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# The Artificial Cultivation of Medicinal Caterpillar Fungus, *Ophiocordyceps sinensis* (Ascomycetes): A Review

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**ABSTRACT:** Caterpillar fungus, *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*), is highly valued in China as a dietary supplement or tonic food and natural remedy. The combination of the fungus and dead insect has been used as a traditional Chinese medicine for centuries, and evidence shows its efficacy on immunomodulatory potentials. The price of *O. sinensis* has continued to increase over the last few years due to growing worldwide demand, driving research to determine methods of artificial cultivation to make *O. sinensis* a more affordable material for commercial trade. This study highlights many aspects of artificial cultivation of *O. sinensis*, including separation of the anamorph, culture of the mycelium, cultivation of the fruiting bodies, bioecological characteristics of the host insect, and two patterns of artificial cultivation. In addition, this review discusses the current state, limitations, remedies, and future prospects, aiming to draw researchers' attention to the new frontier of research needs in this context.

**KEY WORDS**: medicinal mushrooms, *Ophiocordyceps sinensis*, artificial cultivation

**ABBREVIATIONS: ITS,** internal transcribed spacers; **PDA,** potato dextrose agar; **SDA,** Sabouraud agar; **TCM,** traditional Chinese medicines

## I. INTRODUCTION

*Ophiocordyceps sinensis* (Berk.) G.H. Sung et al. (syn. *Cordyceps sinensis* (Berk.) Sacc., Hypocreales, Ophiocordycipitaceae, Ascomycetes)[1] is one of the most valued Chinese natural remedies, and it has been known and used as a medicine in China for over 300 years. In China, this fungus is called *Dong Chong Xia Cao* and the name is likely translated from the Tibetan term *Yartsa gunbu*, meaning "summer grass winter worm." This fungus was first recorded in Tibet by Nyamnyi Dorje in the late 15th century.[2] This species parasitizes larvae of *Thitarodes* (*Hepialus*) moths, which takes over the whole body and grows the fruiting body out of the head of the larvae. Currently, more than 50 species are considered as recognizable potential host species of *O. sinensis.*[3] *O. sinensis* was first introduced in Western society during the 17th century. In 1878, Saccardo named *Cordyceps* derived from China officially as *Cordyceps sinensis* (Berk.) Sacc.; however, this nomenclature has been changed to *Ophiocordyceps sinensis* (Berk.) G.H. Sung et al.[1] *O. sinensis* is grown in a very restricted habitat, and is usually found in prairie soil at an altitude of 3500–5000 m, mainly in provinces such as Sichuan, Qinghai, Yunnan, Gansu, and Tibet Autonomous Region in China. *O. sinensis* has also been recorded in Nepal, Bhutan, and India.[4]

*O. sinensis* has been described as an abundant resource of useful medicinal mushrooms with various bioactivities in traditional Chinese and Tibetan medicine, and it has been used extensively as a tonic and health supplement for patients with subhealth conditions, especially seniors, both in China and other Asian countries. Recently, with traditional Chinese medicines (TCM) growing in popularity, *O. sinensis* seems to have become increasingly popular and important in public and scientific communities. Many bioactive constituents have been reported, such as polysaccharides, mannitol, cordycepin, aminophenol, and ergosterol. A vast literature has demonstrated that the chemical constituents extracted from *O. sinensis* have various pharmacological actions, such as nephroprotective, hepatoprotective, and anti-inflammatory effects, antioxidant and antiapoptotic properties, as well as effects on asthma, diabetes, male erectile dysfunction, cough and cold, and so forth.[5,6] However, due to the scarcity of this resource and the immaturity of artificial cultivation, *O. sinensis* is unable to fully meet the demands of medical use.

In the early 1980s, many scientific institutes began studying the artificial cultivation of *O. sinensis* and some great achievements have been made. Due to the strict parasitism and the special geographical environment in which it grows, the output of natural *O. sinensis* cannot increasingly meet market demand and thus its price is unusually high. In recent years, natural *O. sinensis* has been excessively excavated, which leads to serious damage to *Cordyceps* resources and the environment. *Cordyceps* resources have significantly declined, rendering them unable to meet the demand for health care and medicinal use. As a result, investigation of the artificial cultivation of *O. sinensis* appears particularly significant. With the increasing interest in *O. sinensis* both for mycology and medicine, research is necessary to obtain an overview about the cultivation of this mushroom. Therefore, this article reviews many aspects of the artificial cultivation of *O. sinensis*, aiming to draw researchers' attention to the new frontier of research needs in this context.

## II. RESEARCH ON *OPHIOCORDYCEPS SINENSIS*

### A. Isolation of the Anamorph

The establishment of the anamorph of *O. sinensis* is of great importance for large-scale cultivation to meet the increasing demands for medicinal use and to ease exploitation of natural populations. The results of our literature survey illustrated that over 20 names in 13 different genera were shown to be related to the anamorph of *O. sinensis* or used for isolates from collections of the fungus (Table 1).[7] On the basis of previous nomenclature studies, eight anamorphic names were proposed as new, including six valid and two invalid names and four names that were mentioned as new species but lacked formal publication. Five isolates were given a generic name with no species identification. Three names were proven not to be anamorphs of *O. sinensis*, and the other names remain to be proved. Several independent molecular studies have suggested that *Hirsutella sinensis* Liu et al. is the anamorph of *O. sinensis*.

Liu et al.[8] used the ascospores, stromata, and endosclerotia of 14 samples of *O. sinensis* collected from Kangding, Sichuan Province, China, to isolate the anamorphic state of *O. sinensis*. The authors used 1% peptone potato dextrose agar (PDA) and reformative Sabouraud agar (SAB). Their results suggested that over 90% of the cultures were the same fungus at their conidium stages. This fungus was identified as *H. sinensis*, and was tested through numerous experiments such as a host of inocula, multipath and repeated continuous separation, and the isolation of ascospore. Mo et al.[9] isolated strains of *H. sinensis* from several fruiting bodies of *O. sinensis* collected in the Yunnan Deqin Baima Snow Mountain by amended methods. The process of ascospore microcycle conidiation was illustrated and taken as an evidence for determining their isolates as the anamorph of *O. sinensis*. The relationship between the teleomorph of *O. sinensis* and its presumed anamorph was investigated by an analysis of 5.8S and internal transcribed spacer (ITS) rDNA sequences.[10] The morphological and sequence data confirmed that *H. sinensis* is the anamorph of *O. sinensis*. Furthermore, Zhao et al.[11] and Li et al.[12] certified this conclusion via molecular biotechnology as well.

To isolate the anamorph of *O. sinensis*, aseptic bags sheathing the fruiting bodies are used to collect emitted ascospores, and an inoculating needle is then used to isolate and culture immediately or conserve ascospores at a temperature of 0–4°C after they are dried for reservation. In

**TABLE 1. The Reported Anamorphic Species Related to *Ophiocordyceps sinensis***

| Category | Nomenclature |
|---|---|
| Valid names | *Chrysosporium sinense* Liang |
| | *Hirsutella sinensis* Liu, Guo, Yu et Zeng |
| | *Paecilomyces sinensis* Chen, Xiao et Shi |
| | *Mortierella hepiali* Chen et Liu |
| | *Scytalidium hepiali* C. L. Li |
| | *Tolypocladium sinense* C. L. Li |
| | *Metarhizium anisopliae* (Metschn.) Sorokin |
| | *Paecilomyces hepiali* Chen et Dai |
| | *Sporothrix insectorum* de Hong et Evans |
| Invalid names or names should be synonyms | *Cephalosporium dongchongxiacae* |
| | *Cephalosporium sinensis* |
| | *Hirsutella hepialid* Chen et Shen |
| | *Synnematium sinensis* Yin, Shen |
| | *Paecilomyces lingi* |
| | *Verticillium sinensis* |
| Synonyms | *Cephalosporium acremonium* Corda = *Acremonium strictum* |
| | *Isaria farinose* (Holmsk.) Fr. = *Paecilomyces farinosus* |
| Names with no species identification | *Verticillium* sp. |
| | *Isaria* sp. |
| | *Stachybotrys* sp. |
| | *Scydalium* sp. |
| | *Cephalosporium* sp. |

addition, sterilized culture slides can also be used to collect emitted ascospores for isolation in a humid house. The ideal media for isolation and culture include S31 agar, glycerol meal peptone agar, and milk agar. Moreover, using 1% peptone PDA and SAB to isolate can achieve ideal results as well.[7]

## B. Culture of Mycelia

Reports about submerged cultivation of *O. sinensis* mycelia have long been available. Lu[13] investigated the culture medium, culture conditions, technological process, and equipment for the submerged cultivation of *O. sinensis*, and compared the chemical constituents of natural *O. sinensis* and mycelia cultured in this way. Their results suggested that the constituents of cultured mycelia were the same as those of natural *O. sinensis*. The liquid culture media of *O. sinensis* mycelia were optimized by means of orthogonal analysis.[14] The results showed that the optimal medium for the mycelia was 1.25% glucose, 1.25% sucrose, 0.02% peptone, 0.062 5% yeast powder, 0.025% $KH_2PO_4$, 0.012 5% $MgSO_4 \cdot 7H_2O$, 0.002 5% vitamin $B_1$, and natural pH (without debugging the pH) . In the cultural condition of 24°C and 192 h, the mycelia biomass reached 19.5 g/L, which was as 1.2–1.5 times the amount with the previous method. In addition, the optimal cultivation medium achieved by Shang et al.[15] by means of orthogonal analysis was composed of 20% potato, 0.08% beef extract, 0.2% peptone, 0.15% $KH_2PO_4$, 0.15% $MgSO_4 \cdot 7H_2O$, 1.5% sucrose, 2.5% glucose, and natural pH. In the cultural condition of 23°C, 130 r/min, and 4 d, the mycelia biomass could gain

19.5 g/L, which was reported to be 2 times higher than that of the former optimization.

Liu et al.[16] studied the effect of flask culture and nitrogen source on polysaccharide content and mycelium weight in culture mycelium using the phenol-sulphuric acid method. Their results showed that the polysaccharide content was inhibited by the flask culture, but mycelium weight was increased during 0–16 days of shaking. The content examination of polysaccharides and mycelium weight by different nitrogen sources showed that $NH_4NO_3$ was the appropriate source. The hyphal growth of *O. sinensis* strains from three different origins cultured in different culture media was studied.[17] The results showed that there were discrepancies among different culture media, hyphal germ initiation time of different strains, diameters of hyphae at 40 days, and hypha morphology. At the same time, the growth hyphae in the optimal medium selected was 2–3 times faster than those reported in the media, and the hyphae were white, stout, and of better quality. Moreover, Liu and Cao[18] studied the solid fermentation of *O. sinensis* mycelium, and their results showed that through solid fermentation, the content of polysaccharide of cultured mycelium was more than that of natural *O. sinensis*, and the amino acid contents were near that of natural ones.

In summary, in large-scale production of mycelia, higher technical requirements are needed due to high energy consumptions, long production cycles, and increasing risk of contamination. Therefore, the majority of the current commercial preparations of *O. sinensis* sold are not the fermented products of *H. sinensis*. Consequently, it is vital and urgent to cultivate and domesticate industrial production strains that are fast growing and suitable for room temperature.

## III. RESEARCH OF HOST INSECTS

In 1965, Chu[19] first reported that the host insect of *O. sinensis* is *Hepialus armoricanus* Oberthür (syn. *Thitarodes armoricanus* Oberthür). Three new genera and 14 new species were then reported, and *Hepialus* were indicated to be the main host insects of *O. sinensis*.[20] To date, more than 50 species of *Thitarodes* have been discovered and identified as the host insects of *O. sinensis*.

### A. Species and Distribution

The genus *Thitarodes* are the main host insects of *O. sinensis*. To date, among the more than 50 species identified, 12 species were found in Sichuan, 14 in Tibet, 9 in Qinhai, 3 in Gansu, 2 in Heilongjiang, and 1 in Xinjiang. In addition, a few species of *Hepialiscus*, *Forkalus*, and *Bipectilus* were found to be related to the parasitism of *O. sinensis*. *Hepialus oblifurcus* Chu et Wang is the main host swift moth of *O. sinensis* collected in Kangding and Sichuan. *Hepialus baimaensis* Liang, *H. renzhiensis* Yang, *H. yulongensis* Liang, and *H. deqinensis* Liang are the main host insects of *O. sinensis* collected in Yunnan.[21]

The distribution of *Cordyceps* is cosmopolitan, including all terrestrial regions except Antarctica, with the height of known species diversity occurring in subtropical and tropical regions, especially East and Southeast Asia.[22–24] Yang et al.[25] reported that the Chinese *Hepialus* mainly occur in the alpine grasslands of Tibet, Qinghai, Yunnan, Sichuan, and Gansu (Table 2). While a small amount of them are scattered in the pastures of Xinjiang, Heilongjiang, and Inner Mongolia, nearly 95% of Chinese *Thitarodes* have a very narrow range of distribution and different species are usually known among different mountain ranges.[25] The vertical distribution of these lepidopterans ranges from the lowest elevation of 3000 m in southern areas and approximately 2500 m in northern areas to the highest elevation of 5100 m, with an optimal elevation range from 4000 m to 4800 m. The distributional range of *Thitarodes* is mainly affected by food, vegetation, soil structure, temperature, and humidity. However, due to changes in the global climate and ecological environment of the Tibetan Plateau in recent years, the distribution pattern of *O. sinensis* shows polarization in which large *O. sinensis* is distributed in the region above 4600 m in altitude, small and poor quality *O. sinensis* is distributed

**TABLE 2. Characters of Geographic and Ecological Distribution of *Ophiocordyceps sinensis* Host Insects**

| Distribution area | Common host insects | Altitude (m) | Vegetation type | Soil type |
|---|---|---|---|---|
| Sichuan | *Thitarodes armoricanus* Oberthür; *Hepialus gonggaensis* Fu et Huang; *H. kangdingensis* Chu et Wang; *H. kangdingroides* Chu et Wang; *H. sicuanus* Chu et Wang; *H. alticola* Oberthür, *H. nubifer* Lederer | 3000–5000 | Alpine and subalpine | Alpine grasslands |
| Yunnan | *H. yulongensis* Liang; *H. albipictus* Liang; *H. renzhiensis* Yang; *H. lijiangensis* Chu et Wang; *H. baimaensis* Liang; *H. deqinensis* Liang; *H. yunnanensis* Yang, Li et Shen; *H. zhongzhiensis* Liang; *Bipectilus yunnanensis* Chu et Wang | 3200–5200 | Alpine grasslands | Alpine grasslands |
| Tibet | *H. baqingensis* Yang et Jiang; *H. damxvngensis* Yang; *H. zhangmoensis* Chu et Wang; *H. jialangensis* Yang; *H. flavus* Chu et Wang; *H. zaliensis* Yang; *H. zhayuensis* Chu et Wang | 2200–5000 | Alpine grasslands | Alpine grasslands |
| Qinghai | *H. yushuensis* Chu et Wang; *H. oblifurcus* Chu et Wang; *H. guidera* Yan; *H. menyuanicus* Chu et Wang | 3400–5100 | Alpine grasslands and alpine shrub | Alpine grasslands |
| Gansu | *H. luquensis* Yang et Yang; *H. cingalatus* Yang et Zhang; *H. maquensis* Chu et Wang | 3000–3600 | Alpine grasslands | Subalpine grasslands |

in the region under 3600 m in altitude, and some species have been distributed in dark coniferous forest and alpine shrubs at low altitude.[26] The vegetation types in the distribution areas of *O. sinensis* are mainly alpine grasslands, subalpine grasslands, and alpine shrub, and the majority of the soil types are alpine grasslands and subalpine grasslands.[27] This makes the introduction of host insects of *O. sinensis* from the same altitude or different altitudes possible in the process of artificial cultivation.

## B. Biology

Chen et al.[28] reported the biological characteristics of *H. armoricanus* for the first time in 1973. Research on biological properties of *O. sinensis* host insects was then conducted relatively systematically.[29–32] The *Thitarodes* moth, passing through the stages of being an egg, larva, pupa, and imago, is a holometabolous insect that lives in soil most of its life at the larva stage. The biological characteristics are summarized as follows: 1) Eggs incubate at a temperature >10°C under moisture-keeping conditions. The incubation period is 30–40 days in Sichuan, Qinghai, Yunnan, and Gansu, and approximately 70 days under natural conditions in Nagqu, Tibet. The hatching rate of this insect is between 70% and 90% around the distribution areas, and the color of egg shells changes from white to black over the hatching process after oviposition. 2) Larvae mostly live in soil at a depth of approximately 15 cm, presenting an aggregating distribution. Newly hatched larvae are milk white, and body lengths are approximately 2 mm. The head capsules of mature larvae are light red, the body is beige, and body lengths are approximately 3–4 cm. The survival rate of larvae under natural conditions is usually <10% because of the attack of natural enemies. Larval instars are aged 6–8 years in different distribution areas, and the development durations are diverse according to instar. 3) Pupa occurs in June and July, and the pupal stage is approximately 30 days, varying according to different types, areas, and altitudes. When the temperature is 10–15°C and humidity is 40%–50%, the pupal period increases to approximately 40 days. While molting for the last time, mature larva becomes early pupa, which is milk white, and the color then gradually becomes light yellow, tawny, and puce. 4) Generally, the sex ratio of female *Thitarodes* moths is higher than that of males, and calling and mating activity is at 6 to 9:30 p.m., while the copulate climax of *Hepialus gonggaensis* is at approximately 10:30 a.m. that day. Females only mate once through their whole lives, but the males usually mate 2–3 times. The time interval between mating and oviposition is 5–40 min, and mating is beneficial to the females' oviposition. Female moths spawn approximately 5–45 eggs each time, and then die shortly after spawning; however, the life span of a mature female is longer than that of a male. Furthermore, males have phototaxis while females rarely have this feature, and all imagoes do not eat.

### C. Artificial Rearing

The food, temperature, humidity, and disease aspects of artificial rearing of the host insects of *O. sinensis* have been investigated. Huang et al.[33] investigated the feeding habits of *Hepialus* in Kangding, and their results suggested that the major foods of larvae are tender roots and buds of plants of Polygonaceae such as *Polygonum viviparum* L., *P. sphaerostachyum* Meisn., and *P. capitatum* Ham ex D. Don. Other plants in nine different families (e.g., Ranunculaceae, Juncaceae, and Cyperaceae) are foods of the larvae, so the feeding habit of the *Thitarodes* moth is diverse. Yu[34] reported that host insects of *O. sinensis* have been successfully trained on a large scale at a low altitude indoor environment, and could finish a cycle of generation in 1 year with large larvae. However, no further information was reported, and data about food were not revealed. Malt, millet sprout, and carrot are efficacious foods in indoor cultivation as well.

In the process of artificial cultivation, different insect states require temperature and humidity differently. Favorable temperatures are 15–20°C for incubation and 10–18°C for the larvae period. Temperatures that are too high can cause mutual killing and death, while feeding activities will reduce and growth will retard at lower temperatures. The temperature for the pupal period should be higher than that of the larvae period, which could be controlled at approximately 20°C. Humidity should be maintained at 36%–45% in larval phase, and the soil moisture content is better kept at 42%–45%.

Diseases in the cultivation process are mainly caused by fungi, such as green and white muscardine, species of genus *Paecilomyces*.[35–37] Nematodes, mites, and a smaller insects acting as transmitting vectors are also harmful to the rearing. To ensure livability of larvae, the food and rearing location should be disinfected and sterilized at regular intervals and the soil used for rearing should be exposed in the blazing sun for 1–2 hours.

## IV. ARTIFICIAL CULTIVATION OF FRUITING BODIES

Because previous work was mainly focused on the anamorphic fungi related to *O. sinensis*, reports about the cultivation of fruiting bodies were rare, and only a few papers are available. Shen Nanying isolated 35 strains through the ascospore, sclerotium, stroma, and hyphae of the insect *in vitro*, and then put them in 23 different types of culture media for experimentation. During culture indoors with light and at the temperature of 8–17°C, one of the H1 strains in S31 media, which was rich in nutrients, grew into fruiting bodies with mature perithecium after 7 months. These results showed that several factors should be at least taken into consideration if fruiting bodies of *O. sinensis* are to be successfully cultivated: heredity of strains, suitable culture temperature, right amount of light, and culture medium with plenty of biological active substances and organic nitrogen sources.[38] The former Sichuan TCM Institute (currently the Chongqing Academy of Chinese Materia Medica) also achieved the cultivation of *O. sinensis*. However, because of the high cost and low stability, commercial production has not yet been carried out.[39] Great progress on the cultivation of *O. sinensis* was reported by Liu Xin at the Tibetan Plateau Characteristic Resource Science Workstation of Sun Yat-Sen University in 2010.[40] The station, which is placed in Nyingchi Prefecture, Tibet, at an altitude of 4156 m, investigated the climate, soil, vegetation, microorganism, insect community of the optimum area, and biological characteristics. This research led to over 10 scientific breakthroughs, as well as authorization of 12 Chinese patents.

Currently, the research methodology in laboratory is that *T. armoricanus* larvae are inoculated with mature fruiting bodies or cultured strains, and then the infected larvae are reared in well-drained and moist pits with plants which are larvae's favorite foods. The larvae are collected from natrual fields or cultured, and all the experiments are done under the field conditions of producing areas of *O. sinensis*. In summary, to successfully cultivate *O. sinensis*, virulent asexual spores must be cultivated in the first place. Meanwhile, issues such as how to detect the quality of conidiospores and how to produce a large number of spores also require immediate solutions.

## V. TWO CULTIVATION PATTERNS

Current artificial cultivation of *O. sinensis* has two patterns: complete artificial cultivation and semi-natural cultivation. In complete artificial cultivation, reared larvae are inoculated with cultured strains and the infected larvae are then fed indoors. After 1–2 years, *O. sinensis* can be harvested. All processes of this pattern are conducted under artificial conditions. Although the complete artificial pattern can improve the survival rate of larvae and shorten the growth period of *O. sinensis* compared to natural *O. sinensis*, the cultivation cost is too high. With regard to semi-natural cultivation, the infected larvae are released to natural habitats, allowing them to grow freely. After 3–5 years, *O. sinensis* can be harvested in the releasing areas. The semi-natural cultivation pattern not only makes the most of natural ecological resources but also reduces the cultivation cost significantly, although the cultivation period is too long. Due to factors such as bad weather and natural enemies, the survival rate of released larvae is unstable, which are some limitations to cultivation. The commercial production of these two cultivation patterns has not yet been carried out.

## VI. SUBSTITUTES OF *OPHIOCORDYCEPS SINENSIS*

On account of the immaturity of commercial artificial cultivation, identifying substitutes of *O. sinensis* seems to be an effective way to address the issues of resource scarcity and supply-demand contradiction in the natural remedy market. Related research has been conducted worldwide. Experimental evidence and scientific explanations indicate that the chemical constituents of *Cordyceps militaris* (L.:Fr.) Link are approximately the same as those of *O. sinensis*.[41] Compared with *O. sinensis*, the artificial cultivation of *C. militaris*, which produces cordycepin and has similar pharmacological activity to *O. sinensis*, is easier and was successfully achieved in the early 1980s; multiproduct batch manufacturing has also been achieved. Now the mycelia can grow in rice medium and produce fruit bodies. The process of producing *C. militaris* fruit bodies, which is similar to that of other cultivated edible mushrooms, can be divided into two main stages. The first stage involves the preparation of the fruiting culture, stock culture, mother spawn, and planting spawn, while the second stage entails the preparation of growth substrates for mushroom cultivation.[42,43] Currently, there are many types of cultures in the cultivation of *C. militaris*, including storage culture, slant and plate culture, popular/indigenous culture, and special culture/laboratory culture; in addition, a number of solid and liquid media are used to culture *C. militaris*.[44] Commercial preparations of *O. sinensis* have also been reported, including CordyMax™ Cs-4, WH30$^+$, and Bailing capsules.[45–47]

## VII. CURRENT STATE AND EXTANT ISSUES

Due to environmental and ecological factors, the annual harvest of natural *O. sinensis* cannot increasingly meet worldwide demand. This situation has driven *O. sinensis* prices into an ever-increasing spiral over the last few years, propelling research to determine ways of cultivating *O. sinensis* to make it a more affordable material for commercial trade.[48] Reports on *O. sinensis* thus far are mainly concentrated on chemical constituents, biological activities, and pharmacology, yet the artificial cultivation is rarely reported. Although the artificial cultivation of *O. sinensis* has reportedly been achieved, it is not likely to reach commercial levels and many scientific and technical issues remain to be solved, such as the mechanisms and approaches of parasitizing and the screening of highly virulent strains. Overall, our challenge in the modern age is to scientifically unravel the claims and issues, such as research on biological screening, artificial cultivation of the fungus, better understanding of its status in natural habitats, and differences between the fungus and the insect components. Solutions of these issues are of great significance for reasonable and better use of *O. sinensis* and artificial cultivation.

## VIII. CONCLUSIONS

With the current "return to nature" theory, individuals are more willing to take natural medicines rather than the synthetic drugs. Natural remedies, such as medicinal mushrooms, can conquer life-threatening diseases with few side effects on human health. *O. sinensis* has been used as a traditional medicine in China for over 300 years, and it seems logical that there is quite likely some truth behind the myths. Although the commercial cultivation of *O. sinensis* has not been completely achieved, the highest cordycepin production now can be obtained in surface liquid culture using the *C. militaris* mutant.[49] Due to advances of science and technology, the pharmaceutical industries are able to maintain high output rates on low-cost materials with reasonable safety through innovation. Therefore, biometabolites extracted from medicinal mushrooms like *O. sinensis* will be the key future driving force in the realm of green pharmacology and pharmacognosy. We generally know only some of the wonders of *O. sinensis*, and it still has more in store for us. Only through scientific theories and technologies can industrialization and large-scale production be achieved, and then rational utilization and sustainable development of *O. sinensis* resources can be well conducted.

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