Pharmacogn. Rev.
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
www.phcogrev.com | www.phcog.net

REVIEW ARTICLE

Review of Naturopathy of Medical Mushroom, *Ophiocordyceps Sinensis*, in Sexual Dysfunction

Kanitta Jiraungkoorskul, Wannee Jiraungkoorskul

Department of Pathobiology, Faculty of Science, Mahidol University, Bangkok, Thailand

ABSTRACT

Sexual dysfunctions including desire, arousal, orgasm, and pain disorders are increasing worldwide due to etiological factors and aging. Several types of treatment are claimed in modern medicine, but they have serious side effects and higher costs. In fact, alternative approaches, such as the intake of plants, fungi, and insects, or their extracts, have also been practiced to enhance sexuality and ameliorate illness with notable successes. However, the scientific evidence related to the mechanisms and efficacy of these alternative medicines is both scarce and all too often unconvincing. *Ophiocordyceps sinensis* is an Ascomycetes fungus parasitic to Lepidoptera larvae, and has long been used as medicine to treat many illnesses and promote longevity in Chinese society. Previous investigations have shown that *O. sinensis* has many pharmacological activities. This review has focused on illustrating that *O. sinensis* can enhance libido and sexual performance, and can restore impaired reproductive functions, such as impotency or infertility, in both sexes.

Key words: Aphrodisiac, fungi, mushroom, *Ophiocordyceps sinensis*, sexual dysfunction

APHRODISIAC PLANTS

The third International Consultation on Sexual Medicine held in Paris in July 2009 defined the disorders of sexual function as a problem or situation that occurs during any phase of the sexual response cycle that makes the individual or couple unhappy in the sexual activity.[1-3] The sexual response cycle consists of four stages: Excitement, plateau, orgasm, and resolution.[4,5] From this cycle, sexual dysfunction can be classified into four patterns: (i) Desire disorders, or the lack of sexual desire or moody in sex or lack of libido; (ii) Arousal disorders, or nonstimulation during sexual activity due to vaginal dryness or impotence; (iii) Orgasm disorders, or the delay or absence of the feeling of pleasure or climax; (iv) Pain disorders, or feeling hurt during intercourse, dyspareunia, vaginismus.[6,7] Among many therapeutic approaches is the use of sildanefil citrate (Viagra), which has been reported to successfully modify the hemodynamics in the penis,[8,9] but with limited efficacy, unpleasant side effects, and contraindications in certain disease conditions.[10,11] Many plants have been reported to possess aphrodisiac potential, being employed as remedies for sexual dysfunction and also reviewed by researchers from many countries such as Africa,[12] Canada,[13] India,[14-17] Nigeria,[18] Thailand,[19] Turkey,[20] and USA.[21] The aphrodisiac plants can be classified into three groups depend on the phytochemical substances: (i) Substances that enhance libido, i.e., sexual desire, arousal; (ii) substances that enhance sexual potency, i.e., effectiveness of erection; and (iii) substances that enhance sexual pleasure.[14]

Ophiocordyceps sinensis, one of the medicinal mushrooms, has long been in ethnomycological medicinal use in Bhutan,[22] China,[23] India,[24] Nepal,[25,26] and Tibet.[27] Its synonym with *Sphaeria sinensis* and *Cordyceps sinensis*. It is used worldwide as traditional medicinal mushrooms and fungi to relieve symptoms of various diseases.[28] It is commonly known as caterpillar fungus or Cordyceps mushroom. Its taxonomy is as follows: Fungi (Kingdom), Dikarya (Subkingdom), Ascomycota (Phylum), Pezizomycotina (Subphylum), Sordariomycetes (Class), Hypocreomycetidae (Subclass), Hypocreales (Order), Ophiocordycipitaceae (Family), *Ophiocordyceps* (Genus).[29] There are around 140 widespread species belonging to the genus *Ophiocordyceps*, first described scientifically by British mycologist Tom Petch (1870–1948).[30]

NOMENCLATURE

The name *Cordyceps* comes from Latin words *Cordl-* "club," *ceps-* "head," and *sinensis* "Chinese."[31] *Cordyceps sinensis* was discovered about 2000 years ago as an exotic medicinal mushroom described in traditional Chinese and Tibetan medicine. The British mycologist Miles Joseph Berkeley (1803–1889) first described it in 1843 as *Sphaeria sinesis* Berk. Later in 1878, Italian mycologist Pier Andrea Saccardo (1845–1920) renamed it as *Cordyceps sinensis* (Berk.) Sacc.[32] Based on molecular phylogenetic study, "Cordyceps" was separated into four genera: *Cordyceps*, *Ophiocordyceps*, *Metacordyceps*, and *Elaphocordyceps*, and it was also shown that *C. sinesis* is part of a clade based on the

Correspondence:
Dr. Wannee Jiraungkoorskul,
Department of Pathobiology, Faculty of Science,
Mahidol University, Rama VI Road, Bangkok - 10400, Thailand.
E-mail: wannee.jir@mahidol.ac.th

Access this article online

Quick Response Code:

Website: www.phcogrev.com

DOI: 10.4103/0973-7847.176566

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Jiraungkoorskul K, Jiraungkoorskul W. Review of naturopathy of medical mushroom, *Ophiocordyceps sinensis*, in sexual dysfunction. Phcog Rev 2016;10:1-5.

concept of *Ophiocordyceps* Petch; the correct name for it now is *Ophiocordyceps sinensis* (Berk.) G.H. Sung, J.M. Sung, Hywel-Jones and Spatafora.[33] The vernacular name of *O. sinensis* is *dōng chóng xià cǎo* meaning "winter-worm, summer-plant, or summer-grass, winter-insect" in Chinese. Other names are *bub* (Bhutanese), *ruspendooder* (Dutch), *kiinanloisikka* (Finnish), *ghaas fafoond* (Hindi), to *chu kaso* (Japanese), *dong chug ha cho* (Korean), *jeevan buti*, *keeda ghass*, *chyou kira*, *sanjeevani bhooti*, *keera jhar* (Nepali), *dbyar rtswa dgun bu* or *yartsa gunbu* (Tibetan), and *chong cao* (Thai).[34]

MORPHOLOGICAL CHARACTERISTICS

O. sinensis is the composite of a genus of fungus that grows on the larva of insects. To date, more than 350 related species have been found worldwide based on fungus and insect hosts. The most widespread insect is in order Lepidoptera, especially Thitarodes, formerly classified as Hepialus.[35] In the winter season, the infected larva will be changed into a sclerotium and covered by the intact exoskeleton to withstand the cold temperature, which is regarded as "winter worm." In the summer season, a clavate stroma of the fungus grows from the sclerotium and emerged from the ground appearing as an herb, which is regarded as "summer grass." *Hepialus armoricanus* Oberthur is the host insect species of *O sinensis*. It consists of two parts, the fruiting body (fungus) and the worm (caterpillar). The caterpillar is invaded by *O. sinensis* mycelia and thus the two parts show similar constituents and pharmacological functions.[36]

PHYTOCHEMICAL SUBSTANCES

The major phytochemical constituents of *O. sinensis* are (i) Proteins: Cadaverine, carboline, cordymin, flazin, methylpyrimidine, perlolyrine, putrescine, spermidine, spermine, tryptophan;[37,38] (ii) Nitrogenous compounds: Adenine, adenosine, cordyceamides, cordycedipeptide, cordycepin, cordymin, cordysinin, dideoxyadenosine, guanine, guanosine, hypoxanthine, inosine, thymidine, thymine, uracil, uridine;[39-44] (iii) Sterols: Campesterol, cholesterol, daucosterol, ergosterol, sitisterol, stigmasterol;[45,46] (iv) Fatty acids: Docosanoic acid, lauric acid, lignoceric acid, linoleic acid, myristic acid, oleic acid, palmitic acid, palmitoleic acid, pentadecanoic acid, stearic acid, succinic acid;[47,48] (v) Phenolic acids: Acetovanillone, hydroxybenzoic acid, protocatechuic acid, salicylic acid, syringic acid, vanillic acid49; (vi) Isoflavones: Daidzein, genistein, glycitein, orobol;[49] (vii) Polysaccharides and sugar derivatives: Cordysinocan, glucan, heteroglycan, mannitol, mannoglucan;[50-54] (viii) Vitamins, inorganic and volatile compounds.[55]

TRADITIONAL USES

O. sinensis is traditionally used[56,57] as antidiabetic,[58-62] antiinflammatory,[49,54,63] antimicrobial,[64,65] antioxidant,[66-68] and antitumor agent;[44,69-71] against hypocholesterolemia;[72,73] and for immunomodulatory properties.[74,75] It is also used for treatment in several diseases such as cardiovascular,[76-79] gastrointestinal,[80] hepatic,[81-83] neuromuscular,[84,85] renal,[59,85,86] and respiratory diseases.[87]

Meena *et al.*[88] reported that laboratory-cultured mycelia powders of *O. sinensis* are safe and nontoxic up to 2 g/kg body weight dose. Oral administration of laboratory-cultured mycelia powders of *O. sinensis* did not show any sign of toxicity, as no significant change was observed in organ weight and serological parameters in rats. However, there was a significant increase in food intake, body weight gain, and hematological parameters such as white and red blood cells, hemoglobin, and lymphocytes in treated groups. Histopathology of vital organs also supported the nontoxic effect of *O. sinensis*.

SEXUAL PERFORMANCE ENHANCEMENT AND/OR IMPROVEMENT

Medicinal plants have attracted great interest from researchers around the world because of their positive bioactive effects.[89] However, there are still not many data available about the positive action on sexual dysfunction of this medicinal mushroom, *O. sinensis*. During the review, searches were done on scientific databases such as ScienceDirect, SpringerLink, PubMed, Google Scholar. Moreover, internet searches were performed on the search engine. Different combinations of keywords as well as synonyms for keywords were used during the searches. This review has illustrated the properties of *O. sinensis* in sexual performance as follows.

In vitro and *in vivo* animal study

Several reports have previously demonstrated that *C. sinensis* could stimulate steroid production or steroidogenesis in both primary normal mouse Leydig cells and tumor cells[90-95] and also in human granulosa lutein cells.[96] Huang *et al.*[97] reported that *C. sinensis* (0.02 mg and 0. 2 mg) were fed per gram of body weight to immature or mature mice for 7 days, significantly can induced the plasma testosterone levels but did not have that effect on the weights of reproductive organs. Ji *et al.*[98] reported that the hot water extract of *C. sinensis* has a mild beneficial effect on sexual function in castrated rats.

CLINICAL STUDY

Guo[99] reported that when *C. sinensis* supplement was administered to 22 males for 8 weeks, it showed 33% increase in sperm count and 29% decrease in the sperm malformations, and 79% increase in the sperm survival rate. Huang *et al.*[100] reported that *C. sinensis* dietary supplement can cause the prevention and improvement of adrenal glands and thymus hormones, and the infertile sperm count improved by 300%. Wan *et al.*[101] reported that when *C. sinensis* supplement to 189 both men and women, libido decreased and there was improvement of symptoms and desire by 66%. Dong and Yao[102] reported that *C. sinensis* supplement caused improvement of libido and desire at 86% in women.

MECHANISM

Steroidogenesis stimulation

The carbohydrate moiety of the glycoprotein luteinizing hormone/chorionic gonadotropin plays an important role in recognizing luteinizing hormone receptor to activate a signal pathway for steroidogenesis.[103] Therefore, the polysaccharides and/or glycoproteins in *C. sinensis* may be similar to luteinizing hormone in structure and have the ability to recognize luteinizing hormone receptors on Leydig cells to stimulate testosterone production.[97]

Luteinizing hormone binds to its receptors to activate G-proteins and, in turn, adenylate cyclase, which can increase cyclic AMP formation. cAMP will then stimulate protein kinase A (PKA), which will phosphorylate proteins. The phosphorylated proteins will further phosphorylate other proteins or induce new protein synthesis, i.e. steroidogenic acute regulatory protein.[104] The function of steroidogenic acute regulatory protein is to transfer free cholesterol from the cytoplasm into the inner membrane of mitochondria, where cytochrome P450 side-chain cleavage enzyme converts cholesterol to pregnenolone.[105,106] Pregnenolone will then be transported to smooth endoplasmic reticulum for testosterone synthesis, which is an essential steroid hormone for reproduction in males.[107] It has also been shown that activation of the protein kinase C (PKC) signal pathway can strongly modulate Leydig cell

steroidogenesis.[108] Chen *et al*.[109] explained that *C. sinensis* activated both PKA and PKC signal transduction pathways to stimulate cell steroidogenesis.

Hypothalamus–pituitary–gonad axis

Aphrodisiac activity of *C. sinensis* has been reported because of the testosterone-like metabolites and libido-promoting activity. Moreover, Wang *et al*.[110] reported that *C. sinensis* contains a factor that enhances corticosteroid hormone. In the study, the water-crude extract of *C. sinensis* was investigated for its pharmacological function on primary rat adrenal cell cultures. However, the authors are not sure about the mechanism of *C. sinensis*-induced steriodogenesis, whether its mechanism acts on the adrenal glands or via the hypothalamus–pituitary axis.

Phytochemical substance

It is possible that the *C. sinensis* supplement might affect spermatogenesis through the effect of cordycepin (3'deoxyadenosine), because the increased serum cordycepin concentration paralleled the enhancement of sperm production and increased testosterone levels.[111] Leu *et al*.[112] and Tuli *et al*.[113] reported that cordycepin was as an adenosine analog that increased the plasma testosterone concentration and associated with adenosine receptors to activate the cAMP-PKA-StAR signal pathway and steroidogenesis in mouse Leydig cells.

CONCLUSION

In conclusion, sexual dysfunction is one of the important health problems affecting men and women. Of the available treatments, several are pharmacologically proven and tested medications. However, there are significant users of unproven medical plants and mushrooms for sexual health. *Ophiocordyceps* species have been traditionally used as for the enhancement of sexual function, but direct evidence is lacking. This review paper descriptively highlights the naturopathy of the medicinal mushroom, *O. sinensis*, in sexual dysfunction. This review shows that *O. sinensis* supplementation increased the total sperm number, the percentage of motile sperm cells, and serum testosterone.

Acknowledgments

This review article was funded in part by the Thailand Research Fund and the Commission on Higher Education: Research Grant for Mid-Career University Faculty. Thanks should be addressed to the members of the Fish Research Unit, Department of Pathobiology, Faculty of Science, Mahidol University for their support. The authors also give many thanks to the anonymous referees and the editor for their perceptive comments on and positive criticism of this review article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Montorsi F, Basson R, Adaikan G, Becher E, Clayton A, Giuliano F, *et al*. Sexual Medicine Sexual Dysfunctions in Men and Women. The 3rd International Consultation on Sexua Medicine. Paris: Health Publication Ltd; 2010. p. 1300.
2. Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira ED Jr, *et al*. Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med 2010;7:1598-607.
3. Akinloye OO, Yinusa R. Assessment of complementary and alternative medicine (CAM) usage to enhance male sexual performance in Ogbomoso metropolis. J Public Health Epidemiol 2011;3:271-4.
4. Basson R. Human sex-response cycles. J Sex Marital Ther 2001;27:33-43.
5. Basson R, Brotto LA, Laan E, Redmond G, Utian WH. Assessment and management of women's sexual dysfunctions: Problematic desire and arousal. J Sex Med 2005;2:291-300.
6. Hatzimouratidis K, Hatzichristou D. Sexual dysfunctions: Classifications and definitions. J Sex Med 2007;4:241-50.
7. Bhugra D, Colombini G. Sexual dysfunction: Classification and assessment. BJPsych Adv 2013;19:48-55.
8. Mulhall J, Barnas J, Aviv N, Anderson M, Parker M. Sidenafil citrate response correlates with the nature and the severity of penile vascular insufficiency. J Sex Med 2005;2:104-8.
9. Elhanbly SM, Elkholy AA, Alghobary M, Abou Al-Ghar M. Clinical predictive factors of sildenafil response: A penile hemodynamic study. Andrology 2015;3:241-6.
10. Ishikura F, Beppu S, Hamada T, Khandheria BK, Seward JB, Nehra A. Effects of sildenafil cirate (Viagra) combined with nitrate on the heart. Circulation 2000;102:2516-21.
11. Shinlapawittayatorn K, Chattipakorn S, Chattipakorn N. Effect of sildenafil citrate on the cardiovascular system. Braz J Med Biol Res 2005;38:1303-11.
12. Gundidza GM, Mmbengwa VM, Magwa ML, Ramalivhana NJ, Mukwevho NT, Ndaradzi W, *et al*. Aphrodisiac properties of some Zimbabwean medicinal plants formulations. Afr J Biotechnol 2009;8:6402-7.
13. Bella AJ, Shamloul R. Traditional plant aphrodisiacs and male sexual dysfunction. Phytother Res 2014;28:831-5.
14. Malviya N, Jain S, Gupta VB, Vyas S. Recent studies on aphrodisiac herbs for the management of male sexual dysfunction--a review. Acta Pol Pharm 2011;68:3-8.
15. Singh R, Singh S, Jeyabalan G, Ali A. An overview on traditional medicinal plants as aphrodisiac agent. J Pharm Phytochem 2012;1:43-56.
16. Singh R, Singh S, Jeyabalan G, Ali A, Semwal A. Medicinal plants used to treat sexual dysfunction: A review. Int J Rec Adv Pharm Res 2013;3:29-35.
17. Chauhan NS, Sharma V, Dixit VK, Thakur M. A review on plants used for improvement of sexual performance and virility. Biomed Res Int 2014;2014:868062.
18. Erhabor JO, Idu M, Udo FO. Ethnomedicinal survey of medicinal plants used in the treatment of male infertilty among the IFA Nkari people of Ini local government area of Akwa Ibom State, Nigeria. Res J Recent Sci 2013;2:5-11.
19. Wattanathorn J, Pangphukiew P, Muchimapura S, Sripanidkulchai K, Sripanidkulchai B. Aphrodisiac activity of *Kaempferia parviflora*. Am J Agricult Biol Sci 2012;7:114-20.
20. Abudayyak M, Özdemir Nath E, Özhan G. Toxic potentials of ten herbs commonly used for aphrodisiac effect in Turkey. Turk J Med Sci 2015;45:496-506.
21. Oketch-Rabah HA. *Mondia whitei,* a medicinal plant from Africa with aphrodisiac and antidepressant properties: A review. J Diet Suppl 2012;9:272-84.
22. Cannon PF, Hywel-Jones NL, Maczey N, Norbu L, Samdup TT, Lhendup P. Steps towards sustainable harvest of *Ophiocordyceps sinensis* in Bhutan. Biodivers Conserv 2009;18:2263-81.
23. Chen J, Lee S, Cao Y, Peng Y, Winkler D, Yang D. Ethnomycological 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.
24. Panda AK, Swain KC. Traditional uses and medicinal potential of *Cordyceps sinensis* of Sikkim. J Ayurveda Integr Med 2011;2:9-13.
25. Devkota S. Yarsagumba [*Cordyceps sinensis* (Berk.) Sacc.]; Traditional utilization in Dolpa district, Western Nepal. Our Nature 2006;4:48-52.
26. Childs G, Choedup N. Indigenous management strategies and socioeconomic impacts of Yartsa Gunbu (*Ophiocordyceps sinensis*) harvesting in Nubri and Tsum, Nepal. Himalaya 2014;34:8-22.
27. Winkler D. Yartsa Gunbu (Cordyceps sinensis) and the fungal commodification of Tibet's rural economy. Econ Bot 2008;62:291-305.
28. Vaidya JG, Lamrood PY. Traditional medicinal mushrooms and fungi of India. Int J Med Mushrooms 2000;2:6.
29. Mishra RN, Upadhyay Y. *Cordiceps sinensis*: The Chinese Rasayan-Current research scenario. Int J Res Pharm Biomed Sci 2011;2:1503-19.
30. Xing X, Guo S. The structure and histochemistry of sclerotia of Ophiocordyceps sinesis. Mycologia 2008;100:616-25.
31. Chakraborty S, Chowdhury S, Nandi G. Review on Yarsagumba (*Cordyceps sinensis*)-an exotic medicinal mushroom. Int J Pharmacogn Phytochem Res 2014;6:339-46.
32. Shrestha B, Tanaka E, Han JG, Oh J, Han SK, Lee KH, *et al*. A brief chronicle of the genus Cordyceps Fr., the oldest valid genus in Cordycipitaceae (Hypocreales, Ascomycota). Mycobiol 2014;42:93-9.
33. Sung GH, Hywel-Jones NL, Sung JM, Luangsa-aard JJ, Shrestha B, Spatafora JW. Phylogenetic classification of Cordyceps and the clavicipitaceous fungi. Stud Mycol 2007;57:5-59.
34. Shrestha S, Shrestha AK, Park JH, Lee DY, Cho JG, Shrestha B, *et al*. Review on pharmacologically active metabolites from Yarsagumba (*Ophiocordyceps sinensis*), an Epitome of Himalayan Elixir. Nepal J Sci Technol 2013;14:49-58.
35. Siddique SS, Arif M, Babu R, Shamim M. Wonder drug - An insect and fungus relationship (Hepialus-Cordyceps) through biotechnological approaches. Biol Med 2011;3:70-5.
36. Wang XL, Yao YJ. Host insect species of *Ophiocordyceps sinensis*: A review. Zookeys 2011;43-59.
37. Qi W, Zhang Y, Yan YB, Lei W, Wu ZX, Liu N, *et al*. The protective effect of cordymin, a peptide purified from the medicinal mushroom *Cordyceps sinensis*, on diabetic osteopenia in alloxan-induced diabetic rats. Evid Based Complement Alternat Med 2013;2013:985636.
38. Wei X, Xu N, Wu D, He Y. Determination of branched-amino acid content in fermented *Cordyceps sinensis* mycelium by using FT-NIR spectroscopy technique. Food Bioprocess Technol 2014;7:184-90.

39. Huang LF, Guo FQ, Liang YZ, Chen BM. Determination of adenosine and cordycepin in *Cordyceps sinensis* and *C. militarris* with HPLC-ESI-MS. Zhongguo Zhong Yao Za Zhi 2004;29:762-4.
40. 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.
41. Mang CY, Liu CP, Liu GM, Jiang B, Lan H, Wu KC, *et al.* Theoretical searches and spectral computations of preferred conformations of various absolute configurations for a cyclodipeptide, cordycedipeptide A from the culture liquid of *Cordyceps sinensis*. Spectrochim Acta A Mol Biomol Spectrosc 2014;136PC: 1401-8.
42. Ryu E, Son M, Lee M, Lee K, Cho JY, Cho S, *et al.* Cordycepin is a novel chemical suppressor of Epstein-Barr virus replication. Oncoscience 2014;1:866-81. eCollection 2014.
43. Aramwit P, Porasuphatana S, Srichana T, Nakpheng T. Toxicity evaluation of cordycepin and its delivery system for sustained *in vitro* anti-lung cancer activity. Nanoscale Res Lett 2015;10:152.
44. Nakamura K, Shinozuka K, Yoshikawa N. Anticancer and antimetastatic effects of cordycepin, an active component of *Cordyceps sinensis*. J Pharmacol Sci 2015;127:53-6.
45. Bok JW, Lermer L, Chilton J, Klingeman HG, Towers GH. Antitumor sterols from the mycelia of *Cordyceps sinensis*. Phytochemistry 1999;51:891-8.
46. Yuan JP, Wang JH, Liu X, Kuang HC, Zhao SY. Simultaneous determination of free ergosterol and ergosteryl esters in *Cordyceps sinensis* by HPLC. Food Chem 2007;105:1755-9.
47. 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.
48. Guo LX, Xu XM, Liang FR, Yuan JP, Peng J, Wu CF, *et al.* Morphological observations and fatty acid composition of indoor-cultivated *Cordyceps sinensis* at a high-altitude laboratory on Sejila Mountain, Tibet. PLoS One 2015;10:e0126095.
49. Yang ML, Kuo PC, Hwang TL, Wu TS. Anti-inflammatory principles from *Cordyceps sinensis*. J Nat Prod 2011;74:1996-2000.
50. Shaoping N, Cui SW, Xie M, Phillips AO, Phillips GO. Bioactive polysaccharides from *Cordyceps sinensis: Isolation*, structure features and bioactivities. Bioact Carbohydr Dietary Fibre 2013;1:38-52.
51. Lu WJ, Chang NC, Jayakumar T, Liao JC, Lin MJ, Wang SH, *et al. Ex vivo* and *in vivo* studies of CME-1, a novel polysaccharide purified from the mycelia of *Cordyceps sinensis* that inhibits human platelet activation by activating adenylate cyclase/cyclic AMP. Thromb Res 2014;134:1301-10.
52. Mei YX, Yang W, Zhu PX, Peng N, Zhu H, Liang YX. Isolation, characterization, and antitumor activity of a novel heteroglycan from cultured mycelia of *Cordyceps sinensis*. Planta Med 2014;80:1107-12.
53. Yan JK, Wang WQ, Wu JY. Recent advances in *Cordyceps sinensis* polysaccharides: Mycelial fermentation, isolation, structure, and bioactivities: A review. J Funct Foods 2014;6:33-47.
54. Wang LY, Cheong KL, Wu DT, Meng LZ, Zhao J, Li SP. Fermentation optimization for the production of bioactive polysaccharides from *Cordyceps sinensis* fungus UM01. Int J Biol Macromol 2015;79:180-5.
55. Yu SJ, Zhang Y, Fan MZ. Analysis of volatile compounds of mycelia of *Hirsutella sinensis*, the anamorph of *Ophiocordyceps sinensis*. Appl Mech Mater 2012;140:253-7.
56. Wang SY, Shiao MS. Pharmacological functions of Chinese medicinal fungus *Cordyceps sinensis* and related species. J Food Drug Anal 2000;8:253-7.
57. Seth R, Haider SZ, Mohan M. Pharmacology, phytochemistry and traditional uses of *Cordyceps sinensis* (Berk.) Sacc: A recent update for future prospects. Indian J Tradit Knowl 2014;13:551-6.
58. El Zahraa Z El Ashry F, 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.
59. Wang HP, Liu CW, Chang HW, Tsai JW, Sung YZ, Chang LC. *Cordyceps sinensis* protects against renal ischemia/reperfusion injury in rats. Mol Biol Rep 2013;40:2347-55.
60. Hao L, Pan MS, Zheng Y, Wang RF. Effect of *Cordyceps sinensis* and *Tripterygium wilfordii* polyglycosidium on podocytes in rats with diabetic nephropathy. Exp Ther Med 2014;7:1465-70.
61. Tianzhu Z, Shihai Y, Juan D. Antidepressant-like effects of cordycepin in a mice model of chronic unpredictable mild stress. Evid Based Complement Alternat Med 2014;2014:438506.
62. Luo Y, Yang SK, Zhou X, Wang M, Tang D, Liu FY, *et al.* Use of *Ophiocordyceps sinensis* (syn. *Cordyceps sinensis*) combined with angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) versus ACEI/ARB alone in the treatment of diabetic kidney disease: A meta-analysis. Ren Fail 2015;37:614-34.
63. Wang J, Liu YM, Cao W, Yao KW, Liu ZQ, Guo JY. Anti-inflammation and antioxidant effect of cordymin, a peptide purified from the medicinal mushroom *Cordyceps sinensis*, in middle cerbral artery occlusion-induced focal cerebral ischemia in rats. Metab Brain Dis 2012;27:159-65.
64. Negi CS, Pant M, Joshi P, Bohra S. Yar tsa Gunbu [*Ophiocordyceps sinensis* (Berk.) G.H. Sung *et al.*: The issue of its sustainability. Curr Sci 2014;107:882-7.
65. Mamta, Mehrotra S, Amitabh, Kirar V, Vats P, Nandi SP, *et al.* Phytochemical and antimicrobial activities of Himalayan *Cordyceps sinensis* (Berk.) Sacc. Indian J Exp Biol 2015;53:36-43.
66. Wang Y, Wang M, Ling Y, Fan W, Wang Y, Yin H. Structural determination and antioxidant activity of a polysaccharide from the fruiting bodies of cultured *Cordyceps sinensis*. Am J Chin Med 2009;37:977-89.
67. Yan JK, Wang WQ, Ma HL, Wu JY. Sulfation and enhanced antioxidant capacity of an exopolysaccharide produced by the medicinal fungus *Cordyceps sinensis*. Molecules 2012;18:167-77.
68. Zheng L, Hao L, Ma H, Tian C, Li T, Sun X, *et al.* Production and *in vivo* antioxidant activity of Zn, Ge, Se-enriched mycelia by *Cordyceps sinensis* SU-01. Curr Microbiol 2014;69:270-6.
69. Jayakumar T, Chiu CC, Wang SH, Chou DS, Huang YK, Sheu JR. Anti-cancer effects of CME-1, a novel polysaccharide, purified from the mycelia of *Cordyceps sinensis* against B16-F10 melanoma cells. J Cancer Res Ther 2014;10:43-9.
70. Ji J, Liu J, Liu H, Wang Y. Effects of fermented mushroom of *Cordyceps sinensis*, rich in selenium, on uterine cervix cancer. Evid Based Complement Alternat Med 2014;2014:173180.
71. Li XG, Pan WD, Lou HY, Liu RM, Xiao JH, Zhong JJ. New cytochalasins from medicinal macrofungus *Crodyceps taii* and their inhibitory activities against human cancer cells. Bioorg Med Chem Lett 2015;25:1823-6.
72. Yamaguchi Y, Kagota S, Nakamura K, Shinozuka K, Kunitomo M. Antioxidant activity of the extracts from fruiting bodies of cultured *Cordyceps sinensis*. Phytother Res 2000;14:647-9.
73. Koh JH, Kim JM, Chang UJ, Suh HJ. Hypocholesterolemic effect of hot-water extract from mycelia of *Cordyceps sinensis*. Biol Pharm Bull 2003;26:84-7.
74. Kuo YC, Tsai WJ, Wang JY, 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.
75. Wu DT, Meng LZ, Wang LY, Lv GP, Cheong KL, Hu DJ, *et al.* Chain conformation and immunomodulatory activity of a hyperbranched polysaccharide from *Cordyceps sinensis*. Carbohydr Polym 2014;110:405-14.
76. Chiou 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.
77. Yan XF, Zhang ZM, Yao HY, Guan Y, Zhu JP, Zhang LH, *et al.* Cardiovascular protection and antioxidant activity of the extracts from the mycelia of *Cordyceps sinensis* act partially via adenosine receptors. Phytother Res 2013;27:1597-604.
78. Zhao K, Lin Y, Li YJ, Gao S. Efficacy of short-term *Cordyceps sinensis* for prevention of contrast-induced nephropathy in patients with acute coronary syndrome undergoing elective percutaneous coronary intervention. Int J Clin Exp Med 2014;7:5558-64.
79. Chang Y, Hsu WH, Lu WJ, Jayakumar T, Liao JC, Lin MJ, *et al.* Inhibitory mechanisms of CME-1, a novel polysaccharide from the mycelia of *Cordyceps sinensis*, in platelet activation. Curr Pharm Biotechnol 2015;16:451-61.
80. 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.
81. Liu YK, Shen W. Inhibitive effect of *Cordyceps sinensis* on experimental hepatic fibrosis and its possible mechanism. World J Gastroenterol 2003;9:529-33.
82. Cheng YJ, Shyu WC, Teng YH, Lan YH, Lee SD. Antagonistic interaction between *Cordyceps sinensis* and exercise on protection in fulminant hepatic failure. Am J Chin Med 2014;42:1199-213.
83. Peng Y, Tao Y, Wang Q, Shen L, Yang T, Liu Z, *et al.* Ergosterol is the active compound of cultured mycelium *Cordyceps sinensis* on antiliver fibrosis. Evid Based Complement Alternat Med 2014;2014:537234.
84. Singh KP, Meena HS, Negi PS. Enhancement of neuromuscular activity by natural specimens and cultured mycelia of *Cordyceps sinensis* in mice. Indian J Pharm Sci 2014;76:458-61.
85. Zhang DW, Wang ZL, Qi W, Zhao GY. The effects of *Cordyceps sinensis* phytoestrogen on estrogen deficiency-induced osteoporosis in ovariectomized rats. BMC Complement Altern Med 2014;14:484.
86. Liu X, Zhong F, Tang XL, Lian FL, Zhou Q, Guo SM, *et al. Cordyceps sinensis* protects against liver and heart injuries in a rat model of chronic kidney disease: A metabolomic analysis. Acta Pharmacol Sin 2014;35:697-706.
87. Singh M, Tulsawani R, Koganti P, Chauhan A, Manickam M, Misra K. *Cordyceps sinensis* increases hypoxia tolerance by inducing heme oxygenase-1 and metallothionein via Nrf2 activation in human lung epithelial cells. Biomed Res Int 2013;2013:569206.
88. Meena H, Singh KP, Negi PS, Ahmed Z. Sub-acute toxicity of cultured mycelia of Himalayan entomogenous fungus *Cordyceps sinesis* (Berk.) Sacc. in rats. Indian J Exp Biol 2013;51:381-7.
89. Gurib-Fakim A. Medicinal plants: Traditions of yesterday and drugs of tomorrow. Mol Aspects Med 2006;27:1-93.
90. Huang BM, Chuang YM, Chen CF, Leu SF. Effects of extracted *Cordyceps sinensis* on steroidogenesis in MA-10 mouse Leydig tumor cells. Biol Pharm Bull 2000;23:1532-5.
91. Huang BM, Ju SY, Wu CS, Chuang WJ, Sheu CC, Leu SF. *Cordyceps sinensis* and its fractions stimulated MA-10 mouse Leydig tumor cell steroidogenesis. J Androl 2001;22:831-7.
92. Huang BM, Hsu CC, Tsai SJ, Sheu CC, Leu SF. Effects of Cordyceps sinensis on testosterone production in normal mouse Leydig cells. Life Sci 2001;69:2593-602.
93. Hsu CC, Tsai SJ, Huang YL, Huang BM. Regulatory mechanism of *Cordyceps sinensis* mycelium on mouse Leydig cell steroidogenesis. FEBS Lett 2003;543:140-3.
94. Hsu CC, Huang YL, Tsai SC, Sheu CC, Huang BM. *In vivo* and *in vitro* stimulatory effects of *Cordyceps sinensis* on testosterone production in mouse Leydig cells. Life Sci 2003;73:2127-36.
95. Wong KL, So EC, Chen CC, Wu RS, Huang BM. Regulation of steroidogenesis by *Cordyceps sinensis* mycelium extracted fractions with (hCG) treatment in mouse Leydig cells. Arch Androl 2007;53:75-7.
96. Huang BM, Hsiao KY, Chuang PC, Wu MH, Pan HA, Tsai SJ. Upregulation of steroidogenic enzymes and ovarian 17 beta-estradiol in human granulosa-lutein cells by *Cordyceps sinensis* mycelium. Biol Reprod 2004;70:1358-64.
97. Huang YL, Leu SF, Liu BC, Sheu CC, Huang BM. *In vivo* stimulatory effect of *Cordyceps sinensis* mycelium and its fractions on reproductive functions in male mouse. Life Sci 2004;75:1051-62.
98. Ji DB, Ye J, Li CL, Wang YH, Zhao J, Cai SQ. Antiaging effect of *Cordyceps sinensis* extract. Phytother Res 2009;23:116-22.
99. Guo Y. Medicinal chemistry, pharmacology and clinical applications of fermented mycelia of *Cordyceps sinensis* and JinShuBao capsule. J Mod Diag Ther 1986;1:60-5.
100. Huang Y, Lu J, Zhu B, Wen Q, Jia F, Zeng S, *et al.* Prevention and improvement of adrenal glands and thymus hormones, and infertile sperm count improve by 300% after *Cordyceps supplement*. Zhong Cheng Yao Yan Jiu 1987;10:24-5.
101. Wan F, Guo Y, Deng X. Sex hormone like effects of Jin Shui Bao [Cs-4] capsule: Pharmacological and clinical studies. Chinese Trad Patent Med 1988;9:29-31.

102. Dong CH, Yao YJ. *In vitro* evaluation of antioxidant activities of aqueous extracts from natural and cultured mycelia of *Cordyceps sinensis*. LWT-Food Sci Technol 2008;41:669-77.
103. Kokk K, Kuuslahti M, Keisaka T, Purmonen S, Kaipia A, Tammela T, *et al.* Expression of luteinizing hormone receptors in the mouse penis. J Androl 2011;32:49-54.
104. Manna PR, Slominski AT, King SR, Stetson CL, Stocco DM. Synergistic activation of steroidogenic acute regulatory protein expression and steroid biosynthesis by retinoids: Involvement of cAMP/PKA signaling. Endocrinology 2014;155:576-91.
105. Stocco DM. Clinical disorders associated with abnormal cholesterol transport: Mutations in the steroidogenic acute regulatory protein. Mol Cell Endocrinol 2002;191:19-25.
106. Manna PR, Stocco DM. Regulation of the steroidogenic acute regulatory protein expression: Functional and physiological consequences. Curr Drug Targets Immune Endocr Metabol Disord 2005;5:93-108.
107. Liu T, Wimalasena J, Bowen RL, Atwood CS. Luteinizing hormone receptor mediates neuronal pregnenolone production via up-regulation of steroidogenic acute regulatory protein expression. J Neurochem 2007;100:1329-39.
108. Hirakawa T, Galet C, Ascoli M. MA-10 cells transfected with the human lutropin/choriogonadotropin receptor (hLHR): A novel experimental paradigm to study the functional properties of the hLHR. Endocrinol 2002;143:1026-35.
109. Chen YC, Huang YL, Huang BM. *Cordyceps sinensis* mycelium activates PKA and PKC signal pathways to stimulate steroidogenesis in MA-10 mouse Leydig tumor cells. Int J Biochem Cell Biol 2005;37:214-23.
110. Wang SM, Lee LJ, Lin WW, Chang CM. Effects of a water-soluble extract of *Cordyceps sinensis* on steroidogenesis and capsular morphology of lipid droplets in cultured rat adrenocortical cells. J Cell Biochem 1998;69:483-9.
111. Chang Y, Jeng KC, Huang KF, Lee YC, Hou CW, Chen KH, *et al.* Effect of *Cordyceps militaris* supplementation on sperm production, sperm motility and hormones in sprague-dawley rats. Am J Chinese Med 2008;36:849-59.
112. Leu SF, Poon SL, Pao HY, Huang BM. The *in vivo* and *in vitro* stimulatory effects of coedycepin on mouse leydig cell steroidogenesis. Biosci Biotechnol Biochem 2011;75:723-31.
113. Tuli HS, Sandhu SS, Sharma AK. Pharmacological and therapeutic potential of *Cordyceps* with special reference to Cordycepin. 3 Biotech 2014;4:1-12.

Kanitta Jiraungkoorskul

Wannee Jiraungkoorskul

ABOUT AUTHORS

Kanitta Jiraungkoorskul, received her B.PH. in Environmental Science and Technology, and M.Sc. in Industrial Hygiene and Safety with thesis in title "Factors affecting urinary cadmium level and health risk assessment among farmer in Phrathatphadaeng Subdistrict, Mae Sod District, Tak Province.

Wannee Jiraungkoorskul, is currently working as Assistant Professor in Department of Pathobiology, Faculty of Science, Mahidol University, Thailand. She received her B.Sc. in Medical Technology, M.Sc. in Physiology, and Ph.D. in Biology. Dr. Wannee Jiraungkoorskul's current research interests are aquatic toxicopathology and efficiency of medicinal herbs.