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Review Paper

Unveiling the secrets of Himalayan Viagra (Ophiocordyceps Sinesis)

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ABSTRACT

Himalayan viagra is a commonly known as yarshagumba. It is one of the most important entomopathogenic fungus. It is found in the parts of himalaya and nepal, tibet and china. In nepal it is one of the largest exporters of cordyceps in the world after china and it influence on the economic as well as livelihood of himalayan people. due to over harvesting and climate changes has now been in the list of endangered species. Cordyceps sinensis is a fungus that parasitizes ghost moth larvae and produces a fruiting body prized as herbal medicine, to Ophiocordycipitaceae family. It has wide application in pharmaceutical and health sectors. Its unusual lifecycle and wide range of medical application raised curiosity towards scientific community. The main constituent of the extract derived from this fungus comprises of Cordycepin (3'deoxyadenosine) which has a very potent anti-cancer, anti-oxidant and anti-inflammatory activities.

INTRODUCTION

Nature has always served as a leading example of the remarkable occurrence of symbiosis, and in addition to the three basic essential needs - food, shelter, and clothes nature has offered a perfect storehouse of remedies to cure all human diseases. medicinal plants are important part of the traditional system of medicine. natural therapies are now used to treat the majority of common ailments and some nutritional issues. when it comes to medicinal values, however our interest are not limited to plants or herbs. aside from plants, numerous traditional system of medicine have

suggested various alternative sources for treating human illness. fungus is one such example, which has shown medical potential in many circumstances and has the ability to produce novel chemicals with therapeutic use. The fungus yarsagumba parasitizes the larvae of 'ghost moth'. live caterpillars are used to germinate the fungus. infected insects lift their heads up from earth tunnels towards the surface. fungal stromae grow from the caterpillar's mouth and extend above ground when they die. this allows ascospores to disperse. Cordyceps is also known as keeda jadi (caterpillar fungus) india, found in subalpine

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region of grassy land of himaayas mainly in uttarakhand. It is also reffered as himalayan gold. chinese name of this mushroom is Dong-Chong-Xio-Cao. In tiebetian lands it is identified as Yarsa-Gunba. Himalayan Viagra is the worlds most expensive fungi, it is used since millenium of years. Price of 1 KG of Himalayan Viagra is about 20 lakh.(1) The word cordyceps originated from greek term 'kordyle' means- club and latin etyman 'ceps' - means head. cordyceps sinesis is a medicinal fungi which incresingly used as nuritional source. there have been a variety of pharmacologically active compunds (cordycepin) has recieved much attention due to its broad spectrum biological activities.It contains majority of chemical constituents like cordycepin, cordycepic acid,Adenosine, ergosterol, hypoxanthine, polysaccharides, myriocin, cordymin etc. In recent decades interest in cordyceps species has been amplified due to its other pharmacological activities like antioxidant, antiaging, in cvs, as hypocholesterolemic, hypotensive,and vasorelaxation activities, it boost immunity, boosts respiratory function, supports liver function, increase energy (anti-fatigue) and boost exercise capacity, improves renal health, antiviral and antitumor effects, aphrodisiac.(3)

Lifecycle:

Its a fungi that's growing on a ghost moth larva, a lepidopteran insect. during summer and early autumn, adult yarsagumba fruiting bodies release millions of ascospores in the air, which and

germinate inside the larvae's self defence mechanism weakens, the fungal cells spread throughout the body via the circulatory system. because the larva is subterranean by nature, it digest further into the soil and enteers from the back in a vertical position.(2) this is why the yarsagumba host larva is constantly upright, and the herb develops from the larva's head. during the winter, fungal cells develop fast inside the larva's body, consuminf everything of the larva's internal organs except its exoskeleton. The fungal cells then transform into endosclerotium is a dormant stage in yarsagumba's life cycle that can withstand unfavourable climatic condition, most notably snowcold temperatures when spring arives, outside temperture gradully rises, causing the endosclertium to germinate and extrude through the prothorax region of the head, eventually researching the soil. the stroma is the proportion of yarsagumba that emerges from the host alive the stalk, stipe, or stem at the base of the stroma, and the head, or fertile section at the apex, make up a mature stroma. stroma reach complete maturity in the summer. when the fertile section of the head generates asscospore which infect larvae in that area particularly this is the time of the year when the collectors start to collect yarsagumba. as a result, yarsagumba's life cycle takes one year to commplete. it develops from the host larva and forms a mushroom fruiting body above ground in the spring and summer but grows inside the host larva in the autumn and winter.



Fig. 1. Image of yarsagumba

third position carbon of ribose sugar. cordycepic acid is D-mannitol. it is structurally similar to an isomer of quinic acid it differs mainly from quinic acid as it forms dextrorotatory instead of forming lactone. it belongs to chemical class of organic acid and it can increase nutrient absorption and have potential health benefits when consumed in moderation. (3)

Polysaccharides

The fruiting bodies of cordyceps spp. contains 3-8% polysaccharide. the polysaccharides obtained from cordyceps species are medicinally important and play as main constituent in drug formulation.

the polysaccharides obtained from edible, medicinal mushroom were successfully shown to exhibit antitumor and immunomodulating properties.

Protein and nitrogenous compounds

It contains essential amino acids, proteins, peptides, polyamines. additionally, the cordyceps . contains rare cyclic dipeptides, including cyclo-[gly-pro], cyclo-[leu-pro], cyclo-[val-pro], cyclo-[ala-leu], and cyclo-[thr-leu]. these cyclic dipeptides are known to have immunomodulatory, antioxidant, and antitumor property.

Amino acid composition	Mycelium powders	Mycelia	Fruit body A	Fruit body B
Asp	2.47	1.05	1.67	1.84
Thr	0.95	0.65	1.47	0.83
Ser	0.82	0.49	1.51	0.78
Glu	3.55	1.12	3.44	2.66
Pro	0.90	0.72	0.96	0.95
Gly	1.19	0.58	1.25	0.73
Ala	1.21	0.75	1.40	0.95
Cys	0.25		0.43	
Val	1.42	0.63	1.13	0.80
Met	0.47	0.18	0.25	0.18
Ile	1.14	0.44	0.62	0.53
Leu	1.84	0.69	1.20	0.95
Tyr	0.89	0.31	0.88	0.67
Phe	1.84	0.51	0.71	0.61
Lys	1.27	0.81	1.66	1.15
His	0.58	0.28	1.71	1.13
Arg	1.47	0.04	2.88	1.6
Total content	21.59	9.23	23.15	16.40

Nucleotides

Cordyceps sinensis is rich in nucleotide and its derivative. nucleotides like adenine, adenosine, inosine, cytidine, cytosine, guanine, uridine, thymidine, uracil, hypoxanthine, and guanosine have been isolated from c. sinensis. among all these nucleotides guanosine has highest ratio than other component. Nucleotides are essential for cellular metabolism and have been linked to improved immune function and overall health.

Sterols and fatty acids

As cordyceps is in the class of fungi it contains sterol in the form of ergosterol as it is important

part of fungal cell wall. sterols is essential part of vitamin D2. in cordyceps species the ergosterol was 1.44mg/g in mycelium, while 10.68mg/g in fruiting bodies. sterols have potential benefits for skin health, cholesterol management, and may possess anti-inflammatory properties.

The fatty acids found in cordyceps spp. can be classified in two that is saturated and unsaturated . fatty acids such as lauric acid, myrtic acid, pentadecanoic acid, palmitic acid, linolic acid, oleic acid, steric acid, docosanoic acid, are reported in cordyceps.

Fatty acid	Content (% of total FA)	
	Fruiting body	Corpus
Palmitic acid (C16:0)	24.5	21.5
Palmitoic acid (C16:1)	2.3	2.1
Stearic acid (C18:0)	5.8	5.0
Oleic acid (C18:1)	6.0	17.7
Linoleic acid (C18:2)	61.3	33.0
Linolenic acid (C18:3)	–	20.6

Pharmacological potential of cordyceps species : Recent research has been revealed that yarsagumba has pharmacological potential due to its unique bioactive components(6)

1)Cardioprotective activity-

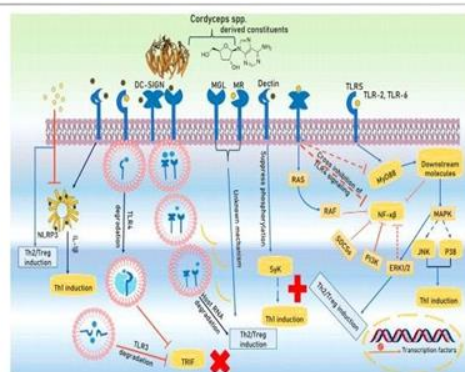
As the mycelia and fruiting bodies of cordyceps sinesis is rich in adenosine, mild hypotensive effect and platelet aggregation inhibition are expected. the ethanolic extract of yarsagunba mycelium (CsB851) also inhibits thrombus formation in abdominal aorta in rabbits. It shows anti arrhythmic, vasodilating effect, negative inotropic effect and also inhibits thrombus formation. It also found to stimulate erythropoiesis in mouse bone marrow so for future purspective it can be used in humans.(3)

2)Immunomodulatory activity:

Immunomodulators are the chemicals or compounds that helps in regulation of immune system of the body. there are various compounds in cordyceps spp which possess immunomodulatory activity. active constituents present in cordyceps spp. are spotted by Toll- like receptors (TLRs) and C- type lectin receptors (CLRs) during initiation of initiation of immunomodulation and hyporesponsiveness in antigen-presenting cells APCs. these active constituents not only alter the TLRs and CLRs expression in APCs but also masterfully manipulate their intracellular signalling. TLRs use the Toll/IL1receptor (TIR)-domain covering adapter proteins such as MyD88 and TRIF (TIR domain- containing adapter inducing IFN- β).

The active constituent of cordyceps spp.) transmit TLR4 signaling to MAPK pathway and extracellular signal-related kinase one and 2 (ERK1/2) activation backing Treg/Th2 induction. Furthermore, coherence of DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) along with TLR4enables active constituents of Cordyceps spp. to trigger unknown intracellular pathways that cross-inhibit MyD88 and NF- κ B activation. These constituents are further restrained NF- κ B activity via the upregulation of negative regulators of TLRs signaling like a suppressor of cytokine signaling (SOCS) and phosphatidylinsoitol-3-kinase (PI3K) along with DC-SIGN mediated rapidly accelerated fibrosarcoma (RAF) signaling. In the prevention of priming Th1 cells, the role of NF- κ B is a core factor due to its support's inflammation by inhibition. The multiplicity of signaling pathways is improved by co-receptors' involvement of CLRs (DDC-SIGN). Activated mannose receptor (MR) and macrophage galactose-type C-type lectin (MGL) helps for the differentiation of Treg/Th2. Degrading host key intracellular molecules is another strategy that Cordyceps spp. exploit to reprogram host immunity. Polysaccharide constituents of Cordyceps spp. degrades endosomal TLR2, TLR3, TLR4, TLR6, and host mRNA which provides Treg/Th2 responses support. The active bio-constituents stimulate Treg/Th2 cell priming which have been stated by CLRs involvements. NLRP3 inflammasome (NLRP3 and caspase-1) modulate inflammatory

processes via secretion of IL-1 β and Th1 intensification. (2)



JRE 2 | Signal pathway activation by TLRs and CLRIs and its interaction with the Cordyceps spp. derived constituents.

Various species of cordyceps spp. exhibit immunostimulatory activity in various parts of body as it triggers the immune system of body through inducing its components. Ethanolic extract of *c. sinensis* enhance phagocytosis activity as evidenced by carbon clearance in tumor bearing mice. It also caused a remarkable increment in an acid phosphatase activity and lysosomal enzyme in macrophages identifies its antitumor acting via the immuno stimulating function.(9)

3)Anticancer or antitumor effect

cordycepin has been hypothesized to have anticancer effect as it exhibits structural similarity to adenosine, and other bioactive compounds like polysaccharides, sterols. it has been documented as it shows capability to restrain the growth of tumors. cordycepin is a nucleoside analogue that can affect DNA or RNA polymerase function (3). it transforms into mono, di and tri phosphates of 3-deoxyadenosine after it enters the cell. it is probable that cordycepin monophosphate causes termination of elongation by integrating into the place where nucleic acids are meant to incorporate because of the structural similarity to adenosine monophosphate. additionally, phosphoribosyl-pyrophosphate amidotransferase activity may be inhibited by cordycepin monophosphate, which would prevent de novo purine synthesis.

cordycepin restrain the growth of cancer cells by triggering adenosine A3 receptors followed by the

Wnt signalling pathway, including glycogen synthase kinase three beta pathway activation and cyclin D1 inhibition. the antiproliferative response of cordycepin is documented to be mediated via the mammalian target of rapamycin (mTOR) and 5' AMP- activated protein kinase (AMPK) signaling. it has also been documented that *c. sinensis* inhibits tumor-cell proliferation activities in different types of cancer cell lines, such as jurkat, HepG2, PC3, colon 205, and MCF-7(2) (9)

4)Aphrodisiac potential

Cordyceps species are highly energetic source in sexual dysfunction and sexual stimulant and specially known as himalayan viagra. it stimulates release of sexual hormones like testosterone, estrogen, and progesteron, controlling reproductive activity, and restore impaired sexual functions. cordyceps *sinensis* induce steroidogenesis, administration of cordycepin can increase the weight of epididymis, sperm motility, movement, and the number, quality and quantity of mature sperm. it increases the steroidogenesis through PKA and PKC signal transduction pathways, plasma testosteron level and testesteron synthesis.(12) cordyceps *sinensis* activated the cAMP-protein kinase A signal pathway, but not protein kinase C, and arrenuated P450 side-chain cleavage enzyme (P450_{scc}) activity to reduce human chorionic gonadotropin-stimulated steroidogenesis in purified mouse leydig cells.

9(15) Similarly, the effect of *C. sinensis* was shown on female reproductive system, it is explored as *C. sinensis* stimulates E2 production in human granulosa-lutein cells (GLCs) by upregulating the expression of several key enzymes specially *stAR* and *aromatase*, making person for enhanced fecundity of women.

5) Antifatigue and antidepressant activity

Yarsagumba facilitates efficient oxygen utilization, enhance energy metabolism in the mitochondria and also increase level of beta-ATP, hence it shows anti-fatigue and antidepressant activity. Athletes use *Cordyceps* spp. to deal with fatigue and weakness thus increase energy levels and extra endurance performed by study to evaluate the effect of *Cordymax*TM Cs-4, A mycelial fermentation product of *C. sinensis*, on energy metabolism. It is well known that fatigue is closely related with depression, the antioxidant properties of *Cordyceps* enhance energy metabolism in the mitochondria and facilitate the efficient utilization of limited oxygen supply.

6) Hypotensive, Hypocholesterolemic and vasorelaxative activities

The presence of protein in *C. sinensis* the mean arterial pressure and induce a direct endothelium-dependent vasorelaxant effects the production and stimulation of NO and endothelium derived hyperpolarizing factor. Along with this *C. sinensis* possess potent anti-lipid peroxidation activity and prevent accumulation of cholesterol ester in macrophages via suppression of LDL oxidation. Yamaguchi et al. (10) performed this study, on water extract of *Cordyceps militaris* on serum lipid and lipid peroxide levels and aortic cholesterol accumulation using an atherosclerosis mouse model and concluded that CMW prevent cholesterol deposition in aorta by lowering performing LDL oxidation via scavenging free radicals.

7) Hypoglycemic effect

Kiho et al. displayed that polysaccharide obtained from the cultivated mycelium of *C. sinensis* (CS-F30) lower the plasma glucose level in the normal and streptozotocin (STZ) induced diabetic mice by intraperitoneal administration. (17) also it is identified as CS-F30 potentiate the activity of *glycokinase*, *hexokinase*, and *glucose-6-phosphate dehydrogenase* thus accelerating the glucose metabolism, which is responsible for its antidiabetic activity. (16) the industrial fermentation product that is *Cordymax*TM Cs-4 (a proprietary mycelial strain from natural *C. sinensis*) improves the metabolism of glucose by increasing insulin sensitivity and improving oral glucose tolerance.

8) Hepatic protection

Cordyceps sinensis is valuable to regulate the imbalances of kidney for example for the reduction of hematuria and proteinuria with the evident restoration of the tissue evidenced by histological analysis (Ding et al., 2011). It supports kidney transplantation in combination with drugs such as cyclosporin

A. the combination is very helpful because of cyclosporin in high doses induce kidney damage.

9) Nutraceutical applications

Cordyceps is nutritionally important components including various types of essential amino acid, vitamins like B1, B2, B12, and K different kinds of carbohydrates such as monosaccharides, oligosaccharides, and various medicinally important polysaccharides, proteins, sterols, nucleosides, and other trace elements (Hyun 2008; Yang et al. 2009, 2010; Li et al. 2011). The fruiting body harbors many abundant amino acids such as lysine, glutamic acid, proline and threonine as well as it is rich in unsaturated fatty acids like linoleic acid. Hence it is highly nutritious and very useful for human for their nourishment. It is a natural medicinal fungi which is widely liked by people now a days as we believe more in natural therapy than chemotherapy because its least side effects.



CONCLUSION:

Recent years have witnessed a growing preference for natural and herbal medicine over synthetic alternatives. Cordyceps, an ancient mushroom, has long been used in traditional medicine for various health benefits, however, its potential, particularly through modern cultivation techniques is still largely untapped. This fungus is a rich source of bioactive metabolites with over 21 clinically approved health benefits. Although some of its traditional uses are now supported by scientific evidence, research and development remain largely confined to specific regions. Cordyceps spp. genus comprises a plethora of compounds and some of them showed therapeutic and pharmacological activities in pre-clinical, in vitro and in vivo studies like its immunomodulatory activity, antitumor, vasorelaxation and hypercholesterolemic activity, hepato-protective action, antiaging potential, aphrodisiac potential etc. Hence it can be useful for future perspective.

Future Prospectus:

Cordyceps is a natural medicinal mushroom that is currently favoured by individuals as they tend to trust natural therapy more than chemotherapy due to its reduced side effects. The growth characteristics of cordyceps must be investigated thoroughly to cultivate this mushroom for mass scale production, enabling the collection of sufficient biomolecules from its mycelium extract. There exists a significant motivation to employ interdisciplinary biotechnological and chemical methods to isolate and enhance the bioactivity of the metabolites derived from this entomopathogenic fungus. Cordycepin's structure indicates that it contains five N and three O atoms, which could potentially form transition metal complexes in the form of di-, tri-, and tetradentate ligands since metals can incorporate the lone pair of electrons from donor atoms into their vacant d-orbital. Additionally, the other pharmacologically

active compounds aside from cordycepin also need to be identified, and their structure-function relationship must be elucidated.

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