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Cordyceps militaris (L.: Fr.) Link – An Important Medicinal Mushroom.

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Cordyceps militaris is an important medicinal mushroom useful for the extraction of several bio-metabolites for natural drugs to revitalize the various physiological systems of the body from the ancient era. The constituents of *C. militaris* are now using widely in the modern pharmaceutical industries. The active principles of *C. militaris* are beneficial to act principally as pro-sexual, anti- cancer, immunomodulatory, and anti-oxidant agent, let alone its others beneficial activities for most of the systems of the body. In addition, it has lots of clinical applications. The prospects of this novel mushroom could be used not only for modern medicinal manufacturers, but also for the community people for the betterment of their health.

Keyword: *Cordyceps militaris*, Cordycepin, Immunomodulatory.

1. Introduction

Medicinal mushroom is a field involving the study of their biology, chemistry as well as their practical applications in the field of pharmacology, in order to prepare novel drugs by biotechnological means. The medicinal mushroom (*Cordyceps* species) is a valuable source of useful natural products having diverse biological activities^[1]. *Cordyceps militaris* (an entomopathogenic fungus), is one of the most important medicinal mushrooms, belonging to the class Ascomycetes, has been used popularly as a crude drug and a folk tonic food in East Asia^[2]. It possesses many kinds of active components (such as cordycepin, polysaccharides, ergosterol, and mannitol), and due to its several physiological activities, it is currently using for multiple medicinal purposes^[3, 4, 5]. It is widely distrib-

uted in North America, South America, Europe and Asia (6), from sub-tropical to temperate regions around the world.

2. Biological activities of *Cordyceps militaris*

The main active constituent of *C. militaris* fruiting bodies is cordycepin, which was first extracted from *C. militaris* and then found to be present in *Cordyceps sinensis*^[7] and *Cordyceps kyushuensis*^[8]. The cordycepin (3' - deoxyadenosine, C₁₀H₁₃N₅O₃, m. pt. 225 °C, [α]_D-47 °C), a nucleoside analogue^[7, 9], is considered as a nucleic acid antibiotic that might inhibit canceration of cells and thus contribute to the normalization of cancer cells as one of constituents of gene DNA^[7].

In addition, it has been reported that the cordycepin is intracellularly converted into its 5' -

mono-, di- and triphosphates that inhibit the activity of several enzymes in the purine biosynthetic pathway^[10].

3. Medicinal values

I. Anticancer Agent

Cordycepin (3'-deoxyadenosine) exhibits antimicrobial, anticancer, antimetastatic, immunomodulatory and insecticidal effects, and is one of the most important bioactive anticancer agents found in *Cordyceps* species (summer grass-winter worm). However, due to the requirements of specific hosts and strict growth environments, *Cordyceps militaris* is very scarce in nature. Therefore, the production of the anticancer agent cordycepin from *Cordyceps militaris* in a large scale is currently an acute issue that might be solved by a repeated batch operation of surface liquid culture^[11].

II. Antioxidant activity

Antioxidant activities of CM-hs-CPS2 were evaluated by various methods *in vitro*. Results showed that DPPH-scavenging activity, reducing power and ferrous ion chelating activity of CM-hs-CPS2 (8 mg/ml) were 89%, 1.188 and 85%, respectively^[12].

III. Improvement of Sperm Production

The present study shows that the CM supplement increased the total sperm number, the percentage of motile sperm cells and normal morphology in subfertile adult boars. The beneficial effect of CM supplement continued after stopping the supplement for 2 weeks. Since plasma concentration of cordycepin was increased by the supplementation with CM mycelium, it is suggested that cordycepin might be responsible for the increased semen production and sperm quality in boars^[13].

IV. Anti-influenza Virus Activity

An acidic polysaccharide (APS) was isolated from the extract of *Cordyceps militaris* grown on germinated soybeans. APS might have beneficial therapeutic effects on influenza A virus infection at least in part by modulation of the immune function of macrophages^[14].

V. Antifungal and Anticancer Activities

A cytotoxic antifungal protease was purified from the dried fruiting bodies of *C. militaris* using anion-exchange chromatography on a DEAE-Sepharose column. Electrophoretic analyses indicated that this protein, designated *C. militaris* protein (CMP), has a molecular mass of 12 kDa and a pI of 5.1. The optimum conditions for protease activity were a temperature of 37°C and pH of 7.0~9.0. The enzyme activity was specifically inhibited by the serine protease inhibitor phenylmethylsulfonyl fluoride. Amino acid composition of intact CMP and amino acid sequences of three major peptides from a tryptic digest of CMP were determined. CMP exerted strong antifungal effect against the growth of the fungus *Fusarium oxysporum*, and exhibited cytotoxicity against human breast and bladder cancer cells^[15].

VI. *Cordyceps militaris* against *Clostridium* spp.

Naturally occurring antibacterial agent, cordycepin could be useful as a new preventive agent against various diseases caused by clostridia. *C. militaris*-derived materials would be expected to alter the growth and composition of the intestinal flora and modulate the genesis of potentially harmful agents, thus maintaining optimal human health^[16].

VII. Cordycepin Suppresses Expression of Diabetes Regulating Genes

Based on these observations, cordycepin suppressed T2D regulating genes

through the inactivation of NF- κ B dependent inflammatory responses and suggesting that cordycepin will provide potential use as an immunomodulatory agent for treating immunological diseases^[17].

VIII. Fibrin binding activity

The fibrinolytic enzyme derived from the edible and medicinal mushroom *Cordyceps militaris* has fibrin binding activity, which allows for the local activation of the fibrin degradation pathway. It may be useful for thrombolytic therapy similar to other potent fibrinolytic enzymes such as nattokinase and earthworm enzyme. This enzyme could provide an adjunct to the costly fibrinolytic enzymes that are currently used for managing heart disease since large quantities can be conveniently and efficiently produced^[18].

IX. Anti-inflammatory effect

To determine the in vitro anti-inflammatory effect of hot water extract from *Cordyceps militaris* fruiting bodies (CMWE) on lipopolysaccharide (LPS)-stimulated nitric oxide (NO) production, tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) release in RAW 264.7 cells. The treatment of macrophages with various concentrations of hot CMWE significantly reduced LPS-induced production as well as NO, TNF- α and IL-6 secretion in a concentration-dependent manner. These results suggest that CMWE have potent inhibitory effects on the production of these inflammatory mediators^[19].

4. Clinical applications of *Cordyceps militaris*

Although *Cordyceps sinensis* was used more extensively than *Cordyceps militaris*, their clinical applications are more or less similar. Therefore, the extracts of *Cordyceps militaris* can be used in the cases of insufficient pulmonary function, coughing and sputum, dizziness,

memory failure, myodesopsia, vision failure, cold virus, inappetence, night sweat, pale face, pale lips, buzzing in the ears, toothache and loose teeth, insomnia and thirsty, cold or hot limbs, lumbago or pain in knees, nervous prostration, diabetes, night enuresis, sexual impotence, anemia and, slow recovery from illness^[3]. There might be some other clinical applications yet to be unveiled.

5. Cultivation

The natural fruiting bodies of *Cordyceps* are very rare and costly to collect. Fruiting body production in vitro is not repeatable and cordycepin content of natural *Cordyceps* is much lower than that of cultured mycelia^[20]. Cultivation of *C. militaris* mycelium using artificial media has recently been developed in which several methods have been reported for cordycepin production such as surface culture^[21] and submerged culture^[22]. The first method^[21] gave higher cordycepin yields. However, only a single *C. militaris* strain was employed and cordycepin production may vary with different strains.

5. *Cordyceps militaris* cultures have two main uses

First, the fruiting-bodies can be directly consumed as food. *C. militaris* can be used in stewed chicken, stewed duck, soup, hot pot, tea, and so on. Use of *C. militaris* in soup is very popular in Southeast Asia, especially in Guangdong, Hong Kong, and Taiwan, China. This use has been shown to be safe if consumption is less than 2.5 g/kg of body weight^[23]. Second, *C. militaris* fruiting-bodies and mycelia can be used as health products and drugs. In China, many health products contain *C. militaris*, and these include oral liquids, capsules, wines, vinegars, teas, yogurt, and soy sauce^[24]. Cultures of *C. militaris* are also used to produce drugs for maintenance of kidney and lung function, anti-aging, regulation of sleep, and chronic bronchitis^[25]. Currently, more than 30 kinds of *C. militaris* health products and drugs are available on the market^[26].

6. Conclusion

The ancient medicinal mushroom *C. militaris*, which has been used as a tonic drug in the old civilization, is now a prospective source to explore much mysterious potential. The novel components obtained from *C. militaris* already have significant number of clinically approved beneficial effects for human health^[3]. Especially, the anti-cancer agent cordycepin from *C. militaris* is expected to play evolutionary roles in the pharmacognosy sector which can lead to create a viable base for pharmaceutical industries as some emerging diseases like CANCER, SARS, AIDS, SWINE FLU have no complete remedies till now. In this context, this novel medicinal mushroom *Cordyceps militaris* needs further study, pharmacological investigations, clinical trials and public awareness.

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