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Medicinal Value of *Cordyceps sinensis*

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Abstract

Cordyceps, a caterpillar fungus is found to be used as high medicinal value by the people around the world. It is known as Yartsa Gunbu in Tibeto-Bhutanese, words originating from Tibetan language, meaning Yartsa: grass in summer and Gunbu: worm in winter, it is called "Dong chong Xia cao" in China and "Tockukaso" in Japan, words meaning the same. It grows on high Himalayan plateau, altitude between 3500 to 5000 meters. Well known species of genus cordyceps is *cordyceps sinensis* (CS) which is being widely used for clinical treatments and researches. *Cordyceps sinensis* is a dead remain of Himalayan Ghost moth belonging to a species *Hepialis aromoricanus*, also called as bat moth. It is considered to have high medicinal value and used to treat diseases like cancer, diabetes, pulmonary diseases, cardiovascular disorder, sexual dysfunction, renal disease and many other diseases for centuries in Chinese Traditional Medicine and Bhutanese Indigenous Medicine. Advanced Biotechnology has revealed that CS has wide range of bioactive constituents and minerals. There are numbers of researches conducted and have seen good impact of this CS on animals, cell cultures and on some cases of human patients, many researches demonstrated its ability in suppressing the tumor cells of various types of cancer. However, few hypotheses contradicted that CS suppresses the immunity. Due to lack of proper trials and studies on human, there is no authenticated or standard protocol that has been formulated for its prescription and clinical use in modern medicine.

Keywords: Diabetes; Asthma; Cancer; Pulmonary diseases; Cardiovascular disorder; Sexual dysfunction; Renal disease; Anti-aging

Introduction

Cordyceps Sinensis is an Ascomycete fungus which parasitizes moth caterpillar of species *Hepialis aromoricanis* [1] by its mycelia and forms stroma or fruiting body. Club shape mycelia is the head of CS and the caterpillar moth forms its body. Use of CS in Tibetan Traditional Medicine was documented in 15th century. However, the use of Cordyceps dates back to AD 620 in China, a written literature stating as magical creature describing its nature to transform from animal to plant [2]. Consistent popularity through ages in healing people provokes our interest in studying its molecular constituents and its effect on human health.

CS constitutes of numerous bioactive molecule, macro and micro molecules and different chemical components. Cordycepin (-3'-deoxyadenosine) [3,4] and cordycepic acid (D-mannitol) are spot light as the most active component among others as of now in respect to pharmaceutical effects [5], other chemical components and bioactive constituent includes all types of essential amino acids, vitamins mainly E, K, B1, B2, B12; carbohydrates, proteins, sterols, nucleosides and essential elements (Mg, Fe, Cu, Mn, Zn, Pi, Se, Al, Si, Ni, Sr, Ti, Cr, K, Na, Ca) To elucidate the role of CS in treating various diseases, it is imperative to know the nature of the components and understand its mode of action in molecular level.

As a matter of fact, its scarcity, difficulty in harvesting and higher demand in the market has rocketed up the price of CS in recent years costing more than US $15000 per kilogram. This has affected even the researchers limiting to conduct studies certainly due to financial issue and further leading to compromise in sample size.

As of now most of the studies were carried out by Chinese and Japanese researchers, this is perhaps because cordyceps entered the western world lately and cordyceps are not easily available in the west, so ostracized by default, creating custody to unawareness among the western community unlike Asians where it is used widely at homes and by local healers beside pharmaceutical purpose. But over the time cordyceps is gaining popularity in the west for its good healing power and least side effects, especially because of the people believing in more of Herbal than chemicals or synthetic drugs nowadays.

Literature Review

Effect of CS on various cancer cells

Apoptosis mediated by cordycepin was experimented *in vitro* by Chun-Yi Jen and team in Taiwan [6] using MA-10 cells (Mouse Leydig tumor cell) The viability of MA-10 cells was measured by MTT test after cordycepin treatment (CT) with different concentration and various time period. The viability

of cells was observed to be decreasing in time and concentration dependent manner. Morphology of the cells were studied using light microscope Olympus CK 40, morphology of apoptosis was characterized by plasma membrane blebbing and detachment from ground matrix. Significant decrease in cell cycle G1 phase and G2 phase were observed in MA-10 cells after subjecting the cell to the cordycepin of different doses suggesting that cell apoptosis in Mouse Leydig cell was induced by cordycepin. Further the pathway of -cordycepin induced apoptosis was investigated and it was found that caspase 7,3 and 9 expressions were activated by cordycepin. However, no prominent change in characteristics were observed in caspase 8 [6].

Inhibition of human colorectal cancer cells with cordycepin was demonstrated by Wei HE and team in Zhejiang University of Technology using SW480 and SW620 cells *in vitro* [7]. Different concentrations (1, 10, 100, 1000 µmol/L against the control with 0.2% (v/v) dimethyl sulfoxide medium) of cordycepin treatment were given in cell culture after 24 hours of its incubation, cells were counted after 24, 48 and 72 hours using trypan blue. The viability of the cell decreased with increasing dose of cordycepin treatment (CT) with time dependent manner. Cell cycle analysis using flow cytometry revealed that apoptosis was induced by cessation of cell cycle progression in the G0/ G1 phase with significant increase in caspase 3/7 and 9 activities. Some suggestions were also made that increase in c-Jun N-terminal Kinase(JNK), P38 kinase activity and protein expression levels of Bcl-2 pro apoptotic molecules played a role in cell apoptosis. The conclusion was drawn that inhibition of cell proliferation and further apoptosis of SW480 and SW620 cells were induced by cordycepin [7].

Similar action of cordycepin was also demonstrated in gallbladder cancer cells *in vitro* with its additional effect in down regulation of multidrug resistance (MDR) expression [8]. Its mode of action was by activation of AMPK (adenosine monophosphate activated protein kinase) signaling which lead to degradation of MDR/ HIF-1α (hypoxia inducible factor), cordycepin also inhibited the mTORC1 (mammalian target of rapamycin complex 1) in gallbladder cancer cell which leads to loss of cancer cell viability and apoptosis. MDR/HIF-1α and mTORC1 are factor responsible for chemo resistance.

Improvised complex of Selenium and CS (Se-CS) was produced and experimented its efficacy in treating Uterine cervix cancer [9]. The experiment was set up on mice using methylcholanthrene to induce uterine cervix cancer and Murphy's string method was followed for the same. Experiment included a control group also. Study parameters were compared among the group treated with Se-CS, CS only and sodium selenium only. Although there was no evidence of direct or prominent anti-tumor effect, the result suggested that Se-CS suppressed oxidative stress. This anti oxidizing activity was supported by the significant findings like decrease in lactate dehydrogenase (LDH), increase in glutathione (GSH) and decrease in lipid peroxidation (LPO) Restoration of endogenous antioxidants enzymes were also noted in Se-CS treatment group expressing immune stimulus to combat malignancy [10].

CS for treatment of Alzheimer's Disease (AD)

Treatment with *Cordyceps sinensis* on memory impairment related to Alzheimer's Disease (AD) was observed by studying the role of M1 muscarinic acetylcholine receptor (M1 mAChR) on F11 neurohybrid cells [11].

ERK (Extracellular-signal regulated kinase) phosphorylation was induced in F11 neurohybrid cells by muscarinic agonist carbachol (CCh), used as a ligand for M1 mAChR. Various types of CS extract were prepared and used; hot water extract of CS (HWCS), an ethanol extract of CS (ECS) and a mixed extract of both (HW+E) for the treatment of the cell *in vitro* and to administer orally for *in vivo* test. The constituent of ECS comprised of oleic acid, triglycerides, cholesterol, ergosterol and palmitic acid, whereas carbohydrate and protein were main component in HWCS. It was found that treatment with mixed extract (HW+E) of CS of 100 mg/ml had maximum effect on ERK phosphorylation. Expansion of ERK phosphorylation induced by CCh was observed to be dose dependent with CS extract treatment.

To study the role of M1mAchR in ERK, phosphorylation induced by CCh, Dicyclomine (DCM) and Pirenzepine (PIR) were used to treat F11 cells which are highly competitive antagonists to M1mAchR. The result suggested that stimulation of the M1mAchR by CCh was the key factor leading to ERK phosphorylation enhanced by extract of CS. Pretreatment with DCM and PIR exhibited drastic inhibition of CCh induced ERK phosphorylation [12].

Effect of M1mAchR by the extract of CS was further confirmed *in vivo* experimenting on amnesia mice model Memory impairment in the mice was induced by injecting anti-cholinergic drug scopolamine which is reported to malfunction the mAChR activity. Than the extract of CS (HW+E) was administered orally and memory test results were compared, result suggested that action of scopolamine induced memory impairment was dominantly attenuated by the treatment by CS extract, suggesting the enhancement of mAChR activity.

CS as an anti-aging formulation

D-galactose induced aged mice were used along with control group in the series of experiment to demonstrate the effect of *Cordyceps sinensis* extract (CSE) on the aspect of anti-aging factors characterized by oxidative stress, sexual dysfunction, memory impairment and age-related enzymes.

Mice treated with CSE showed an improved learning and memory in water maze test. Improved sexual response was exhibited after a CSE in dose dependent manner in castrated and sham castrated rats.

In the enzymatic test, the effect of CSE was reported to have significant reduction of lipid peroxidation level and monoamine oxidase acting with batten activity of superoxide dismutase, GSH-px and catalase in a dose dependent manner suggesting an affirmative effect on anti-aging enzymes.

Electron microscopy of hippocampus found that neurons and cellular organelles were well conserved with less

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degeneration in mice treated with CSE compared to control group mice, suggesting the enhancement of brain function by CSE [12,13].

CS reduces progression of diabetes mellitus

Drastic improvement in fasting blood glucose, glucose tolerance test, polydipsia and related hypoglycemic activity were demonstrated in numbers of research conducted on genetic and streptozotocin induced diabetic animal models after administration of *cordyceps sinensis* extract [14-16].

The protective nature of CS to pancreatic β-cell and its stimulation was demonstrated using extract from solid-state fermented CS on type 2 Diabetes mellitus by a Team in Taiwan [17]. The cell viability was seen to be improved in *in vitro* experiment on mouse pancreas insulinoma β-cells treated with CS extract, where comparison set was done with Streptozotocin (STZ) alone, CS and combination of CS and STZ. The toxicity of STZ was being suppressed by CS. Moreover, findings suggested that CS reduced the complication related to Diabetes Mellitus like improvement in electrolyte balance and decrease in deposition of collagen fibril in histopathological examination of renal cortical over the control model which is a typical feature of Diabetic nephropathy [12].

A study was conducted on Diabetic Nephropathy rat models to see the effect of CS with *Triptorium wilfordii polyglycosidium* and with CS alone focusing on podocytes, set in different grouped mice. Significant improvement was observed in relation to glomerular disorder, tubulointerstitial damage and glomerular podocyte [16]. On evaluation after the administration of CS and TWP, better protective effect was witnessed with CS and TWP treatment than CS alone. Tubular deformation and glomerular hypertrophy were drastically suppressed. Comparative study with TWP affect suggested that CS suppressed the toxicity nature of TWP, which is a limiting factor for clinical use [9].

Effect of CS on liver fibrosis

In an experiment conducted by Yuan Peng and his team in Shanghai, China [18]. They made a finding that ergosterol in cultured mycelium *Cordyceps sinensis* (CMCS) has an anti-fibrotic and anti-inflammatory effect on carbon tetrachloride model of liver fibrosis in mice. Deposition of collagen were decreased and inflammatory cell infiltration was attenuated with the treatment of CMCS. Liver fibrosis was induced in mice by injecting 10% carbon tetrachloride intraperitoneally. Result evaluation showed a marked betterment in serum liver function parameters and ratios of liver/body weight and spleen/body weight percentage. Expression of α-SMA which is an important marker of liver fibrosis was observed to be suppressed with CMCS treatment. In *in vitro* test of cell culture to see the action of ergosterol suggested it's good potential in resisting liver fibrosis by inhibition of hepatocytes and hepatic stellate cell activation in dose dependent manner [18].

Effect of CS on osteoporosis

A plant chemical, Isoflavones, belonging to phytoestrogen and also a component of CS was extracted using ethyl acetate and used against ovariectomized rat to see its effect on estrogen deficiency osteoporosis, experiment setup also included sham control group [19]. Manifold changes were exhibited by the rat with Isoflavones extracted from CS (CSIF) treatment:

- Increase in osteocalcin
- Decrease of calcium in urine and plasma
- Decrease of inorganic phosphate in plasma
- Decrease in collagen type I and interferon-ϒ
- Decrease in mineral dissolution than control group in a solubility test.
- Picture of trabecular bone was comparatively normal than control group.

All these evidences indicate that the osteoporosis is being prevented with treatment of CSIF by its potential in stimulating formation of bones and down regulation of resorption.

Effect of CS as energy booster

It was long believed by the people that CS has immune stimulation and energy boosting potential. Beside the use of CS in pharmaceutical purposes, it was also accustomed as a healthy food for centuries in china, Bhutan, Nepal, India etc. and more often given to the elderly or aged people for their betterment of their health in general aspect. Some outstanding performances among the athletes and sports man were reported confessing their credits of performance to the use of CS [3].

20 elderly persons at the age between 50-75 were randomly selected and a small pilot study was conducted in University of California, Los Angeles(UCLA)[13], their evaluation consisted of the measurement of metabolic threshold based on the accumulation of lactate which indicate improved aerobic activity in the particular subject and the other parameter was ventilatory threshold, increase in this factor down regulates the accumulation of lactate and further facilitates buffering of accumulated lactic acid. In the experiment, after 12 weeks of treatment with CS, metabolic threshold and ventilatory threshold were observed to be increased by 10.5% and 8.5% respectively, ultimately leading to decrease in muscle fatigue and improved strength and exercise load. Although the data obtained were limited and it was a small clinical trial in this case, the finding suggested that CS has positive effect on aerobic performance in elderly people further opening a ground for more advanced research on it.

Official supplier of traditional medicines in the kingdom of Bhutan produces a pure herbal supplement called CordyPLUS, which contain six exotic herbs along with CS used for fatigue, weakness, old age, skin, hair radiance, strength and the stimulation of internal organ. The product is gaining popularity over the years indicating a positive result by the consumers after using it. Cordy active is another product having few additional ingredients formulated for sports man.

Artificial cultivation of CS

CS are artificially cultivated and marketed for consumption as a food beside for research and pharmaceutical purpose, especially in China and USA [5]. Mass artificial production of mycelium is done using culture mediums, two methods of cultivation includes liquid culture fermentation and Solid substrate method. Millet, rye grain and silk worm based substrates are used as culture media, these differences in substrate used harvested CS of different composition. As the CS in liquid culture is obtained by straining, most of the vital extracellular components are excluded when harvesting. Low level of cordycepin and stunted growth were also observed among CS grown on rice substrate. To produce the same quality of CS as wild CS has never been possible, because there are many factors influencing the growth of CS. Some researchers also tried hybridization of the CS in respect to the quality and the quantity of bioactive molecules being generated by the mycelia. John C Holliday and team created a hybrid called *Cordyceps sinensis* Alohaensis using a snake venom which proved to be a higher potency than other artificially cultivated CS and it was more easily cultivated on solid substrate [20].

Simulated environment for CS cultivation is very difficult to monitor and to obtain the same quality of CS like wild CS because the wild CS undergoes different growth phases under natural environment during its long stretched growing stages requiring special growth conditions. Major factors influencing its growth are temperature, humidity, soil pressure, air composition and light intensity. For perfect indoor cultivation, it is required to fully understand their life stages and generations such as mechanisms how the fungal infect the caterpillar moth, their spontaneous development, nutrient sources and requirements. Whereas the idea is vague as of now in many aspects for the matter of fact that most of the transformation occur underground under natural condition.

Indoor CS development from the host larva was observed in a High-Altitude Laboratory on Sejila Mountain, Tibet by Lian-Xian Guo and his group [21], the soil used initially to keep larva was from natural habitat sampled from Sejila Mountain only. Their findings regarded that low temperature incubation increases the level of unsaturated fatty acid content and could promote infection by *Hirstutella sinensis* which is a responsible fungal to form this organism. Soil pressure were considered to have impact for stromata to sprout out vertically and in single form from the head of the larva. Adequate sunlight had negative impact on the growth rate of the stromata in the observation made in wild CS. 20% of larva brought into the laboratory died gradually within the period of two weeks however they also observed the transformation of dead larva to CS. Over all approximately 13% of the total larva brought to the laboratory transformed to CS.

Discussion

Side effects of CS

As the CS has been used as food for so long and the trend still continues, logic remains that the side effect is very minimal or it has no side effects at all. As of now major side effects are not being reported, however few people complained of mild gastro intestinal (GI) disturbances, diarrhea and nausea. It is healthy to think that there may be some side effects undiscovered and to work for the same. One hypothesis stated that CS could be either immune stimulating or immune suppressing depending upon the strain of the CS, one strain was pointed out to be strong immune suppressor and comparison of its strength was given as equal as “cyclosporin A” which is used as immunosuppressant drug in organ transplantations [22]. This suggests that detail study of the CS strains may bring light on this contradictory issue. While some proposed contraindications of CS treatment for the patients suffering from autoimmune diseases like SLE (Systemic lupus erythematosus), rheumatoid arthritis and multiple sclerosis, this contemplation was based on the potential of CS in stimulating the immune system, which would worsen the condition of the patient with its increased immune mechanism destroying own cell which is the hallmark of the autoimmune disease. Similar contraindications were also proposed for pregnant and breastfeeding mother to assure their safety beside insufficient data and evidence based scientific research to prove these statements.

Conclusion

The long history and present trend of the use of CS by the people beside being very expensive makes more curious and demands further study and research to elucidate the tangible healing power of the CS for further advancement. High technology research revealing the molecular aspect and the nature of the CS component would open a new ground in formulating drugs for many chronic diseases which is not being able to cure by our modern medicine for now. Although the complete treatment of the chronic diseases was not documented, significant improvement was indicated in most of the research giving light of hope for the treatment regime to eliminate diseases if meticulous formulation is discovered with more advanced researches. There is a risk of getting this species endangered due to overexploitation which is already an issue, alarming us that it cannot continue to serve growing number of human consumption like this for so long, so it is imperative to understand and invest an effort to find or identify the potential feature of this mysterious CS in healing people before its extinction, so that we can switch over to alternative source and reproduce for needy people in substantial way and cheap. As the studies has shown its least side effects, using CS would replace many modern treatments which has high side effects like steroids and Chemo drugs. The results of the research conducted so far has always encouraged and opened a new ground for continuous studies for the same revealing and generating a diverse idea.

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