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Medicinal Value of the Caterpillar Fungi Species of the Genus *Cordyceps* (Fr.) Link (Ascomycetes). A Review

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ABSTRACT: This review looks in depth at the history and medicinal value of the *Cordyceps* species, especially *C. sinensis*. The *C. sinensis* medicinal species, with a long history of use, has only been found growing from the head of one type of subterranean caterpillar, at high altitudes, in the Qinghai-Tibetan plateau. Because of this highly specific growth environment and restricted geographical distribution, *C. sinensis* has a long reputation of being the single-most expensive raw material used in Oriental Medicine. Due to environmental and ecological factors, the annual harvest has been steadily declining, while at the same time the worldwide demand has been increasing. This situation has driven *Cordyceps* spp. prices into an ever-increasing spiral over the last few years, driving research to determine ways of cultivating it to make it a more affordable material for commercial trade. Part of the goal of this research has been to understand the complex biological niche such an organism fills. This is a mushroom that is only found in cohabitation with the larvae of an insect, and it is this unique growth parameter that has made it challenging to produce *Cordyceps* spp. in artificial cultivation. Further complicating this cultivation issue is the rarefied atmosphere, mineral-rich soil, and low temperature in which *Cordyceps* naturally grows, resulting in a unique profile of secondary metabolites possessing interesting biological potential for medical exploitation, but which are not readily reproduced in normal laboratory cultivation. In this article, we attempt to unravel many of the mysteries of *Cordyceps* spp., detailing the history, medicinal uses, chemical composition, and cultivation of *Cordyceps* spp., with special attention to *C. sinensis*, the world's most costly medicinal mushroom.

KEY WORDS: *Cordyceps*, *Cordyceps sinensis*, dongchongxiacao, chongcao, polysaccharides, tumor, immunomodulator, cordycepin, adenosine, hydroxyethyladenosine, deoxynucleosides, cordycepic acid

I. INTRODUCTION

Species of the genus *Cordyceps* (Fr.) Link (Chinese caterpillar fungi, Tochucaso in Japanese; Clavicipitaceae, Ascomycetes) are the fungi found growing on insect larvae (Figs. 1–3), mature insects, or fruiting bodies of truffles of the genus *Elaphomyces*. *Cordyceps* has a long history as a rare and exotic medicinal fungi. It has been a highly regarded cornerstone of Chinese medicine for centuries; one that reportedly has a number of far reaching medicinal effects.[1–4]

ABBREVIATIONS

COPD: chronic obstructive pulmonary disease; **EAC:** Erhlich ascites carcinoma; **NMR:** nuclear magnetic resonance; **IR:** infrared spectroscopy; **PAH:** polyaromatic hydrocarbons; **SOD:** superoxide dismutase; **TCM:** Traditional Chinese Medicine.

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FIGURE 1. *Cordyceps sinensis* in its natural habitat (4550 meters in Tibet, China).

Most people in the West have only come to know about *Cordyceps* within the last 20 years, during which time, modern scientific methods have been increasingly applied to the investigation of its seemingly copious range of medicinal applications in an attempt to validate what Chinese practitioners have noted for centuries.[3]

II. 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* species 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 creature whose annual existence alluded to a transformation from animal to plant, in summer, and then again from plant to animal, in winter.[5] Tibetan scholars wrote of the healing animal/plant through the 15th to 18th 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.[3–4]

A member of the largest subdivision of true fungi, Ascomycotina, hundreds of species of *Cordyceps* have been identified on six continents, in a variety of habitats, and with equally varied food sources.[6]

The name *Cordyceps* comes from the Latin words: *cord* and *ceps*, respectively, meaning "club" and "head." The Latin word-conjunction accurately describes the appearance of these club fungi, whose stroma and fruit body extend from the mummified carcasses of insect larvae, usually that of the Himalayan ghost Moth, *Thitarodes armoricanus* (=*Hepialis armoricanus*).

In historical and general usage, the term "*Cordyceps*" normally specifically refers to the species *C. sinensis*. However, the name "*Cordyceps*" has come to be used for a number of closely related species over the last few years, which have been

FIGURE 2. Close up of wild *Cordyceps* showing spore-bearing surface and slight insect-feeding damage at the tip.

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FIGURE 3. *Cordyceps* market in Ningchi (aka Bayi), Tibet. *Cordyceps* spread out on the road for buyers to view.

found to be much easier to cultivate. Although *C. sinensis* may be the most well-known species, there are many other species in the genus *Cordyceps* in which modern science may have uncovered potentially valuable medicinal properties.

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

The medicinal value of the *Cordyceps* species has been recognized since ancient times in China and the surrounding Orient; but knowledge of this only reached Western scientific audiences in 1726, when it was introduced at a scientific meeting in Paris. The first specimens were carried back to France by a Jesuit priest who chronicled his experiences with the *Cordyceps* mushroom during his stay at the Chinese Emperor's court.[1,4] Although always a rarity in nature, modern technological advancements in cultivation have made the prospect of affordable *Cordyceps* a reality, and its potential medicinal uses continue to augment conventional therapy and gain recognition as clinical trials proceed to probe the famed efficacy of the species of the genus *Cordyceps*.

III. *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 entomopathogenicity of the *Cordyceps* spp. is disputed. A growing body of logical and empirical data is suggesting to many prominent researchers that *C. sinensis* actually has a symbiotic relationship with the host, and that the connection is mutually beneficial, rather than pathogenic. This stands to logical reason, considering the remote and inhospitable environment in which the *Cordyceps*/moth pairing occurs. Nature tends to select against a parasite because a parasite usually results in the death of the host. Perhaps 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 or other benefit from the *Cordyceps* living in its body, as

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is known to occur when other animals consume *Cordyceps*.[7] In cultivation, *Cordyceps* often exhibits a single-celled, yeast-like anamorphic growth stage. Similar yeast-like symbionts of the genus *Cordyceps* (or their anamorphs) have been found in other insects, most logically existing to some benefit of the host insect.[8] 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 fruit body. 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 fruit body. It is most common in the fungal kingdom that fruit body 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.

IV. *CORDYCEPS* SPECIES DIVERSITY AND ARTIFICIAL CULTIVATION

There are currently more than 680 documented species of *Cordyceps*[3,4,6] found on all six inhabited continents and in many climatic zones and habitats and feeding off a range of hosts. As studies of different species of genus *Cordyceps* continue, it has become increasingly apparent that the potential medicinal benefits of *Cordyceps* spp. are not related only to the one species *C. sinensis*. Of the many different species of *Cordyceps*, those presently being cultivated for medicinal purposes and use in health supplements include *C. sinensis, C. militaris, C. sobolifera, C. subssesilus, C. ophioglossoides*, and others.[1,2]

Due to the rarity and high prices of the wild collected variety (2008 price in San Francisco and other major U.S. cities was as high as $75,000 per kilogram), attempts have long been made to cultivate *Cordyceps*. By the mid-1990s, the majority of *Cordyceps* available in the world's marketplace was artificially cultivated.[2,9] Because of the development of modern biotechnology-based cultivation methods, the availability of this previously rare health supplement has greatly increased in the last 20 years. The demand for *Cordyceps* has also compounded exponentially, in this same time frame, partly due to the opening of China to trade with the West in the 1970s, exposing many more people around the world to the concepts and practices of TCM. As *Cordyceps* has always been highly revered in TCM, it is reasonable that with increased exposure to TCM, the demand for this herb has also increased. Such an increase has lead to over-harvesting of the wild stocks and a subsequent shortage of wild collected species of *Cordyceps*.[9–11]

Many companies now produce artificially cultivated *Cordyceps* products, both from the mycelium as well as from the fruit bodies. The increase in supply has given rise to variations in purity and quality, creating a situation in which there are a large number of counterfeit and adulterated products being sold.[4,11] Recently, new methods for assaying the quality of *Cordyceps* products have been introduced.[9]

The large variations in quality found in cultivated *Cordyceps* has led many consumers to believe the wild collected variety is medicinally better than the cultivated type. But with new advances in biotechnology this is rapidly changing. One manufacturer is even growing *Cordyceps* in an artificial environment exactly replicating the natural growth conditions of *Cordyceps* (the high-altitude air composition and low temperature found on the Himalayan plateau).[12] This low-temperature hypoxia cultivation in an atmosphere consisting primarily of nitrogen, carbon dioxide, carbon monoxide, and only low levels of oxygen allows the artificial cultivation of *Cordyceps,* which replicates the chemical analysis of wild *Cordyceps* as closely as can be determined by today's most sensitive analytical instruments, making cultivated *Cordyceps* a realistic substitute for the much higher priced wild *Cordyceps*. These unique cultivation protocols, coupled with the developments of new strains and hybridization between strains, is resulting in *Cordyceps* of a heretofore unprecedented quality and consistency.[12]

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V. CONTAMINATION AND ADULTERATION OF *CORDYCEPS*

Another issue has been raised regarding the quality of *Cordyceps:* lead contamination, stemming from reports of lead poisoning from consumption of *Cordyceps* by people in China and Taiwan.[13] A separate practice of adulteration, long practiced by the collectors of natural *Cordyceps*, introduces excessive lead into the organism. As found in its natural state, *Cordyceps* is attached to the mummified body of the caterpillar from which it arose. It is harvested whole in this way, dried, and supplied into the market. Because *Cordyceps* is sold by weight, the collectors have historically inserted a small bit of twig into many of the caterpillars, resulting in an increase in weight.[9] Better quality *Cordyceps* traditionally had fewer inserted sticks; however, the practice has been so widespread for so long that it is virtually impossible to find wild collected *Cordyceps* without these fillers inserted (Figs. 4 and 5). This is probably a harmless practice, as long as the object inserted is from a nontoxic source. But modern collectors have found that more weight can be gained if a bit of wire is inserted into the caterpillar, rather than the traditional twig. As long as the wire is steel, such a practice, as is the case with the aforementioned wood insertion, is probably not too harmful.

Unfortunately, the wire of choice is now lead solder. A careful examination of the ends of the caterpillars will often reveal the holes where the sticks or wire have been inserted (Fig. 5), and anyone who chooses to use the wild collected *Cordyceps*, rather than the cultivated variety, would be well advised to break each one of the caterpillars in half before use, so that any bits of foreign matter can be readily discerned and removed.

Although the presence of lead or other substances in the growth medium certainly could be absorbed by any growing organism, these authors have conducted chemical analyses on many thousands of *Cordyceps* samples over the years, and it has been our observation that *Cordyceps* does not have any more of a tendency to accumulate lead or other heavy metals than any other fungi. *Cordyceps* cultivated by any of the usual modern practices is very safe from any heavy metal contamination.

FIGURE 4. Wire and twigs inserted into *Cordyceps* to increase weight.

VI. GENERAL NUTRITIONAL COMPONENTS OF *CORDYCEPS*— CHEMICAL CONSTITUENTS

Cordyceps spp. contains a broad range of compounds that are considered nutritional. It contains all of the essential amino acids, vitamins E and K, and the water-soluble vitamins B_1, B_2, and B_{12}.

FIGURE 5. Commercial *Cordyceps* with tell-tale holes in the caterpillars where twigs/wires have been inserted.

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In addition, it contains many sugars, including mono-, di-, and oligosaccharides, and many complex polysaccharides, proteins, sterols, nucleosides, and macro- and microelements (K, Na, Ca, Mg, Fe, Cu, Mn, Zn, Pi, Se, Al, Si, Ni, Sr, Ti, Cr, Ga, V, and Zr).[1,3,9]

A. Potentially Bioactive Constituents of the Species of Genus *Cordyceps*

Cordycepin [3′-deoxyadenosine] and cordycepic acid [d-mannitol] were the initial bioactive compounds first isolated from *C. militaris*. Chen and Chu[14] announced the characterization of cordycepin (3′-deoxyadenosine) and 2′-deoxyadenosine using nuclear magnetic resonance (NMR) and infrared spectroscopy (IR) in an extract of *C. sinensis.* Other components found included various saccharides and polysaccharides, including cyclofurans, which are cyclic rings of five-carbon sugars, whose function is yet unknown; beta-glucans; beta-mannans; cross-linked beta-mannan polymers; and complex polysaccharides consisting of both 5 and 6 carbon sugars joined together in branching chains, employing both alpha- and beta-bonds. These are true heteropolysaccharides. In addition, many nucleosides have been found in *Cordyceps*, including uridine, several distinct structures of deoxyuridines, adenosine, 2′3′-dideoxyadenosine, hydroxyethyladenosine, cordycepin [3′-deoxyadenosine], cordycepin triphosphate, guanidine, deoxyguanidine, and other altered and deoxygenated nucleosides, found no where else in nature (Fig. 6). Of particular note are various immunosuppressive compounds found in *Cordyceps*, including cyclosporin, a derivative of the species *Cordyceps subsessilis* [anamorph: *Tolypocladium infalatum*].[15] Other immunosupressant compounds have also been found in *Isaria sinclairii*, a species closely related to *Cordyceps.*[2]

B. Polysaccharides

In the fungal kingdom, and particularly in *Cordyceps* spp., polysaccharides are perhaps the best known

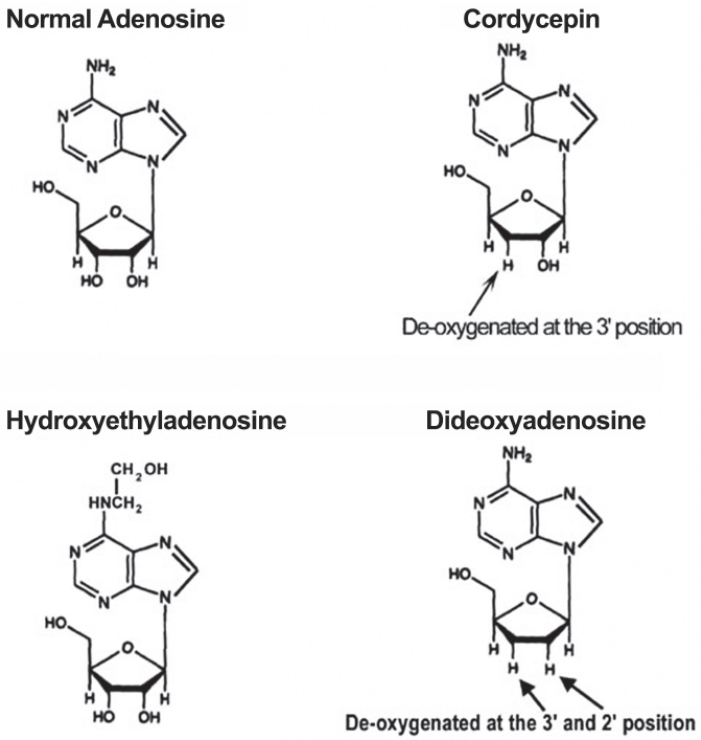

FIGURE 6. Some of the unique nucleosides found in *Cordyceps sinensis*.

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and understood of the medicinally active compounds.[16,17] A number of polysaccharides and other sugar derivatives, such as cordycepic acid [d-mannitol], have been identified. Research has shown these polysaccharides to be effective in regulating blood sugar,[18] and to have antimetastatic and antitumor effects.[19]

C. Proteins and Nitrogenous Compounds

Cordyceps spp. contains proteins, peptides, polyamines, and all essential amino acids. In addition, *Cordyceps* spp. contains some uncommon cyclic dipeptides, including cyclo-[Gly-Pro], cyclo-[Leu-Pro], cyclo-[Val-Pro], cyclo-[Ala-Leu], cyclo-[Ala-Val], and cyclo-[Thr-Leu]. Small amounts of polyamines, such as 1,3-diamino propane, cadaverine, spermidine, spermine, and putrescine, have also been identified.[2]

D. Sterols

A number of sterol-type compounds have been found in *Cordyceps* spp.: ergosterol, Delta-3 ergosterol, ergosterol peroxide, 3-sitosterol, daucosterol, and campeasterol, to name a few.[5]

E. Other Constituents

Twenty-eight saturated and unsaturated fatty acids and their derivatives have been isolated from *C. sinensis.* Polar compounds of *C. sinensis* extracts include many compounds of alcohols and aldehydes.[5] Particularly interesting are the range of polycyclic aromatic hydrocarbons produced by most *C. sinensis* strains as secondary metabolites. These PAH compounds react with the polypropylene used in common mushroom culture bags, resulting in the production of byproducts toxic to *C. sinensis* and stunting growth as time progresses. Eventually, these polypropylene/PAH byproducts kill the organism. For extended periods of growth, *C. sinensis* must be grown in glass or metal containers.[9] The PAH compounds are present in the living culture, but they are volatile compounds and are lost upon drying. Although it is a generally true rule that *Cordyceps* cannot be cultivated in polypropelyne bags, new strains have been developed that produce far lower quantities of PAH, making their cultivation in plastic bags possible.

VII. THERAPEUTIC APPLICATIONS, INDICATIONS, AND USAGE

The range of therapeutic uses claimed for the *Cordyceps* species is far reaching; although many of them have yet to be sufficiently investigated. In TCM, *Cordyceps* has been used to treat conditions including respiration and pulmonary diseases; renal, liver, and cardiovascular diseases; hyposexuality; and hyperlipidemia. It is also used in the treatment of immune disorders and as an adjunct to modern cancer therapies (chemotherapy, radiation treatment and surgery).[5] *Cordyceps* is believed by many, particularly in and around Tibet (its place of origin), to be a remedy for weakness and fatigue, and it is often used as an overall rejuvenator for increased energy while recovering from a serious illness. Many also believe it to be a treatment for impotence, acting as an aphrodisiac in both men and women. *Cordyceps* is often prescribed for the elderly to ease general aches and pains. TCM practitioners also recommend the regular use of *Cordyceps* to strengthen the body's resistance to infections, such as colds and flus, and to generally improve the homeostasis of the patient. Traditionally, *Cordyceps* has most often been used in the treatment of health issues related to or stemming from the kidneys and the lungs. For example, it is used to ease a range of respiratory ailments: cough and phlegm, shortness of breath, bronchial discomfort, chronic obstructive pulmonary disease (COPD), and asthma. Modern science is attempting to confirm the efficacy of *Cordyceps* for most of its traditional uses; however, most medical studies regarding its efficacy remain incomplete.

Today in the West, *Cordyceps* is most widely used by two groups of people: athletes and the elderly. The use of *Cordyceps* by athletes stems from publicity surrounding the performance exhibited by the Chinese Women's Track and Field

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team at the Chinese National games in 1993. In this competition, 9 world records were broken by substantial margins. At first, governing sports authorities suspected that a performance-enhancing drug had been used, but the team's coach attributed their success to *Cordyceps*.[20] Research has shown that the use of *Cordyceps* results in an increase of cellular ATP.[7,21] An increase in cellular ATP results in an increase in useful energy. This is in contrast to the perceived increase in energy that occurs from the use of CNS stimulants, such as caffeine, ephedrine, and amphetamines, which ultimately results in an energy deficiency. However, it should be noted that in a recent study with highly trained professional athletes, *C. sinensis* was shown to have no appreciable effect on increasing performance in this group of people.[22] It is conceivable that these athletes were already performing to the limit of their potential and little increase in performance could be achieved through chemical or herbal supplementation. We are not aware of any test that has been conducted showing a difference in the energy increase potential between highly trained athletes and normal healthy adults using *Cordyceps*.

A. Fatigue

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

In a placebo-controlled clinical study of elderly patients with chronic fatigue, results indicated that most of the subjects treated with *C. sinensis* reported a significant clinical improvement in the areas of fatigue, cold intolerance, dizziness, frequent nocturia, tinnitus, hyposexuality, and amnesia, whereas no improvement was reported in the placebo group.[1,2,23,24,25] Another study involving healthy elderly volunteers, with an average age of 65, tested the output performance and oxygen capacity of subjects while exercising on stationary bicycles. A portion of the volunteers consumed *C. sinensis* for 6 weeks, whereas others consumed a placebo. The results demonstrated that the *Cordyceps* group had a significant increase in energy output and oxygen capacity over the placebo group after 6 weeks.[26]

Among the simplest and most reliable tests used to determine a compound's ability to increase the energy output of a subject or decrease fatigue is the mouse swim test. In this test, two groups of mice (or other animals) are used. One group receives a standard diet, whereas the other receives the same diet, with the addition of the test compound. In this case, the test compound is *Cordyceps*. After a period of time, the two groups are put into a steep-sided container filled with water, from which escape is not possible. In this way, the animals are forced to swim. The time-to-exhaustion is measured for the two groups, and the results are compared and contrasted. If the group receiving the test compound swims longer than the group on the standard diet without the test compound, then it has been determined that they had increased energy output/decreased fatigue, when compared to the control group. Trials of this nature have been conducted using *Cordyceps* as the test compound and have invariably shown the use of *Cordyceps* to significantly increase the time-to-exhaustion in laboratory animals over their control groups.[2]

B. Preclinical and Clinical Data

Therapeutic applications of *Cordyceps* and its extracts are hypothesized to be centered primarily on the key effects of increased oxygen utilization,[5,27] increased ATP production,[5] and the stabilization of blood sugar metabolism.[5] The presence of adenosine, cordycepin, and cordycepic acid [d-mannitol][14]; polysaccharides; vitamins; and trace elements may be, at least partially, the cause for such 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 are still relatively new endeavors. Earlier trials, although few in number, have set the precedent from which modern trials are building, expanding, and cementing our understanding of *Cordyceps.*

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C. Cancer

A possibly valuable therapeutic application of *Cordyceps* is its potential as a treatment for cancer, as well as an adjunct to chemotherapy, radiation, and other conventional and traditional cancer treatments.[1,2,3,17]

1. Animal Studies

The survival time of mice inoculated with murine B16 melanoma cells and treated with a combination of water extracts from *C. sinensis* and the chemotherapy agent, methotrexate, has been shown to be significantly longer than the survival time of either the untreated control group or those treated with methotrexate alone, indicating that some water extracts of *C. sinensis* may be beneficial in the prevention of tumor metastasis.[28]

Antitumor and immunostimulating activities were observed in the treatment of mice inoculated with Sarcoma 180 tumor cells, when treated with an ethanol extract of *C. sinensis,*[29] whereas a study using murine models verified that oral administration of a hot water extract of *C. sinensis* consequently resulted in the activation of macrophages, thereby increasing the production of granulocyte monocyte colony-stimulating factor ([GM-CSF] a naturally occurring substance that is made by the body in response to infection or inflammation) and IL-6, which act on the systemic immune system.[30] In a study of mice subcutaneously implanted with lymphoma cells, oral administration of an extract of *C. sinensis* led to a decrease in tumor size and a prolonged survival time.[31] Furthermore, mice treated with cyclophosphamide, which suppresses immune function, also treated with the same hot water extract, saw their immune function return to normal, as measured by the IgM and IgG response and macrophage activity.[31] Further evidence of the immune-enhancing action of *C. sinensis* was provided by another study treating mice inoculated with Erhlich ascites carcinoma (EAC) cells with a warm water extract of *Cordyceps.* The median survival time of the treated mice compared to untreated controls was over 300%, and the lack of activity of the extract against EAC cells grown in vitro indicated that the antitumor effect in the mice may be attributed to a host-mediated immune response, rather than direct cytotoxicity.[32]

Oral administration of polysaccharide fractions CI-P and CI-A, derived from *C. sinensis*, in doses of 1–10 mg/kg per day, demonstrated antitumor activities in mice inoculated with Sarcoma 180. Similar results were observed with an alkali-soluble polysaccharide (CI-6P), derived from the species *C. sobolifera*, when administered in doses of 10 mg/kg/day.[2] In a related study, β-(1-3)-D-glucan, fraction CO-1, and the galactosaminoglycan fraction CO-N, derived from *C. ophioglossoides*, inhibited the growth of ascitic Sarcoma 180. Increased immune function was noted as well, quantified by an increase in carbon clearance activity.[33,34]

It is well established that numerous fungal-derived simple- and protein-bound polysaccharides exert a significant potentiation of immune function.[17] This is thought to be one of the major mechanisms of antitumor activity in *Cordyceps*. Among the multiple polysaccharides produced by *C. sinensis*, β-D-glucans are one class of polymers that have been shown to increase both innate and cell-mediated immune response. These polysaccharides increase the production of such cytokines as TNF-α, interleukins, interferons, NO, and antibodies by the activated immune cells. This activation of an immune response may be triggered by polysaccharide binding to specific receptors on the surface of the immune system cells, such as the CR3 receptors, and other receptors.[35,36] They are also thought to be involved in cell-to-cell communications, perhaps acting as messenger molecules.

There is evidence of another mechanism at play in the antitumor response of *Cordyceps,* as well, pertaining to the structure of at least one, and possibly more, of the altered nucleosides found in some species of *Cordyceps* and exemplified by the compound cordycepin [3′-deoxyadenosine] (see Fig. 6). These deoxynucleosides interfere with DNA replication in tumor cells. Such interference is reduced in normal healthy cells by the operation of a DNA repair mechanism, which is absent in tumor cells, and by the fact that tumor cells generally multiply at a rate well in excess of that of normal cells.

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2. Clinical Trials

Clinical studies have been conducted in China and Japan involving cancer patients,[37] yielding positive results. In one study of 50 patients with lung cancer who were administered *C. sinensis* at 6 grams per day, in conjunction with chemotherapy, tumors were reduced in size in 46% of the patients studied. A trial involving cancer patients with several different types of tumors found that *C. sinensis*, taken over a 2-month period at 6 g per day, improved subjective symptoms in the majority of patients. White blood cell counts were kept at 3000 per cubic millimeter or higher, and even with radiation or chemotherapy, other immunological parameters showed no significant change, whereas tumor size was significantly reduced in approximately half of the patients observed, indicating an improved tolerance for radiation and/or chemotherapy.[5]

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

The belief in the efficacy of *C. sinensis* against cancer is widespread in the Orient, and many cancer patients in Japan, Korea, and China are taking *Cordyceps* or some other mushroom-derived immunomodulator (such as PSK, PSP, Lentinan, AHCC, heteropolysaccharide complex formula [Immune Assist™], and arabinoxylanes [MGN3™]) while undergoing conventional treatment.[5,37,38]

D. Immunomodulating Effects

The immune-enhancing effects of *C. sinensis* have been alluded to in the above discussions. It is of interest to note that the fungus that produces the immunosuppressive drug cyclosporin, *Tolypocladium inflatum*, was discovered in 1996 to be the asexual stage of yet another *Cordyceps* species, *C. subsessilus*.[15] Thus, the same genus of fungus that was used for centuries to provide immune stimulation was now known to provide an immune suppressant that is valuable in organ transplantation surgery.

Other such experiments demonstrating both inhibiting as well as potentiating effects of *Cordyceps* are controversial, and the effects observed are possibly the result of differing experimental conditions and variables. However, with such evidence of a possibly bi-directional immune-modulating effect, further research is in order.

Although the drug cyclosporin has enabled some advances in medicine by facilitating the transplant of organs, there has been a drawback to its use. The high toxicity of cyclosporin has caused many patients to suffer from serious kidney damage related to the use of the drug. In 1995, a study was undertaken in China in which 69 kidney transplant patients were given either cyclosporin alone or in conjunction with *C. sinensis*, at 3 grams per day. After 15 days it was clearly evident that the group receiving *C. sinensis* in addition to cyclosporin had a much lower incidence of kidney damage than the group receiving only cyclosporin, as measured by the levels of urinary NAG, serum creatinine, and blood urea nitrate.[39]

E. Kidney Ailments

Traditional views of the *Cordyceps* species held that its consumption strengthened the kidneys. Studies have shown that much of the kidney-enhancing potential of *Cordyceps* stems from its ability to increase 17-hydroxy-corticosteroid and 17-ketosteroid levels in the body.[5]

Chronic renal failure is a serious disease, one often affecting the elderly. In a study among 51 patients suffering from chronic renal failure, it was found that the administration of 3–5 grams per day of *C. sinensis* significantly improved both kidney function and overall immune function of treated patients, compared to the untreated control group.[40]

Patients with chronic renal failure or reduced kidney function often suffer from hypertension, proteinuria, and anemia. In a study with such patients, it was found that after one month on *C. sinensis*, a 15% reduction in blood pressure was observed. Urinary protein was also reduced.

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Additionally, increases in superoxide dismutase (SOD) were seen. The increase in SOD, coupled with an observed decrease in serum lipoperoxide, suggests an increase in the oxygen-free radical-scavenging capacity, resulting in reduced oxidative cellular damage.[41]

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 6 days, the group that received *Cordyceps* had recovered 89% of their normal kidney function, whereas 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.[5]

F. Hypoglycemic Effect

Another area of particular interest is the effect of *Cordyceps* spp. on the blood glucose metabolism system. *Cordyceps sinensis* has been tested in animal and human trials to investigate its potential as an agent in blood sugar regulation. In one randomized trial, 95% of patients treated with 3 grams per day of *C. sinensis* saw improvement in their blood sugar profiles, whereas the control group showed only a 54% improvement with treatment by other methods.[42]

In animal studies, isolated polysaccharides have been shown to improve blood glucose metabolism and increase insulin sensitivity in normal animals,[43] to lower blood sugar levels in genetically diabetic animals,[44] and to positively effect blood sugar metabolism in animals with chemically induced diabetes.[45] The common thread throughout all these trials is the increase in insulin sensitivity and hepatic glucose-regulating enzymes, glucokinase, and hexokinase.

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

G. Lung Ailments

Chinese medicine has characterized *C. sinensis* as a guardian of respiratory health for more than a thousand years. There have been trials in humans using *Cordyceps* spp. to treat many respiratory illnesses, including asthma, COPD, and bronchitis, either alone or as an adjunct to standard antibiotic therapy, and in many studies that have been conducted, it appears to be useful for all of these conditions.[26,46–52]

Much of its reputation for protecting the lungs is believed to stem from its ability to promote enhanced oxygen utilization efficacy. In environments lacking sufficient oxygen, mice treated with *Cordyceps* were able to survive up to three times longer than those left untreated, demonstrating a more efficient utilization of the available oxygen. This provides support for the long history of *Cordyceps* use in preventing and treating altitude sickness.[26] Such efficacy alludes to the use of *Cordyceps* as an effective treatment for bronchitis, asthma, and COPD. Extracts of *C. sinensis* have been shown to inhibit tracheal contractions, which is especially important in asthma patients because it allows for increased airflow to the lungs. In addition, its anti-inflammatory properties may prove to bring further relief to asthma patients whose airways become obstructed due to an allergic reaction resulting in the swelling of the bronchial pathways.[1,5,53] In an unpublished clinical trial conducted at the Beijing Medical University involving 50 asthma patients, symptoms among the group treated with *Cordyceps* were reduced by 81.3% within an average of 5 days, whereas among those treated with conventional antihistamines, the rate of symptom reduction averaged only 61.1%, and it took an average of 9 days for symptoms to subside.[46,53]

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H. Heart Ailments

Cordyceps is also a medication used in stabilizing the heartbeat and correcting heart arrhythmias in China. Although the exact mechanism responsible for the reputation of *Cordyceps* with regard to controlling arrhythmias is not completely understood, it is thought to be at least partially due to the presence of adenosine,[54] of which *Cordyceps* often has a significant quantity, along with deoxyadenosine, related adenosine-type nucleotides, and other free nucleosides. It has been shown that these compounds have an effect on coronary and cerebral circulation.[55,56] Although no single drug or herb is equally effective in all patients, it appears rare for a patient's arrhythmia to remain unaffected by the addition of *Cordyceps* to the treatment regimen. *Cordyceps* has been used traditionally to treat patients with heart disease and those recovering from stroke.[1]

In studies of patients suffering from chronic heart failure, the long-term administration of *Cordyceps*, in conjunction with conventional treatments—that is, 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.[25]

I. Liver Ailments

Another area of considerable research interest is the relationship between *Cordyceps* and liver function. *Cordyceps* has been shown in nearly all such studies to increase the efficient functioning of the liver. For example, in the Orient today, *Cordyceps* is commonly used as an adjunct in the treatment of chronic hepatitis B and C. In one study, *Cordyceps* extract was used in combination with several other medicinal mushroom extracts as an adjunct to lamivudine, for the treatment of hepatitis B. Lamivudine is a common antiviral drug used in the treatment of hepatitis. In this study, the group receiving *Cordyceps* along with other medicinal mushroom extracts had much better results, in a shorter period of time than the control group, who received only lamivudine.[37]

In another study using 22 patients who were diagnosed with posthepatic cirrhosis,[57] after 3 months of consuming 6–9 grams of *Cordyceps* per day, each patient showed improvements in liver-function tests.

J. Hypercholesterolemia

Although hypercholesterolemia is not typically considered a disease, it is a clear indicator of metabolism dysfunction and an indicator of increased cardiovascular risk. In both human and animal studies, the administration of *Cordyceps* has been associated with cholesterol and triglyceride reduction and an increase in the ratio of HDL to LDL cholesterol.[1,5,58] Whether the causative mechanism for this lipid-balancing effect is through blood sugar stabilization, from enhancing liver function, or due to some other as yet unknown cause, remains to be seen.

K. Treatment for Male/Female Sexual Dysfunction

Cordyceps has been used for centuries in TCM to treat male and female sexual dysfunction, such as hypolibidinism and impotence. Preclinical data on the effects of *C. sinensis* on mice showed sex-steroid-like effects.[1,2] Human clinical trials have similarly demonstrated the effectiveness of *Cordyceps* in combating decreased sex drive and virility.[26,46,59]

L. Use Against HIV/AIDS

A *Cordyceps*-containing formula, Immune Assist 24-7™, has recently come into popularity throughout West Africa for use in treating HIV infections and other immune-deficient states. This American-made product has been approved as a complementary medicine by the regulatory authorities in a number of African countries and is currently being stocked in most hospitals, clinics, and pharmacies throughout the region and is quite popular with both the doctors and the patients due to its low toxicity

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and cost when compared to the other antiretroviral drug options.

M. Other Uses

Many species of *Cordyceps* and other entomopathogenic fungi have been mentioned in scientific discourse in relation to their potential as biological-control agents.[60]

VIII. DOSAGE

Because clinical data on *Cordyceps* is relatively new, and even more so in Western countries, recommended dosage requirements may vary, depending on the source. In general, clinical trials have been conducted using 3–4.5 g of *C. sinensis* per day, except in cases of severe liver disease, where the dosage has usually been higher, ranging from 6 to 9 g per day.[1,2] There are some practitioners known to this author who keep their cancer patients on 30–50 g of *Cordyceps* per day. Although this may seem excessive, the clinical results seen with this treatment regimen are promising, and *Cordyceps*-related toxicity has never been reported.

It has traditionally been 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 noncapsulated forms. At present, there are no reliable standards by which to compare different brands, but in general, the quality of *Cordyceps* is improving, as methods of more efficient cultivation are investigated, and as more clinical trials are conducted, a clearer picture of recommended dosages for a particular condition will become more standardized. Considering the quality of cultivated *Cordyceps* on the market today and the risk of lead exposure, as well as the cost of the wild Cordyceps, use of natural *Cordyceps* over the artificially cultivated variety is not recommended. Obtaining *Cordyceps* from a reliable source, with complete analytical data provided, is the safest way to purchase *Cordyceps*.

A. Safety Profile

Contraindications. None known.

B. Drug Interactions

There is observational evidence by these authors that the alteration of the body's blood glucose metabolism in patients consuming *Cordyceps* often results in the reduction of oral or injected antidiabetic medications. It is also posited that the naturally occurring antiretroviral compounds found in *Cordyceps* (e.g., 2′3′-dideoxyadenosine, which is found in *C. sinensis* and is marketed as a major anti-HIV drug under the name Videx and Didanosine, as well as 3′-deoxyadenosine, which has the same or at least similar activity) could 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 being selectively cultivated. Many antiretroviral drugs currently on the market are considerably toxic, 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 their efficacy. Although no detrimental drug interactions have yet been noted in the scientific literature, caution is advised, as both the fields of pharmaceutical discovery and *Cordyceps* cultivation are rapidly expanding. As with any substance of considerable bioactivity, some drug interaction is always a possibility.

C. Adverse 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.[5] One study reported that a patient had developed a systemic allergic reaction after taking a strain of *Cordyceps* called Cs-4[61]; however, this type of reaction is not common. There is little published data on the use of *Cordyceps* in pregnant or lactating women,

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or in very young children, and appropriate precautions should be taken with these types of patients.

IX. TOXICITY

Cordyceps has proven to be a nontoxic fungal substance with wide-ranging physical and chemical effects on the body. No human toxicity has been reported, and animal models failed to find an LD_{50} (median lethal dose) injected i.p. in mice at up to 80 g/kg per day, with no fatalities after 7 days.[1,3] Given by mouth to rabbits for 3 months, at 10 g/kg per day (n = 6), no abnormalities were seen from blood tests or in kidney or liver function.[62]

X. REGULATORY STATUS

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

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

XI. CONCLUSIONS

When a natural product such as *Cordyceps* has such a long history of use, it seems logical that there is quite likely some truth behind the myths. Our challenge in the modern age is to scientifically unravel the many claims and conflicts. With *Cordyceps* this challenge has been greater than with many other herbals due to the enormous cost and scarcity of the material. We are fortunate that we live in an age of such rapidly expanding biotechnological progress, for now we have ways at our disposal to produce *Cordyceps* in large enough volume and at a low enough cost that research becomes possible to nearly anyone interested in looking at this unique organism. As time passes, we may find that this once rare fungal species may hold the key to controlling some of our more difficult-to-manage diseases. It is clear from our studies that we know only a little of the wonders of these strange *Cordyceps* creatures. *Cordyceps* still has many secrets in store for us. More research is needed on these and other species of medicinal mushrooms.

REFERENCES

1. Hobbs Ch. Medicinal mushrooms: an exploration of tradition, healing, and culture. Santa Cruz (CA): Botanica Press; 1995. 251 pp.
2. Mizuno T. Medicinal effects and utilization of Cordyceps (Fr.) Link (Ascomycetes) and Isaria Fr. (Mitosporic fungi) Chinese caterpillar fungi, "Tochukaso" (review). Int J Med Mushr. 1999;1:251–62.
3. Holliday J, Cleaver M, Wasser SP. Cordyceps. In: Coates PM, Blackman MR, Cragg G, Levine M, Moss J, White J, editors. Encyclopedia of dietary supplements. New York: Marcel Dekker; 2005. p. 1–13.
4. Halpern GM. Healing mushrooms. Effective treatments for today's illnesses. Garden City (NY): Square One Publishers; 2007.
5. Zhou J-S, Halpern G, Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis. J Altern Complement Med. 1998;4:429–57.
6. Kirk PM, Cannon PF, David JC, Stalpers JA. Dictionary of the fungi. 9th ed. Wallingford (CT): CAB International; 655 p.
7. Dai GW, Bao TT, Xu GF, Cooper R, Zhu GX. CordyMax™ Cs-4 improves steady-state bioenergy status in mouse liver. J Altern Complement Med. 2001;7:231–40.
8. Suh SO, Noda H, Blackwell M. Insect symbiosis: derivation of yeast-like endosymbionts within an entomopathogenic filamentous lineage. Mol Biol Evol. 2001;18(6):995–1000.
9. Holliday J, Cleaver P, Loomis-Powers M, Patel D. Analysis of quality and techniques for hybridization of

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medicinal fungus Cordyceps sinensis. Int J Med Mushr. 2004;6:147–60.
10. Chen K, Li C. Recent advances in studies on traditional Chinese anti-aging Materia Medica. J Tradit Chin Med.1993;13:223–6.
11. Hsu TH, Shiao LH, Hsiea C, Chang DM. 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. 2002;78:463–9.
12. Cleaver P, Holliday JC, Powers ML. Novel method for growing Cordyceps sinensis on a substrate and novel method for hybridizing different strains of Cordyceps sinensis. United States patent application US 20060014267. 2006 .
13. Wu TN, Yang KC, Wang CM, Lai JS, Ko KN, Chang PY, Liou SH. Lead poisoning caused by contaminated Cordyceps, a Chinese herbal medicine: two case reports. Sci Total Environ. 1996;182:193–5.
14. Chen SZ, Chu JZ. [NMR and IR studies on the characterization of cordycepin and 2'deoxyadenosine.] Zhongguo Kangshengsu Zaxhi. 1996;21:9–12 (in Chinese).
15. Segelken R. 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.
16. Ukai S, Kiho T, Hara C, Morita M, Goto A, Imaizumi N, Hasegawa Y. 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). 1983;31:741–4.
17. Wasser SP. Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. Appl Microbiol Biotechnol. 2002;60:258–74.
18. Kiho T, Hui J, Yamane A, Ukai S. Hypoglycemic activity and chemical properties of a polysaccharide from the cultural mycelium of Cordyceps sinensis. Biol Pharm Bull. 1993;16:1291–3.
19. 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. Jpn J Pharmacol. 1999;79:505–8.
20. Chinese women's running coach reveals secret recipe for rejuvenation. World J. 1997.
21. Manabe N, Sugimoto M, Azuma Y, Taketomo N, Yamashita A, Tsuboi H, Tsunoo A, Kinjo N, Nian-Lai H, Miyamoto H. Effects of the mycelial extract of cultured Cordyceps sinensis on in vivo hepatic energy metabolism in the mouse. Jpn J Pharmacol. 1996;70(1):85–8.
22. Parcell A.C, Smith JM, Schulthies SS, Myrer JW, Fellingham G. Cordyceps sinensis (CordyMax Cs-4) supplementation does not improve endurance exercise performance. Int J Sport Nutr Exerc Metab. 2004;14:236–42.
23. Bao ZD, Wu ZG, Zheng F. Amelioration of aminoglycoside nephrotoxicity by Cordyceps sinensis in old patients. Chin J Integr Med. 1994;14:271–3.
24. Chamberlain M. Ethnomycological experiences in South West China. Mycologist. 1996;10:173–6.
25. Chen DG. Effects of JinShuiBao capsule on the quality of life of patients with heart failure. J Admin Trad Chin Med. 1995;5:40–3.
26. Zhu J-S, Rippe J. CordyMax enhances aerobic capability, endurance performance, and exercise metabolism in healthy, mid-age to elderly sedentary humans. Presented at the Annual Scientific Conference of the American Physiological Society (APS). Experimental Biology. 2004 April 17–21; Washington, DC.
27. Wang R, Xu Y, Ji P, Wang X, Holliday J. Clinical trial of a mixture of six medicinal mushroom extracts. Available from: http://www.alohamedicinals.com/clinical_trials.htm 2001.
28. Nakamura K, Konoha K, Yamaguchi Y, Kagota S, Shinozuka K, Kunitomo M. Combined effects of Cordyceps sinensis and methotrexate on hematogenic lung metastasis in mice. Receptors Channels. 2003;9:329–34.
29. Shin KH, Lim SS, Lee S, Lee YS, Jung SH, Cho SY. Anti-tumor and immuno-stimulating activities of the fruiting bodies of Paecilomyces japonica, a new type of Cordyceps spp. Phytother Res. 2003;17:830–3.
30. Koh JH, Yu KW, Suh HJ, Choi YM, Ahn TS. Activation of macrophages and the intestinal immune system by an orally administered decoction from cultured mycelia of Cordyceps sinensis. Biosci Biotechnol Biochem. 2002;66:407–11.
31. Yamaguchi N, Yoshida J, Ren LJ, Chen H, Miyazawa Y, Fujii Y, Huang YX, Takamura S, Suzuki S, Koshimura S. Augmentation of various immune reactivities of tumor bearing hosts with an extract of Cordyceps sinensis. Biotherapy. 1990;2:199–205.
32. Yoshida J, Takamura S, Yamaguchi N, Ren LJ, Chen H, Koshimura S, Suzuki S. Antitumor activity of an extract of Cordyceps sinensis (Berk.) Sacc. against murine tumor cell lines. Jpn J Exp Med. 1989;59:157–61.
33. Ohmori T, Tamura K, Tsuru S, Nomoto K. Antitumor activity of protein-blood polysaccharide from Cordyceps ophioglossoides in mice. Jpn J Cancer Res (Gann). 1986; 77:1256–63.
34. Ohmori T, Tamura K, Furuki K, Kawanishi G, Mitsuyama M, Nomoto K, Miyazaki T. Isolation of galactosaminoglycan moity (CO-N) from protein-bound polysaccharide of Cordyceps ophioglossoides and its effects against murine tumor. Chem Pharmacol Bull. 1989;37:1019–22.
35. Smith JE, Rowen N, Sullivan R. Medicinal mushrooms: their therapeutic properties and current medical usage with special emphasis on cancer treatment. Special report commissioned by Cancer research UK. Glasgow: The University of Strathclyde; 2002. 256 p.
36. Chen J, Seviour R. Medicinal importance of fungal β-(1→3), (1→6)-glucans. Mycol Res. 2007;111:635–52.
37. 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

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Lamivudine [Epivirtm] 2002. Available from: http://www.alohamedicinals.com/Hep_B_Study2.pdf.
38. Xu WZ, Wei JP, Wang NQ, Liu T. [Experimental study of the combined chemotherapy of Zhiling capsules and anticancer agents.] Shanghai Zhongyiyao Zazhi. 1988;6:48 (in Chinese).
39. Xu F, Huang JB, Jiang L, Xu J, Mi J. Amelioration of cyclosporin nephrotoxicity by Cordyceps sinensis in kidney transplanted recipients. Nephrol Dial Transplant.1995;10:142–3.
40. Guan YJ, Hu G, Hou M, Jiang H, Wang X, Zhang C. Effect of Cordyceps sinensis on T- lymphocyte subsets in chronic renal failure. Chin J Integr Med. 1992; 12:338–9.
41. Jiang JC, Gao YF. Summary of treatment of 37 chronic renal dysfunction patients with JinShuiBao. J Admin Trad Chin Med. 1995;5:23–4.
42. Guo QC, Zhang C. Clinical observations of adjunctive treatment of 20 diabetic patients with JinSHuiBao capsule. J Admin Trad Chin Med. 1995;5:22.
43. Zhao CS, Yin WT, Wang JY, Zhang Y, Yu H, Cooper R, Smidt C, Zhu JS. Cordyceps Cs-4 improves glucose metabolism and increases insulin sensitivity in normal rats. J Altern Complement Med. 2002;8:403–5.
44. Kiho T, Yamane A, Hui J, Usui S, Ukai S. 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;4:647–9.
45. Hsu TH, Lo HC. Biological activity of Cordyceps (Fr.) Link species (Ascomycetes) derived from a natural source and from fermented mycelia on diabetes in STZ-induced rats. Int J Med Mushr. 2002;4:111–25.
46. Donohue JF. Recent advances in the treatment of asthma. Curr Opin Pulm Med. 1996;2:1–6.
47. Manfreds J, Mao Y, Litven W. Morbidity and mortality from chronic obstructive pulmonary disease. Ann Rev Respir Dis. 1989;140:S19–26.
48. Han SR. Experiences in treating patients of chronic bronchitis and pulmonary diseases with Cs-4 capsule (JinShuiBao). J Admin Trad Chin Med. 1995;5 Suppl:33–4.
49. Qiuo YL, Ma XC. Treatment of 32 tussive asthma patients with JinShuiBao. Chin J Integr Trad Western Med. (Chung-KuoChungHsi I Chieh Ho Tsa Chih). 1993;13:660.
50. Qu ZY, Song K, Cai WL, Tang J. Evaluation of therapeutic effects of JinShuiBao capsule for treatment of respiratory disease. J Admin Trad Chin Med. 1995;5 Suppl:29–30.
51. Zheng XY, Zhang ZJ, Wen YZ, Liao SZ. Observation on the therapeutic effects of artificial Cordyceps in the treatment of chronic bronchitis and its effects on pulmonary function. In: Collection on the basic medical and clinical studies of submerged culture Cordyceps sinensis. Vol. 2. Beijing, Nanchang, China: Jiangxi TCM/IMM; 1985. p. 95–9.
52. Zheng LY, Deng WW. The clinical efficacy of Cordyceps sinensis Cs-4 capsule in treating chronic bronchitis and its effect on pulmonary function. J Admin Trad Chin Med. 1995; 5 Suppl:9–11.
53. Halpern G. Cordyceps: China's healing mushroom. New York (NY): Avery Publishing; 1999. p. 63–70.
54. Pelleg A, Porter RS. The pharmacology of adenosine. Pharmacotherapy. 1990;10:157–74.
55. Toda N, Okunishi H, Taniyama K, Miyazaki M. Response to adenine nucleotides and related compounds of isolated dog cerebral, coronary and mesenteric arteries. Blood Vessels. 1982;19:226–36.
56. Berne RM. The role of adenosine in the regulation of coronary blood flow. Circ Res. 1980;47:807–13.
57. 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 Chin Materia Medica. 1986;6:30–1.
58. Dai G, Bao T, Xu C, Cooper R, Zhu JS. Cordyceps Cs-4 improves steady-state bioenergy status in mouse liver. J Altern Complement Med. 2001;7:231–40.
59. Guo YZ. Medicinal chemistry, pharmacology and clinical applications of fermented mycelia of Cordyceps sinensis and JinShuBao capsule. J Modern Diagn Ther. 1986;1:60–5.
60. Shah PA, Pell JK. Entomopathogenic fungi as biological control agents. Appl Microbiol Biotechnol. 2003;61:413–23.
61. Xu Y. Drug allergy occured in a patient after orally taken JinShuiBao capsule. China J Chin Materia Medica. 1994;19:503.
62. Huang Y, Lu J, Zhu B, Wen Q, Jia F, Zheng S, Chen T, Li Y, Cheng G, Yi Z. [Toxicity study of fermentation Cordyceps mycelia B414.] Zhongchengyao. 1987;10:24–5 (in Chinese).

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