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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

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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.

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Conflicts of interest

There are no conflicts of interest.

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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.