A Systematic Review of the Mysterious Caterpillar Fungus

*Ophiocordyceps sinensis* in DongChongXiaCao (冬蟲夏草 Dōng Chóng Xià Cǎo) and Related Bioactive Ingredients

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**ABSTRACT**

The caterpillar fungus *Ophiocordyceps sinensis* (syn.¹ *Cordyceps sinensis*), which was originally used in traditional Tibetan and Chinese medicine, is called either “yartsa gunbu” or “DongChongXiaCao (冬蟲夏草 Dōng Chóng Xià Cǎo)” (“winter worm-summer grass”), respectively. The extremely high price of DongChongXiaCao, approximately USD $20,000 to 40,000 per kg, has led to it being regarded as “soft gold” in China. The multi-fungi hypothesis has been proposed for DongChongXiaCao; however, *Hirsutella sinensis* is the anamorph of *O. sinensis*. In Chinese, the meaning of “DongChongXiaCāo” is different for *O. sinensis*, *Cordyceps* spp.,² and *Cordyceps* sp.³ Over 30 bioactivities, such as immunomodulatory, antitumor, anti-inflammatory, and antioxidant activities, have been reported for wild DongChongXiaCao and for the mycelia and culture supernatants of *O. sinensis*. These bioactivities derive from over 20 bioactive ingredients, mainly extracellular polysaccharides, intracellular polysaccharides, cordycepin, adenosine, mannitol, and sterols. Other bioactive components have been found as well, including two peptides (cordymin and myriocin), melanin, lovastatin, γ-aminobutyric acid, and cordysmins. Recently, the bioactivities of *O. sinensis* were described, and they include antiarteriosclerosis, antidepressant, and antiosteoporosis activities, photoprotection, prevention and treatment of bowel injury, promotion of endurance capacity, and learning-memory improvement. *H. sinensis* has the ability to accelerate leukocyte recovery, stimulate lymphocyte proliferation, antiglaucoma, and improve kidney injury. Starting January 1st, 2013, regulation will dictate that one fungus can only have one name, which will end the system of using separate names for anamorphs. The anamorph name “*H. sinensis*” has changed by the *International Code of Nomenclature for algae, fungi, and plants* to *O. sinensis*.

**Key words:** Bioactive Ingredients, *Cordyceps sinensis*, DongChongXiaCao, *Hirsutella sinensis*, *Ophiocordyceps sinensis*

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¹The term “*Cordyceps sinensis*” has been renamed to its synonym “*Ophiocordyceps sinensis*” by Sung *et al.* in 2007. In the discussion, “*Cordyceps sinensis*” is still used to represent “*Ophiocordyceps sinensis*” out of respect to the original authors of the articles that we cited.

²*Cordyceps* spp. indicates any species that belongs to the genus *Cordyceps*.

³*Cordyceps* sp. indicates the unidentified species that belong to the genus *Cordyceps*

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INTRODUCTION

The caterpillar fungus *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*) is one of the entomogenous Ascomycetes and parasitizes the larvae of Lepidoptera to form the well-known traditional Tibetan medicine “yartsa gunbu” or, in traditional Chinese medicine, “DongChongXiaCao (冬虫夏草 Dong Chóng Xià Cǎo)” (“winter worm-summer grass,” [Figure 1]). *DongChongXiaCao* is a well-described remedy that has been used in traditional Chinese medicine for over 700 years.\(^1\) The wild fungus, which possesses a plant-like fruiting body and originates from dead caterpillar that fill with mycelia [Figure 2], has generally been called *C. sinensis* or *Cordyceps* spp. (“ChongCao” in Chinese) due to its insect-shape appearance. *O. sinensis* (previously named *C. sinensis*) is a slow-growing fungus and needs to be grown at a comparatively low temperature, i.e., below 21ºC. Both temperature and growth rate are crucial factors that identify *O. sinensis* from other similar fungi.\(^2\) In recent decades, curative and health-care products derived from the so-called “Cordyceps” are extremely popular in China in various forms such as capsules, oral liquids, and drinks.\(^3\) Most of these products, derived from submerged mycelial *O. sinensis* cultures [Figure 3], are the popular merchandise items on the market.

It has been shown that *O. sinensis* can be used to treat conditions such as hyposexuality, night sweats, hyperglycemia, hyperlipidemia, asthenia, arrhythmias, and other heart, respiratory, renal and liver diseases.\(^4\) Although “natural *O. sinensis* specimens” have significant pharmaceutical effects, the commercial cultivation of this fungus on larvae of moth to produce fruiting body has not yet been successful.\(^4\) Therefore, the biology of *O. sinensis* remains a secret, and its commercial cultivation is still a dream.\(^5\)

In the past years, several new names have been proposed for *O. sinensis*-like species from alpine regions, such as *O. gansuensis*, *O. crassispora*, *O. kangdingensis*, *O. multiaxialis*, *O. nepalensis*, and others, but there is not sufficient to distinguish these species from *O. sinensis*.\(^6\) Fungi other than *O. sinensis* originating...
from natural *O. sinensis* specimens could be important resources for the development of alternative products.\(^{[7]}\) For example, it is claimed that the Bailing Capsule, a cultured product isolated from *DongChongXiaCao*, has a similar chemical composition to natural *O. sinensis*; in addition, the Bailing Capsule possesses anti-inflammatory, anti-hypoxia, and antitumor properties and has the ability to regulate the endocrine system, enhance immune function, and protect the kidneys, lung, liver, and other organs.\(^{[8]}\)

As a traditional oriental medicine, *DongChongXiaCao* is endemic to alpine habitats on the Tibetan Plateau, located predominantly in Tibet, the Tibetan autonomous prefectures of neighboring provinces, and the high Himalayas.\(^{[9]}\) In recent years, *DongChongXiaCao* has been regarded as the Himalayan Viagra, which has caused the price to reach USD $6.77 per piece of wild medicine.\(^{[10]}\) 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.\(^{[11]}\) 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.\(^{[12]}\) Furthermore, it is believed that the price of this fungus reached USD $20,000 to 40,000 per kg in the international market.\(^{[13]}\) As of August 2012, the price per gram of wild *DongChongXiaCao* in Beijing is up to CNY ¥698 [Figure 4], 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, which contributed more than USD $225 million to the Tibet Autonomous Region’s GDP.\(^{[14]}\) These data suggested that about 40% of the rural cash income in the Tibet Autonomous Region comes from *DongChongXiaCao* collection.

### REVIEW ARTICLES AND SPECIAL REPORTS OF CORDYCEPS

Since 1998, there have been more than 25 reviews or special reports published discussing *Cordyceps*, and 14 of them have focused on *C. sinensis*. For example, these studies have emphasized: terminology, life strategy, and ecology;\(^{[5]}\) traditional uses and medicinal potential in Sikkim;\(^{[10]}\) the reliability of fungal materials;\(^{[2]}\) ecology, trade, and development in Tibet;\(^{[15]}\) production and sustainability on the Tibetan Plateau and in the Himalayas;\(^{[16]}\) origin of scientific name, morphological characteristics, micromorphological characteristics of the teleomorph, identification, hosts, and synonymy;\(^{[6]}\) ethnomycological use, collection, discovery, protection, and the range of diseases treated in Northern Yunnan Province in China;\(^{[9]}\) host spectrum, distribution, artificial rearing host, infection technology, and substitute products;\(^{[17]}\) clinical efficacy for chronic kidney diseases;\(^{[18]}\) markers and analytical methods for quality control;\(^{[19]}\) history, use, and implications;\(^{[20]}\) pharmacological functions;\(^{[21]}\) safety, effects on the nervous system, glucose metabolism, effects on the respiratory, hepatic, cardiovascular, immune systems, immunological disease, inflammatory conditions, cancer, and diseases of the kidney;\(^{[22]}\) and *in vitro* and *in vivo* studies, open-label and double-blinded clinical trials on the respiratory, renal, hepatic, cardiovascular, immunological, and nervous systems, and in its effects on cancer, glucose metabolism, inflammatory conditions, and toxicological studies.\(^{[23]}\) Two papers have focused on *C. militaris*, placing emphasis on: biological aspects including the host range, mating system, cytology and genetics, insect- and noninsect nutritional requirements, environmental influence on stroma development, and commercial development;\(^{[24]}\) and active principles and culture techniques.\(^{[25]}\)

The other publications focus on *Cordyceps*, examining: pharmacological functions and development of products;\(^{[21]}\) production, isolation, purification, structure elucidation, and pharmacological action of polysaccharides;\(^{[1]}\) chemical constituents;\(^{[20]}\) preparations and chemical structures of polysaccharides;\(^{[27]}\) taxonomic concepts, preparations, apoptosis, chemical constituent profiling, hosts, and poisoning;\(^{[28]}\) history, medicinal uses, chemical composition, and cultivation;\(^{[29]}\) pharmacological actions;\(^{[30]}\) and the pharmacological basis of “Yin-nourishing (養陰)" and "Yang-invigorating (壯陽)" actions.\(^{[31]}\)

### TERMINOLOGY OF “DONGCHONGXIACAO” WITH REGARD TO CORDYCEPS

“DongChongXiaCao” is commonly known as “yarsa gumba” in Tibetan, because “yarsa” means winter and “gumba” means summer. “Gumba” or “gonba” has also been used to replace “gumba,” and the fungus is named “keera jhar” (insect herb) in the Indian mountains.\(^{[13]}\)

However, the term “DongChongXiaCao” in Chinese has been recognized as having different meanings, as follows:

1. The traditional Chinese medicine originating from *O. sinensis* (syn. *C. sinensis*).
2. The health food originating from *O. sinensis*.
3. The fungus *O. sinensis*.
4. The fungi *Cordyceps* spp.
5. The fungus *Cordyceps* sp.
6. The fungi *Ophiocordyceps* spp.
7. The fungi *Ophiocordyceps* sp.
8. The wild and crude medicine that has a caterpillar shape with fruiting body.
9. The mycelia of *O. sinensis* derived from submerged culture.
10. The mycelia of *H. sinensis* derived from submerged culture.
11. The traditional Chinese medicine originating from the larvae of Hepialidae (Lepidoptera) infected by *O. sinensis*.
12. The traditional Chinese medicine originating from the larvae of *Thitarodes* (syn. *Hepialus*) infected by *O. sinensis*.
13. The traditional Chinese medicine originating from the larvae of *T. armoricanus* (syn. *H. armoricanus*) infected by *O. sinensis*.
14. The traditional Chinese medicine originating from the larvae of Hepialidae (Lepidoptera) infected by *Ophiocordyceps* spp.
15. The traditional Chinese medicine originating from the larvae of Hepialidae (Lepidoptera) infected by *Cordyceps* spp.

The term “ChongCao” (meaning Insect Grass) in Chinese is
the abbreviation of “DongChongXiaCao,” which related products is popular in the market in Taiwan. For consumers, it is confusing whether “ChongCao” is equivalent to “DongChongXiaCao,” the traditional Chinese medicine “DongChongXiaCao,” or the fungi Cordyceps spp. In addition, C. militaris, a type species of Cordyceps, has been regarded as a substitute for “DongChongXiaCao” and is named “North DongChongXiaCao,” “BeiChongCao,” “ChongCao mycelium,” or “ChongCao fruiting body.” There is no doubt that O. sinensis is not equivalent to the traditional Chinese medicine “DongChongXiaCao,” because the latter has a caterpillar shape with a fruiting body. In the market, natural products with caterpillar shapes and fruiting bodies that are called “DongChongXiaCao” are extensively distributed; however, the origins of most of these microorganisms and their hosts remain uncertain. In the scientific view, the traditional Chinese medicine wild “DongChongXiaCao” is not strictly equivalent to O. sinensis unless the species has been identified. In fact, for most literature, the term “C. sinensis” used in the materials section might refer to wild DongChongXiaCao or to its fruiting bodies or cultured mycelia. Dong and Yao[2] reviewed 152 papers from PubMed on O. sinensis since 1998 and found that at least 116 papers (over three-quarters) used unreliable, uncertain, or unspecified materials, including so-called cultivated fruit bodies that were apparently not O. sinensis strains, based on temperature and growth period.

RENAME, ANAMORPH, AND GENETIC DIVERSIFICATION OF C. SINENSIS

Renaming of C. sinensis

The colony characteristics of O. sinensis cultures are significant different from Cordyceps spp. Mostly Cordyceps species possess brightly colored and fleshy stromata. The family of Cordycipitaceae has been validated based on the type species of Cordyceps, C. militaris, and a new family, Ophiocordycipitaceae, based on the Genus Ophiocordyceps Petch, the majority of whose species produce dark pigments and tough to pliant stromata, often possesses aperithecial apices including C. sinensis.[32] Based on the publication referenced above, C. sinensis has been transferred to Ophiocordyceps and has been renamed O. sinensis.

The anamorph of C. sinensis

Twenty-two names spanning 13 genera associated with the anamorph of C. sinensis have been described.[33] However, H. sinensis and C. sinensis belong to different stages of the life cycle of the same organism: H. sinensis is the anamorph of C. sinensis, rather than Paecilomyces sinensis or other species.[34] The rDNA ITS sequences of C. sinensis collected from different geographical regions are almost identical and are significantly different from substitutes.[35] H. sinensis has been confirmed as the anamorph of C. sinensis by both DNA sequences and microcyclic conidiation, and additionally, two species, C. multiaxialis and C. nepalesis, were shown to share identical or almost identical ITS sequences with C. sinensis.[36] The relationship between teleomorphs of Cordyceps spp. and their presumed anamorphs has been investigated by analyzing 5.8S and ITS rDNA sequences. Both sequence analyzes demonstrated that H. sinensis is the anamorph of C. sinensis.[37] When analyzing the sequences of ITS1, ITS2 and 5.8S rDNA regions, some species with different names had similar morphologies to C. sinensis, which suggested that these species might be synonymous with C. sinensis.[38] Based on the results of the 5.8S rDNA and ITS region analyses, it is clear that the ITS sequences within C. sinensis are highly homologous, regardless of the geographical origin. The evolutionary distance values between C. sinensis and H. sinensis were found to be the same as those for C. sinensis from different geographic regions, and C. sinensis should only have H. sinensis as its asexual stage, regardless of sample origin.[39] Even though many studies indicate that H. sinensis is the only anamorph of C. sinensis, molecular evidence demonstrates the existence of both H. sinensis and Paecilomyces heipiai DNA in the caterpillars and fruiting bodies of natural C. sinensis, strongly supports the multi-fungi hypothesis for natural C. sinensis.[40]

Genetic diversification of C. sinensis

A high diversity in the fungal community structure occurs in natural O. sinensis.[5] The significant genetic divergence in O. sinensis was found to be greater among southern isolates than among northern isolates in China.[41] The genetic similarity indices range from 0.282 to 0.782, which indicate that there is a high level of diversity among natural C. sinensis samples.[42] In addition, a total of 141 markers, 99.3% of which were polymorphic, were identified in 180 individual samples of natural C. sinensis from 18 populations, and these 18 populations can be divided into five groups based on genetic distance and by grouping pattern matches with geographic distributions along the latitudinal gradient.[43] It has been observed that differences in medicinal effects among C. sinensis populations may be attributed to the existence of genetically differentiated chemotypes in morphotaxon.[44]

CHEMICAL CONSTITUENTS, PROXIMATE COMPOSITION AND VOLATILE COMPOUNDS

Chemical constituents

The chemical constituents of natural Cordyceps include cordycepic acid, glutamic acid, amino acids, polyamines, cyclic dipeptides, saccharides and sugar derivatives, sterols, nucleotides and nucleosides, 28 saturated and unsaturated fatty acids, fatty acid derivatives and other organic acids, vitamins, and inorganic elements.[13] Palmitic acid, linoleic acid, oleic acid, stearic acid, and ergosterol are the main components of natural and cultured Cordyceps, these fatty acids, as well as 14 investigated compounds, can be used to discriminate the hierarchical cluster, as the palmitic acid and oleic acid contents in natural Cordyceps are significantly higher than those in the cultured Cordyceps.[45]

Proximate composition and others

Significant differences in proximate composition, such as for protein, fat, carbohydrate, and moisture content, were observed between the corpus and the fruiting body of wild DongChongXiaCao and the fermented mycelia of C. sinensis. There is a conspicuously high carbohydrate content of 39.4% for fermented mycelia, whereas carbohydrates comprise 24.20% of the corpus.
and 24.9% of the fruiting body in wild DongChongXiaCao.[46] Fermented mycelia had lower protein and fat contents (14.8 and 6.63%, respectively) than the corpus (29.1 and 8.62%, respectively) and the fruiting body (30.4 and 9.09%, respectively) of wild DongChongXiaCao.[46] However, Smirnov et al.[47] showed that the mycelia of C. sinensis had high protein (29%) and low lipid contents (7%), and, similar to other studies. They also indicated that the mycelia were rich in endopolysaccharides (EPS, 15%), phospholipids (up to 28% of total lipids), and unsaturated fatty acids (C18:1 - up to 44%; C18:2 - 53% of total fatty acids).

The compositions of natural fruiting bodies of C. sinensis (NFCS) and mycelia from submerged cultures (MSMC) and shaking cultures (MSKC) of H. sinensis were compared by Li et al.[48] They indicated that the crude fat, crude protein, total, and essential amino acid contents could be ranked in the following descending order: MSKC > MSMC > NFCS, and additionally, unsaturated fatty acids in MSMC account for 65.9% of total fatty acids, which is noticeably lower than for NFCS (86.9%) and MSKC (76.5%). The total content of four nucleosides (adenosine, guanosine, uridine, and inosine) in MSMC (6.20 mg/g) was significantly higher than NFCS (1.80 mg/g) and MSKC (1.60 mg/g).[49] Moreover, the sugar and protein contents of EPS from Hirsutella sp. were 92.7 and 5.2%, respectively, and the monosaccharide components of EPS are mannose, galactose, and glucose with a molar ratio of 4.0:8.2:1.0, and its molecular weight is 23 kDa.[49]

**Volatile compounds**

From the mycelia of H. sinensis cultured with solid-state media (SSM) and submerged fermentation (SF), 51 volatile compounds were identified, and phenols, acids, and alkanes were the major classes of compounds, while butylated hydroxytoluene was the most abundant volatile compound and accounted for 47.38% and 46.12% of the total volatile compounds in mycelia cultured by SSM and SF, respectively.[50]

### BIOACTIVE INGREDIENTS AND BIOACTIVITIES

A review of the literature regarding the bioactive ingredients and bioactivities of O. sinensis reveals that eight types of materials have been used, including (1) the crude powder, (2) the crude powder of the fruiting body, (3) the extracts from the crude powder, (4) the extracts from the crude powder of the fruiting body, (5) the crude powder of mycelia, (6) mycelial extracts, (7) the supernatants of submerged fermented cultures, and (8) the whole broth of submerged fermented cultures. The diversity of these materials brings up the major concern of whether the knowledge we have acquired regarding O. sinensis is applicable to wild “Dong Chong Xia Cao” or the fermented mycelia or mycelial fermentation products (including cultured broth) of O. sinensis, H. sinensis, or other species.

Over 20 bioactive ingredients from mycelia, culture supernatants, or fruiting bodies have been published, as shown in Table 1. In summary, these ingredients include (1) extracellular polysaccharides, (2) intracellular polysaccharides, (3) cordycepin, (4) adenosine, (5) guanosine, (6) cordymin, (7) lovastatin, (8) γ-aminobutyric acid (GABA), (9) sitosterol, (10) ergosterol, (11) ergosta-4,6,8(14),22-tetraen-3-one (ergone), (12) 5a,8a-epidioxy-22E-ergosta-6,22-dien-3β-ol, (13) 5a, 8a-epidioxy-22E-ergosta-6,9(11),22-trien-3β-ol, (14) 5a,6a-epoxy-5a-ergosta-7,22-dien-3β-ol, (15) 5a,8a-epidioxy-24(R)-methylcholesta-6,22-dien-3β-D-glucopyranoside, (16) 6-epoxy-24(R)-methylcholesta-7,22-dien-3β-ol, (17) myrician, (18) melatin, (19) cordyssin A, (20) cordysin B, (21) cordysin C, (22) cordysin D, (23) cordysin E, and (24) serine protease.

The bioactivities of O. sinensis, which have been identified from materials derived from different preparations or extracts that were tested in in vitro, in vivo, or ex vivo studies, are shown in Table 2. Over 30 different bioactivities have been reported for O. sinensis, including (1) immunomodulatory, (2) immunosuppressive, (3) anticomplementary, (4) antitumor, (5) anti-inflammatory, (6) antioxidant, (7) antibacterial, (8) hepatoprotection, (9) kidney benefitting, (10) antibacterial, (11) hypcholesterolemia, (12) antiarthritis, (13) antithrombus, (14) hypotension and vasorelaxant, (15) lung benefitting, (16) photoprotection, (17) antidepression, (18) antioestrogen, (19) antiebetal plasma, (20) antifatigue, (21) antiasthma, (22) steroidogenesis, (23) erythropoiesis, (24) antiarrhythmia, (25) aortic, (26) testosterone production, (27) sedation, and (28) adrenals, as well as the ability to do the following: (29) prevent and treat injury to the bowel, (30) promote endurance capacity, (31) improve learning-memory, (32) prevent allograft rejection, and (33) attenuate lupus.

It has been found that most local folk/traditional healers use Cordyceps to treat 21 ailments, including erectile dysfunction, female aphrodisia, benign tumors, bronchial asthma, bronchitis, diabetes, cough and cold, jaundice, alcoholic hepatitis, and others.[10] The traditional uses of caterpillar fungus among the Bai, Naxi, Lisu, and Tibetan people living in the mountainous Northern Yunnan Province are to improve eyesight, to treat calcium deficiency (specific to children), diabetes and associated nephropathy, and indigestion (specific to children), to speed up labor parturition, and to strengthen the immune system.[9] Moreover, C. sinensis exhibits broad biological and pharmacological actions in hepatic, renal, cardiovascular, and immunological systems, and possesses anticancer activity as well.[21]

### Polysaccharides

Evidence indicates that Cordyceps polysaccharides may effectively improve immune system function and possess liver protection, anti hyperglycemia, hyperlipidemia, antitumor and antioxidant activities.[1]

### Extracellular polysaccharides

There are several different Extracellular polysaccharides (EPS) from O. sinensis that are based on their molecular weights (MW). EPS obtained from submerged O. sinensis culture supernatant with MW ranging from 5 to 200 kDa has antioxidant and immunomodulatory activities and may attenuate renal failure, described as follows. The EPS designated EPS-1 with an average MW of 38 kDa was hydrolyzed in diluted sulfuric acid solution at pH 1 and 90°C to yield two major MW fractions: 3.0 kDa and 30 kDa possessed high (30-80%) antioxidant and radical-scavenging
| No. | Bioactive Ingredient                                      | Bioactivities                      | Material Source                      | References |
|-----|----------------------------------------------------------|------------------------------------|-------------------------------------|------------|
| 1   | Extracellular polysaccharides or exopolysaccharide      | Immunomodulatory and antitumor     | Culture supernatant                 | [51-53]    |
|     |                                                          | Immunomodulatory                   |                                     | [54-58]    |
|     |                                                          | Antioxidant                        |                                     | [59,60]    |
| 2   | Intracellular polysaccharides                           | Immunostimulatory and antitumor    | Mycelium                            | [61]       |
|     |                                                          | Immunomodulatory and antioxidant   | Mycelium                            | [62]       |
|     |                                                          | Immunomodulatory                   | Mycelium                            | [63-65]    |
|     |                                                          | Hypoglycemic                       | Mycelium                            | [66,67]    |
|     |                                                          | Hypoglycemic and antioxidant       | Mycelium                            | [68]       |
|     |                                                          | Antioxidant and antitumor          | Mycelium                            | [69]       |
|     |                                                          | Antioxidant                        | Mycelium                            | [70,71]    |
|     |                                                          | Antioxidant                        | Fruiting body                       | [72]       |
|     |                                                          | Protection of chronic renal failure| Mycelium                            | [73]       |
|     |                                                          | Cholesterol esterase inhibitory activity| Mycelium                         | [74]       |
|     |                                                          | Lower plasma triglyceride and cholesterol| Mycelium                      | [75]       |
| 3   | Cordycepin                                               | Steroidogenesis                    | Culture supernatant                 | [76,77]    |
|     |                                                          | Antimetastatic activity            | Culture supernatant                 | [78]       |
|     |                                                          | Antitumor                          | Culture supernatant                 | [79,80]    |
|     |                                                          | Immunomodulatory                   | Culture supernatant                 | [81]       |
| 4   | Adenosine                                                | Immunomodulatory                   | Mycelium                            | [82]       |
| 5   | Guanosine                                                | Immunomodulatory                   | Mycelium                            | [82]       |
| 6   | Cordymin                                                 | Antioxidant; Anti-inflammation      | -                                   | [83]       |
| 7   | Lovastatin                                               | Hypolipidemic                      | Mycelium                            | [19]       |
| 8   | γ-aminobutyric acid (GABA)                              | Neurotransmitter                   | Mycelium                            | [19]       |
| 9   | Sitosterol                                               | Cytotoxic                           | Mycelium                            | [85]       |
| 10  | Ergosterol                                               | Cytotoxic                           | Mycelium                            | [85]       |
| 11  | Ergosta-4,6,8(14),22-tetraen-3-one(ergone)              | Cytotoxic                           | -                                   | [86]       |
| 12  | 5α,8α-epidioxy-22E-ergosta-6,22-dien-3β-ol              | Cytotoxic                           | Mycelium                            | [85]       |
| 13  | 5α,8α-epidioxy-22E-ergosta-6,9(11),22-trien-3β-ol       | Cytotoxic                           | Mycelium                            | [85]       |
| 14  | 5α,6α-epoxy-5α-ergosta-7,22-dien-3β-ol                   | Cytotoxic                           | Mycelium                            | [85]       |
| 15  | 5α,8α-epidioxy-24(R)-methylcholesta-6,22-dien-3β-D-glucopyranoside | Antitumor | Mycelium | [87] |
| 16  | 5,6-epoxy-24(R)-methylcholesta-7,22-dien-3β-ol          | Antitumor                           | Mycelium                            | [87]       |
| 17  | Myrocin                                                  | Immune inhibitor                    | -                                   | [88]       |
| 18  | Serine protease                                          | Fibrinolytic                       | Culture supernatant                 | [89]       |
| 19  | Melanin                                                  | Antioxidant                         | Mycelium                            | [2]        |
| 20  | cordysin A                                               | Anti-inflamatory                    | Mycelium                            | [90]       |
| 21  | cordysin B                                               | Anti-inflamatory                    | Mycelium                            | [90]       |
| 22  | cordysin C                                               | Anti-inflamatory                    | Mycelium                            | [90]       |
| 23  | cordysin D                                               | Anti-inflamatory                    | Mycelium                            | [90]       |
| 24  | cordysin E                                               | Anti-inflamatory                    | Mycelium                            | [90]       |
| 25  | Cordyceamide A                                           | Cytotoxic                           | Culture supernatant                 | [91]       |
| 26  | Cordyceamide B                                           | Cytotoxic                           | Culture supernatant                 | [91]       |

activities. An acidic polysaccharide AEPS-1, fractionated from the EPS produced by *C. sinensis* Cs-HK1 in mycelial culture, was composed of glucopyranose (GlcP) and pyran-glucuronic acid (GlcUp) in an 8:1 M ratio plus a trace amount of mannose, which has an average MW of 36 kDa and significantly stimulated the release of several major cytokines that may have immunomodulatory properties.

The polysaccharide CPS-2, mostly composed of α-(1→4)-d-glucose and α-(1→3)-d-mannose and branched with α-(1→4, 6)-d-glucose every 12 residues, has an average MW of 43.9 kDa and has been shown to significantly relieve renal failure. A polysaccharide with a MW of 82 kDa that was isolated from the culture medium of *Cordyceps*, namely cordysinocan, and contained glucose, mannose, and galactose in a 2:4:2:1 ratio induced cell proliferation and the secretion of interleukin (IL)-2, IL-6, and IL-8. In another study, EPS consisting of mannose, glucose, and galactose in a ratio of 23:1:2:6 with a MW of about 104 kDa had the ability to stimulate cytokine expression in immunocytes. Moreover, EPS composed of polysaccharide-protein complexes with a β-D-glucan backbone and a wide range of MWs (5 kDa to more than 200 kDa) had moderate antioxidant activities.

**Intracellular polysaccharides**

Intracellular polysaccharides (IPS), extracted from *O. sinensis*
| No. | Bioactivity       | Experiment mode | Material                        | Extraction solvent | References |
|-----|------------------|----------------|---------------------------------|-------------------|------------|
| 1   | Immunomodulatory | In vivo        | Artificial CS*¹                 | -                 | [92]       |
|     |                  | In vivo        | CS                              | -                 | [93]       |
|     |                  | In vivo        | CS                              | Water             | [94]       |
|     |                  | In vivo        | CS                              | Water             | [95]       |
|     |                  | In vivo        | CS                              | -                 | [96]       |
|     |                  | Ex vivo        | EPS*²                          | -                 | [97]       |
|     |                  | Ex vivo        | CS                              | -                 | [98]       |
|     |                  | Ex vivo        | EPS                            | -                 | [98]       |
|     |                  | In vitro       | CS                              | -                 | [99]       |
|     |                  | In vitro       | Mycelium                        | -                 | [100]      |
|     |                  | In vitro       | Mycelium                        | Water             | [101]      |
|     |                  | In vitro       | Mycelium                        | Methanol          | [102]      |
|     |                  | In vitro       | Mycelium                        | Methanol          | [103]      |
|     |                  | In vitro       | Mycelium                        | Methanol          | [104]      |
|     |                  | In vitro       | Fruiting body                   | Methanol          | [105]      |
| 2   | Immunosuppression| In vitro       | Mycelium                        | -                 | [106]      |
|     |                  | Clinical       | CS                              | -                 | [107]      |
| 3   | Anticomplementary| In vitro       | EPS                            | -                 | [108]      |
| 4   | Antitumor        | In vitro       | Polysaccharide-rich fraction    | -                 | [109]      |
|     |                  | Clinical       | CS                              | -                 | [110,111] |
|     |                  | In vitro       | Mycelium                        | Methanol          | [112]      |
|     |                  | In vitro       | Mycelium                        | Methanol          | [113]      |
|     |                  | In vivo        | CS                              | -                 | [114]      |
|     |                  | In vitro       | CS                              | Water             | [115]      |
|     |                  | In vitro       | Mycelium                        | Ethyl acetate     | [116]      |
|     |                  | In vitro       | Mycelium                        | Water             | [117]      |
| 5   | Anti-inflammation| In vivo        | Cordymin                        | -                 | [83]       |
|     |                  | In vitro       | Mycelium                        | -                 | [118]      |
|     |                  | In vitro       | Cordysinins A-E from mycelium   | -                 | [90]       |
|     |                  | In vitro       | CS                              | -                 | [119]      |
|     |                  | In vitro       | Mycelium                        | Methanol          | [112]      |
|     |                  | In vivo        | Extract                         | -                 | [120]      |
| 6   | Antioxidation    | In vitro       | EPS                            | -                 | [108]      |
|     |                  | In vitro       | EPS                            | -                 | [109]      |
|     |                  | In vitro       | Mycelium                        | Water             | [121]      |
|     |                  | In vitro       | Mycelium                        | Water             | [122]      |
|     |                  | In vitro       | Fruiting body                   | Water             | [123]      |
|     |                  | In vivo        | Cordymin                        | -                 | [83]       |
|     |                  | In vivo        | Mycelium                        | -                 | [124]      |
| 7   | Antibacterial    | In vitro       | Mycelium                        | -                 | [125]      |
|     |                  | In vivo        | Mycelium                        | -                 | [126]      |
| 8   | Hepatoprotection| In vitro       | Fruiting body                   | -                 | [167]      |
|     |                  | In vivo        | Compound Codysceps-TCM-700C     | -                 | [128]      |
|     |                  | In vivo        | The fruiting bodies             | -                 | [129]      |
|     |                  | In vivo        | CS                              | -                 | [130]      |
|     |                  | In vivo        | CS                              | -                 | [131]      |
|     |                  | In vivo        | Mycelium                        | -                 | [132]      |
|     |                  | In vivo        | Mycelium                        | -                 | [133]      |
| 9   | Kidneys benefits | In vivo        | CS                              | -                 | [134]      |
|     |                  | In vivo        | CS                              | -                 | [135]      |
|     |                  | In vivo        | CS                              | -                 | [136]      |
|     |                  | In vivo        | CS                              | -                 | [137]      |
|     |                  | In vivo        | CS                              | -                 | [138]      |
|     |                  | In vitro       | CS                              | -                 | [139,140] |
|     |                  | In vitro       | Natural product of CS (H1-A)    | -                 | [141]      |
| No. | Bioactivity                  | Experiment mode | Material                                      | Extraction solvent               | References |
|-----|------------------------------|-----------------|-----------------------------------------------|----------------------------------|------------|
| 10  | Antidiabetic                 | Clinical        | Bailing Capsule, fermented agent of CS        | -                                | [142]      |
|     |                              | In vivo         | Mycelium                                      | -                                | [143]      |
|     |                              | In vivo         | CS                                            | -                                | [144]      |
|     |                              | In vivo         | Vanadium-enriched CS (VECS)                   | -                                | [145]      |
|     |                              | In vivo         | Vanadium-enriched CS(VECS)                    | -                                | [146]      |
|     |                              | In vivo         | Fruiting body                                 | -                                | [147,148] |
|     |                              | In vivo         | Fruiting body                                 | -                                | [149]      |
|     |                              | In vivo         | Mycelium(cordyceps Cs-4)                      | -                                | [150]      |
| 11  | Hypcholesterolemic           | In vivo         | Mycelium                                      | Water                            | [152]      |
| 12  | Antiarteriosclerosis         | In vivo         | Extract                                       | -                                | [153]      |
|     |                              | In vivo         | Fruiting body                                 | Water                            | [154]      |
| 13  | Antithrombus                 | In vivo         | Mycelium                                      | Alcohol                          | [155]      |
| 14  | Hypotensive and vasorelaxant | In vivo         | CS                                            | Phosphate buffer saline          | [156]      |
| 15  | Lung benefit                 | In vivo         | CS                                            | -                                | [157]      |
|     |                              | In vivo         | CS                                            | -                                | [158]      |
|     |                              | In vivo         | Cultured CS                                   | -                                | [159]      |
|     |                              | In vivo         | CS                                            | Alcohol                          | [160]      |
|     |                              | In vivo         | Mycelium                                      | -                                | [161]      |
| 16  | Photoprotection              | In vitro        | Mycelium                                      | Methanol                         | [162]      |
|     |                              | In vivo         | Mycelium                                      | Water                            | [163]      |
|     |                              | In vivo         | Vanadium-enriched Mycelium                    | -                                | [145,146] |
| 17  | Antidepress                    | In vivo         | Mycelium                                      | Water                            | [164]      |
|     |                              | Clinical        | Mycelium                                      | -                                | [165]      |
| 18  | Antiostecoporosis            | In vivo         | CS                                            | -                                | [166]      |
| 19  | Anticerebral ischemia        | In vivo         | Extract                                       | -                                | [167]      |
| 20  | Prevention and treatment of injury to the bowel | In vivo         | Extract                                       | Water                            | [168]      |
| 21  | Promotion to endurance capacity | In vivo         | Mycelium                                      | -                                | [169]      |
|     |                              | Clinical        | Mycelium(cordyceps Cs-4)                      | -                                | [63]       |
| 22  | Antifatigue                  | Clinical        | Cultured CS                                   | -                                | [170]      |
| 23  | Antiasthmatic                | In vitro        | Extract                                       | -                                | [171]      |
| 24  | Learning-memory Improvement  | In vivo         | Extracts                                      | -                                | [172]      |
| 25  | Steroidogenesis              | In vitro        | CS                                            | -                                | [173]      |
|     |                              | In vivo         | CS                                            | -                                | [174]      |
|     |                              | In vitro        | Mycelium                                      | -                                | [175]      |
|     |                              | In vitro        | Mycelium                                      | -                                | [176]      |
|     |                              | In vitro        | CS                                            | Water                            | [177]      |
| 26  | Erythropoiesis               | In vitro        | CS                                            | -                                | [178]      |
| 27  | Antiarhythmic                | In vivo         | CS                                            | Alcohol                          | [179]      |
| 28  | Antiaging                    | In vivo         | Extract                                       | -                                | [180]      |
| 29  | Allograft rejection prevention | In vivo         | CS                                            | -                                | [181]      |
| 30  | Lupus attenuation            | In vivo         | Mycelium                                      | -                                | [182]      |
|     |                              | In vitro        | A pure compound (H1-A) from CS                | -                                | [183]      |
| 31  | Testosterone production      | In vivo         | CS                                            | -                                | [176,184] |
| 32  | Sedation                     | In vivo         | Natural CS                                    | -                                | [185]      |
| 33  | Adjunction                   | Clinical        | CS                                            | -                                | [186]      |

* CS: Cordyceps sinensis
* EPS: Extracellular polysaccharide
mycelia and containing 1,3-β-D-, 1,3-α-D-, or 1,4-α-D-glucan with 1,6-branched chains, had MWs ranging from 7.7 to 11,800 kDa depending on the extract conditions. Structural analyses showed that insoluble polysaccharides with 1, 3-β-D-glucan contained some 1, 6-branched chains with an average particle diameter of 1.5 μm.\[187]\ The D-glucan consisted of a backbone with (1→4)-D-glucosyl residues and carried a single (1→6)-linked D-glucosyl residue; and these α-D-glucosidic linkages were present in the polysaccharide with short exterior chains.\[189]\ The neutral mannoglucon with a MW of 7.7 kDa consisted of Man and Glc units in the molar ratio of 1:9, a α-D-glucan backbone with (1→4) and (1→3)-linkages, and side chains of α-D-(1→6)-Manp, which attached to the backbone via O-6 of α-(1→3)-Glcp residues.\[189]\ The polysaccharide CS-F10, purified from a hot water extract, was composed of galactose, glucose, and mannose in a molar ratio of 43:33:24, and its MW was estimated to be about 15 kDa, which has a comb-type structure with α-D-glucopyranosyl residues on the termini of the side-chains and characteristic sugar residues, such as 1, 5-linked β-D-galactofuranosyl residues.\[190]\ Hot water extracts of mycelia (WIPS) and alkaline extracts of mycelia (AIPS) were characterized as α-D-glucons with a backbone of (1→4)-linked α-D-Glcp and similar MWs (WIPS 1180 kDa; AIPS 1150 kDa); and WIPS had a short branch of (1→6)-linked α-D-Glcp, and AIPS was a linear glucan, which is different from the branched structures of most glucons from medicinal fungi.\[61]\ IPS from C. sinensis mycelia with MWs ranging from 8.1 to 460 kDa have antioxidant, anti-inflammatory, immunomodulatory, hypoglycemic, and hypocholesterolemic activities, described as following. Antioxidant polysaccharide CPS1 was found to be a glucomannogalactan with a monosaccharide composed of glucose, mannose, and galactose in a ratio of 2:8:2:9:1, and its total carbohydrate content and average MW were 99.0% and 8.1 kDa, respectively.\[172]\ The anti-inflammatory polysaccharide fraction CME-1, has a MW of 27.6 kDa and containing mannose and galactose in a ratio of 4:6.\[193]\ The hypoglycemic polysaccharides obtained from a hot-water extract and alkaline extracts were found to be composed of galactose, glucose, and mannose in a ratio of 62:28:10 with a MW 45 kDa.\[197\] In addition, the isolated IPS composed of D-Glc, D-Man, L-Ara, and D-Gal in a molar ratio of 8:90:1:1 with an average MW of 83 kDa has been shown to have immunomodulatory potential.\[65]\ A polysaccharide with MW 210 kDa may protect Against free radical-induced neuronal cell toxicity.\[192]\ Another polysaccharide with a MW of 210 kDa that was isolated and named CSP-1 is composed of glucose, mannose, and galactose in the ratio of 1:0.6:0.75 and was shown to have strong antioxidation activity and the abilities to decrease blood glucose and insulin secretion in diabetic animals.\[66]\ The heteropolysaccharide PS-A, composed of D-glucose, D-galactose, and D-mannose in a molar ratio of 2:1:1 with a MW of 460 kDa, was shown to possess strong inhibitory activity against cholesterol esterase and may be a potential agent to control hypercholesterolemia.\[74]\ Nucleosides

It has been demonstrated that the nucleoside contents, including uracil, uridine, hypoxanthine, inosine, guanosine, adenosine, adenine, and cordycepin, of natural and cultured Cordyceps could be separated into two individual sub-groups, which suggested that the chemical characteristics of the cultured mycelia of different fungal strains isolated from natural C. sinensis were similar but were different from natural mycelia.\[191]\ The perithecium of C. sinensis was found to have considerably higher amounts of total nucleosides and nucleobases compared to other parts of this fungus.\[194]\ The content of the four active nucleosides, specifically adenosine, guanosine, cytidine, and thymidine, in C. sinensis was lower than that of cultured Cordyceps.\[185]\ Moreover, there is a positive correlation between nucleoside content in C. sinensis and the growth altitude.\[46]\ Adenosine

Adenosine was abundant in the fruiting body and was considerably more abundant than in the corpus of natural DongChongXi-aCao and the mycelia of C. sinensis.\[196]\ It has been shown that the amount of adenosine in Cordyceps ranges from 0.28 to 14.15 mg/g.\[197]\ The concentration of adenosine 2.45 ± 0.03 mg/g in C. militaris fruiting bodies was found to be higher than those of 1.643 ± 0.03 mg/g in natural C. sinensis, while the content of the fermented mycelia 1.592 ± 0.03 mg/g of C. militaris was similar to those of natural C. sinensis.\[198]\ Cordycepin

Studies have shown that cordycepin is abundant in cultured C. militaris (2.28 ± 0.84 mg/g) and sparse in natural C. sinensis; however, there is an undetectable amount in cultured C. sinensis.\[199]\ The amount of cordycepin in Cordyceps was found to range from 0.006 mg/g to 6.36 mg/g.\[190]\ In cultured mycelia and the fruiting body of Cordyceps, cordycepin contents were lower and varied from 0.006 to 1.64 mg/g.\[196,198]\ The cordycepin content of the mycelia of C. sinensis cultured in potato dextrose agar (PDA) medium and Finger millet medium were 0.075 mg/g and 0.021 mg/g, respectively; however, the cordycepin content in natural C. sinensis was higher than in the mycelia of C. sinensis cultured with PDA medium.\[200]\ It has been indicated that the concentration of cordycepin in C. militaris fruiting bodies is higher than in natural C. sinensis, and the concentration of cordycepin in fermented C. militaris mycelia is similar to that in natural C. sinensis: the mean cordycepin contents in the fruiting bodies of C. militaris and C. sinensis were found to be 2.65 and 1.64 mg/g, respectively, and the content in C. militaris mycelia was 1.59 mg/g.\[198]\ In addition, cultured mycelia and natural specimens of C. sinensis contained similar amounts of cordycepin.\[42]\ When extracted with 50% methanol-chloroform, the cordycepin content of cultured mycelia varied from 0.002% to 0.029% (i.e., 0.02-0.29 mg/g) in twenty-one isolates, and the cordycepin content of natural Dong Chong Xia Cao varied from 0.004% to 0.006% (i.e., 0.04-0.06 mg/g).\[201]\ Mannitol

Mannitol is the so-called “ChongCao Acid” in Chinese and is also improperly named as “cordycepic acid.” When searching for the terms “mannitol” plus “Cordyceps” in the Scopus database, a limited number of articles can be found. Li et al.,\[202]\ indicated that the D-mannitol contents in natural fruiting bodies of C. sinensis, mycelia from shaking cultures, and fruiting bodies from
artificial cultivation of *H. beakdumountainsi* were 8.9, 11.5, and 10.2%, respectively. For *in vitro*-cultured *C. sinensis*, the amount of D-mannitol yielded was almost the same as that in natural samples.[42] Moreover, when *C. sinensis* was cultured with millet, the D-mannitol content achieved levels as high as that in *C. militaris* fruiting bodies.[203] There was no obvious difference in the amount of nucleosides between cultured *O. sinensis* mycelia and natural products; however, natural products were shown to have a significantly higher D-mannitol content compared with submerged culture mycelia.[204]

Likewise, when searching for the terms "cordycepic acid" plus "Cordyceps" in the Scopus database, a limited articles can be found. The chemical constituents of natural *Cordyceps*, including cordycepic acid, have been described.[13] Dong et al.[205] showed that the superoxide dismutase activity and the content of cordycepic acid in the fruiting bodies of *C. militaris* were dependent on the sodium selenite concentration in the culture medium. It has been reported that *C. sinensis* has many bioactive components, such as 3′-deoxyadenosine, cordycepic acid, and *Cordyceps* polysaccharides.[5] In addition, yields of cordycepic acid from *C. jiangxiensis*, *C. taii*, and *C. gunnii* were found to be 11.81%, 8.72%, and 4.73%, respectively, of the dry weight of mycelia.[206]

**Amino acids**

The total amount of amino acids in fermented mycelia was determined to be 9.23%, which is lower than that in wild *DongChongXiaCao* (18.1%) but is similar to that in the fruiting body of wild *DongChongXiaCao*. [46] The three principal amino acids in the corpus-fruiting body are glutamic acid, aspartic acid, and arginine, and their contents are 2.64–2.66%, 1.70–1.84%, and 1.53–1.60%, respectively.[46] A mixture with 18 synthetic amino acids to mimic the amino acid composition in natural *C. sinensis* showed the same sedative action as natural *C. sinensis*.[185]

**Sterols**

The ergosterol content in the stroma of *C. sinensis* was found to be approximately 0.92 g/L and was about three times higher than that found in the sclerotium.[207] The fruiting body (CsA) and the host caterpillar (CsB) of *C. sinensis* had similar ergosterol compositions, but the level of ergosteryl esters in CsB was much higher than in CsA, these data indicated that CsA and CsB might exist in different growth phases and have different physiological functions for the growth and multiplication of *C. sinensis*.[208] It has been shown that ergosta-4,6,8(14),22-tetraen-3-ol may induce G2/M cell cycle arrest and apoptosis in human hepatocellular carcinoma HepG2 cells.[86] 5α,8α-epidioxy-22E-ergosta-6,22-dien-3β-ol, 5α,8α-epidioxy-22E-ergosta-6,9(11),22-trien-3β-ol, and 5α,6α-epoxy-5α-ergosta-7,22-dien-3β-ol isolated from the ethyl acetate fraction with a peroxide ring or an epoxide ring had substantial cytotoxic activity.[209] In addition, 5α,8α-epidioxy-24R-methylcholesta-6,22-dien-3β-D-glucopyranoside, and 5,6-epoxy-24R-methylcholesta-7,22-dien-3β-ol from the methanol extract of *C. sinensis* had antitumor activity.[87]

**Aurantiamides**

Two aurantiamides, a new class of potent analgesic and anti-inflammatory agents, named cordyceamides A and B were isolated from the culture liquid of *C. sinensis* along with one known compound, aurantiamide acetate. The structures of these compounds were elucidated as N-benzoyl-l-tyrosyl-l-phenylalaninol acetate and N-benzoyl-l-tyrosyl-l-p-hydroxyphenylalaninol acetate by 1D and 2D-NMR techniques and by the comparison with the literature.[91]

**Peptides**

**Cyclodipeptides**

A cyclodipeptide named cordycedipeptide A, which is a natural compound that was isolated from the culture liquid of *C. sinensis*, had cytotoxic activity against L-929, A375, and Hela cells.[210]

**Cordymin**

The peptide cordymin from *C. sinensis*, which has a neuroprotective effect in the ischemic brain due to inhibited inflammation and increased antioxidant activity related to lesion pathogenesis, can be used as a potential preventive agent against cerebral ischemia-reperfusion injury.[83]

**Myricin**

Myricin (also known as the antibiotic ISP-1) is a new type of immune inhibitor extracted from *C. sinensis*, it was shown to significantly inhibit the upregulated expression of cyclin D1 induced by high concentrations of glucose, restoring the expression of cyclin D1.[88]

**Melanin**

The antioxidant activity of melanin, derived from a black pigment, was isolated from the fermentation broth of *O. sinensis* and showed much stronger scavenging abilities for 1,1-diphenyl-2-picrylhydrazyl (DPPH•) and ferrous ion chelation compared to the mycelial water extract.[211]

**Lovastatin, γ-aminobutyric acid (GABA), and ergothioneine**

Lovastatin, GABA, and ergothioneine are secondary metabolites of fungal growth. Chen et al.[84] indicated that mycelia of *C. sinensis* contained 1365 mg/kg of lovastatin, 220.5 mg/kg GABA, and detectable ergothioneine and had different hypolipidemia, hypotension, and antioxidant activities.

**Cordysinins**

Five cordysinins, A-E, from the mycelia of *C. sinensis* have been identified and have been shown to have anti-inflammatory activities, and 1-(5-Hydroxymethyl-2-furyl)-β-carboline was shown to most significantly inhibit superoxide anion generation and elastase release.[86]

**SHAKING CULTURE AND SUBMERGED FERMENTATION OF O. SINENSIS**

The maximal production of mycelia, EPS, and exo-biopolymer are important concerns for producers, especially for industry. Several factors that may affect the production of *O. sinensis* in shaking culture and submerged fermentation, including strain, medium, and culture conditions, have been discussed in different studies.
The amounts of mycelial biomass, EPS, and exo-biopolymer range from 11.10 to 62.3 g/l, 0.43 to 3.21 g/l and 22.0 to 28.4 g/l, respectively, described as follows.

It has been observed that Tween 80 can exhibit a remarkable effect on EPS production by increasing EPS yield more than two-fold at 1.5% (w/v); the effects of Tween 80 can probably be attributed to the stimulation of EPS biosynthesis and release from fungal cells.[212] In addition, evidence has shown that palmitic acid may significantly increase the production of biomass and extracellular polysaccharides to 11.10 g/l and 0.43 g/l, respectively[101]. Adding ammonium to the mycelial culture of strain Cs-HK1 may enhance intracellular cordycepin accumulation, which may be attributed to the uptake of ammonia for nucleoside synthesis, and EPS production, which may be attributed to the increased uptake of glucose for EPS biosynthesis.[213]

The optimal medium for the production of mycelia and exobiopolymers by strain CS 16 is 2% sucrose, 0.9% yeast extract, 0.3% K2HPO4, and 0.4% CaCl2, and this medium was shown to yield maximal mycelia and exo-biopolymer productions of 54.0 g/l and 28.4 g/l, respectively, in shaking-flask cultures.[214] In bioreactor cultures, rapid differentiation and cell lysis occurred when agitation speed was increased. When the agitation speed was maintained at 350 rpm, 62.3 g/l of mycelia and 22.0 g/l of exo-biopolymers were obtained from strain CS 16 in submerged fermentation.[215] In shaking cultures, the maximum polysaccharide production was 3.05 and 3.21 g/l in a flask and a 5-L jar fermentor, respectively, when fungi were supplied with optimal medium.[216] It is believed that the optimal medium for mycelial growth is 50 g/l sucrose, 10 g/l peptone, and 3 g/l yeast extract, which would produce over 22 g/l of mycelial biomass after 40 days of submerged culture at a temperature below 20°C.[217]

CULTURE AND BIOACTIVITY OF HIRSUTELLA SINENSIS OR HIRSUTELLA SP.

There is little literature published on H. sinensis, the anamorph of O. sinensis. This might be due to geographic limitations, difficulty in isolation and cultivation, and slow growth under low temperatures.

Culture

It was shown that most strains of H. sinensis prefer to grow on Sabouraun’s dextrose agar, and some of the strains prefer potato-dextrose agar as the medium for optimal development.[218] The optimized conditions and medium for submerged fermentation of Hirsutella sp. have been described as follows: initial pH 5.5, potato extract 20% (w/v), sucrose 2.5%, peptone 0.5%, K2HPO4 0.2%, MgSO4 0.05%, and fermentation for 4 days, the highest production of EPS and mycelial biomass may reach 2.17 and 10.06 g/l, respectively.[249]

Bioactivity

H. sinensis extract (HSW) was shown to have a remarkable action in vitro and in vivo in a model of kidney injury.[219] The extract downregulated transforming growth factor-β1 in renal tissue, antagonized tubular epithelial-myofibroblast transdifferentiation and renal interstitial fibrosis, and improved renal function in chronic aristolochic acid nephropathy rats.[220] Furthermore, the fermented mycelia of H. sinensis significantly prevented spontaneous type 1 diabetes in non-obese diabetic mice.[221] Additionally, H. sinensis was shown to significantly increase animal survival after a lethal dose of radiation, accelerate leukocyte recovery, and stimulate immune lymphocyte proliferation.[222]

ECOLOGY AND HOSTS

O. sinensis is confined to the Tibetan Plateau and its surrounding regions, including Tibet, Gansu, Qinghai, Sichuan, and Yunnan provinces in China, in certain areas of the southern flank of the Himalayas, and in the countries of Bhutan, India, and Nepal. These regions are at altitudes of over 3,000 m. The fungus is distributed from the southernmost site in Yulong Naxi Autonomous County in northwestern Yunnan Province to the northernmost site in the Qilian Mountains in Qilian County, Qinghai Province and from the east edge of the Tibetan Plateau in Wudu County, Gansu Province to the westernmost site in Uttarakhand, India.[202] The yearly yield of C. sinensis in the Naqu district, which is the principal growth zone in Tibet, is 7000 kg, and the elevation of the distribution area is from 5000 m to 4100 m, and the ecological geographical distribution is mainly affected by vegetation, soil, temperature, and humidity.[223]

As hosts, the larvae of Thitarodes spp. play a vital role in supplying nutritional materials for the growth of O. sinensis. In the Tibetan Plateau, more than 40 species of the genus Thitarodes have been recorded since 1958.[224] According to another publication, 57 taxa are recognized as potential hosts of O. sinensis, including 1 Bipectilus, 1 Endoelita, 1 Gazoryctra, 12 Hepialus, 2 Magnificus, 3 Pharmacis, and 37 Thitarodes.[225] The recorded altitude ranges of the recognized potential host insects were found to vary from 2800 to 5100 m, and the distribution areas of these species covered 26 provinces in China and more than 12 other countries.[225] Due to long-term adaptive evolution, O. sinensis and its host insects have developed a living requirement for special high altitude-associated climates and soil conditions, such as sub-ambient atmosphere and soil temperatures and specific solar radiation, barometric pressure, and hypoxic conditions.[224] Studies show that there is genetic differentiation of C. sinensis among different latitudes.[226] The interspecific genetic differentiations are obvious in Hepialus, and the genus Hepialus might be considered the polyphyletic origin for Cyth sequences, which have abundant variations among the host insects of C. sinensis at both the specific and generic levels.[227]

CONCLUSIONS

O. sinensis is a complex fungus with multiple biological functions. Over 20 bioactive ingredients have been found in O. sinensis, such as extracellular polysaccharides, intracellular polysaccharides, cordycepin, adenosine, and sterols, derived from its mycelia, culture supernatant, or fruiting body. In addition, over 30 bioactivities have been indicated, including immunomodulatory, antitumor, anti-inflammatory, and antioxidant activities, in preparations or solvent extracts in in vitro, in vivo, or ex vivo stud-
ies. However, few publications have given regard to the bioactive ingredients, bioactivities, and the medium and culture conditions of *O. sinensis* and *H. sinensis*, which must be incubated for more than 10 days at low temperatures (below 21°C). The slow growth rate at low temperature is a critical characteristic of *O. sinensis* and *H. sinensis*. It has been demonstrated that these fungi grow poorly at temperatures above 21°C and stop growing at 25°C or above.

The fungus *O. sinensis* is not equivalent to the traditional Chinese medicine DongChongXiaCao; the latter develops a fruiting body following the occupation of a dead caterpillar and grows wild in nature. The host caterpillar provides nutrients for *O. sinensis*, resulting in the formation of a fruiting body in the appropriate climate and environment. The morphology of *O. sinensis* in submerged culture can be microscopically visualized as mycelia, without the fruiting body. The relationship between *O. sinensis* and its host in the traditional Chinese medicine DongChongXiaCao, as well as its pathobiology and ecology, still remains unclear.

The mysterious caterpillar fungus *O. sinensis* has been renamed since 2007; however, many publications still use the name *C. sinensis*. When the names “*Ophiocordyceps sinensis*” and “*Cordyceps sinensis*” are searched for in article titles, abstracts, and keywords in the Scopus database from the year 2008 to 2012, 84 and 255 articles can be found, respectively. Even though it has been confirmed that *H. sinensis* is the anamorph of *C. sinensis*, most articles still use the terms “*Cordyceps sinensis*,” “*Cordyceps*,” and “*Cordyceps*” to refer to the traditional Chinese medicine DongChongXiaCao. Among all of these publications, not one successfully obtained fruiting bodies from caterpillars artificially infected with *O. sinensis* or *H. sinensis*. The key identification characteristics for *O. sinensis* are the existence of a perithecium, ascus, and ascospore in the fruiting body. If the fruiting body cannot be formed from caterpillars infected by *O. sinensis* or *H. sinensis*, these key characteristics cannot be identified by microscope. Beginning January 1st, 2013, regulations will allow one fungus to have only one name, and the system of permitting separate names for anamorphs will end.[228] The anamorph name *H. sinensis* will be changed by the International Code of Nomenclature for algae, fungi, and plants (formerly called the International Code of Botanical Nomenclature)[229] to *O. sinensis*.

## REFERENCES

1. Zhong S, Pan H, Fan L, Lv G, Wu Y, Parmeswaran B, et al. Advances in research of polysaccharides in *Cordyceps* species. Food Technol Biotechnol 2009;47:304-12.
2. Dong CH, Yao YI. On the reliability of fungal materials used in studies on *Ophiocordyceps sinensis*. J Ind Microbiol Biotechnol 2011;38:1027-35.
3. Zhou X, Gong Z, Su Y, Lin J, Tang K. *Cordyceps* fungi: Natural products, pharmacological functions and developmental products. J Pharm Pharmacol 2009;61:279-91.
4. Zhang Y, Zhang S, Wang M, Bai F, Liu X. High diversity of the fungal community structure in naturally-occurring *Ophiocordyceps sinensis*. PLoS ONE 2010;5:1-8.
5. Zhang Y, Li E, Wang C, Li Y, Liu X. *Ophiocordyceps sinensis*, the flagship fungus of China: Terminology, life strategy and ecology. Mycology 2012;3:2-10.
6. Shrestha B, Zhang W, Zhang Y, Liu X. What is the Chinese caterpillar fungus *Ophiocordyceps sinensis* (*Ophiocordycipitaceae*)? Mycology 2010;1:228-36.
7. Jin C, Wu X, Chen G. Clinical application of Jinshuibao capsule. Cap Med 2005;12:42-3.
8. Xu H, Li S. Pharmacological effects of Bailing capsule and its application in lung disease research. Zhongguo Zhong Yao Za Zhi 2010;35:2777-81.
9. Chen J, Lee S, Cao Y, Peng Y, Winkler D, Yang D. Ethnopharmacological use of medicinal chinese caterpillar fungus, *Ophiocordyceps sinensis* (Berk.) G. H. Sung et al. (ascomycetes) in Northern Yunnan Province, SW China. Int J Med Mushrooms 2010;12:427-34.
10. Panda AK, Swain KC. Traditional uses and medicinal potential of *Cordyceps sinensis* of Sikkim. J Ayurveda Integr Med 2011;2:9-13.
11. Cannon PF, Hywel-Jones NL, Maczey N, Norbul L, Tshtita, Samdup T, et al. Steps towards sustainable harvest of *Ophiocordyceps sinensis* in Bhutan. Biodivers Conserv 2009;18:2263-81.
12. Au D, Wang L, Yang D, Mok DK, Chan AS, Xu H. Application of microscopy in authentication of valuable Chinese medicine I-Cordyceps sinensis, its counterfeiters, and related products. Microsc Res Tech 2012;75:54-64.
13. Sharma S. Trade of *Cordyceps sinensis* from high altitudes of the Indian Himalaya: Conservation and biotechnological priorities. Curr Sci 2004;86:1614-9.
14. Winkler D. Yartsa Gunbu (*Cordyceps sinensis*) and the fungal commodification of Tibet’s rural economy. Econ Bot 2008;62:291-305.
15. Winkler D. *Cordyceps sinensis*: A precious parasitic fungus infecting Tibet. Field Mycol 2010;11:60-7.
16. Winkler D. Caterpillar fungus (*Ophiocordyceps sinensis*) production and sustainability on the Tibetan Plateau and in the Himalayas. Asian Med 2009;5:291-316.
17. Liu F, Wu XL, Chen SJ, Yin DH, Zeng W, Zhong GY. Advances in studies on artificial culture of *Cordyceps sinensis*. Chin Tradit Herb Drugs 2007;38:302-5.
18. Xu FL, Huan WY, Wu TX, Qiu X, Zhang H, Liu XH. Clinical efficacy of *Cordyceps sinensis* for chronic kidney diseases: A systematic review. Chin J Evid Based Med 2006;6:804-8.
19. Li SP, Yang FQ, Tsim KW. Quality control of *Cordyceps sinensis*, a valued traditional Chinese medicine. J Pharm Biomed Anal 2006;41:1571-84.
20. Canney S. *Cordyceps sinensis* animal, vegetable or both? J Chin Med 2006;80:43-9.
21. Wang SY, Shiao MS. Pharmacological functions of Chinese medicinal fungus *Cordyceps sinensis* and related species. J Food Drug Anal 2000;8:248-57.
22. Zhu JS, Halpern GM, Jones K. The scientific rediscovery of a precious ancient Chinese herbal regimen: *Cordyceps sinensis* Part II. J Altern Complement Med 1998;4:429-57.
23. Zhu JS, Halpern GM, Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis* part I. J Altern Complement Med 1998;4:289-303.
24. Shrestha B, Zhang W, Zhang Y, Liu X. The medicinal fungus *Cordyceps militaris*: Research and development. Mycol Prog 2012;11:599-614.
25. Das SK, Masuda M, Sakurai A, Sakakibara M. Medicinal uses of the mushroom *Cordyceps militaris*: Current state and prospects. Fitosfera 2010;81:961-8.
26. Wang Z, Liu JL. Advances in studies on chemical constituents of *Cordyceps*. Chin Tradit Herb Drugs 2009;40:1157-60.
27. Xiao JH. Current status and ponderation on preparations and chemical structures of polysaccharide in fungi of *Cordyceps* (Fr.) Link. Chin Tradit Herb Drugs 2008;39:454-60.
28. Paterson RRM. *Cordyceps* - A traditional Chinese medicine and another fungal therapeutic biofactory? Phytochemistry 2008;69:1469-95.
29. Holloway JC, Cleaver M. Medicinal value of the caterpillar fungus species of the genus *Cordyceps* (Fr.) link (Ascomycetes). A review. Int J Med Mushrooms 2008;10:219-34.
30. Ng TB, Wang HX. Pharmacological actions of *Cordyceps*, a prized folk medicine. J Pharm Pharmacol 2005;57:1509-19.
31. Siu KM, Mak DH, Chiu PY, Poon MK, Du Y, Ko KM. Pharmacological basis of ‘Yin-nourishing’ and ‘Yang-invigorating’ actions of *Cordyceps*, a Chinese tonifying herb. Life Sci 2004;76:385-95.
32. Sung GH, Hywel-Jones NL, Sung JM, Luangsa-Ard JJ, Shrestha
B. Spatafora JW. Phylogenetic classification of Cordyceps and the clavicipitaceous fungi. Stud Mycol 2007;57:5-59.
33. Jiang Y, Yao YJ. Names related to Cordyceps sinensis anamorph. Mycotaxon 2002;84:245-54.
34. Chen YQ, Wang N, Qu LH, Li TH, Zhang WM. Determination of the anamorph of Cordyceps sinensis inferred from the analysis of the ribosomal DNA internal transcribed spacers and 5.8S rDNA. Biochem Syst Ecol 2001;29:597-607.
35. Chen YQ, Wang N, Zhou H, Qu LH. Differentiation of medicinal Cordyceps species by rDNA ITS sequence analysis. Planta Med 2002;68:635-9.
36. Liu ZY, Yao YJ, Liang ZQ, Liu YJ, Pegler DN, Chase MW. Molecular evidence for the anamorph-teleomorph connection in Cordyceps sinensis. Mycoscience 2001;42:567-74.
37. Liu ZY, Liang ZQ, Liu YJ, Hyde KD, Yu ZN. Molecular evidence for teleomorph-teleomorph connections in Cordyceps based on ITS-5.8S rDNA sequences. Mycoscience 2002;43:1100-8.
38. Kinjo N, Zang M. Morphological and phylogenetic studies on Cordyceps sinensis distributed in southwestern China. Mycoscience 2001;42:567-74.
39. Chen YQ, Hu B, Xu F, Zhang W, Zhou H, Qu LH. Genetic variation of Cordyceps sinensis, a fruit-body-producing entomopathogenic species from different geographical regions in China. FEMS Microbiol Lett 2004;230:153-8.
40. Zhu JS, Yao YS, Chen W, Zheng TY, Lu JH, Guo YL. Molecular co-existence of Paecilomyces hepialii and Hirustella sinicella in caterpillar and fruiting bodies of Cordyceps sinensis. FASEB J 2007;21:A1079.
41. Zhang Y, Xu L, Zhang S, Liu X, An Z, Wang M, et al. Genetic diversity of Ophiocordyceps sinensis, a medicinal fungus endemic to the Tibetan Plateau: Implications for its evolution and conservation. BMC Evol Biol 2009;9:290.
42. Singh R, Negi PS, Ahmed Z. Genetic variability assessment in medicinal caterpillar fungi Cordyceps spp. (Ascomycetes) in central himalayas, India. Int J Med Mushrooms 2009;11:185-9.
43. Liang H, Cheng Z, Yang XL, Li S, Ding ZQ, Zhou TS, et al. Genetic diversity and structure of Cordyceps sinensis populations from extensive geographical regions in China as revealed by inter-simple sequence repeat markers. J Microbiol Biochem 2008;46:549-56.
44. Stensrud Ø, Schumacher T, Shalchian-Tabrizi K, Svegården IB, Kauserud H. Accelerated rDNA evolution and profound AT bias in the medicinal fungus Cordyceps sinensis. Mycoscience 2007;48:110-15.
45. Yang FQ, Feng K, Zhao J, Li SP. Analysis of sterols and fatty acids in natural and cultured Cordyceps by one-step derivatization followed with gas chromatography-mass spectrometry. J Pharm Biomed Anal 2009;49:1172-8.
46. Hsu TH, Shiao LH, Hsieh 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.
47. Smirnov DA, Shcherba TV, Bisko NA, Poyedinok NL. Some Biologically Active Substances from a Mycelial Biomass of Medicinal Caterpillar Mushroom Hirsutella sinensis (Berk.) Sacc. (Ascomycetes). Int J Med Mushrooms 2009;11:65-69.
48. Li C, Li Z, Fan M, Cheng W, Long Y, Ding T, et al. The composition of Hirustella sinensis, anamorph of Cordyceps sinensis. J Food Compost Anal 2006;19:800-5.
49. Li R, Jiang XL, Guan HS. Optimization of mycelium biomass and exopolysaccharides production by Hirustella sp in submerged fermentation and evaluation of exopolysaccharides antibacterial activity. Afr J Biotechnol 2010;9:196-203.
50. Yu S, Zhang Y, Fan M. Analysis of volatile compounds of mycelia of Hirustella sinensis, the anamorph of Ophiocordyceps sinensis. Appl Mech Mater 2012;140:253-7.
51. Song D, He Z, Wang C, Yuan F, Dong P, Zhang W. Regulation of the exopolysaccharide from an anamorph of Cordyceps sinensis on dendritic cell sarcoma (DCS) cell line. Eur J Nutr 2012 [Epub ahead of print].
52. Yoon TJ, Yu KW, Shin KS, Suh HJ. Innate immune stimulation of epxolymers prepared from Cordyceps sinensis by submerged culture. Appl Microbiol Biotechnol 2008;80:1087-93.
53. Zhang W, Yang J, Chen J, Hou Y, Han X. Immunomodulatory and antitumour effects of an exopolysaccharide fraction from cultivated Cordyceps sinensis (Chinese caterpillar fungus) on tumour-bearing mice. Biotechnol Appl Biochem 2005;42:9-15.
54. Cheung JK, Li J, Cheung AW, Zhu Y, Zheng KY, Bi CW, et al. Cordysinocan, a polysaccharide isolated from cultured Cordyceps, activates immune responses in cultured T-lymphocytes and macrophages: Signaling cascade and induction of cytokines. J Ethnopharmacol 2009;124:61-8.
55. Kuo MC, Chang CY, Cheng TL, Wu MJ. Immunomodulatory effect of exo-polysaccharides from submerged cultured Cordyceps sinensis: Enhancement of cytokine synthesis, CD11b expression, and phagocytosis. Appl Microbiol Biotechnol 2007;75:769-75.
56. Sheng L, Chen J, Li J, Zhang W. An exopolysaccharide from cultivated Cordyceps sinensis and its effects on cytokine expressions of immuneocytes. Appl Microbiol Biotechnol 2011;86:669-78.
57. Wang ZM, Peng X, Lee KL, Tang JC, Cheung PC, Wu JY. Structural characterisation and immunomodulatory property of an acidic polysaccharide from mycelial culture of Cordyceps sinensis fungus Cs-HK1. Food Chem 2011;125:637-43.
58. Zhang W, Li J, Qiu S, Chen J, Zheng Y. Effects of the exopolysaccharide fraction (EPSF) from a cultivated Cordyceps sinensis on immunocytes of H22 tumor bearing mice. Fitoterapia 2008;79:168-73.
59. Leung PH, Zhao S, Ho KP, Wu JY. Chemical properties and antioxidant activity of exopolysaccharides from mycelial culture of Cordyceps sinensis fungus Cs-HK1. Food Chem 2009;114:1251-6.
60. Yan JK, Li L, Wang ZM, Leung PH, Wang WQ, Wu JY. Acidic degradation and enhanced antioxidant activities of exopolysaccharides from Cordyceps sinensis mycelial culture. Food Chem 2009;117:641-6.
61. Yan JK, Wang WQ, Li L, Wu JY. Physiochemical properties and antitumor activities of two α-glucans isolated from hot water and alkaline extracts of Cordyceps (Cs-HK1) fungal mycelia. Carbohydr Polym 2011;85:753-8.
62. Chen SD, Lin SY, Lai YS, Cheng YH. Effect of Cordyceps sinensis adlay fermentative products on antioxidant activities and macrophage functions. Taiwan J Agric Chem Food Sci 2008;46:223-33.
63. Chen S, Li Z, Krochmal R, Abrazado M, Kim W, Cooper CB. Effect of Cs-4® (Cordyceps sinensis) on exercise performance in healthy elderly subjects: A double-blind, placebo-controlled trial. J Altern Complement Med 2010;16:585-90.
64. Chen W, Zhang W, Shen W, Wang K. Effects of the acid polysaccharide fraction isolated from a cultivated Cordyceps sinensis on macrophages in vitro. Cell Immunol 2010;262:69-74.
65. Wu Y, Sun H, Qiu F, Pan Y, Sun C. Effect of various extracts and a polysaccharide from the edible mycelia of Cordyceps sinensis on cellular and humoral immune response against ovalbumin in mice. Phytother Res 2006;20:646-52.
66. Huang ZJ, Ji H, Li P, Xie L, Zhao XC. Hypoglycemic effect and mechanism of polysaccharides from cultured mycelium of Cordyceps sinensis. J China Pharm Univ 2002;33:51-4.
67. Kiho T, Hui J, Yamane A, Ukai S. Polysaccharides in Fungi. XXXII. Hypoglycemic activity and chemical properties of a polysaccharide from the cultural mycelium of Cordyceps sinensis. Biol Pharm Bull 1993;16:1291-3.
68. Li SP, Zhang GH, Zeng Q, Huang ZG, Wang YT, Dong TT, et al. Hypoglycemic activity of polysaccharide, with antioxidation, isolated from cultured Cordyceps sinensis mycelia. Phytochemistry 2006;71:428-33.
69. Chen J, Zhang W, Lu T, Li J, Zheng Y, Kong L. Morphological and genetic characterization of a cultivated Cordyceps sinensis fungus and its polysaccharide component possessing antioxidiant property in H22 tumor-bearing mice. Life Sci 2006;78:2742-50.
70. Wang L, Wang G, Zhang J, Zhang G, Jia L, Liu X, et al. Extraction optimization and antioxidiant activity of intracellular selenium polysaccharide by Cordyceps sinensis SU-02. Carbohydr Polym 2011;86:1745-50.
71. Wang SH, Yang WB, Liu YC, Chiu YH, Chen CT, Kao PF, et al. A potent sphingomyelinase inhibitor from Cordyceps mycelia contributes its
cytoprotective effect against oxidative stress in macrophages. J Lipid Res 2011;52:471-9.
72. Wang Y, Wang M, Ling Y, Fan W, Yin H. Structural determination and antioxidative activity of a polysaccharide from the fruiting bodies of cultured Cordyceps sinensis. Am J Chin Med 2009;37:977-89.
73. Wang Y, Yin H, Lv X, Gao H, Wang M. Protection of chronic renal failure by a polysaccharide from Cordyceps sinensis. Fitoterapia 2010;81:397-402.
74. Kim SD. Isolation, structure and cholesterol esterase inhibitory activity of a polysaccharide, PS-A, from Cordyceps sinensis. J Appl Biol Chem 2010;53:784-9.
75. Kihío T, Yamane A, Hui J, Usai S, Ukai S. Polysaccharides in fungi. XXXVI. Hypoglycemic activity of a polysaccharide (CS-F30) from the cultural mycelium of Cordyceps sinensis and its effect on glucose metabolism in mouse liver. Biol Pharm Bull 1996;19:294-6.
76. Leu SF, Poon SL, Pao HY, Huang BM. The in vivo and in vitro stimulatory effects of cordycepin on mouse Leydig cell steroidogenesis. Biosci Biotechnol Biochem 2011;75:723-31.
77. Pao HY, Pan BS, Leu SF, Huang BM. Cordycepin stimulated steroidogenesis in MA-10 mouse Leydig tumor cells through the protein kinase C pathway. J Agric Food Chem 2012;60:4905-13.
78. Kudo E, Sato A, Yoshikawa N, Kagata S, Shinozuka K, Nakamura K. Effect of Cordyceps sinensis on TIMP-1 secretion from murine melanoma cell. Cent Eur J Biol 2012;7:167-71.
79. Chen Y, Chen YC, Lin YT, Huang SH, Wang SM. Cordycepin induces apoptosis of CGT11 W-2 thyroid carcinoma cells through the calcium-calpain-caspase 7-PARP pathway. J Agric Food Chem 2010;58:11645-52.
80. Yoshikawa N, Nakamura K, Yamaguchi Y, Kagata S, Shinozuka K, Kunimoto M. Cordycepin and Cordyceps sinensis reduce the growth of human promyelocytic leukemia cells through the Wnt signalling pathway. Clin Exp Pharmacol Physiol 2007;34:861-3.
81. Zhou X, Luo L, Dressel W, Shadler G, Krumbiegel D, Schmidtke P, et al. Cordycepin is an immunomodulatory active ingredient of Cordyceps sinensis. Am J Chin Med 2008;36:967-80.
82. Yu L, Zhao J, Zhu Q, Li SP. Macrophage biospecific extraction and high performance liquid chromatography for hypothesis of immunomodulatory active components in Cordyceps sinensis. J Pharm Biomed Anal 2007;44:439-43.
83. Wang J, Liu YM, Cao W, Yao KW, Liu QZ, Guo JY. Anti-inflammation and antioxidant effect of cordymin, a peptide purified from the medicinal mushroom Cordyceps sinensis, in middle cerebral artery occlusion-induced focal cerebral ischemia in rats. Metab Brain Dis 2012;27:159-65.
84. Chen SY, Ho KJ, Hsieh YJ, Wang LT, Mau JL. Contents of lovastatin, γ-aminobutyric acid and ergothioneine in mushroom fruiting bodies and mycelia. LWT - Food Sci Technol 2012;47:274-8.
85. Matsuda H, Akaki J, Nakamura S, Okazaki Y, Kojima H, Tamasada M, et al. Apoptosis-inducing effects of sterols from the dried powder of cultured Cordyceps sinensis mycelium. Chem Pharm Bull 2009;57:411-4.
86. Zhao YY, Shen X, Chao X, Ho CC, Cheng XL, Zhang Y, et al. Ergosta-4,6,8(14),22-tetraene-3-one induces G2/M cell cycle arrest and apoptosis in human hepatocellular carcinoma HepG2 cells. Biochem Biophys Acta 2011;1810:384-92.
87. Bok JW, Lermer L, Chilton J, Kligerman HG, Towers GH. Antitumor sterols from the mycelia of Cordyceps sinensis. Phytochemistry 1999;51:891-8.
88. Xiao ZH, Zhou JH, Wu HS. Effect of myricin on the expression of cyclinD1 in high glucose-induced hypertrophy mesangial cells. Zhongguo Dang Dai Er Ke Za Zhi 2011;13:677-9.
89. Li HP, Hu Z, Yuan JL, Fan HD, Chen W, Wang SJ, et al. A novel extracellular protease with fibrinolytic activity from the culture supernatant of Cordyceps sinensis: Purification and characterization. Phytother Res 2007;21:1234-41.
90. Yang ML, Kuo PC, Hwang TL, Wu TS. Anti-inflammatory principles from Cordyceps sinensis. J Nat Prod 2011;74:1996-2000.
91. Jia JM, Tao HH, Feng BM. Cordyceamides A and B from the culture liquid of Cordyceps sinensis (Berk.) Sacc. Chem Pharm Bull (Tokyo) 2009;57:99-101.
92. Zhong J, Zhang Y, Ding Z, Ye K. Effect of polysaccharide extract from artificial Cordyceps sinensis on immune function of mouse. Zhongguo Da Xue Xue Bao Zi Ran Ke Xue Ban 2011;50:99-102.
93. Shi B, Wang Z, Jin H, Chen YW, Wang Q, Qian Y. Immunoregulatory Cordyceps sinensis increases regulatory T cells to Th17 cell ratio and delays diabetes in NOD mice. Int Immunopharmacol 2009;9:582-6.
94. Park DK, Choi WS, Park PJ, Kim EK, Jeong YJ, Choi SY, et al. Immunoglobulin and cytokine production from mesenteric lymph node lymphocytes is regulated by extracts of Cordyceps sinensis in C57Bl/6N mice. J Med Food 2008;11:784-8.
95. Liu WC, Chuang WL, Tsai ML, Hong JH, Mchride WH, Chiang CS. Cordyceps sinensis health supplement enhances recovery from taxol-induced leukopenia. Exp Biol Med 2008;233:447-55.
96. Cheng Q. Effect of Cordyceps sinensis on cellular immunity in rats with chronic renal insufficiency. Zhonghua Yi Xue Za Zhi 1992;72:23-9.
97. Song D, Lin J, Yuan F, Zhang W. Ex vivo stimulation of murine dendritic cells by an exopolysaccharide from one of the anamorph of Cordyceps sinensis. Cell Biochem Funct 2011;29:55-61.
98. Huang Z, Jin J, Tong X, Yang Q, Gu B, Wang J, et al. The immunomodulatory effects of Cordyceps sinensis on dendritic cells derived from chronic myelogenous leukemia (CML). J Med Plant Res 2011;5:5925-32.
99. Kawanishi T, Ikeda-Dentusui Y, Nagayama A. Effects of two basidiozyme species on interleukin 1 and interleukin 2 production by macrophage and T cell lines. Immunobiology 2010;215:16-20.
100. Jordan JL, Sullivan AM, Lee TD. Immune activation by a sterile aqueous extract of Cordyceps sinensis: Mechanism of action. Immunopharmacol Immunotoxicol 2008;30:53-70.
101. Kuo CF, Chen CC, Lin CF, Jan MS, Huang YR, Luo YH, et al. Abrogation of streptococcal pyrogenic exotoxin B-mediated suppression of phagocytosis in U937 cells by Cordyceps sinensis mycelium via production of cytokines. Food Chem Toxicol 2007;45:278-85.
102. Koh JJ, Yu KW, Sui 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 2006;70:407-11.
103. Kuo YC, Tsai WJ, Wang YJ, Chang SC, Lin CY, Shiao MS. Regulation of bronchoalveolar lavage fluids cell function by the immunomodulatory agents from Cordyceps sinensis. Life Sci 2001;68:1067-82.
104. Chiu JH. Cordyceps sinensis increases the expression of major histocompatibility complex class ii antigens on human hepatoma cell line HA227/VGH Cells. Am J Chin Med 1998;26:159-70.
105. Kuo YC, Tsai WJ, Shiao MS, Chen CF, Lin CY. Cordyceps sinensis as an immunomodulatory agent. Am J Chin Med 1996;24:111-25.
106. Tang J, Tian D, Liu G. Immunosuppressive effect of Cordyceps CS-4 on human monocyte-derived dendritic cells in vitro. Am J Chin Med 2010;38:961-72.
107. Li Y, Xue WJ, Tian PX, Ding XM, Yan H, Pan XM, et al. Clinical Application of Cordyceps sinensis on Immunosuppressive Therapy in Renal Transplantation. Transplant Proc 2009;41:1565-9.
108. Choi JW, Ra KS, Kim SY, Yoon TJ, Yu KW, Shin KS, et al. Enhancement of anti-complementary and radical scavenging activities in the submerged culture of Cordyceps sinensis by addition of citrus peel. Bioresearch Technol 2010;101:6028-34.
109. Ji NF, Yao LS, Li Y, He W, Yi KS, Huang M. Polysaccharide of Cordyceps sinensis enhances cisplatin cytotoxicity in non-small cell lung cancer H157 cell line. Integr Cancer Ther 2011;10:359-67.
110. Hao L, Wang Q, Kobayashi M, Tamasada M, Wang HJ. Effectiveness of Cordyceps sinensis alone or in combination with chemotherapy in patients with non-small cell lung cancer. Biotherapy 2008;22:345-9.
111. Hao L, Wang Q, Wang B, Wang HJ. Clinical observation of Cordyceps combined with NP regimen in treatment of advanced non-small cell lung cancer. J Dalian Med Univ 2007;29:563-5.
112. Rao YK, Fang SH, Tzeng YM. Evaluation of the anti-inflammatory and anti-proliferation tumoral cells activities of Antrodia camphorata, Cordyceps sinensis, and Cinnamomum osmophloeum bark extracts. J Ethnopharmacol 2007;114:78-85.
113. Kuo YC, Lin CY, Tsai WJ, Wu CL, Chen CF, Shiao MS. Growth inhibitors
against tumor cells in *Cordyceps sinensis* other than cordycepin and polysaccharides. Cancer Invest 1994;12:611-5.

114. Jordan JL, Nowak A, Lee TD. Activation of innate immunity to reduce lung metastases in breast cancer. Cancer Immunol Immunother 2010;59:789-97.

115. Kubo E, Yoshikawa N, Kunitomo M, Katagata S, Shinozuka K, Nakamura K. Inhibitory effect of *Cordyceps sinensis* on experimental hepatic metastasis of melanoma by suppressing tumor cell invasion. Anticancer Res 2010;30:3429-33.

116. Wu YY, Zhang QX, Leung PH. Inhibitory effects of ethyl acetate extract of *Cordyceps sinensis* mycelium on various cancer cells in culture and B16 melanoma in C57BL/6 mice. Phytomedicine 2007;14:43-9.

117. Nakamura K, Yamaguchi Y, Katagata S, Kwon YM, Shinozuka K, Kunitomo M. Inhibitory effect of *Cordyceps sinensis* on spontaneous liver metastasis of Lewis lung carcinoma and B16 melanoma cells in syngeneic mice. Jpn J Pharmacol 1999;79:335-41.

118. Liu Z, Li P, Zhao D, Tang H, Guo J. Anti-inflammation effects of *Cordyceps sinensis* mycelium in focal cerebral ischemic injury rats. Inflammation 2011;34:639-44.

119. Li CY, Chiang CS, Tsai ML, Hseu RS, Shu WY, Chuang CY, et al. Two-sided effect of *Cordyceps sinensis* on dendritic cells in different physiological stages. J Leukoc Biol 2009;85:987-95.

120. Chou YL, Lin CY. The extract of *Cordyceps sinensis* inhibited airway inflammation by blocking NF-κB activity. Inflammation 2012;35:985-93.

121. Dong CH, Yao YJ. *In vitro* evaluation of antioxidant activities of aqueous extracts from natural and cultured mycelia of *Cordyceps sinensis*. Lebenswiss Technol 2008;41:669-77.

122. Li SP, Li P, Dong TTX, Tsim KW. Anti-oxidation activity of different types of natural *Cordyceps sinensis* and cultured *Cordyceps* mycelia. Phytomedicine 2001;8:207-12.

123. Li SP, Su ZR, Dong TTX, Tsim KW. The fruiting body and its caterpillar host of *Cordyceps sinensis* show close resemblance in main constituents and anti-oxidation activity. Phytomedicine 2002;9:319-24.

124. Zhang L, Chen SZ, Liu SS. Prosecutible function of *Cordyceps sinensis* extracts for hepatic mitochondrial oxidative injuries in diabetic mice. Chin J Clin Rehabil 2006;10:132-4.

125. Hu Z, Ye M, Xia L, Tu W, Li L, Zou G. Purification and characterization of an antibacterial protein from the cultured mycelia of *Cordyceps sinensis*. Wuhan Da Xue Xue Bao Zi Ran Ke Xue Ban 2006;11:709-14.

126. Kuo CF, Chen CC, Luo YH, Huang RY, Chuang WJ, Sheu CC, et al. *Cordyceps sinensis* mycelium protects mice from group A Streptococcal infection. J Med Microbiol 2005;54:795-802.

127. Wang BS, Lee CP, Chen ZT, Yu HM, Duh PD. Comparison of the hepatoprotective activity between cultured *Cordyceps militaris* and natural *Cordyceps sinensis*. J Funct Foods 2012;4:489-95.

128. Ko WS, Hsu SL, Chyau CC, Chen KC, Peng RY. Compound *Cordyceps* TCM-700C exhibits potent hepatoprotective capability in animal model. Fitoterapia 2010;81:1-7.

129. Jung SH, Lee YS, Lim SS, Kim YS, Lee S, Shin KH. Hepatoprotective and antioxidant capacities of *Paeoniae japonica* and *Cordyceps sinensis* in rats with CCl₄-induced hepatic injury. Korean J Hortic Sci 2009;27:668-72.

130. Li FH, Liu P, Xiong WG, Xu GF. Effects of *Cordyceps sinensis* on dimethylthiourea-induced liver fibrosis in rats. Zhong Xi Yi Jie He Xue Bao 2006;4:514-7.

131. Liu YK, Shen W. Inhibitive effect of *Cordyceps sinensis* on experimental hepatic fibrosis and its possible mechanism. World J Gastroenterol 2003;9:529-33.

132. Manabe N, Azuma Y, Sugimoto M, Uchio K, Miyamoto M, Taketomo N, et al. Effects of the mycelial extract of cultured *Cordyceps sinensis* on *in vivo* hepatic energy metabolism and blood flow in dietary hypoferric anaemic mice. Br J Nutr 2000;83:197-204.

133. Manabe N, Sugimoto M, Azuma Y, Taketomo N, Yamashita A, Tsuibo H, et al. Effects of the mycelial extract of cultured *Cordyceps sinensis* on *in vivo* hepatic energy metabolism in the mouse. Jpn J Pharmacol 1996;70:85-8.

134. Zhong F, Liu X, Zhou Q, Hao X, Lu Y, Guo S, et al. ¹H NMR spectroscopy analysis of metabolites in the kidneys provides new insight into pathophysiological mechanisms: Applications for treatment with *Cordyceps sinensis*. Nephrol Dial Transplant 2012;27:556-65.

135. Yu H, Zhou Q, Huang R, Yuan M, Ao X, Yang J. Effect of *Cordyceps sinensis* on the expression of HIF-1α and NGAL in rats with renal ischemia-reperfusion injury. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2012;37:57-68.

136. Wu R, Zhou Q, Lin S, Ao X, Chen X, Yang J. Effect of *Cordyceps sinensis* on the expression of ICAM-1 and VCAM-1 in the kidney of spontaneously hypertensive rats. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2010;35:152-8.

137. Song LQ, Si-Ming Y, Xiao-Peng M, Li-Xia J. The protective effects of *Cordyceps sinensis* extract on extracellular matrix accumulation of glomerular sclerosis in rats. Afr J Pharm Pharmac 2010;4:471-8.

138. Zhao X, Li L. *Cordyceps sinensis* in protection of the kidney from cyclosporine A nephrotoxicity. Zhonghua Yi Xue Za Zhi 1993;73:410-2, 447.

139. Wang Y, Yin HP, Chen T, Wang M. Preliminary structural identification and protection on renal cell injury of acidic polysaccharide from *Cordyceps sinensis*. J China Pharm Univ 2009;40:559-64.

140. Zhang XL, Bi-Cheng L, Al-Assaf S, Phillips GO, Phillips AO. *Cordyceps sinensis* decreases TGF-β1 dependent epithelial to mesenchymal transdifferentiation and attenuates renal fibrosis. Food Hydrocoll 2012;28:200-12.

141. Lin CY, Ku FM, Kuo YC, Chen CF, Chen WP, Chen A, et al. Inhibition of activated human mesangial cell proliferation by the natural product of *Cordyceps sinensis* (H1-A): An implication for treatment of iga mesangial nephropathy. Transl Res 1999;133:55-63.

142. Guo SM, Zhong F, Zhou Q, Lu Y, Hao X, Wang WM, et al. Renal protective effect of *Cordyceps sinensis* on 5/6 nephrectomy-induced renal fibrosis in rats. J Shanghai Jiaotong Univ 2012;32:1-8.

143. Kan WC, Wang HY, Chien CC, Li SL, Chen YC, Chang LH, et al. Effects of extract from solid-state fermented *Cordyceps sinensis* on type 2 diabetes mellitus. Evid Based Complement Alternat Med 2012;1:1-10.

144. El Ashry FE, Mahmoud MF, El Maraghy NN, Ahmed AF. Effect of *Cordyceps sinensis* and taurine either alone or in combination on streptozotocin induced diabetes. Food Chem Toxicol 2012;50:1159-65.

145. Guo J, Li C, Wang J, Liu Y, Zhang J. Vanadium-enriched *Cordyceps sinensis*, a contemporary treatment approach to both diabetes and depression in rats. Evid Based Complement Alternat Med 2011;2011:450316.

146. Guo JY, Han CC, Liu YM. A contemporary treatment approach to both diabetes and depression by *Cordyceps sinensis*, rich in vanadium. Evid Based Complement Alternat Med 2010;7:387-9.

147. Lo HC, Hsu TH, Tu ST, Lin KC. Anti-hyperglycemic activity of natural and fermented *Cordyceps sinensis* in rats with diabetes induced by nicotinamide and streptozotocin. Am J Chin Med 2006;34:819-32.

148. Lo HC, Tu ST, Lin KC, Lin SC. The anti-hyperglycemic activity of the fruiting body of *Cordyceps* in diabetic rats induced by nicotinamide and streptozotocin. Life Sci 2004;74:2897-908.

149. Wang NN, Wang YJ, Zhang X. Effects of *Cordyceps sinensis* on blood glucose, plasma insulin, histology of liver and kidney in rats. Chin Pharm J 2003;38:924-6.

150. Balon TW, Jasman AP, Zhu JS. A fermentation product of *Cordyceps sinensis* increases whole-body insulin sensitivity in rats. J Altern Complement Med 2002;8:315-23.

151. Ji H, Tu HH, Li NS, Liu GQ. Study on hypoglycemic activity of alkaline extract from cultural mycelium of *Cordyceps sinensis*. Chin Pharmacol Bull 1993;9:386-9.

152. Koh JJ, Kim JM, Chang UJ, Suh HJ. Hypocholesterolemic effect of hot-water extract from mycelia of *Cordyceps sinensis*. Biol Pharm Bull 2003;26:847-7.
Cordyceps sinensis on raised serum lipid peroxide levels and aortic cholesterol deposition in atherosclerotic mice. Phtyoother Res 2000;14:650-2.

155. Zhao Y. Inhibitory effects of alcoholic extract of Cordyceps sinensis on abdominal aortic thrombus formation in rabbits. Zhonghua Yi Xue Za Zhi 1991;71:612-5,642.

156. Chiu WF, Chang PC, Chou CJ, Chen CF. Protein constituent contributes to the hypotensive and vasorelaxant activities of Cordyceps sinensis. Life Sci 2000;66:1369-76.

157. Chen M, Cheung FW, Chan MH, Hui PK, Ip SP, Ling YH, et al. Protective roles of Cordyceps on lung fibrosis in cellular and rat models. J Ethnopharmacol 2012;143:448-54.

158. Zhang YS, Feng YZ, Cao ZF, Gu ZL, Yang QY, Yang XT, et al. Effect of Cordyceps sinensis on Panax notoginseng compound extracts on Bleomycin-induced pulmonary fibrosis in rats and its mechanisms. Chin Tradit Herb Drugs 2011;42:1766-72.

159. Xu H, Li S, Lin Y, Liu R, Gu Y, Liao D. Effectiveness of cultured Cordyceps sinensis combined with glucocorticosteroid on pulmonary fibrosis induced by bleomycin in rats. Zhongguo Zhong Yao Za Zhi 2011;36:2265-70.

160. Lin XX, Xie QM, Shen WH, Chen Y. Effects of fermented Cordyceps powder on pulmonary function in sensitized guinea pigs and airway inflammation in sensitized rats. Zhongguo Zhong Yao Za Zhi 2001;26:624-5.

161. Wong WC, Wu JY, Benzie IF. Photoprotective potential of Cordyceps polysaccharides against ultraviolet B radiation-induced DNA damage to human skin cells. Br J Dermatol 2011;164:980-6.

162. Lin CC, Pumsangwan G, Koo MM, Huang HB, Lee MS. Radiation protective effects of Cordyceps sinensis in blood cells. Tzu Chi Med J 2007;19:226-32.

163. Liu WC, Wang SC, Tsai ML, Chen MC, Wang YC, Hong JH, et al. Protection against radiation-induced bone marrow and intestinal injuries by Cordyceps sinensis, a Chinese herbal medicine. Radiat Res 2006;166:900-7.

164. Nishizawa K, Torii K, Kawasaki A, Ito M, Terashiba K, et al. Antidepressant-like effect of Cordyceps sinensis in the mouse tail suspension test. Biol Pharm Bull 2007;30:1758-62.

165. Morikubo K, Uchida M, Kume A, Tsunoo H, Tajima T, Nagata A. Effect of a mixture of mycelial extract of cultured Cordyceps sinensis and Ayamurasaki anthocyanin on the mental condition of middle-aged people. Jpn Pharmacol Ther 2005;33:729-34.

166. Qi W, Wang PJ, Guo WJ, Yan YB, Zhang Y, Lei W. The mechanism of Cordyceps sinensis and strontium in prevention of osteoporosis in rats. Biol Trace Elem Res 2011;143:302-9.

167. Liu Z, Li P, Zhao D, Tang H, Guo J. Protective effect of extract of Cordyceps sinensis in middle cerebral artery occlusion-induced focal cerebral ischemia in rats. Behav Brain Funct 2010;6:61.

168. Marchbank T, Ojobo E, Playford CJ, Playford RJ. Reparative properties of the traditional Chinese medicine Cordyceps sinensis (Chinese caterpillar mushroom) using HT29 cell culture and rat gastric damage models of injury. Br J Nutr 2011;105:1303-10.

169. Kumar R, Neel PS, Singh B, Ilavazhagan G, Bhargava K, Sathy NK. Cordyceps sinensis promotes exercise endurance capacity of rats by activating skeletal muscle metabolic regulators. J Ethnopharmacol 2011;136:260-6.

170. Nagata A, Tajima T, Uchida M. Supplemental anti-fatigue effects of Cordyceps sinensis (Tochu-Kaso) extract powder during three stepwise exercise of human. Jpn J Phys Fitness Sports Med 2006;55:145-51.

171. Sun W, Yu J, Shi YM, Zhang H, Wang Y, Wu BB. Effects of Cordyceps extract on cytokines and transcription factors in peripheral blood mononuclear cells of asthmatic children during remission stage. Zhong Xi Yi Jie He Xue Bao 2010;8:341-6.

172. Gong MF, Xu JP, Chu ZY, Luan J. Effect of Cordyceps sinensis spornacor on learning-memory in mice. Zhong Yao Cai 2011;34:1403-5.

173. Chen YC, Huang BM. Regulatory mechanisms of Cordyceps sinensis on steroidogenesis in MA-10 mouse Leydig tumors cells. Biosci Biotechnol Biochem 2010;74:1855-9.
195. Lei N, Du SS, Ni XM, Zhang WS, Guo ER, Li Q. Determination of nucleosides in natural *Cordyceps sinensis* and cultured *Cordyceps* by RP-HPLC. Chin Pharm J 2006;41:948-51.

196. Ikeda R, Nishimura M, Sun Y, Wada M, Nakashima K. Simple HPLC-UV determination of nucleosides and its application to the authentication of *Cordyceps* and its allies. Biomed Chromatogr 2008;22:630-6.

197. Li J, Feng CQ, Ni XM, Zhang WS. Determination of nucleosides of natural *Cordyceps sinensis* in Qinghai Province by capillary electrophoresis. Chin Pharm J 2008;43:1105-7.

198. Huang L, Li Q, Chen Y, Wang X, Zhou X. Determination and analysis of cordycepin and adenosine in the products of *Cordyceps* spp. Afr J Microbiol Res 2009;3:957-61.

199. Yang FQ, Ge L, Yong JW, Tan SN, Li SP. Determination of nucleosides and nucleobases in different species of *Cordyceps* by capillary electrophoresis-mass spectrometry. J Pharm Biomed Anal 2009;50:307-14.

200. Meena H, Mohsin M, Pandey HK, Negi PS, Ahmed Z. Estimation of cordycepin by improved HPLC method in the natural and cultured mycelia of high medicinal value Himalayan entomogenous fungus *Cordyceps sinensis*. Electron Environ Agric Food Chem 2010;9:1598-603.

201. Varshney VK, Pandey A, Kumar A, Rathod D, Kannojia P. Chemical screening and identification of high cordycepin containing cultured isolate(s) of medicinal chinese caterpillar mushroom, *Ophiocordyceps sinensis* (Berk.) G.H. Sung et al. Int J Med Mushrooms 2011;13:327-33.

202. Li Y, Wang XL, Jiao L, Jiang Y, Li H, Jiang SP, et al. A survey of the geographic distribution of *Ophiocordyceps sinensis*. J Microbiol 2011;49:913-9.

203. Lim L, Lee C, Chang E. Optimization of solid state culture conditions for the production of adenosine, cordycepin, and D-mannitol in fruiting bodies of medicinal caterpillar fungus *Cordyceps militaris* (L.:Fr.) Link (Ascomycetes). Int J Med Mushrooms 2012;14:181-7.

204. Dong CH, Yao YJ. Comparison of some metabolites among cultured mycelia of medicinal fungus, *Ophiocordyceps sinensis* (Ascomycetes) from different geographical regions. Int J Med Mushrooms 2010;12:287-97.

205. Dong JZ, Lei C, Ai XR, Wang Y. Selenium enrichment on *Cordyceps militaris* link and analysis on its main active components. Appl Biochem Biotechnol 2012;166:1215-24.

206. Xiao JH, Xiao DM, Xiong Q, Liang QZ, Zhong JJ. Optimum extraction and high-throughput detection of cordycepic acid from medicinal macrofungi *Cordyceps jiangxiensis*, *Cordyceps taii* and *Cordyceps* gymnii. J Food Agric Environ 2009;7:328-33.

207. Chen LC, Hseu RS, Guo JH. Determination of ergosterol and its derivatives in *Cordyceps sinensis*-associated products by high performance liquid chromatography and liquid chromatography-mass spectrometry. Chin J Anal Chem 2011;39:1380-6.

208. Yuan JP, Wang JH, Liu X, Kuang HC, Zhao SY. Simultaneous determination of free ergosterol and ergosterol esters in *Cordyceps sinensis* by HPLC. Food Chem 2007;105:1755-9.

209. Matsuda H, Akaki J, Nakamura S, Okazaki Y, Kojima H, Tamesada M, et al. Apoptosis-inducing effects of sterols from the dried powder of cultured *Cordyceps* and cultured *Cordyceps*, *Cordyceps* spp. Afr J Biotech 2011;103:1942-9.

210. Liu J, Cong Z, Liu X, Li Y, Liu J, Chen H, et al. Determination of free nucleosides and nucleobases in different species of *Cordyceps* by capillary electrophoresis-mass spectrometry. J Pharm Biomed Anal 2009;50:307-14.

211. Dong C, Yao Y. Isolation, characterization of melamin derived from *Ophiocordyceps sinensis*, an entomogenous fungus endemic to the Tibetan Plateau. J Biosci Bioeng 2012;113:474-9.

212. Liu YS, Wu JY. Effect of Tween 80 and pH on mycelial pellets and exopolysaccharide production in liquid culture of a medicinal fungus. J Ind Microbiol Biotechnol 2012;39:623-8.

213. Leung PH, Wu JY. Effects of ammonium feeding on the production of bioactive metabolites (cordycepin and exopolysaccharides) in mycelial culture of a *Cordyceps sinensis* fungus. J Appl Microbiol 2007;103:1942-9.

214. Cha SH, Lim JS, Yoon CS, Koh JH, Chang HI, Kim SW. Production ofmycelia and exo-biopolymer from molasses by *Cordyceps sinensis* in submerged culture. Bioresour Technol 2007;98:165-8.

215. Cha SH, Kim JC, Lim JS, Yoon CS, Koh JH, Chang HI, et al. Morphological characteristics of *Cordyceps sinensis* 16 and production of mycelia and exo-biopolymer from molasses in submerged culture. J Ind Engg Chem Chem 2006;12:115-20.

216. Hsieh C, Tsai MJ, Hsu TH, Chang DM, Lo CT. Medium optimization for polysaccharide production of *Cordyceps sinensis*. Appl Biochem Biotechnol 2005;120:145-57.

217. Dong CH, Yao YJ. Nutritional requirements of mycelial growth of *Cordyceps sinensis* in submerged culture. J Appl Microbiol 2005;99:483-92.

218. Barseghyan GS, Holliday JC, Price TC, Madison LM, Wassert SP. Growth and cultural-morphological characteristics of vegetative mycelia of medicinal caterpillar fungus *Ophiocordyceps sinensis* GH Sung et al. (Ascomycetes) Isolates from Tibetan Plateau (PR China). Int J Med Mushrooms 2011;13:565-81.

219. Shen LH, An YT, Yang QY, Yang XT, Shen X, Ding H. In vitro and in vivo study of *Hirsutella sinensis* extract on kidney injury. Chin Pharmacol Bull 2011;27:1537-40.

220. Chai JJ, Chen YP, Rui HL. Effects of *Hirsutella sinensis* on TGF-betall and Snail expressions and transdifferentiation of tubular epithelial-myofibroblast in renal tissue of rats with chronic arteriolosclerotic acid nephropathy. Zhongguo Zhong Xi Jie He Za Zhi 2009;29:325-9.

221. Shou QY, Fu HY, Chen FM, Zhou WM, Zhang CQ, Chen ML. Prevention of strain fermentation in *Hirsutella sinensis* on type 1 diabetes of non-obese diabetic mice. Chin Tradit Herb Drugs 2010;41:1311-5.

222. Cao X, Shen N, Li B, Zhang Y, Wang F, Yang Y, et al. Radiation mitigation effect of cultured mushroom fungus *Hirsutella sinensis* (CorImmune) isolated from a Chinese/Tibetan herbal preparation - *Cordyceps sinensis*. Int J Radiat Biol 2008;84:139-49.

223. Chen S, Yin D, Li L, Zha X, Shuen J, Zhamal C. Resources and distribution of *Cordyceps sinensis* in Naqu Tibet. Zhong Yao Cai 2000;23:673-5.

224. Zheng G, Yu J, Wu G, Liu X. Factors influencing the occurrence of *Ophiocordyceps* in Naqu Tibet. Zhong Yao Cai 2000;23:673-5.

225. Wang XL, Yao YJ. Host insect species of *Ophiocordyceps* sinensis: A review. ZooKeys 2011;127:43-59.

226. Hao JH, Cheng Z, Liang HH, Yang XL, Li S, Zhou TS, et al. Genetic differentiation and distributing pattern of *Cordyceps sinensis* in China revealed by rDNA ITS sequences. Chin Tradit Herb Drugs 2009;40:112-6.

227. Cheng Z, Geng Y, Liang H, Yang X, Li S, Zhu Y, et al. Phylogenetic relationships of host insects of *Cordyceps sinensis* inferred from mitochondrial cytochrome b sequences. Prog Nat Sci 2007;17:789-97.

228. Hawksworth DL. A new dawn for the naming of fungi: impacts of decisions made in Melbourne in July 2011 on the future publication and registration of fungal names. MycoKeys 2011;1:7-20.

229. McNeill J, Turland NJ. Major changes to the Code of Nomenclature-Melbourne, July 2011. Taxon 2011;60:1495-7.