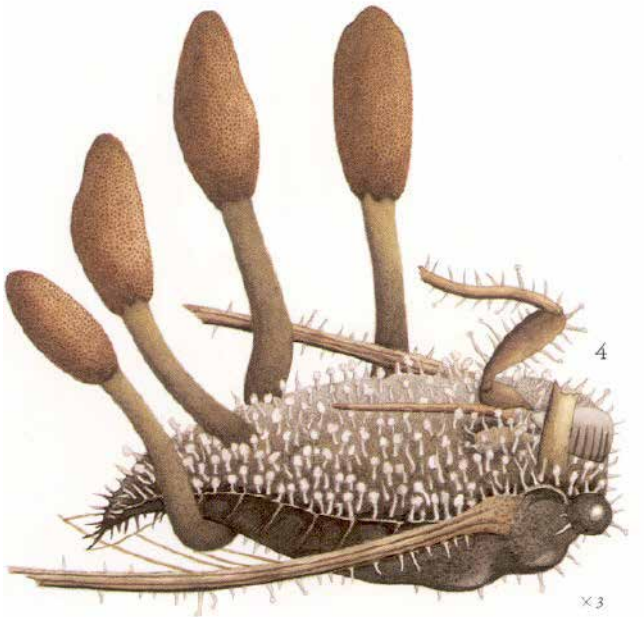
Traditional views of the *Cordyceps* mushroom held that its consumption strengthened the kidneys. Given its vast array of uses, it is interesting to note that what is being discovered today is that kidney health, perhaps more than that of any other organ, is a virtual cornerstone of the body's health. When the kidneys fail, the effects are normally felt via other organs and systems consequently affected. In this way, taking into consideration only its effect on the kidneys, *Cordyceps* truly was a promoter of overall health and homeostasis. Many other traditional uses for this mushroom can be traced back to proper kidney health. Fatigue, impotence, joint and back pain, even ringing in the ears are all symptoms of degenerative kidney health. It has been shown that much of *Cordyceps* kidney enhancing potential comes from its ability to increase 17-hydroxy-corticosteroid and 17-ketosteroid levels. (Zhou et al 1998)

Chronic renal failure is a serious disease, one often affecting the elderly. In a study with 51 patients suffering Chronic Renal Failure, it was found that the administration of 3-5 grams per day of *Cordyceps sinensis* significantly improved both the kidney function and the overall immune function of the patients

receiving *Cordyceps,* as compared to the control group who did not receive the *Cordyceps*. (Guan et al 1992)

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 *Cordyceps*, a 15% reduction in blood pressure was observed. Urinary protein was also significantly reduced. Additionally, increases in superoxide dismutase (SOD) were seen. This increase in SOD coupled to an observed decrease in serum lipoperoxide suggests an increase in the oxygen free radical scavenging capacity, which results in reduced oxidative cellular damage. (Jiang and Gao, 1995)

In another human clinical study, 57 patients with gentamicin-induced kidney damage were either treated with 4.5 grams 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 to the control group.



***Cordyceps minuta* on beetle**

Represented here are just a few of the many tests conducted on kidney function with *Cordyceps*, both animal and human, showing *Cordyceps* to be of particular value in maintaining kidney health and in restoring function to diseased and damaged kidneys. It appears to be a low cost, low toxicity medicinal that is well tolerated and has real value for clinical application in this field.

Hypoglycelmic Effect

Another area where there has been a lot of research done is in the effect of *Cordyceps* on the blood glucose metabolism system. Diabetes is a serious problem, especially in countries with a Western diet. The present estimate of the number of type 2, or adult onset, diabetics in the United States alone is greater than 25 million, and it is one of the fastest growing health problems we face. Worldwide the number of diabetics is estimated at more than 350 million. Another disease that seems to be closely related to diabetes is alcoholism. Alcoholic tend to have a much higher rate of diabetes and hypoglycemia than is found in society as a whole. Whether the alcohol causes the blood sugar metabolism disorders, or if people with blood sugar metabolism disorders have a greater tendency to abuse alcohol is unclear. In either case, *Cordyceps* has been shown to help both diabetics and alcoholics.

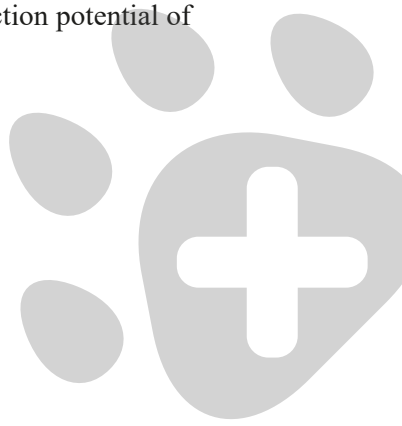
Traditionally Diabetes has been classified into two main types (Type 1 and Type 2). Type 1 diabetes causes the affected person to be dependant for life upon the use of insulin. It usually begins early in life and is caused when the immune system attacks and destroys the insulin producing cells of the pancreas. Type 1 Diabetes accounts for about 10% of all people who have the disease. Type 2, or adult onset diabetes, accounts for the other 90%. This type of diabetes usually begins later in life (adult onset) and is caused by the development of cellular resistance to the action of insulin (insulin desensitization). This appears to be caused by the consumption of too much sugar and refined carbohydrate over long periods of time. While this cause and effect relationship is still controversial, there is mounting evidence that the over-consumption of these refined carbohydrates will cause a state of chronic hyperinsulinemia in the body, and this in turn could be what causes the loss of insulin sensitivity at the cellular level. Whatever the cause or classification, diabetes is a very serious disease. It is the leading cause of blindness, end stage kidney disease and lower limb amputations. It also increases the risk of stroke, high blood pressure,

increases in blood cholesterol levels and cardiovascular disease. Diabetes not only causes its own list of deleterious effects, but it also increases the likelihood and severity of many other diseases as well.

Cordyceps has been tested in a number of animal and human trials for the potential as a blood sugar regulation agent, and it has performed very well in this roll indeed. In one randomized trial, 95% of the patients treated with 3 grams per day of *Cordyceps* saw improvement in their blood sugar profiles, while the control group showed only 54% improving with treatment by other methods. (Guo and Zhang 1995)

In animal trials, it has been shown to improve blood glucose metabolism and increase insulin sensitivity in normal animals (Zhao et al 2002), to lower blood sugar levels in genetically diabetic animals (Kiho et al 2000) and to positively effect blood sugar metabolism in animals with chemically induced diabetes. (Tai-Hao and Hui-Chen, 2002). The common thread throughout all of these trials is the increase in insulin sensitivity and the increase in the livers' output of the glucose regulating enzymes glucokinase and hexokinase. In short, it appears that whatever the cause or classification, *Cordyceps* can be useful in the control of the diabetic patient, either as a single agent or in conjunction with other drugs.

In one unpublished trial conducted by this author on non-diabetic patients treated with 3 grams/day of *Cordyceps*, it was found that the normal blood sugar swings which occur throughout the day, that is the increase in blood glucose levels after eating and the dropping of glucose levels between meals, was significantly dampened in the *Cordyceps* group. The blood sugar did not go as high after eating, and it did not drop down as low between meals. This would indicate an increase in efficiency of the blood sugar regulation mechanism. Even more interesting was the finding in this study that the subjects who also happened to be alcoholics, all lost their desire for alcohol with 48 hrs of commencing the *Cordyceps* regimen. Subsequent studies have confirmed this observation in the alcohol-craving reduction potential of *Cordyceps*. Further research into this area is clearly indicated.



Lung

Chinese medicine has characterized Cordyceps as a guardian of respiratory health for more than a thousand years. Much of its reputation for protecting the lungs is believed to come from its ability to promote enhanced oxygen utilization efficacy. In environments lacking sufficient oxygen levels, 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 is objective confirmation of *Cordyceps* long history of use in preventing and treating altitude sickness. (Zhu et al 1998) Such efficacy alludes to the use of *Cordyceps* as an effective treatment for Bronchitis, Asthma, and Chronic Obstructive Pulmonary Disease (COPD). Extracts of *Cordyceps sinensis* have been shown to inhibit tracheal contractions, especially important for asthma patients in that it allows for increased airflow to the lungs. In addition, its anti-inflammatory properties bring further relief to asthma patients, whose airways become obstructed, due to an allergic reaction resulting in swelling of the bronchial pathways. In a clinical trial involving fifty asthma patients, efficacy against symptoms among the group treated with *Cordyceps* was 81.3%, within an average of five days; while among those treated with conventional antihistamines the rate was only 61.1%, and took an average of nine days for symptoms to subside (Halpern 1999).

There has been very extensive trials in humans, using *Cordyceps* to treat all manner of respiratory illnesses, including asthma, COPD, and bronchitis, either alone or as an adjunct to standard antibiotic therapy. It has proven useful for all of these conditions. (Zhu, et al 1998) What has been observed for centuries by thousands of TCM practitioners, that *Cordyceps* improves respiratory function, is now a well-proven and well-accepted scientific fact.

Cordyceps Myrmecophila

Heart

One of the more profound actions of *Cordyceps*, both traditionally and in modern practice is its ability to stabilize the heart beat and correct heart arrhythmias. This herb is one of the first line medications of choice for this serious condition in China today. While the exact reasons and mechanism for *Cordyceps* excellent reputation in controlling arrhythmias are only partly understood, it is thought to be at least partially due to the presence of adenosine. (Pelleg et al 1990). *Cordyceps* often contains a significant quantity of adenosine, deoxyadenosine and related adenosine type nucleotides and nucleosides present. It has been shown that these compounds have a widespread effect on coronary and cerebral circulation. (Toda et al 1982) (Bern 1980) While no single drug or herb is equally effective in all patients, it is rare that a patient's arrhythmia does not benefited from the addition of *Cordyceps* to the treatment regimen. *Cordyceps* is not known to adversely react with any other arrhythmia medication, and with its low toxicity, it seems to be an excellent choice for this condition. *Cordyceps* has been used traditionally for heart disease and stroke patients.

In studies of patients suffering from chronic heart failure the long-term administration of *Cordyceps* in combination 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 (Chen, 1995).

Liver

Another area where a considerable amount of research has been done is in the area of *Cordyceps* and liver function. It has been shown in nearly all such studies that *Cordyceps* increases the efficient functioning of this major organ. 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 the *Cordyceps* and other medicinal mushroom extract*s* had a much better outcome in a shorter period of time than the control group who received only the lamivudine. (Wang et al 2002)

Liu et al (1986) reported on another study done with 22 patients who were diagnosed with post hepatic cirrhosis. After 3 months of consuming 6-9 grams of Cordyceps per day, all patients showed dramatic improvement in liver function tests.

Another interesting study was done in 1994 in China, where 70 patients with chronic hepatitis B and post hepatic cirrhosis were treated either with *Cordyceps* or with another herbal combination of proven effectiveness against liver disease, whose main ingredient was the medicinal mushroom *Ganoderma applanatum*. In that study a significant clinical response was seen in 68% of the *Cordyceps* patients and in 57% of the *Ganoderma* patients. This shows that *Cordyceps* is a bit better at treating this type of liver disease than is the *Ganoderma applanatum*, which is a type of Reishi. (Yang et al 1994)

Hypercholesterolemia

While hypercholesterolemia is usually not considered a disease in its own right, it is certainly a clear indicator of dysfunction of the metabolism and an indicator of increased cardiovascular risk. The mechanism by which cholesterol, and indeed all blood lipids, becomes out of balance is only partly understood. The liver is the main source of both cholesterol production and elimination; therefore it stands to reason that any disorders of the liver could affect the blood levels of cholesterol and triglycerides. It is also well known that diabetes can and usually does lead to hyperlipidemia. Dietary fats can influence the amount of lipids in the blood, but it is now known that dietary fat consumption is not as great a factor in hypercholesterolemia and hyperlipidemia as was once thought. In both human and animal studies, administration of *Cordyceps* has been associated with cholesterol and triglyceride reduction and an increase in ratio of HDL to LDL cholesterol. Whether the causative mechanism for this lipid balancing effect is through blood sugar stabilization, or from enhancing liver function, or whether it is due to some other as yet unknown cause remains to be seen. The main importance though is that *Cordyceps* is well proven through many formal trials and clinical observations to act in a positive way with regards to maintaining healthy cholesterol and triglyceride levels. It is interesting to note other fungal-derived compounds that also have a profound effect on hypercholesterolemia: The statin drugs, which are the

number one class of drugs used worldwide for lowering cholesterol, are produced by several types of fungi, particularly the oyster mushrooms of the genus *Pleurotus*. (Wasser, 2002) There is another compound found in the shiitake mushroom (*Lentinula edodes*) called eritadenine, which also has a major effect on hypercholesterolemia, although it acts through a different mechanism than that of the statins. While the statins interfere with the production of cholesterol in the liver by inhibiting certain enzymes, eritadenine appears to act by increasing the breakdown and elimination of cholesterol. The fungi as a group then have shown considerable potential in lowering excessive cholesterol and triglycerides, and perhaps the best approach to take would be to try a mixture of *Cordyceps* with other medicinal mushrooms such as oyster mushrooms and shiitakes for patients that have a problem with hypercholesterolemia.

Cordyceps canadensis

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 *Cordyceps sinensis* on mice showed sex-steroid-like effects (Wan et. al., 1988). Human clinical trials have demonstrated similarly the effectiveness of *Cordyceps* in combating decreased sex-drive. The results of one such study (Yang et al., 1995) showed an increase in 24-hour urine 17-keto-steroid, compared to the control group.

“These results indicated that CS-4 might affect patients' sexual drive and functions, either via sex hormone systems or by directly acting on the sexual organs, in parallel with the effects on the hypothalomo-pituitary-adrenocortical axis." (Zhu, 1998) The presence of amino acids, vitamins, zinc, and other trace elements found in Cordyceps are hypothesized to account for increased sperm survival rates, as demonstrated in clinical and preclinical studies (Guo, 1986). In three separate studies done in China on a total of 756 patients who were reporting decreased sex drive (hypolibidinism); the patients were given either a placebo or *Cordyceps sinensis* at 3 grams per day for 40 days. By the completion of the 40-day study, 64.8% of the patients in the *Cordyceps* groups reported improvement in their sex drive, while only 23.8% showed improvement in the placebo group. In these three related studies alone, 492 patients with a noted lack of sex drive found relief from this condition by using *Cordyceps.* In another study on both elderly men and women with complaints of decreased libido, impotence and other sexual malfunctions, *Cordyceps* was given at 3 grams per day for 40 days, and several measurements were taken to determine the degree of improvement. Increased sperm survival time, increased sperm count and decreased number of malformed sperm were noted in the majority of male subjects, as well as more than double the number of patients reporting reversal of their impotence. Improvements in hypoleukorrhagia, menoxenia and sex drive were noted in the majority of women subjects. (Zhu et al 1998) *Cordyceps* is clearly indicated as a therapeutic agent in treating hypolibidenism and other sexual malfunction in both men and women.

Dosage

Because clinical data on *Cordyceps* is relatively new, recommended dosage requirements may vary, depending on the source. In general, the clinical trials have been conducted on 3 – 4.5 grams of *Cordyceps* per day, except in cases of severe liver disease, when the dosage used has usually been higher, in the range of 6-9 grams per day. There are some practitioners known to this author that keep their cancer patients on 30-50 grams of *Cordyceps* per day. While this may seem a bit excessive, the clinical results seen with this treatment regimen are excellent, and no *Cordyceps* related toxicity has been reported. It has been traditionally taken in tea or eaten 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 non-capsulated form. At present there are no reliable standards by which to compare different brands of *Cordyceps*, but generally *Cordyceps* quality is improving. As more clinical trials are reported on, the dosages for particular conditions will become more standardized. Considering the excellent 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 the natural *Cordyceps* rather than the cultivated type makes little sense. Buying *Cordyceps* from a reliable supplier with complete analytical data provided is the best and most cost effective way to get this once rare herbal medicine.

Safety Profile

Contraindications. None known. Caution should be used in insulin dependent diabetics as hypoglycemia can occur in diabetics taking insulin or other oral anti-diabetes drugs due to *Cordyceps* increasing the insulin receptivity of the cells.

Drug Interactions

There is some observational evidence that alteration of the body's blood glucose metabolism in patients consuming *Cordyceps* often results in 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) could result in increased effectiveness or decreased 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 they are being selectively cultivated for. Many of the 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 some of these more toxic synthetic drugs, while sacrificing none of the efficacy. While no detrimental drug interactions have yet been noted in the scientific literature, caution should be advised, as both the fields of pharmaceutical discovery and *Cordyceps* cultivation are both rapidly expanding. With any substance of such considerable bioactivity as *Cordyceps* has proven to be, 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. Increased libido is the most common side effect reported by people under treatment with *Cordyceps*, however few people will complain about that. Many people find that when they first take *Cordyceps*, they will experience a feeling of mental clarity, sometimes bordering on the state induced in the early stages of LSD intoxication, where the colors all seem brighter and everything seems to stand out with crystal clarity. These effects usually clear up within a couple of days of *Cordyceps* use. There have been reported very occasional allergic reactions to *Cordyceps*, but this type of reaction is not common. There is little published data on the use of *Cordyceps* in pregnant or lactating women, or in very young children, so normal appropriate precautions should be taken with these types of patients.

Toxicity

Cordyceps has proven to be a very non-toxic herbal substance for something with the obviously wide-ranging physical effects on the body. While no human toxicity has been reported, animal models have found an LD_{50} of 27 g/kg when injected i.p. in mice. Given by mouth to rabbits for 3 months at 80 grams/day, no abnormalities were seen from blood tests or in kidney or liver function. (Huang et al 1987). *Cordyceps* is thought to be a very safe substance with a minimal potential of toxicity.

Commercially available wild Cordyceps sinensis

General Nutritional Components Of *Cordyceps*

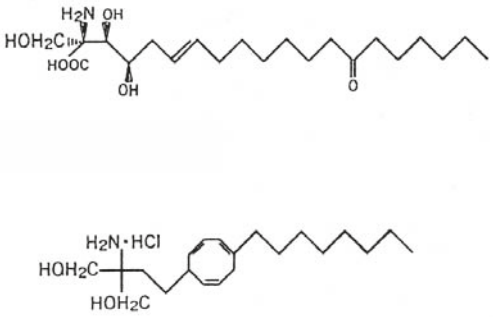
Cordyceps contains a wide range of compounds considered nutritional. It contains all of the essential amino acids, vitamins B_1, B_2, B_{12}, E, and K, a wide range of sugars including mono-, di- and oligiosaccharides and many different polysaccharides (some of amazing and unique complexity), proteins, sterols, nucleosides, and a wide range of trace elements (K, Na, Ca, Mg, Fe, Cu, Mn, Zn, Pi, Se, Al, Si, Ni, Sr, Ti, Cr, Ga, V, and Zr.).

Major Bioactive Constituents

Cordycepin [3'-deoxyadenosine] and cordycepic acid [d-mannitol] were the initial bioactive compounds first isolated from the *Cordyceps militaris* species (Cunningham et al., 1951). A study by Chen and Chu (1996), announced the characterization of cordycepin [3' deoxyadenosine] and 2'-deoxyadenosine, using nuclear magnetic resonance (NMR) and infrared spectroscopy (IR) in an extract of *Cordyceps sinensis.* Other components found included various saccharides, and polysaccharides of varied and amazing complexities (including cyclofurans - cyclic rings of five-carbon sugars of unknown function), beta-glucans, beta-mannans, cross-linked beta-mannan polymers, and complex polysaccharides consisting of

both 5 and 6 carbon sugars joined together in branching chains comprising both alpha- and beta-bonds. Many nucleosides have been found in *Cordyceps*, including uridine, several distinct structures of deoxyuridines, adenosine, 2',3'dideoxyadenosine (which is marketed worldwide as a primary antiretroviral drug for the treatment of HIV infections under the names Didanosine™, Videx™ and others) hydroxyethyladenosine, cordycepin [3'deoxyadenosine], cordycepin triphosphate, guanidine, deoxyguanidine, and a variety of other very unique altered and deoxygenated nucleosides that are found no where else in nature. (see illustration on page 23) Of particular note are various immunosuppressive compounds found in *Cordyceps*, including cyclosporin, which is the main anti-rejection drug used for human organ transplants and which comes from the species *Cordyceps subsessilis.* [anamorph: *Tolypocladium infalatum*] (Segelken 1996) Other immunosupressant compounds have been found in a species closely related to *Cordyceps*, named *Isaria sinclairii* (Mizuno 1999). See illustration on next page.

Another *Cordyceps sp.* which infects honeybees



Non-Cyclosporin immunosuppressive compounds found in Cordyceps

Polysaccharides

In the fungal kingdom, and particularly in *Cordyceps*, the polysaccharides are perhaps the best known and understood of the medicinally active compounds. (Ukai et al 1983) (Wasser, 2002) A number of polysaccharides and other sugar derivatives such as cordycepic acid [d-mannitol] have been identified and their pharmacological activity has been reported. Research has shown these polysaccharides to be effective in regulating blood sugar (Kiho et al 1996) to have anti-metastatic effect (Nakamura et al 1999) and antitumor effect. (Bok et al 1999)

Proteins And Nitragenous Compounds

Cordyceps contains proteins, peptides, all the essential amino acids, and several polyamines. In addition to all the essential amino acids, *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, including 1,3-diamino propane, cadaverine, spermidine, spermine, and putrescine, have been identified.

Sterols

A number of sterol type compounds have been found in *Cordyceps*. Some of these are ergosterol, Delta-3 ergosterol, ergosterol peroxide, 3-sitosterol, daucosterol, and campasterol. (Zhou et al 1998)

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 hydrocarbons, alcohols, and aldehydes. (Zhou et al 1998) Particularly interesting are the range of polycyclic aromatic hydrocarbons (PAH) produced by *Cordyceps 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 the *Cordyceps* that stunts the growth as the growing time progresses. Eventually, these polypropelene/PAH byproduct will kill the organism, making the cultivation of *C. sinensis* in this type of bag impractical. For extended periods of growth, *C. sinensis* must be grown in glass or metal containers. (Holliday et al 2004). These PAH compounds are present in the living culture, but are highly volatile compounds and are lost upon drying.

Cultivation Details And Growth Parameters

There are two methods used today in the cultivation of *Cordyceps*. The method primarily used in China is known as Liquid Culture or Fermentation, in which a small bit of Cordyceps tissue is inoculated into a sterilized liquid medium. It grows in this liquid environment very rapidly and is usually ready for harvest in about 5 days. The *Cordyceps* mycelium is harvested by filtering out from the liquid broth, after which it is dried and ground to a fine powder. After it is dried, it can be used as is, or further processed by extracting it with hot water or some other solvent, and the resulting extract either supplied as a liquid or again dried and powdered. The majority of *Cordyceps* available on the market is liquid cultured in this way. This results in a fairly good product, since this is a very economical method for large-scale production and the ease of controlling the growth parameters in large sealed tanks of liquid results in a very consistent product with very little variation in quality from batch to batch.

However there is a major drawback to the fermented *Cordyceps*; which is the loss of the extra-cellular compounds which *Cordyceps* produces. When the mycelium is filtered out of the culture broth and the residual liquid discarded, all of the bioactive extra-cellular compounds produced throughout the growth process are lost. These are many of the unique secondary metabolites produced by *Cordyceps* that have

some of the most potent medicinal effects. Consider for a moment: In the fungal kingdom nearly everything of biological importance happens outside of the cell wall. This has to be so, since the fungi have no mouths. In order for it to feed, the mycelium grows up alongside a food source and exudes out through the cell - wall compounds to digest that food. Then it exudes other compounds that act as transport molecules, ones that bring the nutrients back across the cell wall and into the cell for use. And all the while it is exuding antimicrobial compounds to keep other organisms from competing with it for the food (these are the compounds we refer to as antibiotics). And other compounds which act in significant ways such as adjusting the pH of its surrounding environment. Probably as much as 90% of the bioactive compounds of interest that are produced by the *Cordyceps* are in the liquid that is discarded after the mycelium is harvested. In the wild collected *Cordyceps,* the caterpillar body, which is harvested along with the fruitbody, is fully mummified with the *Cordyceps* mycelium. But more importantly, it acts as a natural reservoir for all of those exuded extra-cellular compound that were produced. The compounds, which were exuded outside of the mycelium, still remain in the caterpillar body. That is probably the main reason why wild collected *Cordyceps* is thought to be more potent than cultivated *Cordyceps*. It is the presence of these bioactive extra-cellular compounds, which were lost in the harvesting process of the liquid-cultivated type.

There is a second method of *Cordyceps* cultivation practiced, called the solid-substrate method or biomass method. In this type of cultivation, the *Cordyceps* is inoculated onto some type of sterilized solid nutrient source, usually a cereal grain or mixture of grains. It grows much more slowly on solid material than it does in liquid, but eventually the growth of the mycelium consumes most or all of the substrate and is ready for harvest. At this point, the entire contents of the growing container is harvested and dried; the mycelium, the residual substrate and the entire compliment of all the extra-cellular compounds which were produced throughout the entire growth process. In this way it is possible to capture these unique compounds, which are naturally lost when cultivated by fermentation technique.

The quality potential would seem to be much greater when cultivated under solid substrate method verses liquid fermentation method. However, it is not always that simple as to say *Cordyceps* produced by one

method is better than the other. The final quality of the *Cordyceps* is determined by a number of factors, among which the most important are the particular strain chosen for cultivation, the substrate composition, the culture parameters (such as temperature and oxygen content) and the length of time that it is grown. When all the conditions are correct, there is less than 5% residual substrate in the solid substrate grown variety, and better than 95% *Cordyceps* material, including all of the extra-cellular compounds. When grown this way the quality is high indeed, often exceeding the potency of wild *Cordyceps* by a factor of five times! (Holliday 2004)

Due to the longer growing time required, it is much more costly to produce *Cordyceps* with the solid substrate method than by fermentation, and it is therefore generally more expensive in the marketplace. This creates a situation where many solid substrate cultivators are forced to harvest their *Cordyceps* crop earlier than is optimum, in order to keep their cost competitive with the fermented products on the market. This means that they are producing a less-than-ideal product, which may or may not be better than the fermented variety. In some cases the residual grain present in solid substrate *Cordyceps* is greater than 80%. This is one of the reasons it is so important that buyers demand a standardized analysis of the *Cordyceps* they are contemplating purchasing. At present this standardized analysis is not commonplace, but it is becoming more so, as more people become educated in the uses and potential of this medicinal herb. As time progresses, we can expect to see the overall quality of cultivated *Cordyceps* to continue to increase.

Solid Substrate Cordyceps Cultivation in Glass

Medium for maintaining stock cultures: The usual nutrient agar mixtures used in maintaining mycological cultures can almost all be used for maintaining *Cordyceps* cultures. It is worth noting that *Cordyceps* will usually adapt quickly to a new medium, which is both a blessing and a curse. A blessing in that almost any medium used to propagate the culture will support growth, but a curse in that the organism rapidly develops a preference to this new medium, probably through the generation of enzymes specific to the character of that particular medium. This will result in the culture loosing its growth vigor for a time when transferred to another medium. This also leads to early culture senescence when the culture is repeatedly grown generation after generation on the same medium. The easy way around this issue is to constantly challenge the culture by transferring it onto a new medium with each successive generation. In this way, the culture is forced to maintain a broader spectrum of digestive enzymes to deal with the varying food sources, much as happens in nature. It also helps quite a bit to introduce some of the final substrate upon which the *Cordyceps* is to be grown into the maintenance medium. For example, if the *Cordyceps* is to be grown on a substrate of brown rice, it helps to add some finely ground brown rice to the agar upon which the culture is stored. That way, the *Cordyceps* has already been exposed to the end substrate and will have had time to develop the necessary enzymes to deal with this food source beforehand. When the organism is transferred from the agar onto the final substrate, a quicker growth is achieved, since the organism does not have to develop a new set of enzymes, as would be the case if it were seeing brown rice for the first time.

Some of the nutrient agar mediums that have been found to support good mycelial growth are:

Standard Malt Extract Agar

Standard Potato Dextrose Agar

Catfood Agar (10 grams dry catfood and 20 grams agar per L water)

Dogfood Agar (10 grams dry dogfood and 20 grams agar per L water)

Ovaltine Agar (10 grams Ovaltine drink mix, 20 grams agar per L water)

Mycelial Characteristics: Longitudinally radial, non-aerial, initially white, rapid growing, becoming densely matted. Some variations will turn yellowish to brown, and still some develop a translucent pink to orange tint, especially prominent upon exposure of the growing mycelium to sunlight but not to artificial light; and eventually, as the food source is completely consumed, the mycelium becomes increasingly dark and mud-like (30+ days). At approximately 14 days of growth or a bit later, the mycelium of some strains of *Cordyceps sinensis* begins to form small nodules (perhaps sclerotia?) on the surface of the substrate, appearing orange-brown to tan in color. Most strains of *Cordyceps sinensis* tend to rapidly change growth characteristics in cultivation, sectoring readily and sometimes growing densely, while other times growing light. Changes in color occur in the mycelial growth, even when the tissue inoculums are taken from the same petri dish. These changes are not permanent, that is, they change from one growth form to another and back again with seemingly no reason. One possible explanation for this is the possibility that *Cordyceps sinensis* (and possibly other *Cordyceps* species as well) are not single organisms, but rather symbiotic colonies of two or more organisms, perhaps fungi and bacterial pairings. (Chen 2001) The changing growth characteristic can then perhaps be seen as different primacy growth stages, where one of the separate organisms out-grows the other(s), while later in time, or perhaps in a different container, the other organism(s) gain dominance in the culture. Further study is necessary to better understand the growth cycle of the *Cordyceps sinensis* mycelium in its varying forms.

Some scientists question whether the species of the genus *Cordyceps* are in fact single organisms. This conclusion is drawn from several factors, including the changing growth patterns in culture as noted above, and also the appearance under microscopic examination of what appears to be endosymbionts. Or perhaps they are endoparasites. Small, spherical, rapidly moving, apparently single-celled organism living within the long, bamboo-like, hyphal cells, with anywhere from one to five individually moving spheres per mycelial cell. Often times these inner-cellular organisms can be observed under normal light magnification or phase contrast microscopy of living *Cordyceps* mycelial tissue. (Holliday 2004)

DNA Analysis

It would seem that DNA sequencing could easily answer this question of whether *Cordyceps* is a single organism or a symbiotic colony, however DNA sequencing has proven somewhat inconclusive in this regard. In recent DNA analysis of 29 samples of *Cordyceps sinensis* from the Qinghai-Tibet plateau, there was found to be an average genetic variation of nearly 50% between different specimens tested! And none of the specimens tested matched the "type specimen" kept at the Herbarium of the Royal Botanic Garden in Kew, England. Further DNA sequencing of the various anamorphs compared to the parent *Cordyceps sinensis* also showed great variation. So great in fact that the investigators concluded that of more than twenty different strains currently being commercially cultivated as *Cordyceps sinensis*, only *Hirsutella sinensis* is an actual anamorphs of *Cordyceps sinensis*! Further confusion in the DNA analysis results from the non-repeatability of the DNA sequences of *Cordyceps* over time. The DNA sequence is apparently rather variable in Cordyceps. It appears that the Cordyceps may even incorporate some of the insects' own DNA in order to fruit, then loses this insect DNA sequencing when grown from the spores produced or from tissue specimens of the fruitbody. Clearly, further genetic testing will needed before we can depend on this method of analysis to reveal much about what is, or what is not, *Cordyceps*. (Yue-Qin 2002, Chen 2001)

Substrate:

The substrates used for the commercial cultivation of *Cordyceps* are primarily either silkworm residue based (in China, Korea and Japan), or cereal grain based in the European countries and the Americas. While both substrates work well and produce good quality *Cordyceps*, the insect based substrates are, strictly speaking, not allowed in the United States under FDA guidelines. This is somewhat of a moot point, since the substrate upon which the *Cordyceps* was grown is rarely listed in the accompanying literature. It is likely that in the future, as more and more producers are importing *Cordyceps* into North America, that the insect-based substrates will be legally challenged under FDA law, and either they will be allowed, or what is more likely considering the aversion of the American people to the consumption of insects, they will be denied. The substrates that are used to grow *Cordyceps* will then become more standardized between different cultivators. Cereal grains will likely become the prominent type.

Incubation Temperature: Optimal temperature for mycelial growth is dependent on the goals of the cultivator: 21-27 C for fast production, or 3-5 C for slower growth with an emphasis on the production of medicinal target compounds such as Cordycepin (3'deoxyadenosine) or Hydroxyethyladenosine.

Relative Humidity: 95-100% with substrate moisture content of 45-50% for solid substrate growth.

Duration: In liquid culture, satisfactory mycelium production can take place in as little as 84-96 hours when grown at 21 or 22 C with sufficient aeration and heat dissipation. If the temperature of the growth medium is dropped to 4 C, the growth cycle lengthens to approximately 70 days to achieve an equal quantity of mycelium, but yielding a much greater concentration of Cordycepin. In solid substrate culture, harvest of the mycelium is usually between day 18 and day 25, unless the production of specific target compounds is the goal, in which case growth can take up to 180 days, or even longer depending on the desired compounds targeted.

Optimum CO_2 concentration: This is entirely dependent on the desired outcome of the growth. While *Cordyceps* will grow under both aerobic and anaerobic conditions, the secondary metabolites are entirely different when grown under differing conditions. Each cultivator has his or her own system and each is as different from the other as can be. Some cultivators find that an initial low CO_2 concentration, favoring the production of adenosine type compounds, followed by a high CO and CO_2 environment yields a higher quality end product. It is difficult to generalize about the optimum concentration of metabolically active gases for *Cordyceps* cultivation, as so much depends on the target compounds desired.(Holliday et al 2004)

Light Requirements: none

Primordia Formation: Perhaps not applicable, although reference is made to the formation of nodules as outlined earlier. Whether these are true primordia or not is unknown. These sometimes develop into

fruitbodies, although fruitbodies can also form directly from the mycelium, sometimes right next to these nodules.

Cropping Cycle: not applicable, as the form of product usually harvested in cultivation is the mycelium. In the case of *Cordyceps militaris*, only one crop is generally possible, as the *C. militaris* readily fruits from grains when grown directly from the spore, but fails to fruit a second time and so far has usually resisted attempts to fruit from tissue culture. (But not always – as you can see from the illustration below)

***Cordyceps militaris* fruiting on grain**

Other Interesting Possibilities For The Genus *Cordyceps*

Use As A Bio-pesticide

Among the first possible applications for the *Cordyceps* fungus, devised by Western scientists shortly after its having been brought to Europe by the French Jesuit, was as that of an insect pest control agent. Today, further analysis of the *Cordyceps* genus and the efficacy of different species against specific host organisms is encouraging the development of related biological control techniques as an alternative to those of a chemical nature, with the goal of possibly eliminating chemical pesticides altogether. *Metarhyzium anasopliae*, recently described as an anamorphs of *Cordyceps brittlebankosoides*, together with species of the *Termitomyces* genus, is currently being marketed for termite control in the United States; *Metarhyzium anasopliae*, being the destructive entamopathogenic agent and *Termitomyces albuminosa*, being the termite attractant.

Possible Uses As Agent In Mummification

The potential of *Cordyceps* as an agent in mummification is realized through the observation of the host animal, after the total consumption of available nutrients by the C*ordyceps* mycelium. Such observation of the well-preserved (mummified) state of the host animal has led to suggestions for further study.

Conclusion

Cordyceps is an amazing substance. Once so rare that only the emperor of China could afford to use it, it is now within the reach of everybody. 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 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 smart that we think that 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 now have instruments that can detect what you ate for dinner a month ago. And 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 scientific proof. But it is clear from our studies, that we know almost nothing of the wonders of these strange *Cordyceps* creatures. It seems that the more we learn, the more questions that we are presented with. *Cordyceps* yet has many secrets in store for us.

REFERENCES

Bao, Z.D., Wu, Z.G., and Zheng, F. (1994). [Amelioration of aminoglycoside nephrotoxicity by *Cordyceps Sinensis* in old patients]. *Chinese Journal of Integrated Medicine* 14: 259,271-273.

Berne, R.M., 1980: The role of Adenosine in the regulation of coronary blood flow. Circ. Res. 47: 807-813, 1980

Bok JW, Lermer L, Chilton J, Klingeman HG, Towers GH., (1999) *Antitumor sterols from the mycelia of Cordyceps sinensis.* Phytochemistry 1999 Aug;51(7):891-8

Chamberlain, M. (1996). Ethnomycological experiences in South West China. *Mycologist* 10 (4): 173-176.

Chang, H.M. and But, P.P.H. (Eds.) (1986). *Pharmacology and Applications of Chinese Materia Medica,* 1. Philadelphia, PA: World Scientific, pp. 410-413.

Chen, J.R., Yen, J.H., Lin, C.C., Tsai, W.J., Liu, W.J., Tsai, J.J., Lin, S.F., and Liu, H.W. (1993). The effects of Chinese herbs on improving survival and inhibiting anti-ads DNA antibody production in lupus mice. *American Journal of Chinese Medicine* 21: 257-262.

Chen K, Li C. (1993) Recent advances in studies on traditional Chinese anti-aging Materia Medica. J Tradit Chin Med 1993 Sep;13(3):223-6,

Chen D.G., (1995) Effects of JinShuiBao Capsule on the Quality of Life of Patients with Heart Failure. *Journal of Administration of Traditional Chinese Medicine* 5 (1995): 40-43

Chen, S.Z. and Chu, J.Z. (1996). [NMR an IR studies on the characterization of cordycepin and 2'deoxyadenosine]. *Zhongguo Kangshengsu Zaxhi* 21: 9-12.

Chen, Y.J., Shiao, M.S., Lee, S.S., and Wang, S.Y. (1997). Effect of *Cordyceps sinensis* on the proliferation and differentiation of human leukemic U937 cells. *Life Sciences* 60: 2349-2359.

Chen, Y.Q., Wang, N., Qu, L., Li., T., and Zhang, W. (2001). Determination of the anamorph of *Cordyceps sinensis* inferred from the analysis of the ribosomal DNA internal transcribed spacers and 5.85 rDNA. *Biochemical Systematics and Ecology* 29: 597-607.

Chen, Y., Zhang, Y.P., Yang, Y., and Yang, D. (1999). Genetic diversity and taxonomic implication of *Cordyceps sinensis* as revealed by RAPD markers. *Biochemical Genetics* 37: 201-213.

Chen, K. T., Su, C.H., Chang, H.C., and Huang, J.Y. (1998). Differentiation of genuines and counterfeits of *Cordyceps* species using random amplified polymorphic DNA. *Planta Medica* 64: 451-453.

Chen YJ, Shiao MS, Lee SS, Wang SY. (1997) Effect of Cordyceps sinensis on the proliferation and differentiation of human leukemic U937 cells. Life Sci. 1997;60(25):2349-59.

Creadon, M. and Dam, J. (1996). " Drink up." *Time* (August 19): 55. a biologically active compound from cultures mycelia of *Cordyceps* and *Isaria* species. *Phytochemistry* 22: 2509-2512.

Gist Gee, N. (1918). Notes on *Cordyceps sinensis. Mycological Notes* 54: 767-768.

Gordon, D. (1993). : The rumored dope on Beijing's Women." *Newsweek* September 27): 63.

Grey, P. and Barker, R. (1993). *Cordyceps* or plant eats animal! *The Victorian Naturalist* 110: 98-107.

Guan, Y.J., Hu, G., Hou, M., Jiang, H., Wang, X., and Zhang, C. (1992). Effect of *Cordyceps sinensis* on T- lymphocyte subsets in chronic renal railure. *Chinese Journal of Integrated Medicine* 12: 323, 338-339.

Guo, Y. Z. (1986). [Medicinal chemistry, pharmacology and clinical applications of fermented mycelia of *Cordyceps sinensis* and JinShuBao capsule]. *Journal of Modern Diagnostics and Therapeutics* (1): 60-65.

Guo QC, Zhang C. (1995) Clinical Observations of Adjunctive Treatment of 20 Diabetic Patients with JinSHuiBao Capsule. J Administration Traditional Chinese Medicine 1995:5(suppl):22

Guowei Dai, Tiantong Bao, Changfu Xu, Raymond Cooper, and Jia Xi Zhu, CordyMax™ Cs-4 Improves Steady-State Bioenergy Status in Mouse Liver. *The Journal Of Alternative And Complementary Medicine* Volume 7, Number 3, 2001, pp. 231–240

Halpern, G., (1999) Cordyceps, Chinas healing mushroom. Avery Publishig 1999: 63-70

Hammerschmidt, D.E. (1980). Szechwan purpura. *New England Journal of Medicine* 302: 1191-1193.

Holliday, J., Cleaver, P., Loomis-Powers, M., and Patel, D., *Analysis of Quality and Techniques for Hybridization of Medicinal Fungus Cordyceps sinensis,* International Journal of Medicinal Mushrooms, Vol. 6, pp. 147–160 (2004)

Holliday, J., (2004b) Investigation into mechanism of action with Aloha Medicinals Inc. hybrid Cordyceps altered nucleosides. unpublished research , 2002-2004

Huang, Q., Li, D., Liang, J., Liao, S., and Liang S., (1991). {Weak polar chemical components in *Cordyceps*]. *Journal of Chinese Medical Materials* 14: 33-34.

Ikumoto, T., Sasaki, S., Namba, H., Toyama, R., Moritoki, H., and Mouri, T. (1991). [Physiologically active compounds in the extracts from tochukaso and cultured mycelia of *Cordyceps* and *Isaria*]. *Yakugaku Zasshi* 111: 504-509.

Huang , Y. et al (1987) Toxicology studies on cultured Cordyceps sinensis strain B414. Zhongchengyao Yanjiu 10:24-25 From Abstracts of Chinese Medicine 2:321

Jia-Shi Zhu, M.D., Ph.D. and James Rippe, M.D. (2004) Presented at the American Physiological Society's (APS) annual scientific conference, Experimental Biology 2003, held April 17-21, 2004, in Washington, D.C.

Kadota, S., Shima, T., and Kikuchi, T. (1986) [Steroidal components of "I-Tiam-Hong" and *Cordyceps sinensis.* Separation and identification by high-performance liquid chromatography]. *Yakugaku Zasshi* 106: 1092-1097.

Kiho, T., Tabata , H., Ukai, S., and Hara, C., (1986). A minor protein-containing galactomannan from a sodium carbonate extracted of *Cordyceps sinensis. Corbohydrate Reseach* 156: 189-197.

Kiho T, Hui J, Yamane A, Ukai S. (1993) Hypoglycemic activity and chemical properties of a polysaccharide from the cultural mycelium of *Cordyceps* sinensis. Biol Pharm Bull 1993 Dec;16(12):1291-3

Kiho T, Yamane A, Hui J, Usui S, Ukai S. (2000) Hypoglycemic activity of a polysaccharide (CS-F30) from the cultural mycelium of *Cordyceps sinensis* and its effect on glucose metabolism in mouse liver. Phytother Res 2000 Dec;14(8):647-9

Koh JH, Yu KW, Suh HJ, Choi YM, Ahn TS. (2002) Activation of macrophages and the intestinal immune system by an orally administered decoction from cultured mycelia of Cordyceps sinensis. Biosci Biotechnol Biochem. 2002 Feb;66(2):407-11

Kuo, Y.C., Tsai, W.J., Shiao, M.S., Chen, C.F., and Lin, C.Y. (1996) *Cordyceps sinensis* as an immunomodulatary agent. *American Journal of Chinese Medicine* 24: 111-125.

Kuo, Y.C., Tsai, W.J., Wang , J.Y., Chang, S.C., Lin, C.Y., and Shiao, M.S. (2001). Regulation of bronchoalveolar lavage fluids cell function by the immunomodulatory agents from *Cordyceps sinensis*. Life *Sciences* 68; 1067-1082.

Hawksworth D. L., et al. 1995 *Ainsworth and Bisbi's Dictionary of the Fungi:* 8th ed. International, University Press and Cambridge, 616 pp.

Hirose K., and Yahagi N. 1997. *Japan tochukaso, Shock to Disappear of Cancer.* Metamoru shyupan, Tokyo, 175 pp.

Itami H., and Yahagi N. 1996. *Japan tochukaso*, Challenge for Terminal Cancer. Metamoru shyupan, Tokyo, 140pp.

Jiang, JC, Gao, YF. Summary of treatment of 37 chronic renal disfunction patients with JinShuiBao. J Administration Traditional Chinese Med 1995: 5(suppl):23-24

Kiho T., and Ukai S. 1995. Tochukaso (Semitake and others), *Cordyceps* species. *Food Rev Int,* 11, 231-234.

Kiho T., Hui, J., Yamane A., and Ukai S. 1993. Hypoglycemic activity and chemical properties of a polysaccharide from the cultural medium of *Cordyceps sinensis. Bio Pharmacol Bull,* 16 1291-1293.

Hiho T., Yamane A., Hui J., Usui S., and Ukai S. 1996. Hypoglycemic activity of a polysaccharide (CS-F30) from the cultural mycelium of *Cordyceps sinensis* and its effect on glucose metabolism in mouse liver. *Biol Pharmacol Bull,* 19, 294-296.

Hsu T. H., Shiao L. H., Hsiea C., and Chang D. M. 2002. A comparison of the chemical composition and bioactive ingredients of the Chinese medicinal mushroom DongChongXiaCao, its counterfeit and mimic, and fermented mycelium of *Cordyceps sinensis*. *Food Chem,* 78, 463–469.

Kim Y., ed. 1998.Ipact experiences for 50 people came back from the depths of death with vegetable wasps and plant worms. From the last stages of cancer. Nishinhodo, Tokyo, 207pp.

Koh JH, Yu KW, Suh HJ, Choi YM, Ahn TS. (2002) Activation of macrophages and the intestinal immune system by an orally administered decoction from cultured mycelia of Cordyceps sinensis. Biosci Biotechnol Biochem. 2002 Feb;66(2):407-11

Kobayashi Y., and Shimizu D., 1983. *Iconography of Vegetable Wasps and Plant Worms.* Hoikusha Tokyo, 208 pp.

Kubo M. 1996 *Tochukaso. Its secret and its Power. Hoikusha,, Tokyo, pp. 128, 152.*

Li, L.S. and Zheng, F. (1992). Clinical protection of aminoglycoside neophrotoxiciry by *Cordyceps sinensis* (CS). *Journal of the American Society of Nephrology* 3: 726 (ABSTRACT 24p).

Liu FA, Zheng X, (1993) Study of Cordyceps sinensis on anti-laryngeal carcinoma. J. Norman Bethune University Med Sci 1993; 19(1):57-58

Liu, C., Xue, HM., Xu, LM., Zhao, PZ., Zhang, LB., Tang, MG., Treatment of 22 patients with post hepatic cirrhosis with a preparation of fermented mycelia of *Cordyceps sinensis.* Shanghai J Chinese Materia Medica 1986;6:30-31

Leung, A.K., Gong, F., and Chau, F. (2000). Analysis of the water soluble constituents of *Cordyceps sinensis* with heuristic evolving latent projections. *Analytical Letters* 33: 3195-3211.

The Merck Index, 11 Edition, 1989. 2524 Cordycepin. *Merk and Co., 395 pp.*

Mizuno T.1997. Development and ultilization of bioactive substances from medical and edible mushrooms fungi (10) Charga, Sclerotiana of *Fuscopotia oblique* (Fr) Aoshima. *The Chemical Times,* 163, 9-15.

Mizuno T. 1998. *Immunological Diet for Cancer Serious Disease.* Gendaishorin, Tokyo, 188 pp.

Nakamura K, Yamaguchi Y, Kagota S, Shinozuka K, Kunitomo M., Activation of in-vivo Kupffer cell function by oral administration of Cordyceps sinensis in rats. (1999) *Jpn J Pharmacol 1999 Apr;79(4):505-8*

Nakamura K, Konoha K, Yamaguchi Y, Kagota S, Shinozuka K, Kunitomo M. *(2003)* Combined effects of Cordyceps sinensis and methotrexate on hematogenic lung metastasis in mice. Receptors Channels. 2003;9(5):329-34

Ohmori T., Tamura K., Tsuru S., and Nomoto K., 1986. Antitumor activity of protein-blood polysaccharide from *Cordyceps ophioglossoides* in mice. *Jnp J Cancer* Res (Gann), 77, 1256-1263.

Ohmori T., Tamura K., Furuki K., Kawanishi G., Mitsuyama M., Nomoto K., Miyazaki t, 1989. Isolation of galactosaminoglycan moity (CO-N) from protein-bound polysaccharide of *Cordyceps ophioglossoides* and its effects against murine tumor. *Chem Pharmacol Bull,* 37, 1019-1022.

Parcell AC, Smith JM, Schulthies SS, Myrer JW, Fellingham G. (2004) Cordyceps Sinensis (CordyMax Cs-4) supplementation does not improve endurance exercise performance. Int J Sport Nutr Exerc Metab. 2004 Apr;14(2):236-42

Pelleg, A., Porter, R.S. (1990) The pharmacology of adenosine. Pharmacotherapy 10: 157-174, 1990

Shin KH, Lim SS, Lee SH, Lee YS, Cho SY (2001) Antioxidant and immunostimulating activities of the fruiting bodies of Paecilomyces japonica, a new type of Cordyceps sp.
Ann N Y Acad Sci. 2001 Apr;928:261-73.

Shin KH, Lim SS, Lee S, Lee YS, Jung SH, Cho SY. (2003) Anti-tumour and immuno-stimulating activities of the fruiting bodies of Paecilomyces japonica, a new type of Cordyceps spp. Phytother Res. 2003 Aug;17(7):830-3.

Shimizu D. 1994. *Color Iconography of Vegetable Wasps and Plant Worms.* Seibundoshinksosha, Tokyo, 381 pp.

Suh SO, Noda H, Blackwell M (2001)Insect symbiosis: derivation of yeast-like endosymbionts within an entomopathogenic filamentous lineage. Mol Biol Evol. 2001 Jun;18(6):995-1000.

Takeuchi N. 1998. Pharmacological effect of Tochukaso and its utilization for food. *Kagaku to Kogyo,* 51, 1614-161.

Toda, N., Okunishi, H., Taniyama, K., Miyazaki, M., (1982) Response to adenine nucleotides and related compounds of isolated dog cereberal, coronary and mesenteric arteries. Blood Vessels 19: 226-236 1982

Ukai S, Kiho T, Hara C, Morita M, Goto A, Imaizumi N, Hasegawa Y (1983) Polysaccharides in fungi: XIII. Antitumor activity of various polysaccharides isolated from *Dictyophora indusiata*, *Ganoderma japonicum*, *Cordyceps cicadae*, *Auricularia uricula-judae* and *Auricularia* sp. Chem Pharma Bull (Tokyo) 31:741–744

Yamanaka K., and Inatomi S, 1997. Cultivation of *Isaria japonica* fruit bodies on mixed plant/insect media. *Food Rev Int,* 13, 455-460.

Segelken, R. (2002) Cyclosporin mold's 'sexual state' found in New York forest Cornell students' discovery could target additional sources of nature-based pharmaceuticals *Cornell University Science News, Sept 16, 1996*

Smith, Rowen and Sullivan (2002), Medicinal Mushrooms: Their Therapeutic Properties and Current Medical Usage with Special Emphasis on Cancer Treatment, May 2002, 106-141

Tai-Hao, H., Hui-Chen, L., Biological activity of Cordyceps (Fr.) Link Species (Ascomycetes) Derived from a Natural Source and from Fermented Mycelia on Diabetes in STZ-Induced Rats. Inter J of Med Mush 4; 111-125

Wang, R., Xu, Y., Ji, P., Wang, X., Holliday, J (2001) Clinical Trial Of A Mixture of Six Medicinal Mushroom Extracts. http://alohamedicinals.com/clinical_trials.html 2001

Wang, R., Xie, J., Ji, P., Li, S., Zhan, H., Xia, J., Sun, H., Lei, L., Yu, J., Wang, Y., Holliday, J., Clinical Trial report on Chronic Hepatitis treatment using Immune-Assist brand mushroom extract mixture in conjunction with the drug *Lamivudine* http://alohamedicinals.com/Hep_B_Study2.htm

Wasser, S.P., (2002) Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. Appl Microbiol Biotechnol (2002) 60:258–274

Wu T. N., Yang K. C., Wang C. M., Lai J. S., Ko K. N., Chang P. Y., and Liou S. H. 1996. Lead poisoning caused by contaminated *Cordyceps*, a Chinese herbal medicine: two case reports. *Sci Total Environ*, 182, 193–195.

Xu, W.Z., Wei, J.P., Wang N. Q., Liu T., (1988) Experimental study of the combined chemotherapy of Zhiling Capsules and Anticancer agents. Shanghai Zhongyiyao Zazhi 1988; (6): 48

Xu, F., Huang JB., Jiang, L., Xu, J., Mi, J., (1995) Amelioration of cyclosporin nephrotoxicity by *Cordyceps sinensis* in kidney transplanted recipients. Nephrol Dial Transplant 1995; 10(1):142-143

Yamada H., Kawaguchi N., Ohmori T., Takeshita Y., Teneya S., and Miyazaji t. 1984. Structure and antitumor activity if an alkali-soluble polysaccharide from *Cordyceps ophioglossoides. Carbohydr Res,* 125, 107-115.

Yamaguchi N., et al, (1990) Augmentation of various immune reactivities of tumor bearing hosts with an extract of *Cordyceps sinensis*. Biotherapy, 2: 199-205

Yang, YZ., Wang, LS., Deng, HY., Ma, YS., Wu, HS., Short term observation of treating chronic hepatitis B and post hepatic cirrhosis with XinGanBao. Res Chinese Materia Medica 1994;(1):19-20

Yoshida J et al (1989) Antitumor activity of an extract of Cordyceps sinensis (Berk.) Sacc. Against murine tumor cell lines Jpn J Exp Med 59:157-161

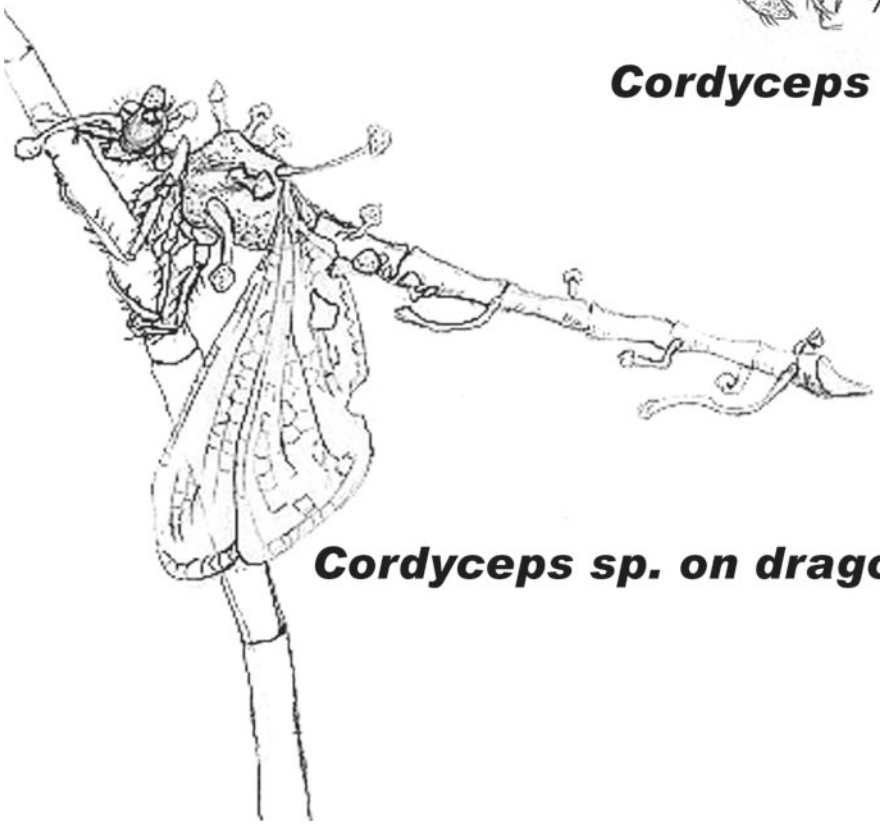
Yue-Qin C, Ning W, Hui Z, Liang-Hu Q. (2002) Differentiation of medicinal Cordyceps species by rDNA ITS sequence analysis. *Planta Med. 2002 Jul;68(7):635-9.*

Zhao CS, Yin WT, Wang JY, Zhang Y, Yu H, Cooper R, Smidt C, Zhu JS. (2002) Cordyceps Cs-4 improves glucose metabolism and increases insulin sensitivity in normal rats. J Altern Complement Med. 2002 Aug;8(4):403-5.

Zhu, Jia-Shi, Halpern, G., Jones ,K (1998) The Scientific Rediscovery of an Ancient Chinese Herbal Medicine: *Cordyceps sinensis* The Journal Of Alternative And Complementary Medicine [part 1]Volume 4, Number 3, 1998, pp. 289—303 [part 2] Volume 4, Number 4, 1998, pp. 429 - 457

Cordyceps sobolifera

Cordyceps sp. on ant



Cordyceps sp. on dragonfly