

Review articles

Cordyceps fungi as natural killers, new hopes for Medicine and biological control factors

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ABSTRACT. The *Cordyceps* genus includes many species of fungi, most of which are endoparasitoids on arthropods. The distribution of these fungi is cosmopolitan, but many occur in regions such as Asia with a hot, humid climate. These pathogens of insect pests are promising candidates for use as biological control factors. Entomopathogenic fungi including the famous *Cordyceps sinensis* produce bioactive compounds. Lately *Cordyceps sinensis* was renamed *Ophiocordyceps sinensis*. This fungus has a long history as a medicinal fungus. It germinates in a living host, kills and mummifies the larva, and then grows from the body of the host. Is known in Tibet as the "winter worm, summer grass", or "Caterpillar fungus" (Yartsa gunbu). Collecting *Ophiocordyceps* has become an important source of money for local households in Nepal. *Ophiocordyceps sinensis* is cultivated as an anamorph for its medicinal and pharmaceutical properties in an artificial medium on an industrial scale. *Ophiocordyceps* compounds have immunostimulating properties and antitumor activity.

Key words: *Cordyceps*, entomopathogenic fungi, medical fungi, cordycepin

Introduction

The *Cordyceps* genus includes many identified species of fungi [1–3]. All *Cordyceps* species are entomopathogenic, in that they are endoparasitic on arthropods, and some are parasitic on other fungi. These fungi belong to the division Ascomycota, class Sordariomycetes, order Hypocreales, Family Clavicipitaceae. The order Hypocreales includes fungi pathogenic to arthropods (AP) [4–8]. The distribution of these forest fungi is cosmopolitan. The greatest species diversity is found in subtropical and tropical regions like Asia with a hot and humid climate.

Some studies note the occurrence of *Cordyceps* in Poland and Slovakia, as well as the rest of Europe, although these are mainly pathogens of insect pests [3,8,9]. These species of *Cordyceps* are promising candidates for use as biological control factors. Many species of *Cordyceps* produce numerous biologically-active compounds, the most famous being *Cordyceps sinensis* [3,8,9]. Most compounds, particularly cordycepin – 3'deoxyadenosine, have been exploited for use in traditional and modern ethnomedicine, for the treatment of various diseases like diarrhea, headache, muscle pain and cancer [10–14].

Morphology and reproduction of *Cordyceps* fungi

Hypocrealean AP fungi may be poly- and pleomorphic. Their life cycle, may contain a meiotic (teleomorphic, perfect) stage and many mitotic (anamorphic, unperfect) stages. Both the teleomorph and anamorph forms may have different morphologies and receive individual Latin names [1,2,15–20].

Arthropod Pathogenic (AP) fungi produce a stroma (fruiting body) that erupts from the infected arthropod. The colour of the stroma may vary from orange to red or brown to black, depending on the species, and often produces a stipe, which serves to bring the spores away from the host, which is often buried in the soil or dead trees. The fertile region of the stroma is usually terminal and has a club-like or head-like appearance. Spores derived from sexual reproduction are produced internally inside sacs, or asci, housed in flask-shaped structures called perithecia. Ascospores and asci are microscopic structures, a single perithecium is smaller than half of millimeter in diameter, which collectively give the stroma a small blade-like shape [3,5,9,20–23]. Infection of the surface of the insect in winter leads to the formation of a fruiting body in summer ("winter worm, summer grass") followed by the spores becoming airborne. The elongated stroma may be cylindrical or branched and is often found bursting from the head of the host (Fig.1). The fruiting body, or ascocarp, bears many perithecia containing ascospores, which are infectious. Many *Cordyceps* species are able to grow on artificial media and some can be isolated just from soil [24–28].

Fig. 1. *Ophiocordyceps forquignonii*, stroma emerging from insect

Pathogenicity

Usually each species of the 1200 known AP [30,31] fungi attack only one species of host, or a group of related species, but collectively these fungi attack hosts from many orders, although these are mainly arthropods such as Lepidoptera [3,14,30,31]. The insect may become infected at various stages of development ranging from larvae and pupae to adult. Infection starts with the dispersion of fungus conidia on insect`s cuticle. The spores then adhere to the exoskeleton of the insect and germination begins within a few hours [3,31]. To protect the fungus from ultraviolet environmental radiation, protective enzymes like superoxide dismutase (SOD) and peroxidases are secreted by the conidia, as well as other hydrolytic enzymes such as proteases, chitinases and lipases during germination [31–35]. The conidia start producing a germ tube with an appressorium, a flattened disc-like structure on the end. The appressorium penetrates the exoskeleton by a combination of mechanical pressure and the production of enzymes, allowing it to enter the haemocoel of the insect. Once inside the host, the fungus grows, resulting in the death of the host. During growth, the fungus produces toxic

Fig. 2. *Ophiocordyceps gracilis*, stroma emerging from insect larva

secondary metabolites with insecticidal properties. The fungal hyphae then feed on the insect, growing throughout all visceral organs. Finally, the tissue of the host is replaced with a fungal mycelium, and only the host exocuticula supports the fungal stroma. The fruiting body, consisting of the stroma and ascocarp, arising from the corpses of the victims presents a most unusual appearance [3,5,31–35] (Fig. 2).

Aberrant behavior of the host after *Cordyceps* infection

Infection often results in aberrant behavior of the host (Zombi ant), such as causing the host to climb before death [23,31,37]. Near the time of death, *Cordyceps* grows in a filamentous stage producing a mass of mycelium, the endosclerotium. Infected ants (*Camponotus leonardi*) living in the trees of the tropical rainforest will climb down from its normal habitat and bite down, with a "death grip", on a leaf and then die [23,37]. The death grip occurs in very precise locations on the leaf: the ants bite down on the underside of a leaf, on a vein, then move to the north side of the plant and bite down on a leaf above the ground, with the leaf being in an environment with high humidity [23,31,37]. After the death of the ant, the fungus produces hyphae inside the corpse, with the hyphae erupting from the exoskeleton from a specific point at the back of the head after a few days. The fungus starts sexual reproduction. When the fungus releases spores, it creates an infectious "killing field" of about one square meter, below which ants or similar species may be infected [23,31,37].

Classification

For many years, the arthropod pathogenic (AP) fungi were classified in the genus *Cordyceps* in the family Clavicipitaceae [3,17]. This classification was based on the morphology of cylindrical asci and filiform ascospores that often separate into part-spores. A molecular investigation of DNA revealed that the famous *Cordyceps sinensis* is unrelated to the rest of the members of the genus. As a result, *Cordyceps sinensis* was renamed *Ophiocordyceps sinensis* and placed in a new family, the Ophiocordycipitaceae. The latest phylogenetic studies have rejected the monophyly of both *Cordyceps* and Clavicipitaceae, however, and three clavicipitaceous clades were created: Clavicipitaceae s.s., Cordycipitaceae and Ophiocordycipitaceae [3]. *Cordyceps sensu lato* was divided into four genera (*Cordyceps s.s.*, *Elaphocordyceps*, *Metacordyceps* and *Ophiocordyceps*) based on DNA analysis of five gene regions: SSU rDNA, LSU rDNA, TEF1, RPB1 and RPB2 [3,15,21,38–48].

Cordyceps s.s. consists of species that produce soft fleshy stromata (e.g., *C. militaris*). Most species attack the larvae and pupae of arthropods [3]. *Elaphocordyceps* includes all species that infect *Elaphomyces* and any closely-related species that attack the nymphs of cicadas [3]. The stromatal color of *Metacordyceps* ranges from white to lilac, purple or green, and the darker pigments are almost black in dried specimens. The texture of the stroma is fibrous and the hosts are almost always buried in soil. *Ophiocordyceps* is the largest genus of arthropod pathogenic fungi [3]. The majority of species are darkly pigmented and occur on immature stages of hosts buried in soil or in decaying wood. However, exceptions exist for species that attack adult stages of hosts. *Ophiocordyceps unilateralis* is common on adult ants and occurs on the undersides of leaves, and *O. sphecocephala* is common on adult wasps and is found in leaf litter [3]. Their life cycle may comprise more than one spore-producing stage. Both the teleomorph and anamorph may receive separate Latin names [3,15,21,38–48].

Below are some examples of different names for pleomorphic life cycles among the hypocrealean AP fungi (http://cordyceps.us) [3].

Teleomorph	**Anamorph**
Cordyceps militaris	*Lecanicillium*
Metacordyceps taii	*Metarhizium anisopliae*
	Tolypocladium inflatum
Elaphocordyceps subsessilis	*Hirsutella sinensis*

History of *Ophiocordyceps* production

Several species of *Cordyceps* are considered as medicinal mushrooms in classical Asian pharmacologies such as Traditional Chinese Medicine (TCM) and Traditional Tibetan Medicine (TTM) [3,10,26–28,48]. *Ophiocordyceps sinensis* (earlier *Cordyceps sinensis*) has a long history as a medicinal fungus. There are over 600 documented species of the genus *Ophiocordyceps* or *Cordyceps*, and the best known of these is *Ophiocordyceps sinensis,* a fungus which is known in Tibet as "winter worm, summer grass" or as "Caterpillar fungus" (Yartsa gunbu). It is a parasite of the *Thitarodes* ghost moth larva and similar species which live on the Tibetan Plateau and the Himalayas throughout India, Nepal and Bhutan [27,28,31,48]. The fungus germinates in a living host, kills and mummifies the larva, and then grows from the body of the host.

Searching for Yartsa gunbu begins in Tibet in May and June at a height of 3–4 thousand meters and this period lasts for approximately only 5 weeks. Whole villages are involved. Collecting Yartsa gunbu in Nepal was only legalised in 2001, and demand is highest in Asian countries [27,28]. The search for *Ophiocordyceps sinensis* is often perceived to pose a threat to the environment of the Tibetan Plateau. [27,28]. Current collection rates are much higher than in historical times. In rural Tibet, Yartsa gunbu has become the most important source of money, representing nearly half of the annual income of local households. In 2008, one kilogram traded for 3,000 USD (lowest quality) to over 18,000 USD (best quality, largest larvae) [27,28]. The annual production on the Tibetan Plateau was estimated to be 80–175 tons in 2009 [27,28,31,48]. The Himalayan *Ophiocordyceps* production might not exceed a few tons. Because of its high value, inter-village conflicts have become a problem for the local government, with people being killed in some cases [27,28,31,48].

The earliest record outlining the tonic properities of *Ophiocordyceps sinensis* especially as an aphrodisiac is a 15th Century Tibetan medical. In Chinese medicine, it is regarded as a fungus improving the balance of "yin and yang" [49]. The fungus was made famous in 1993 by the performance of three female Chinese athletes who broke five world records for long-distance running; the coach told the reporters that the runners were taking *Ophiocordyceps sinensis* and turtle blood at his request [27,28,31,48,49].

Biological activity and industrial culture of *Ophiocordyceps sinensis*

One of the useful products which can be obtained from *Cordyceps* species is cyclosporine: a drug which can be used as an immunosuppressor in human organ transplants [50,51]. Many different species of *Cordyceps,* including *Ophiocordyceps sinensis,* are cultivated from anamorphic mycelia for their medicinal and pharmaceutical properties in bioreactors [14,35,50,51]; this production is on an industrial scale with the world output being several millions tonnes per year [5,50]. Most of these medicinal products are extracted from the cultivated fruiting bodies of the fungus [50].

This biotechnology industry is growing rapidly and a variety of methods for this cultivation have been proposed by many research groups [51]. All artificial products are derived from mycelia grown on solid or liquid medium after 100 days at different temperatures [52]. Laboratory-grown *Ophiocordyceps sinensis* mycelia have similar clinical efficacy as those grown in the wild and less associated toxicity. As a drug, *Ophiocordyceps* is available in capsules, tincture, and extract forms and the recommended dosage is two to three grams taken with meals [31,50,51].

Cordycepin (opiocordin) and the exopolysaccharides are some of the major pharmacologically and biological active compounds of this fungus. The most important properties of *Cordyceps* compounds are its immunostimulation and antitumor activities [14,31,53]. Commercial products contain high concentrations of active ingredients including cyclosporine, D-mannitol, sterols, vitamins A, B, C and E, 16 amino acids, peroxide dysmutase (SOD) and minerals [14,31]. The structure of cordycepin is very similar to the cellular nucleoside, adenosine; it also acts like a nucleoside analogue, and inhibits the purine biosynthesis pathway. Cordycepin also provokes RNA or DNA chain termination [14,31,53] and interferes with receptors for mTOR, "the mammalian Target of Rapamycin", for signal transduction in cells. mTOR inhibitors such as rapamycin have been tested as anticancer drugs. mTOR plays an important role in the regulation of protein synthesis [54]. The active fungal components are thought to be incorporated in cellular signaling pathways, as well as involved in boosting the number of small-part ATP and cAMP. Recent studies further confirm that *Cordyceps* supplies energy to cells in the form of ATP. Upon hydrolysis of phosphates from ATP, a large amount of energy is released and then used by the cell [55].

It seemed that biocompounds isolated from fungus grown in bioreactors poses a wide spectrum of biological activity to that of naturally-collected *Cordyceps.* Previous studies on *Cordyceps* have showed it to possess antibacterial, antifungal, larvacidal, anti-inflammatory, antidiabetic, antioxidant, antitumor, prosexual, apoptotic and immunomodulatory activities [31,56–62]. Administration of *Cordyceps* may be able to improve movement, relieve fatigue, lower high cholesterol, dilate blood vessels, calm the body, prevent and treat infertility and impotence as well as improve strength; it may also be effective against ome symptoms of HIV/AIDS [11,31,56–62]. The caterpillar fungus *Ophiocordyceps sinensis* is promoted as a natural Viagra [49]. Research includes substances as nucleosides, 3'deoksyadenozyna, ergosterol, D-mannitol, amino acids and polysaccharydes, all of which are well known fungal products. Many studies have shown *Cordyceps* to have beneficial effects on the cardiovascular system [24,25,59–61], possibly through lowering high blood pressure by direct dilatory effects, or their mediation through M-cholinergic receptors, which may result in improved coronary and cerebral circulation [24,25]. *Cordyceps* is available in supplement form and although no adverse reactions have been reported, the compounds are rapidly degraded by the body [31].

Biological control agents – biopesticide

Other Hypocrealean AP fungi are also known to produce biologically-active secondary metabolites that are involved in arthropod pathogenicity [30,32,34,63,64]. These secondary metabolites have attracted significant attention in modern agriculture and Medicine as potential sources of novel pharmaceuticals [63,64].

Several mitotic or anamorphic species have received attention as biological control agents of insect pests. Candidate species have largely come from the Cordycipitaceae or Clavicipitaceae [30,32,34,63,64]. Anamorphic forms of Ophiocordycipitaceae are often difficult to culture and are slow growing. In the Clavicipitaceae, species of the genera *Metarhizium*, *Nomuraea* and *Pochonia* (anamorphs) have all proven useful against a range of pests [30,32,34,63–65] (Fig. 3).

The commercial biopesticide for the control of locusts in Africa was developed from *Metarhizium anisopliae* var. *acridum* as an alternative to synthetic pesticides [13,66]. Some isolates of this fungus are under development for control of a wide array of pests including mosquito vectors of malaria. Closely related to *M. anisopliae*, *Nomuraea rileyi* has also shown potential as a biological control organism [13,33,66]. This fungus is now under development for the control of pests [66]. *Pochonia chlamydosporia* has been used against nematode pests of potato [66]. In the Cordycipitaceae, several species of *Beauveria* have been developed, the most common of which is *B. bassiana*. This species has shown activity against a wide range of hosts, including beetle and moth larvae [33,66].

Fig. 3. *Cordyceps tuberculata* covering insect

Conclusion

Medicinal fungi are used or studied as possible factors for treatment of many diseases. Research shows that various species of fungi contain antiviral, antimicrobial, anticancer, antihyperglycemic, cardioprotective and anti-inflammatory compounds. Lentinan and PSK are well known extracts from fungi which are licensed in certain countries as immunomodulators. Fungi were the original sources of penicillin, griseofulvin, mycophenolate, ciclosporin, mizoribine, mycophenolic acid, the first statins, and cephalosporins [50].

A broad range of medical practices share common theoretical concepts developed in China and are based on a tradition of more than 2000 years, including various forms of herbal medicine, acupuncture, massage and dietary therapy. Traditional Chinese Medicine is mainly concerned with the identification of functional entities which regulate such processes as digestion, breathing and aging. While health is perceived as harmonious interaction of these entities and the outside world, disease is interpreted as a disharmony in interaction. Different natural biocompounds, such as fungal bioproducts, give hope that this harmony may once again be recovered.

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References

[1] Kobayasi Y. 1941.The genus *Cordyceps* and its allies. *Science reports of the Tokyo Bunrika Daigaku* 84: 53-260.

[2] Hodge K.T., Humber RA, Wozniak CA. 1998. *Cordyceps variabilis* and the genus *Syngliocladium. Mycologia* 90: 743-753.

[3] http://cordyceps.us/ an electronic monograph of *Cordyceps* and related fungi. Spatafora Lab., Department of Botany and Plant Pathology, Oregon State University.

[4] Sung G.H., Sung J.M., Hywel-Jones N.L., Spatafora J.W. 2007. A multi-gene phylogeny of Clavicipitaceae (Ascomycota, Fungi): Identification of localized incongruence using a combinational bootstrap approach. *Molecular Phylogenetics and Evolution* .44: 1204-1223.

[5] Hodge K.T., Krasnoff S.B., Humber R.A. 1996. *Tolypocladium inflatum* is the anamorph of *Cordyceps subsessilis*. *Mycologia* 88: 715-719.

[6] Kobayasi Y., Shimizu D. 1982. *Cordyceps* species from Japan 4. *Bulletin of the National Science Museum*, Tokyo, B. 8: 79-91.

[7] Kobayasi Y. 1982. Keys to the taxa of the genera *Cordyceps* and *Torrubiella*. *Transaction of the Mycological Society of Japan* 23: 329-364.

[8] http://mushroaming.com/Cordyceps

[9] http://nagrzyby.pl

[10] http://www.medicalmushrooms.net

[11] http://www.cordycepssinensis.org

[12] Sung G.H., Poinar J.G.O., Spatafora J.W. 2008.The oldest fossil evidence of animal parasitism by fungi supports a Cretaceous diversification of fungal-arthropod symbioses. *Molecular Phylogenetics and Evolution* 49: 495-502.

[13] Namasivayam K.R., Bharani R.S.A, Ansari M.R. 2013. Natural occurrence of potential fungal biopesticide *Nomuraea rileyi* (Farlow) Samson associated with agriculture fields of Tamil Nadu, India and it's compatibility with metallic nanoparticles. *Journal of Biofertilizers and Biopesticides* 4: 132.

[14] Karpińska E. 2012. Biostymulujące właściwości entomopatogenicznych grzybów z rodzaju *Cordyceps. Borgis - Postępy Fitoterapii* 4: 254-264.

[15] Liu Z., Yao Y., J, Kiang Z.O., Liu A.Y., Pegler D., Chase M. 2001. Molecular evidence for the anamorph-teleomorph connection in *Cordyceps sinensis*. *Mycological Research* 105: 27-832.

[16] Artjariyasripong S., Mitchell J.I,. Hywe-Jones N.L., Gareth Jones E.B. 2001. Relationship of the genus *Cordyceps* and related genera, based on parsimony and spectral analysis of partial 18S and 28S ribosomal gene sequences. *Mycoscience* 42: 503-517.

[17] Spatafora J.W., Blackwell M. 1993. Molecular systematics of unitunicate perithecial ascomycetes: The Clavicipitales-Hypocreales connection. *Mycologia* 85: 912-922.

[18] Hodge K.T. 2003. Clavicipitaceous anamorphs. In: *Clavicepitalean fungi: Evolutionary Biology, Chemistry, Biocontrol and Cultural Impacts.* (Eds. J.F. White, C.W. Bacon, N. Hywel-Jones, J.W. Spatafora): 75-123, New York, Marcel Dekker.

[19] Kepler R.M., Bruck D.J. 2006. Examination of the interaction between the Black Vine Weevil (Coleoptera: Curculionidae) and an entomopathogenic fungus reveals a new tritrophic interaction. *Environmental Entomology* 35: 1021-1029.

[20] Kobayasi Y., Shimizu D. 1960. Monographic studies of *Cordyceps* 1. Group parasitic on *Elaphomyces. Bulletin of the National Science Museum*, *Tokyo* 5: 69-85.

[21] Liang Z.Q., Liu A.Y., Liu J.L. 1991. A new species of the genus *Cordyceps* and its *Metarhizium* anamorph. *Acta Mycologica Sinica* 10: 257-262.

[22] Liu Z.Y., Liang Z.Q., Whalley A.J.S., Liu A.Y., Yao Y.J. 2001. A new species of *Beauveria*, the anamorph of *Cordyceps sobolifera*. *Fungal Diversity* 7: 61-70.

[23] Evans H.C., Elliot S.I., Hughes D.P. 2011. *Ophiocordyceps unilateralis*. A keystone species for unraveling ecosystem functioning and biodiversity of fungi in tropical forests? *Communicative and Integrative Biology* 4: 598-602.

[24] Zhu J.S., Halpern G.M., Jones K. 1998. The scientific rediscovery of an ancient Chinese herbal

medicine: *Cordyceps sinensis*, part I. *Journal of Alternative and Complementary Medicine* 4: 289-303.

[25] Zhu J.S., Halpern G.M., Jones K. 1998. The scientific rediscovery of an ancient Chinese herbal regimen: *Cordyceps sinensis*, part II. *Journal of Alternative and Complementary Medicine* 4: 429-457.

[26] Winkler D. 2008. Yartsa gunbu (*Cordyceps sinensis*) and the fungal commodification of the rural economy in Tibet. *Economic Botany* 62: 291-305.

[27] Winkler D. 2010. Caterpillar fungus (*Ophiocordyceps sinensis*) production and sustainability on the Tibetan Plateau and in the Himalayas. *Chinese Journal of Grassland* (Supl.) 32: 96-108.

[28] Wang I., Zhang W.M., Hu B., Chen Y.Q., Qu L.H. 2008. Genetic variantion of *Cordyceps militaris* and its allies based on phylogenetic analysis of rDNA ITS sequence data. *Fungal Divers* 31: 147-156.

[29] http://nagrzyby.pl/atlas/515

[30] Humber R.A. 2000. Fungal pathogens and parasites of insects. In: *Applied microbial systematics*. (Eds. F. Priest, M. Goodfellow). Kluwer Academic Publishers, Dordrecht: 203-230.

[31] Hardeep S., Tuli-Sardul S., Sandhu-A.K.Sharma. 2014. Pharmacological and therapeutic potential of *Cordyceps* with special reference to Cordycepin, 3. *Biotechnology* 4: 1-12.

[32] Ali S., Ren S., Huang Z., Wu J. 2010. Purification of enzymes related to host penetrations and pathogenesis from entomopathogenic fungi. In: *Current Research, Technology and Education Topics in Applied Microbiology and Microbial Biotechnology.* (Ed. A. Mendez-Vilas). Formatex Research Center, Spain: 15-22.

[33] Holder D.J., Keyhani N.O. 2005. Adhesion of the entomopathogenic fungus *Beauveria* (*Cordyceps*) *bassiana* to substrata. *Applied and Environmental Microbiology* 71: 5260-5266.

[34] Isaka M., Jaturapat A., Ruksereee K., Danwisetkanjana K., Tanticharoen M., Thebtar Anonth Y. 2001. Phomoxanthones A and B, novel xanthone dimers from the endophytic fungus *Phomopsis* species. *Journal of Natural Products* 64: 1015-1018.

[35] Wanga Z., Heb Z., Lib S., Yuanb Q. 2005. Purification and partial characterization of Cu, Zn containing superoxide dismutase from entomogenousfungal species *Cordyceps militaris*. *Enzyme and Microbial Technology* 36: 862-869.

[36] http://nagrzyby.pl/atlas/470

[37] Hughes D., Wappler T., Labandeira C. 2010. Ancient death-grip leaf scars reveal ant-fungal parasitism. *Biology Letters* DOI: 10.1098/rsbl.2010.0521.

[38] Spatafora J.W., Sung G.H., Sung J.M, Hywel-Jones N., White J.F. 2007. Phylogenetic evidence for an animal pathogen origin of ergot and the grass endophytes. *Molecular Ecology* 16**:**1701-1711.

[39] Sung G.H., Hywel-Jones N.L., Sung J.M., Luangsaard J., Shrestha B., Spatafora J.W. 2007. Phylogenetic classification of *Cordyceps* and the clavicipitaceous fungi. *Studies in Mycology* 57: 5-59.

[40] Zare R., Gams W., Evans H.C. 2001. A revision of Verticillium sect. Prostrata. V. The genus *Pochonia*, with notes on Rotiferophthora. *Nova Hedwigia* 73: 51-86.

[41] Liang Z.Q. 1991. Anamorphs of *Cordyceps* and their determination. *Southwest China Journal of Agricultural Sciences* 4: 1-8.

[42] Liang Z.Q. 1991.Verification of identification of the anamorph of *Cordyceps pruinosa Petch. Acta Mycologica Sinica* 10: 104-107.

[43] Liu Z.Y., Liang Z.Q., Liu A.Y., Yao Y.J., Hyde K.D., Yu Z.N. 2002. Molecular evidence for teleomorph-anamorph connections in *Cordyceps* based on ITS-5.8S rDNA sequences. *Mycologial Research* 106: 1100-1108.

[44] Liu Z.Y., Yao Y.J., Liang Z.Q., Liu A-Y., Pegler D.N., Chase M.W. 2001. Molecular evidence for the anamorph-teleomorph connection in *Cordyceps sinensis*. *Mycological Research* 105: 827-832.

[45] Evans H.C. 1982. *Cordyceps* species and their anamorphs pathogenic on ants (Formicidae) in tropical forest ecosystems. *Transaction of the British Mycological Society* 79: 431- 453.

[46] Shrestha B., Zhang W., Zhang Y, Liu X. 2012. The medicinal fungus *Cordyceps militaris*: research and development. *Mycological Progress* DOI 10.1007/s11557-012-0825-y

[47] Gams W., Zare R**.** 2001. A revision of *Verticillium* sect. Prostrata III. Generic classification. *Nova Hedwigia* 72: 329-337.

[48] Zhou X.W., Gong Z.G., Su Y., Lin Y., Tang K. 2009. *Cordyceps* fungi: natural products, pharmacological functions and developmental products. *Journal of Pharmacy and Pharmacology* 61: 279-291.

[49] http://www.danielwinkler.com

[01] Stone R. 2008. Last Stand for the Body Snatcher of the Himalayas? *Science* 322: 1182.

[51] Lindequist U., Niedermayer T.H.J., Julich W.D. 2005. The pharmacological potential of mushrooms. *Evidence Based Complementary and Alternative Medicine* 2: 285-299.

[52] Das S.K., Masuda M., Hatashita M., Sakurai A., Sakakibara M. 2010. Effect of inoculation on production of anticancer drug – cordycepin in surface liquid culture using *Cordyceps militaris* mutant: a minor factor may greatly affect the result. *Indian Journal of Biotechnolology* 9: 427-430.

[53] Ni H., Zhou X.H., Li H.H., Huang W.F. 2009. Column chromatographic extraction and preparation of cordycepin from *Cordyceps militaris* waster medium. *Journal of Chromatography B* 877: 2135-2141.

[54] Chen L.S., Stellrecht C.M., Gandhi V. 2008. RNA-direct agent cordycepin induces cell death in multiple myeloma cells. *British Journal of Hematology* 140: 391-682.

[55] Wong Y.Y., Moon A., Duffin R., Barther-Barateig A., Meijer H.A., Clemens M.J., de Moor C.H. 2010. Cordycepin inhibits protein synthesis and cell adhesion throught effects on signal transduction. *Journal of Biological Chemistry* 285: 2610-2621.

[56] Siu K.M., Mak H.F.D., Chiu P.Y., Poon K.T.M., Du Y., Ko K.M. 2004. Pharmacological basis of Yin-nourishing and Yang-invigorating actions of *Cordyceps*, a Chinese tonifying herb. *Life Sciences* 76: 385-395.

[57] Kuo M.C., Chang C.Y., Cheng T.L., Wu M.J. 2007. Immunomodulatory effect of exo-polysaccharides from submerged cultured *Cordyceps sinensis* enhancement of cytokine synthesis, CD11b expressions and phagocythosis. *Applied Microbiology and Biotechnolology* 75: 769-775.

[58] Rao Y.K., Fang S.H., Wu W.S., Tzeng Y.M. 2010. Constituents isolated from *Cordyceps militaris* suppress enhanced inflammatory mediators production and human cancer cell proliferation. *Journal of Ethnopharmacology* 131: 363-367.

[59] Chu H.L., Chien J.C., Duh P.D. 2011. Protective effect of *Cordyceps militaris* against high glucose-induced oxidative stress in human umbilical vein endothelial cells. *Food and Chemical Toxicology* 129: 871-876.

[60] Li Y., Chen G.Z., Jiang D.Z. 1993. Effect of *Cordyceps sinensis* on erythropoiesis in mouse bone marrow. *Chinese Medical Journal* 106: 313-316.

[61] Park B.T., Na K.H., Jung E.C., Park J.W., Kim H.H. 2009. Anti-fungal and cancer activities of a protein from the mushroom *Cordyceps militaris*. *Korean Journal of Physiology and Pharmacology* 13: 49-54.

[62] Lee J.H., Hong S.M., Yun J.Y., Myoung H., Kim M.J. 2011. Anti-cancer effects of cordycepin on oral sqamous cell carcinoma proliferation and apoptosis in vitro. *Journal of Cancer Therapy* 2: 224-234.

[63] Thakur A., Hui R., Hongyan Z., Tian Y., Tianjun C., Mingwei C. 2011. Pro-apoptic effects of *Paecilomyces hepiali*, a *Cordyceps sinensis* extract on human lung adenocarcinoma A549 cells in vitro. *Journal of Cancer Research and Therapeutics* 7: 421-426.

[64] http://www.livescience.com/5631-zombie-ants-controlled-fungus.html

[65] http://www.studiesinmycology.org/content/57/1/5/F9.full

[66] http://nagrzyby.pl/atlas/430

[67] http://www.bioworksinc.com/products/shared/bota-nigard. pdf

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