Review Paper

Cordyceps The Fungal Gold - A Review

Abstract

Cordyceps is an entomophagous medicinal mushroom that commands a price close to that of Gold or even more, it is believed that the price of this fungus reached USD $20,000 to 40,000 per kg in the international market. *Cordyceps* spp is mainly endemic to the Tibetian plateau including the adjoining high altitude areas of the central and East Himalayas that includes Nepal, Bhutan and India's Uttaranchal, Sikkim, Himachal and Arunachal Pradesh. However certain species like *Cordyceps militaris* is said to be distributed worldwide from 0 to >2000 m a.s.l. The fungus attacks many lepidopteran larvae especially Thitarodes caterpillars and mummifies it. The larvae along with the mummified insect is highly valued for its medicinal property. The fungus initially navigates the weak body part of the larvae and then penetrates the insect integument which is composed of chitin or it may enter through the mouth region and then dispenses endotoxin to the larval blood, proliferates and finally mummifies the larvae and it's stroma emerges through the larval head. *Cordyceps* sp is the world's most efficient and expensive medicinal mushroom and considered as a traditional Chinese medicine having multiple medicinal and pharmacological properties and is used to treat respiratory and immune disorders, pulmonary diseases, renal, liver and cardiovascular diseases, hyposexuality and hyperlipidema etc. With regard to the various medicinal properties this review is limited to the facts which is substantiated with proofs only. This review further deals with the various methods of artificial production of the fungus.

Keywords :-Cordyceps, entomophagous Ophiocordyceps

Introduction

Cordyceps sinensis is an entomophagous medicinal mushroom. It is a premium Chinese herb that commands a price close to that of Gold or even more [1]. It is basically the costliest fungus or medicinal mushroom throughout the world, hence known as “fungal gold” or “soft gold”. It has great pharmacological properties and has been used for over 2000 years in China for infectious diseases [2]. Early records of *Cordyceps* as a medicine is as old as the Qing Dynasty in China and this information has been mentioned in Ben-Cao-Cong-Xin (New Compilation of Materia Medica) written by Wu-Yiluo in around 1757 [3]. Though the medicinal value of this fungus has been recognized for more than 2000 years in China and the Orient it's knowledge reached Western scientific audiences only in 1726, when it was introduced at a scientific meeting in Paris. The first specimen was 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 [4]. In historical and general usage, the term ‘‘*Cordyceps*’’ refers specifically to the species *Cordyceps.*

sinensis (Berk.) Sacc (syn Ophiocord*yceps sinensis* (Berk.) G.H. Sung, J.M. Sung, Hywel-Jones & Spatafora.) which is the most widely used *Codyceps* species. Berkely the British mycologist first described this fungus in 1843 as *Sphaeria sinensis* Berk., later in 1878 Saccardo renamed it as *Cordyceps sinensis* . The accepted scientific name is *Cordyceps sinensis* (Berk.) Sacc.[5]. It belongs to the phylum Ascomycota (sac fungi), the family Ophiocordycipitaceae, order Hypocreales. It is often referred to as an entomophagous fungus owing to its parasitic nature on insects' larvae. Often the combination of the fungus and dead insect is used as a traditional Chinese medicine(TCM) .The fungus possesses wide host range, killing Lepidopteran larvae of more than 60 different species [6]. Although it can infect 30 of 40 known species of Thitarodes caterpillars [7], the Himalayan bat moth *Hepialus armoricanus* proves to be the usual and common host for this fungus. Because of their high medicinal value they are called medicinal mushroom though they are not mushrooms in the real taxonomic sense. *Cordyceps sinensis* was first recorded as *yartsa gunbu* in Tibet in the text "*An ocean of Aphrodisiacal Qualities"* [9] and known as "*yarsha gumba"* in Nepali ''Dong Chong-XiaCao'' in Chinese ''Tochukaso'' in Japanese and "caterpillar fungus" in English [8]. The generic name *Cordyceps* comes from the latin word "cord" and "ceps", meaning "club" and "head" respectively. The latin word accurately describes the appearance of this club fungus whose stoma and fruiting body extend from the mummified carcasses of the insect larvae.

There are many species that come under the genus *Cordyceps* [10]. There is debate amongmany scientists at present whether the species of the genus *Cordyceps* are in fact single organism or if they are symbiotic colonies of more than one organism. Perhaps what we are calling *Cordyceps sinensis* today, will one day be known as a fungal/bacterial symbiosis. DNA sequencing has proven inconclusive in this regard as the DNA sequence tends to change with time, as if the fungus were incorporating some of the insect DNA into its own DNA code for the initiation of its fruiting body form, then losing the insect DNA when it goes back into its mycelial form [11]. It was found that even though the parent fungus is the same, the resultant asexual mycelial growth forms are characteristically different enough in taxonomy and chemistry that they are considered different species by many taxonomists [11].

Price of *Cordyceps*

Cordyceps sinensis is a premium Chinese herb that commands a price close to that of Gold or even more [1]. Basically the costliest fungus or medicinal mushroom throughout the world is *Cordyceps sinensis* [2]. In the last decade the prices of Cordyceps grew 20% annually, and to date is probably 1000% the price 10 years ago [1]. Pricing is achieved by inspecting the size and firmness of the larval host (posterior part of the specimen), which is often tested by squeezing between two fingers; the stiffer it is, the higher the price [12]. Colours are also observed when pricing, a saturated yellowish-brown colour is preferred to paler colours [13]. Other physical characteristics taken into account when assessing quality are size, weight, smell, taste and robustness [13,14]. The odour of freshly collected specimens is relatively fleshy while the taste is bitter [15].

Since economic liberalization in the early 1980s, *Cordyceps* has developed into one of the most important “cash crops” on the southeastern Tibetian Plateau. *Cordyceps* trade between Tibet and China goes back at least to the 17th century and probably much further. During the Cultural Revolution (1966–1976), the *Cordyceps* market collapsed and 1 kg of *Cordyceps* was traded for CNY 21 (less than US$ 3) in Xining, Qinghai Province [16]. Following the economic liberalization prices increased dramatically (Table 1). In 1985 *Cordyceps* traded wholesale for CNY 1,800 per kg in Lhasa, rising to CNY 8,400 in 1997 (an increase of 366%) and to CNY 36,000 in 2004 (a further increase of 1,900%). Inflation was largely controlled after 1997, and the increase in wholesale price from 1997 to 2004 amounts to 342%, representing an average annual price increase of 21.2% (Table 1) [12].

Table 1. **Cordyceps (Yartsa gunbu) wholesale price development in lhasa (Tibet autonomous region) and Litang (GanziTibetan autonomous prefecture, Sichuan**).

Location	**Year**	**1970**	**1982**	**1985**	**1988**	**1990**	**1992**	**1995**	**1997**
Litang big size		-	600	800	1,800	2,000	2,200	4,600	5,000
Lhasa mid-sized		22	-	1,800	3,800	4,000	4,400	8,000	8,400
	1998	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
Litang big size	5,000	9,000	10,000	14,000	20,000	26,000	30,000	36,000	46,000
Lhasa mid-sized	9,600	12,000	15,000	18,000	24,000	30,000	36,000	42,000	50,000
Lhasa annual price increase	9.5%	25%	20%	20%	33.3%	25%	20%	16.6%	19%

Winkler, (2008) [12].

In recent years, *Cordyceps* has been regarded as the Himalayan Viagra, which has caused the price to reach USD $6.77 per piece of wild medicine [17]. Over the past 10 years, its value has increased dramatically. For example, collectors must pay as much as USD $12,500 per kg for top-quality material [18]. In 2008-2009, the price of *C. sinensis* crude drug was around USD $13,000 per kg, which caused it to be regarded as “soft gold” in China [15]. Furthermore, it is believed that the price of this fungus reached USD $20,000 to 40,000 per kg in the international market [19]. As of August 2012, the price per gram of wild *Cordyceps* in Beijing is up to CNY ¸698 or USD $111,560 per kg. This price already surpasses that of real gold. According to the government statistics for 2004, 50,000 kg of this drug were collected,in Tibet which contributed more than USD $225 million to the Tibet Autonomous Region's GDP.[20].

Distribution

Cordyceps sinensis is endemic to the Tibetian plateau including the adjoining high altitude areas of the central and East Himalayas that includes Nepal, Bhutan and India's Uttaranchal, Sikkim, Himachal and Arunachal Pradesh. In addition [21] reported C*ordyceps sinensis* from Tian Shan and Altai Shan of North West China. C*ordyceps sinensis* is common in the grassland and shrublands of the Tibetian Plateau. The grasslands provides habitat to the *Thitarodes (Hepialus)* moths and thus to *Cordyceps sinensis.* This grassland consist predominantly of *Kobresia* sedges. *Kobresia* can cover up 80-90% of the subalpine grasslands [22]. [21] reported that alpine *Cordyceps* species was associated with *Polygonum affine*, *P. viviparum*, *P. macrophyllum*, *P. glaciale*, *Astragalus balfourianus* and *A. craibianus*. [23] stated that *Thitarodes (Hepialus)* preferred to feed on young roots of plant species of the families of Polygonaceae, Fabaceae, Cyperaceae, Poaceae and Liliaceae. Its favorite fodder species are Nagchu *Polygonum viviparum*, *Rheum pumilum*, *Astragalus yunnanensis* and *Salix lindleyana*. The distribution of *Cordyceps* spp.is limited to areas with an average annual precipitation above 350-400 mm.

It is widely believed that temperature and humidity play important roles in yields, abundance, and the probability of infection and sporulation of *Cordyceps* fungus. Furthermore, *Cordyceps* distribution is also assumed to be affected by winter and summer temperatures and the seasonality of precipitation [24]. This might be the reason that distribution of natural *Cordyceps* has varied with altitude over the past years, it is now reported to occur in lower altitudes also, a common *Cordyceps* species *C.militaris* (L.:Fr.) Link, is said to be distributed worldwide from 0 to >2000 m a.s.l [25,26,27]. *Cordyceps* sp has been reported to naturally parasitize root grub of coconut *Leucopholis coneophora* in the plains of Kerala in India [28].

Mode of Infection

Different preferential modes of infection on young larvae of Himalayan bat moth has been reported [29]. The fungus initially navigates the weak body part of the larvae and then penetrates the insect integument which is composed of chitin (a polysaccharide of N-Acetyl glucosamine through 1-4 linkage), then there is rapid extension of the mycelia network and subsequent dispensation of endotoxins to larval blood vessels. Since the insect cuticle is very tough as it is made up of wax and epicuticle, the fungus sometimes find it difficult to enter and may encroach through its mouth and makes its way to the gut [30]. The insect cuticle provides protection to the fungus from drying out due to solar rays and also protect the fungus from predators. After the *Cordyceps* has colonized the larva asymptotically, it switches to necrotrophic mode once the insect is dead, thus it is not an obligate biotroph but a facultative saprophyte [31]. The fungus may or may not be host specific.

The fungus entry into the insect haemolymph is difficult because of the defense mechanism provided by the larval immune system. The fungus respond to the insect immune system by invoking its own adaptive biochemical process and develop specific morphological structures [6]. Fungal entrance to the haemolymph suppresses the larval immune system and causes cessation of the insect life especially by starvation, convulsion or any physiological or biochemical disruption caused by the developing fungus [32]. Following successful penetration the conidia gives rise to the appresorium and then the secondary hyphae during fungal entrance through the insect haemolymph and extend further to the insects vital organs. Successive events after the fungal establishment and colonization causes the insect to lose vital body chemicals making it to become paralyzed and completely mummified by the fungal mycelium. Owing to the intensive extension of the fungal mycelium the fungus gains maturity and starts to sporulate for its successive generations. Soon after the cadaver (mycosed pupae) is fully occupied by the fungal mycelium the fungus excerts internal pressure, bursting out directly from the anterior part of the larvae giving rise to a single-stem (rarely two) external structure called the mushroom or fruiting body (teleomorph) [33].

Artificial cultivation of *Cordyceps* spp.

As a highly valued medicinal fungus C*ordyceps sinensis* has a long history of being collected and traded [34]. Recent studies have shown that the natural population of *C sinensis* is decreasing rapidly due to over collection [35,36]. Because of the high cost and scarcity of wild *Cordyceps* there is a need for finding an alternative, this led to a lot of research on artificial cultivation of the fungus. Though more than 400 *Cordyceps* species have been described, only about 36 species have been artificially cultivated [37,38,39].

The strain that is known as CS-4 was one of the first commercial strains of *Cordyceps* isolated in 1982 at the Institute of Materia Medica, Chinese Academy of Medical Sciences. Known by the Latin name of *Paecilomyces hepiali* Chen. the aseptically fermented mycelium of this strain underwent extensive human testing and clinical trials during the 1980's and resulted in a commercial product with wide usage in China, known as "Jin Shui Bao" capsules. More than 2000 patients were involved in the clinical trials with CS-4 and the chemical composition, therapeutic activity and toxicity are very well known for this strain. [40]. There are also semi-artificial *Cordyceps sinensis* growing programs under way in Tibet AR (Lhasa), Qinghai and West Sichuan's Kangding. In Kangding, for example, the *Thitarodes (Hepialus)* host larvae are bred and about 100 larvae each are placed into shoe carton-sized plastic containers with lids, which are filled with grassland soil containing the tubers and roots of their favorite natural foods collected from the wild, as well as some other roots from cultivation. After two years spores of *Cordyceps sinensis* are inoculated and about 10% of the larvae are actually taken over by the fungus and grow stromata, reducing the natural growing cycle from 5 to 2 years, later longish stromata were observable in many boxes. This was the first large scale fruiting [41]. [42] succeeded in culturing C*ordyceps sinensis* in submerged conditions under specified conditions of pH 6 and temperature 15ºC. The significant effect of nutritional sources i.e. carbon, nitrogen, vitamins and minerals on the growth of *C.sinensis* in SDY (sabouraud's dextrose with yeast extract) broth medium were also studied [43]. [44] found that the physical stress of frozen-shock, produced the greatest number of conidia, reaching 7.5 times higher than the control. [45] obtained an US patent (number US 2017/0067011A1) for artificial culturing of *Cordyceps sinensis.* He cultured *Cordyceps sinensis* in sterile rice media at 9-13^{o} C for 40-60 days and then provided low temperature induction of 4^0 C for stroma production and at 13^o C for 40 days to develop fruiting bodies.

Cordyceps mycelium is an important part for production of several secondary metabolites used for therapeutic purpose. The mycelium growth depends on several factors such as growth media, pH, temperature, nutrient element and some environmental factors [46]. [47] compared different media like potato dextrose agar (PDA), potato dextrose yeast agar (PDYA), malt extract agar (MEA) and yeast extract agar (YEA) for mycelia growth of *Cordyceps sinensis* and found potato dextrose agar was the best and the best pH was reported to be alkaline pH of 8.5-9.5 and best temperature for growth was 20-25^{o}C. [48] reported that sucrose was the best carbon source for growth of *Cordyceps sinensis* while Beef extract and yeast extract were the best nitrogen sources. Organic nitrogen sources were significantly more productive then inorganic nitrogen sources. Yield obtained with folic acid was significantly higher among vitamin sources used. In all micro nutrients and macro nutrients, calcium chloride and zinc chloride were significantly higher than other variables used. Two patterns of artificial cultivation of *Cordyceps sinensis* was established viz., complete artificial cultivation and semi-natural cultivation. In complete artificial cultivation, reared larvae were inoculated with cultured strains and the infected larvae were then fed indoors. After 1–2 years, *C. sinensis* could be harvested. In semi-natural cultivation, the infected larvae were released to natural habitats, allowing them to grow freely. After 3–5 years, *C sinensis* could be harvested in the released areas [20].

A common *Cordyceps* species *C.militaris* (L.:Fr.) Link, which is distributed worldwide from 0 to >2000 m a.s.l.[25,26,27] commonly called orange caterpillar fungus has all the chemical capacities and medicinal properties of *C.sinensis* [49,50,51,52] They produce many bioactive compounds, including polysaccharides, cordycepin, adenosine, amino acid, organic selenium, ergosterol, sterols, cordycepic acid, superoxide dismutase (SOD), and multivitamins [53,54]. Cordycepin (3-deoxyadenosine), a nucleoside analog, was first isolated from *C.militaris* and is one of the most important biologically active metabolites. *C.militaris* can be very easily cultured in both solid and liquid media with a variety of carbon and nitrogen sources and hence is considered a substitute for *C.sinensis*. Since *C.militaris* can complete its life cycle when cultured in-vitro, it is considered as a model organism for the study of *Cordyceps* species in culture [55,56]. Earlier the researchers have tried to produce the stromata of *C.militaris* on insects [57] and later on different organic substrates [58,59] in the laboratory on an experimental basis. These early studies have greatly contributed to the success of in vitro and large scale cultivation of *C.militaris*. Apart from stroma cultivation, production of mycelia in submerged culture has also been done successfully for the production of bioactive compounds [51,60,61]. Among the different organic substrates tested for commercial production of stromata, cereals with the addition of some organic substances have proven to be good substitute for insects. [25] documented stroma production of *C.militaris* in rice substrate. Since then rice has been widely used for stromata production [58,62,63,64,65]. [66] reported that a ratio of rice to water from 1:1 to 1:1.35 or slightly higher was optimal for stroma production. Whole rice and husked rice has been reported to give maximum fruiting body yield

[64]. Other organic substances used for production of *C militaris* stromata include bean powder, corn grain, corn cobs, cotton seed coats, jowar, millet, sorghum, and wheat grains [67,68,69,70,71]. Rice mixed with silkworm pupae has proved to be superior to other substrates and is now routinely used [72,73,74,75]. *C.militaris* strains require a relatively low level of nitrogen, and excessive nitrogen might suppress differentiation of the fruiting-body [76], this probably explains why yields have been observed to be less on insects than on cereals in the culture. [77,78] have also shown that brown rice, malt, and soybean are better sources of nutrition for *C. militaris* than chemically defined media. [79] produced in vitro stromata of *C. militaris*, by inoculating two mating compatible single ascospore strains in rice pupae medium. It has been shown from cultural studies that *C militaris* dominantly behaves as a bipolar heterothallic fungus [80]. Molecular studies also showed that *Cordyceps* species, including *C.militaris*, are heterothallic consisting of two mating type genes MAT1-1-1 and MAT1-2-1 [81]. [82] reported that Isolates of *C. militaris* could be easily established from both spores and tissues. For isolation of spores, ascospores released from mature stromata has to be trapped in sterile medium. Multi-ascospore isolates, as well as combinations of single ascospore strains, were used for production of fruiting bodies. Progeny ascospore strains could be isolated from artificial fruiting bodies, thus, the cycle of fruiting body production could be continued for a long period of time. They studied the fruiting body production from multi-ascospore isolates and their progeny strains for three generations and found that F1 progeny strains generally produced a larger number of fruiting bodies, compared with their mother multi-ascospore isolates, however, F2 and F3 progeny strains produced fewer fruiting bodies. [83] used a solid media consisting of 30 g rice, 1 g silkworm chrysalis powder and 45 ml nutrition liquid (containing 2% dextrose, 1% peptone, 0.1% KH2PO4, 0.1% $MgSO_4$, 0.01% Vitamin B1) for multiplication of *Cordyceps militaris*. [84] established fruiting body formation of *Cordyceps militaris* in Silk worm pupae by injecting hyphal body suspension, and found that a concentration of more than 2×10^5 (cfu) recorded greater than 96% infection and fruiting body production was also obtained. A dependable method for the isolation and in vitro cultivation of *Cordyceps* sp. was accomplished by [85], they collected pure germinated spores by Shooting ascospores from ant cadaver onto PDA plates, the germinated ascospores or secondary spores were then induced to develop blastospores.

Plant hormones such as 2, 4-D, citric acid triamine, colchicines, and others were found to enhance stroma production by *C.militaris* [69,86]. Similarly, mineral salts such as K+, Mg2+, and Ca2+ at a concentration of 0.1 g/l may increase fruiting yield [69]. Some elements may enhance the production of bioactive compounds of *C. militaris* in culture [52]. Commercial production must also take into account the duration of stroma production. Stromata are usually produced over a period of 35–70 days [68,87]. [68] reported the production period of 35–45 days on rice but 40–70 days on other substrates such as maize, millet, and rice-tussah. Culture duration, however, depends upon the shape and volume of the culture container and the amount of medium. Stroma production has been quantified in some studies [68,88,89]. Nearly 9 g of dry stromata (equivalent to about 68 g of fresh wt.) was produced from 60 g of brown rice supplemented with 10 g of silkworm pupae [79]. *Cordyceps militaris* cultivars with desirable properties such as high production of stromata and high Cordycepin content have recently been developed [90]. [87] reported a cultivar with a cordycepin yield of 24.98mg/g of fruiting body dry weight.

Cordyceps the Medicinal fungus

There has been an outburst of reviews and reports on the medicinal properties of *Cordyceps* since 1980's, but many of them are vague and most of them are not substantiated with evidence, hence in this review I am restricting to medicinal properties to those with supporting evidence and proven facts only.

The range of therapeutic uses claimed for *Cordyceps* species is far reaching, *Cordyceps* has been widely used to treat many conditions including respiration and pulmonary diseases, renal, liver, and cardiovascular diseases, hypo sexuality, and hyperlipidemia etc. It is also used in the treatment of immune disorders and as an adjunct to modern cancer therapies [91], it is also used as an overall rejuvenator for increased energy while recovering from a serious illness. Many also believe it to be a medicine for the treatment for impotence, acting as an aphrodisiac in both men and women. For medication, the fruiting body (fungus) and the worm (caterpillar) are used together. Worm has chemical composition similar to the fruiting body [92].

Antitumour and anticancerous Property

A variety of bioactive compounds isolated from *Cordyceps* were reported to display antitumour activity. Cordycepin displayed an antitumour effect by stimulating adenosine A(3) receptors, followed by activation of a glycogen synthase kinase-3b in the Wnt signalling pathway, and inhibited the growth of B16 melanoma cells inoculated subcutaneously into right murine footpads [93,94]. *C militaris* was found to inhibit cell growth of U937 cells in a dose-dependent manner, which was associated with morphological change and apoptotic cell death such as formation of apoptotic bodies and DNA fragmentation. Moreover, the treatment caused a dose-dependent inhibition of cyclooxygenase-2 and prostaglandin E2 accumulation. Taken together, these results indicated that the antiproliferative effects of these extracts were associated with the induction of apoptotic cell death through regulation of several major growth regulatory gene products such as Bcl-2 family expression and caspase protease activity, and the extracts were found to have therapeutic potential in human leukaemia treatment also [95]. *Cordyceps* is currently being recommended and used by a growing number of doctors worldwide as adjunct to chemotherapy, radiation and other conventional and traditional cancer treatments. It has shown remarkable progress in not only inhibiting the growth of cancer cells [96], but in some cases even dissolves certain types of tumours, [97]. Clinical studies have been conducted in China and Japan involving cancer patients, yielding positive results [98]. In one study of 50 patients with lung cancer who were administered *C. sinensis* at 6 g/day in conjunction with chemotherapy, tumors were reduced in size in 23 patients. In a trial involving cancer patients with several different types of tumors it was found that *C. sinensis*, taken over a two-month period at 6 g/day, improved subjective symptoms in the majority of patients. Even with radiation or chemotherapy, other immunological parameters showed no significant change, while tumor size was significantly reduced in approximately half of the patients observed, indicating an improved tolerance for radiation and/or chemotherapy [91]. A serious side effect of the use of conventional cancer chemotherapy and radiation therapy is the suppression of the patient's immune system. The use of *C. sinensis* in combination with conventional chemotherapy appears to have an immuno-stimulatory effect, which enhances the effectiveness of conventional chemotherapy by balancing its side effects [99]. *Cordyceps sinensis* is found to have anti-leukemia activities and ameliorate suppressive effects of chemotherapy on bone marrow function as a model for cancer treatment [100].

Immunomodulating Property

It was found that mice treated with cyclophosphamide, which suppresses immune function, also treated with the hot water extract of *Cordyceps sinensis* saw their immune function return to normal, as measured by the IgM and IgG response and macrophage activity [101]. Further evidence of the immunoenhancing action of *C. sinensis* was provided by another study treating mice inoculated with Erhlich ascites carcinoma (EAC) cells with a warm water extract of *Cordyceps*. The median survival time of the treated mice compared to untreated controls was over 300%, and the lack of activity of the extract against EAC cells grown in vitro indicated that the antitumor effect in the mice may be mediated through immunoenhancing activity, rather than directly [102].

Cordyceps sinensis can both suppress and enhance various aspects of the immune system, known as immunomodulators [103,104]. 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 are found to drop, while the red blood cells often increase in number. [8]. 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 3g/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 [105].

Hypoglycemic and hypocholesterolaemic effect

Cordyceps has been shown to help both diabetic and cholesterol patients. The caterpillar fungus is found to lower the blood sugar levels by the conservation of hepatic glycogen and improving glucose metabolism [106]. *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. It was efficient in lowering blood sugar levels in genetically diabetic animals and in those with chemically induced diabetes. It increased insulin sensitivity [107] and also the liver's output of the glucose regulating enzymes, glucokinase and hexokinase. In short, *Cordyceps* can be effectively used for the control of diabetes either as a single agent or in conjunction with other drugs [8]. A polysaccharide (CS-F30) obtained from the culture mycelium of *C. sinensis* showed potent hypoglycaemic activity in genetically diabetic mice after intraperitoneal administration. The plasma glucose level was quickly reduced in normal and streptozocininduced diabetic mice after intravenous administration [108]. Crude and neutral polysaccharides of *C. sinensis* exerted hypoglycaemic activity in normal mice, but did not affect the circulating insulin level . A polysaccharide (CS-F10), which was purified from a hot-water extract of the cultured mycelia of *C. sinensis* and composed of galactose, glucose and mannose in a molar ratio of 43:33:24, lowered the plasma glucose level in normal, adrenaline-induced hyperglycaemic and diabetic mice [109].

Hypercholesterolemia is not a disease in true sense but is a clear indicator of dysfunction of the metabolic system and indicates high risk of cardiovascular attack. Studies have demonstrated that *C. sinensis* helps in lowering the total cholesterol level and also the level of triglycerides [110]. It also helps to

increase the ratio of HDL-cholesterol (good cholesterol) to LDL cholesterol (bad cholesterol). The mater extracts of cultured fruiting bodies of *C. sinensis* prevented cholesterol deposition in the aorta of atherosclerotic mice by inhibition of LDL oxidation mediated by free radicals in an investigation into hypolipidaemic activity [111]. A hypocholesterolaemic effect of hot-water extract from mycelia of *C. sinensis* was investigated [112], the results suggested that it lowered the total cholesterol concentration, reduced the concentration of cholesterol carried by LDL and very-low-density lipoprotein, and elevated the high density lipoprotein (HDL)-cholesterol concentration in the serum of mice fed a cholesterol enriched diet.

Improvement in Kidney Functioning

Traditional views of the *Cordyceps* mushroom held that its consumption strengthened the Kidneys. Chronic renal failure is a serious disease, one often affecting the elderly. In a study among 51 patients suffering from chronic renal failure, it was found that the administration of 3–5 g/day of *C. sinensis* significantly improved both the kidney function and overall immune function of treated patients, compared to the untreated control group [113]. In another human clinical study, 57 patients with gentamicin-induced kidney damage were either treated with 4.5 g of *Cordyceps* per day or by other, more conventional methods. After six days, the group that received *Cordyceps* had recovered 89% of their normal kidney function, while the control group had recovered only 45% of normal kidney function. The time-to recover was also significantly shorter in the Cordyceps group when compared with that of the control group [114]. Studies have shown that much of *Cordyceps*' kidney enhancing potential stems from its ability to increase 17-hydroxy-corticosteroid and 17-ketosteroid levels in the body [114]. *C. sinensis* has been found to accelerate the regeneration of tubular cells, protect the sodium pump activity of tubular cells and also reduce the content of calcium in certain tissues [115,116]. It also improved disease conditions in various animal and human clinical trials with renal failure [117], renal insufficiency [113], mesangial nephropathy [118], and nephrotoxicity [119].

H1-A an extract from *Cordyceps sinensis* was reported to inhibit tyrosine phosphorylation of human mesangial proteins [120]. In an earlier report, H1-A alleviated immunoglobulin A nephropathy (Berger's disease) with histological and clinical improvement [118]. H1-A reduced anti-double-stranded DNA production and lymph-adenopathy, delayed progression of proteinuria, improved kidney function and inhibited the proliferation of human mesangial cells, and promoted apoptosis by suppressing tyrosine phosphorylation of Bcl-2 and Bcl-XL [118,120].

Treatment of Respiratory Disorders

Chinese medicine has characterized *C. sinensis* as a guardian of respiratory health for more than a thousand years. There have been trials on humans, using *Cordyceps* to treat many respiratory illnesses, including asthma, COPD, and bronchitis, either alone or as an adjunct to standard antibiotic therapy, and in many studies that have been conducted, it appears to be useful for all of these conditions [34,121,122].

C*ordyceps sinensis* improves pulmonary function and is used to treat respiratory disease [123]. *C. sinensis* has proved to be highly useful in alleviating other symptoms of several respiratory illnesses such as chronic bronchitis, etc [124]. Much of its reputation for protecting the lungs is believed to come from its ability to promote enhanced oxygen utilization efficacy. Such efficacy alludes to the use of *Cordyceps* as an effective treatment for Bronchitis, Asthma, and Chronic Obstructive Pulmonary Disease (COPD). Extracts of *C. sinensis* have been shown to inhibit tracheal contractions, especially important for asthma patients. In addition, its anti-inflammatory properties bring further relief to asthma patient [34].

Improvement in Heart Functioning

Cordyceps is also a medication used in stabilizing the heartbeat and correcting heart arrhythmias. Though the exact mechanism responsible for *Cordyceps*' reputation with regard to controlling arrhythmias is not completely understood, it is thought to be at least partially because of the presence of adenosine [125], of which *Cordyceps* often has a significant quantity, along with deoxyadenosine, related adenosine-type nucleotides, and nucleosides. It has been shown that these compounds have an effect on coronary and cerebral circulation [126]. In studies of patients suffering from chronic heart failure, the long-term administration of *Cordyceps,* in conjunction with conventional treatments—digoxin, hydrochlorothiaside, dopamine, and dobutamine— promoted an increase in the overall quality of life. This included general physical condition, mental health, sexual drive, and cardiac function, compared to the control group [127].

In Liver Disorders

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 extracts had a much better outcome in a shorter period of time than the control group who received only the lamivudine [128]. In another study using 22 patients who were diagnosed with posthepatic cirrhosis,[129] after three months of consuming 6–9 g of *Cordyceps* per day, each patient showed improvement in liver function tests

Reduction of 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, 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, while no improvement was reported in the placebo group [130,131,132]. In another study healthy elderly volunteers, with an average age of 65, were tested for the output performance and oxygen capacity of subjects while exercising on stationary bicycles, a portion of the volunteers consumed *C. sinensis* for six weeks, while others consumed a placebo.The results demonstrated that the group that consumed *Cordyceps* had a significant increase in energy output and oxygen capacity over the other group after six weeks [133].

Cordyceps is a remedy for weakness and fatigue and is often used as an overall rejuvenator for increased energy while recovering from serious illness [8]. It also improves shortness of breath and reduces fatigue in patients suffering from chronic heart failure. It is thus, used by competitive athletes in the treatment of fatigue and weakness, and to improve endurance and increase energy levels [134].

Uses against Male/Female Sexual Dysfunction

Cordyceps has been used for centuries in Traditional Chinese Medicine to treat male and female sexual dysfunction [135], such as hypolibidinism and impotence. Preclinical data on the effects of *C. sinensis* on mice showed sex-steroid-like effects. Human clinical trials have demonstrated similarly the effectiveness of *Cordyceps* in combating decreased sex-drive. *Cordyceps* was clearly indicated as a therapeutic agent in treating hypolibidenism and other sexual malfunction in both men and women [8].

Protection against Free Radical Damage

C. sinensis has powerful antioxidant properties and thus, can protect against the damages caused by free radicals [111,136] and hence acts as an anti-ageing agent [137]. Antioxidant activity in the xanthine oxidase, haemolysis and lipid peroxidation assay systems was demonstrated from a polysaccharide fraction of cultured *C. sinensis* mycelia [136]. Pheochromocytoma PC12 cells were protected against H2O2-induced injury by a 210-kDa polysaccharide from *C. sinensis* mycelia [137]. Treatment of the cells with the polysaccharide at 100 mg/ml before H2O2 exposure significantly elevated the survival of PC12 cells in culture by over

60%. In parallel, the H2O2-induced production of malondialdehyde in cultured cells was markedly reduced by the polysaccharide treatment, and the pretreatment of the polysaccharide significantly attenuated the changes of glutathione peroxidase and superoxide dismutase activity in H2O2-treated cells in a dose-dependent manner [138].

Made Human Organ Transplants Possible

Cyclosporin is an antifungal drug developed from the asexual stage of *Cordyceps* when 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 cyclosporine is acting somehow as an anti-recognition factor. This is virtually the only use of cyclosporin today, as an anti-rejection drug for transplants patients [8,105].

Conclusion

Cordyceps is a medicinal substance of long history and promising potential. Unlike early reports that gave observed facts about it's medicinal value today we have scientific proof for its mode of action and medicinal properties and the principle ingredient responsible for its mode of action. Moreover as the natural Cordyceps is becoming rare we have found different methods of artificial production of this fungus with the same chemical constituents or even better one. The world is now awakening to the importance of this fungus and it's price is shooting up drastically. A lot of research is still pending on this fungus especially from the medical side.

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