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The health benefits of *Cordyceps militaris* - a review

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ABSTRACT

***Cordyceps militaris*, a macro fungus is medicinally important for having potential therapeutic applications. Its medicinal properties are due to variety of therapeutically important constituents including cordycepin, cordymin, ergosterol, glycoprotein, polysaccharides, as a part of its composition. This review focuses on the pharmacological properties of *Cordyceps militaris* explored by different workers from time to time.**

Key words: *Cordyceps militaris*, Bioactive compound, Cancer, Cordymin, Polysaccharides

INTRODUCTION

Edible mushrooms are widely used for their high nutritional and therapeutic value as a functional food. Additionally, they have been highly appreciated for their medicinal and therapeutic applications (Chang and Miles, 2004). Medicinal mushrooms produce a vast diversity of bioactive compounds such as polysaccharides, proteoglucans, terpenoids, phenolic compounds, steroids, and lectins. These compounds have a wide range of therapeutic effects and can act as immuno-modulatory, anticarcinogenic, antiviral, antioxidant, and anti-inflammatory agents (Badalyan, 2012; Villares *et al*., 2012). *Cordyceps* is a highly valued fungus in this regard which thrives at altitudes above 3,800 meters above MSL, in the cold, grassy, alpine meadows on the mountainous Himalayan plateau (Alessandro and Francesca, 2009; Sharma *et al.*, 2015a,b;2016). Because of the difficulties involved in harvesting, it has been expensively priced. Despite its cost and rarity, the unprecedented medicinal applications of *Cordyceps* has made it a highly valued staple component of the traditional Chinese and Tibetan medicine. This review gives a general overview of the modern progress in *C. militaris* research, with regard to evaluation of the active chemical components, the pharmacological effects and the research and development of products in recent years. *C. militaris* is a parasitic fungus on *Lepidoptera* larvae which has been used as a traditional medicine in China. It is well known for its nucleoside, cordycepin (3'-de-oxyadenosine) and its derivatives, ergosterol, polysaccharides, glycoprotein and peptides containing α-aminoisobutyric acid. Polysaccharides and cordycepin present in *C militaris* account for the anti-inflammatory antioxidant, anti-tumor, anti-metastatic, immunomodulatory (Das *et al.*, 2010), hypoglycaemic, steroidogenic and hypolipidaemic effects (Wang *et al.*, 2014). Its biological activity includes anti-tumour (Lee *et al.*, 2015), anti-metastatic, immunomodulatory, antioxidant (Ma *et al.,* 2012), anti-inflammatory, insecticidal, antimicrobial, hypolipidaemic (Mizuno *et al.,* 1999), hypoglycaemic (Ma *et al.*, 2015), anti-ageing, neuroprotective, and renoprotective properties (Patel *et al.,* 2013).

1. INHIBITION OF CELL PROLIFERATION

Cancer is one of the leading causes of death, still needing an effective medicine for its remedy. Cordycepin from *C. militaris* has played an evolutionary change in pharmacognosy, leading to establish as a viable base for the treatment of emerging diseases like cancer, SARS, AIDS and Swine flu. Electrophoresis analysis (SDS PAGE) and gel filtration showed strong inhibition of the viability of human cancer cells such as MCF-7 cells with an IC50 of 15.0 uM,5637 cells with an IC50 of 9.30 uM, A-549 cells with an IC50 of 8.10 uM (Park *et al*., 2009). Zhang *et al.*, (2010) reported that MCMP strain (a water soluble polysaccharide) isolated from mycelium induces anti-tumor activity after 48 hr incubation against Hep-G2 cells, Hela cells, and mesangial cells. Wong *et al*. (2011) purified a protease known as Cordymin from *C. militaris* which showed anti-proliferative activity towards breast cancer cells (MCF-7). It is important to understand that *C. militaris,* inhibits cell proliferation in tumor cells in order to develop it as a new agent for the prevention and treatment of cancer. The A3 adenosine receptor (A_3AR) is a member of the AR family, it has utility in the treatment of cancer. It is reported to be over expressed in cancer and inflammatory cells, as compared to normal cells where expression is low (Wong *et al.*, 2011).

2. THROMBOLYTIC ACTIVITY

Thromboembolic disorders such as pulmonary emboli, deep vein thrombosis, strokes and heart attacks are the main causes of morbidity and mortality in developed countries (Dickneite *et al*., 1995). Current clinical thrombolytic agents are reported to be plasminogen activators that convert the proenzyme plasminogen to the active enzyme plasmin, which degrades fibrin (Collen and Lijnen, 2005). New thrombolytic agents are developed for fibrin-specific property, acting on the surface of thrombus that avoids excessive induction of systemic fibrinolytic system. These agents are reported to reduce bleeding tendency induced by tissue type plasminogen activator (t-PA), single- chain urokinase-type PA (scu-PA) and staphylokinase (Ueshima and Matsuo, 2006). Kim *et al*. (2006) extracted and purified an enzyme which showed fibrinolytic activity from *C. militaris,* this enzyme has been reported to result in rapid hydrolysis of the fibrin alpha chain followed by the gamma-gamma chains, and the reaction is enhanced by Ca^{2+} and Mg^{2+} ions. It was concluded that this enzyme exhibited a high specificity for the chymotrypsin substrate S-2586 indicating it to be a chymotrypsin like serine protease which has a fibrin binding activity which allows for local activation of the fibrin degradation pathway. Patel and Ingalhalli (2013) also witnessed the fibrin binding activity

from the fibrinolytic enyme isolated from *C. militaris* which allowed the fibrin degradation pathway, which might be used in thrombolytic therapy. This property provides an alternative to the other costly fibrinolytic enzymes which are used in humans' age related heart diseases.

3. ANTI-OXIDATIVE PROPERTY

Mushrooms accumulate a variety of secondary metabolites, including phenolic compounds, polyketides, terpenes and steroids. Among the antioxidant compounds, polyphenols have gained importance due to their large array of biological actions that include free radical scavenging, metal chelation, enzyme modulation activities and inhibition of LDL oxidation, among others (Rodrigo and Bosco, 2006). Li and Xu (1997) explained the anti-oxidant property of fruiting bodies of *C. militaris* cultivated artificially under optimized conditions. The effects of *C. militaris* on the activities of catalase (CAT), surperoxide dismutase (SOD), glutathione peroxidase (GPx) and anti-hydroxyl radicals when assayed *in vivo*. It has been documented to show that *C. militaris* could inhibit mitochondrial injury and swelling induced by Fe^{2}(+)-L-Cysteine in a concentration dependent manner along with a significant superoxide anion scavenging effect. Moreover, the activities of CAT, SOD, GPx and anti-hydroxyl radicals in mice liver have been documented to increase significantly by *C. militaris*. These results indicated that *C.militaris* protected mitochondria by scavenging reactive oxygen species inhibiting mitochondrial swelling, and increasing the activity of antioxidases. *C. militaris* have been reported to have pharmaceutical value for mitochondrial protection and anti-aging. Dong *et al.* (2010) showed that the extract of *C. militaris* possessed anti-oxidative property with capability to normalize superoxide dismutase and glutathione peroxide level.

4. ANTI-INFLAMMATORY PROPERTY

Inflammations represent a complex set of interactions among soluble factors and cells that can arise in any tissue in response to trauma, infections, or postischaemic, toxic, or autoimmune injury (Nathan, 2002). In normal cases, the body's response to inflammation has been reported to be self-limiting through the down regulation of proinflammatory protein expression, the increased expression of anti-inflammatory proteins, and a reversal in the vascular changes that facilitated the initial immune cell recruitment process (Cook *et al*., 2005). This beneficial host response to foreign challenge or tissue injury has been reported to result in the restoration of normal tissue structure and function. Wol *et al*. (2010) showed the anti-inflammatory effects of hot water extract of *C. militaris* in traditional herbals, and the effect on the production of NO, IL-6, TNF and LPS stimulated RAW 264.7 cells and concluded that hot extract of *C. militaris* inhibited the production of macrophages derived inflammatory mediators in a dose dependent manner. Fung and Ko (2012) concluded that *C. mililtaris* extract (polysaccharide) and cordycepin exhibited anti-inflammatory effects in the *in-vitro* and *in-vivo* models of inflammation (mice), possibly through suppression of humoral immunity. It has also been reported that by decreasing the level of pro- inflammatory cytokine mediator (TNF-alpha) with the help of *C. militaris* extract, there is a suppression in intestinal inflammation in an acute colitis mouse model. When various concentrations of hot *C. militaris* were examined, the fall was seen in LPS-induced production, TNF-alpha, NO and IL-6 secretion, which showed the potential inhibitory effect on the production of inflammatory mediators (Patel and Ingalhalli, 2013). In addition to the bioactive compounds, anti-inflammatory peptides of different molecular weights have also been isolated from mushrooms. Cordymin, a low molecular weight peptide (10,906 Da), has been purified from *C. militaris* (Wong *et al*., 2011). This peptide has been evaluated to significantly inhibit the infiltration of poly morphonuclear cells and IR-induced upregulation of C3 protein produced in the brain, interleukin- 1β, and tumour necrosis factor-α, which had a neuro protective effect on the ischemic brain, due to the inhibition of inflammation.

5. ANTI- MICROBIAL AGENT

The development of antibiotics has been one of the most important scientific achievements of the last seventy years. These compounds are reported to act in several ways, by interfering in metabolic processes or in the organism structures (Fuchs, 2004). The mechanism of action is mostly related with interferences in the synthesis of the cell wall, modification of plasmatic membrane permeability, interferences in chromosome replication, or in protein synthesis (Tenover, 2006). Park *et al.* (2009) showed that the *C. militaris* protease extract inhibited the growth of *Fusarium oxysporum* in a controlled concentration manner. The purified cytotoxic antifungal protease form *C.militaris* fruiting bodies has been documented to show strong antifungal effect against *Fusarium oxysporum, Bipolaris maydis, Mycosphaerella arachidicola, Rhizoctonia solani* and *Candida albicans* (Wong *et al.*, 2011). Patel and Ingalhalli (2013) suggested that an acidic polysaccharide from *C. militaris* showed therapeutic effects against influenza virus infection when grown on germinated soybeans. Wong *et al.* (2011) reported that cordymin, a protease extracted from *C. militaris* also inhibited HIV-1 reverse transcriptase.

6. FERTILITY ENHANCER

Infertility is a common problem, affecting many peoples, the majority of whom now seek medical care (Glazener *et al*., 1987). The use of herbal extracts as fertility enhancer in animals is now on the rise because of the shifting of attention from synthetic drugs to natural herbal products (Dada and Ajilore, 2009). Chang *et al*. (2008) explained the effect of role of cordycepin from *C. militaris* in increasing the sperm quality and quantity. The *C. militaris* supplementation has been reported to result in an increase of serum cordycepin concentration which simultaneously enhanced the testosterone and estradiol-17, increasing the percentage of motile sperm cells. Patel and Ingalhalli (2013) suggested that cordycepin might be responsible for the increased semen production and sperm quality in boars. Hong *et al*. (2011) documented the stimulatory effect of *C. militaris* on testosterone production in male mouse rats. Results illustrated that changes of the body weight, food and water intake of the rats were not observed in this study but the

concentration of testosterone in the serum of the rats was significantly increased by *C. militaris* ($p<0.05$). Therefore fruiting bodies of *C. militaris* grown on the drone bee medium can serve as an integrative medicine for the treatment of reproductive problems caused by insufficient testosterone levels in human males.

7. ANTI CHOLESTEROL AGENT

Hypercholesterolemia is a major socioeconomic problem in common individuals as well as health professionals due to the strong correlation between cardiovascular diseases and lipid abnormalities (Morsy and Fouad, 2008). In hypercholesterolemia, high levels of low- density lipoprotein (LDL) cholesterol accumulate in the extracellular sub endothelial space of arteries which are highly atherogenic and toxic to vascular cells, leading to atherosclerosis, hypertension, obesity, diabetes and functional depression in organs such as the liver, heart and kidneys (Jain *et al*., 2010). In human as well as animal studies, administration of *Cordyceps* has been associated with reduction in cholesterol and triglyceride and an increase in the ratio of high density lipoprotein to LDL cholesterol. Whether the causative mechanism for this lipid balancing effect is through blood sugar stabilization, enhancing liver function, or any other as hitherto unknown cause, remains to be seen (Patel and Ingalhalli, 2013). This has nurtured research interest in evaluating traditional remedies and alternative medicines as potentially efficacious cholesterol- lowering therapies which have few or no, side- effects.

8. ANTI DIABETIC PROPERTY

Diabetes mellitus (DM) is a chronic metabolic disorder in the endocrine system resulting from defects of insulin secretion (type 1), increased cellular resistance to insulin (type 2), or both. The consequence of this is characterized by an abnormally high level of blood glucose, also known as hyperglycemia, that leads to serious damage of the body organs (Wong *et al*., 2011).Currently, several DM therapeutic drugs are available in the market. This includes various oral antidiabetic agents such as sulfonylureas, biguanides, glinides, tolbutamide, phenformin, rosiglitazone and repaglinide. Even though there are many drugs available, most of them are too toxic and costly and promote negative effects on the patient. Thus, they fail to alter the course of diabetic complications. Some of these drugs may potentially increase the incidence of renal tumors, hepatic injury and acute hepatitis. (Singh *et al*., 2008). Currently, most antidiabetic researches are focused highly on the development of antihyperglycemic agents that are safe and free of adverse effects such as nausea, diarrhoea, liver problems and weight gain. (Malviya *et al*., 2010). Zhang *et al*. (2006) compared the anti-diabetic effects of crude extract obtained from fruiting bodies and mycelia of many medicinal fungi including *C. militaris, C. sinensis, Omphalia lapidescens* and *Tricholoma mongolicum*. Dong *et al*. (2010) induced a water extract or alcohol extract of *Cordyceps militaris* on diabetic Sprague- Dawley rats and concluded that this extract caused significant reduction in blood glucose levels by promoting glucose metabolism and strongly suppressed total cholesterol and triglycerides concentration. Silva *et al*. (2012) showed the anti- diabetic effect of various fractions of *C. militaris* in streptozotocin induced diabetic mice which exhibited reduced blood glucose levels. They concluded that water extract of *C. militaris* contained a compound that acted as an insulin sensitizer (insulin resistance and improved insulin secretion in type II diabetic rats). Patel and Ingalhalli (2013) suggested that cordycepin extracted from *C. militaris* suppressed expression of diabetes regulating genes through the inactivation of NF-Kb dependent inflammatory responses. Diabetes mellitus is reported to be accompanied by hormonal and neurochemical changes that can be associated with anxiety and depression. It has been hypothesized that vanadium complex of vanadium-enriched *C. militaris* (VECM), is beneficial in preventing depression in diabetes, and influences the action of insulin, and mimic further favourable effects on the level of treatment satisfaction and mood. *C. militaris* has been reported to demonstrate an antidepressant- like activity, which attenuates the diabetes induced increase in blood glucose concentrations (Ji *et al*., 2009).

9. MELANOGENASIS

Melanogenesis is reported to be regulated by three specific enzymes viz. tyrosinase, tyrosinase-related protein-1 (TRP-1), and tyrosinase- related protein-2 (TRp-2). Tyrosinase, a copper- containing glycoprotein, is a key enzyme in melanin synthesis and a rate-limiting enzyme in this pathway, and can catalyze three different reactions viz. the hydroxylation of tyrosine to 3, 4- dihydroxyphenylalanine (DOPA), the oxidation of DOPA to DOPA-quinone changes to DOPA-chrome, and then to dihydro- indolizine (DHI) or indole 5,6-quinone2-carboxylic acid (DHICA) (Lee *et al*., 2010; Zaidi *et al*., 2015 a,b). During this biosynthetic pathway, TRP-1 has been documented to catalyze the oxidation of DHICA, and TRP-2 (DOPA chrome tautomerase) catalyzes the conversion of DOPA-chrome to DHICA (Ando *et al*., 2007; Zaidi *et al*, 2014a, b). Additionally, the two enzymes are reported to be regulated by a specific transcription factor, microphthalmia-associated transcription factor (MITF) (Shimoda *et al*., 2010; Hasegawa, 2010). *Cordyceps* is traditionally used in Korea, China and Japan, for the ethno pharmacological treatment of anti-aging activities from various extracts of *Cordyceps* exhibited a wide range of bioactivity *in vivo*, as well as *in vitro* (Ji *et al.*, 2009; Shi *et al.*, 2009; Ko *et al*., 2010). Chien *et al*. (2008) and Ji *et al*. (2009) reported that *Cordyceps* spp. Extract exhibited suppressing effect on the melanin production by tyrosinase- inhibitory activities. The water extract of *C. militaris* has been reported to give 71% inhibitory activity against tyrosinase, 40% L-DOPA (L-3,4-dihydroxyphenylalanine) oxidation and over 50% melanin biosynthesis in B16 mouse melanoma cells (Nam *et al.*, 2010). Jin *et al.* (2012) explored the inhibitory effect of cordycepin on melanogenesis and the relative molecular mechanisms. It has been documented that cordycepin inhibited melanin synthesis related enzymes, such as tyrosinase, tyrosinase related protein-1 (TRP-1) and tyrosinase related protein -2 (TRP -2. α-MSH and IBMX were reported as melanin synthesis enhancers. Aramwit *et al.* (2014) reported that cordycepin isolated from mycelia of *C. militaris* has anti- tyrosinase activity of 13×10^{-4} unity/µl. It

was also shown that, the highest anti tyrosinase activity was of the cordycepin extracted from the *Cordyceps* mycelia. The inhibitory effect of *C. militaris* on melanogenesis was attributed to enhancement of tyrosinase degradation.

A tabulated description of health benefits of *Cordyceps militaris* are listed in the table (**Table 1**).

Table 1: Health benefits of *Cordyceps militaris*

Disease	Fruitbody/Mycelial Extract	Effect	References
Breast Cancer	Fruiting bodies and mycelia	Anti-proliferative activity towards breast cancer cells (MCF-7)	Lee *et al.*, 2015
Diabeties	Fruiting bodies and mycelia	Hypoglycaemic, Anti diabetic	Ma *et al.*, 2015
Oxidative damage	Fruiting bodies	Anti-oxidant	Zhan *et al*., 2006
Hypercholesterolemia	Mycelia extract	Anti cholesterol agent	Jain *et al*.,2010 Patel and Ingalhalli, 2013.
Immune Injury	Mycelia	Immune modulating	Nathan, 2002
Diabetes mellitus	Fruiting bodies and mycelia	Anti diabetic property	Wong *et al*., 2011
Melanogenesis	Mycelia	Anti- tyrosinase activity	Aramwit *et al*., 2014

List of Abbreviations used

C. militaris	*Cordyceps militaris*
MSL	*Mean Sea Level*
SDS PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
MCMP	Multi-Component Multiphase
AIDS	*Acquired Immune Deficiency Syndrome*
AR Family	Adenosine Receptor Family
LDL	*Low-Density Lipoprotein*
CAT	Activities of Catalase
SOD	Surperoxide Dismutase
GPx	Glutathione Peroxidase
NO	Nitric Oxide
IL-6	Interleukin-6
LPS	Lipopolysaccharide
DM	Diabetes Mellitus
NF-kB	Nuclear Factor- kB
VECM	Vanadium- Enriched *C. militaris*
L-DOPA	L-3, 4- Dihydroxyphenylalanine
TRP-1	Tyrosinase-Related Protein-1
MSH	Melanocyte Stimulating Hormones

CONCLUSION

Cordyceps militaris has been widely used since antiquity for pharmacological purposes like immuno-modulation, anti-inflammatory, anti-cancer, anti-diabetic, anti-oxidative and radical scavenging and anti- aging effects. In the recent past more scientific information about it has become available, to support these claims. The potency of *C. militaris* depends chiefly on its chemical constituents, viz. the cordycepin and polysaccharides that make up the fruiting body, mycelium or spores. Its anti-cancer properties have been demonstrated in various human and murine cancer cell lines. However, the mechanisms responsible for the anti-cancer effects of *C. militaris* on cancer cells remain inconclusive. *C. militaris* offers a promising role in cancer prevention and treatment. However, further experimental, epidemiological and clinical studies are needed to identify other molecular targets, resolve the relationships between *C. militaris* intake and cancer risks, and explore the optimum dosing, efficacy and safety-alone and in combination with chemotherapy/ radiotherapy. In addition to the anti-cancer activity, *C. militaris* is being used for the general promotion of health and longevity. The anti-inflammatory and immune- promoting effects described can potentially facilitate the treatments of other diseases such as arthritis, HIV and Crohn's disease. Since this fungi is edible and thus can be a food additive or supplement will play a key role in the prevention and cure of various ailments caused by metabolic disorder or infections.

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REFERENCES

Alessandro, B. and Francesca, C. 2009. *Cordyceps sinensis* medicinal mungus: Traditional use among tibetan people, harvesting techniques, and modern uses; *HerbalGram*: *American Botanical Council* **83**: 52-61.

Ando, H. Kondoh, H. Ichihashi, M. and Hearing, V.J. 2007. Approaches to identify inhibitors of melanin biosynthesis via the quality control of tyrosinase. *J. Invest. Dermatol*. **127**: 751-761.

Aramwit. P. Bang, N., Ratanavaraporn, J., Nakp, T. and Srichana, T. 2014. An anti-cancer cordycepin produced by *Cordyceps militaris* growing on the dead larva of *Bombax mori* silkworm. *Journal of Agricultural Science* 6-6.

Badalyan, S. 2012. Medicinal Aspects of edible ectomycorrhizal mushrooms. *Springer, Verlag, Germany* **34**: 317-334.

Chang, S.T. and Miles, P.G. 2004. *Mushrooms: Cultivation, nutritional value, medicinal effect and environmental impact.* CRC Press, Boca Raton, Fla, USA, 1st edition.

Chang, Y. Jeng, K.C. Huang, F. Lee, Y.C. Hou, C.W. Chen, K.H. Cheng, F.Y. Liao, J.W. and Chen, Y.S. 2008. Effect of *Cordyceps militaris* supplementation on sperm production, sperm motility and hormones in sprague-dawley rats. *The American J. Chinese Medicine* **36** (5):849-859.

Chien, C.C., Tsai, M., Chen, C.C., Chang, S.J. and Tseng, C.H. 2008. Effects on tyrosinase activity by the extracts of *Ganoderma lucidum* and related mushrooms. *Mycopathologia* **166**: 117-120.

Collen, D. and Lijnen, H.R. 2005.Thrombolytic agents.

Thromb. Haemost. **93**: 627-630.

Cook, M., Joan, M. and Deem, T.L. 2005. Active participation of endothelial cells in inflammation. *Journal of Leukocyte Biology* **(4)**:487-495.

Dada, A. A. and Ajilore, V.O. 2009.Use of ethanol extracts of *Garcinia kola* as fertility enhancer in female catfish *Clarias gariepinus* brood stock. *Int. J. Fish. and Aquacul*. **1** (1): 005-010.

Das, S.K., Masuda, M., Sakurai, A. and Sakakibara, M. 2010. Medicinal uses of the mushroom *Cordyceps militaris*: current state and prospects. *Fitoterapia*. **81**(8):961-8.

Dickneite, G., Seiffe, D., Diehl, K.H., Rogers, M. and Czech, J.1995. Pharmacological characterization on a new 4-amidinophenyl-alanine thrombin-inhibitor (CRC220). *Thromb. Res*. **77**:357-368.

Dong, Y.T., Meng, Q., Liu, C., Hu, S., Ma, Y., Liu, Y., Lu, J., Cheng, Y., Wang, D. and Teng, L. 2010. Studies on the anti-diabetic activities of *Cordyceps militaris* extract in diet-streptozotocin-induced diabetic dprague-dawley rats. *Appl. Microbiol. Biotechnol*. **72** (6):1152-1156.

Fuchs, F.D. 2004. Princípios gerais do uso de antimicrobianos. In*: Farmacologia clínica fundamentos da terapeutica racional* (Eds.: Fuchs, F., Wannamacher, I. and Ferreira, M.), 3ªed. Rio de Janeiro, Guanabara Koogan , 342.

Fung, C.K. and Ko, W.H. 2012. *Cordyceps* extracts and the major ingredient, Cordycepin: possible cellular mechanisms of their therapeutic effects on respiratory diseases. In *Respiratory Diseases*, (Ed.: Dr. Mostafa Ghanei). In Tech Open Access Publisher, 3-14.

Glazener, C.M., Kelly, N.J. and Weir, M.J. 1987. The diagnosis of male infertility-prospective time specific study of conception rates related to seminal analysis and post-coital sperm-mucus penetration and survival in otherwise unexplained infertility. *Hum. Reprod*. **2**: 665- 671.

Hasegawa, S. 2010. Characterization and expression analysis of a maltose-utilizing (MAL) cluster in *Aspergillus oryzae*. *Fungal Genet. Biol*. **47**(1):1-9.

Hong, P., Choi1, Y.S., Woo1, S.O., Han, S.M., Kim, H.K., Lee, M.R., Nam, S.H. and Korean, H.N. 2011. Stimulatory effect of *Cordyceps militaris* on testosterone production in male mouse. *Journal of Mycology* **39** (2): 148-150.

Jain, K.S., Kulkarni, R.R. and Jain, D.P. 2010. Current drug targets for antihyperlipidemic therapy. *Mini Reviews in Medicinal Chemistry* **10**(3): 232-262.

Ji, D.B., Ye, J., Li, C.L., Wang, Y.H., Zhao, J. and Cai, S.Q. 2009. Anti-aging effect of *Cordyceps sinensis* extract. *Phytother. Res.* **23**: 116-122.

Jin, M.L., Park, S.Y., Kim, Y.H., Park, G., Son, H. and Lee, S. 2012. Suppression of α-MSH and IBMX-induced melanogenesis by cordycepin via inhibition of CREB and MITF, and activation of PI3K/Akt and ERK-dependent mechanisms. *International J. molecular medicine* **29**: 119-124.

Kim, J.S., Sapkota, K., Park, S.E., Choi, B.S., Kim, S., Hiep, N.T., Kim, C.S., Choi, H.S., Kim, M.K., Chun, H.S., Park, Y. and Kim, S.J. 2006. A Fibrinolytic enzyme from the medicinal mushroom *Cordyceps militaris* .*The Journal of Microbiology* **44** (6):621-623.

Ko, W.S., Hsu, S.L., Chyau, C.C., Chen, K.C. and Peng, R.Y. 2010 .Compound *cordyceps* TCM- 700C exhibits potent hepatoprotective capability in animal model. *Fitoterapia* **81**:1-7.

Lee, Y.S., Kim, H.K., Lee, K.J., Jeon, H.W., Cui, S., Lee, Y.M., Moon, B.J., Kim, Y.H. and Lee, Y.S. 2010. Inhibitory effect of glyceollin isolated from soybean against melanogenesis in B16 melanoma cell. *BMB Reports* **43**: 461-467.

Lee, H., Lee, S., Lee, K., Shin, Y.S. A., Kang, H. and Cho, H. 2015. Anti-cancer effect of *Cordyceps militaris* in human colorectal carcinoma RKO cells via cell cycle arrest and mitochondrial apoptosis. *Daru J. Pharmaceutical Sciences* **23**(1): 35.

Li, X. and Xu, L.1997. Studies on (EPS) fermentation by *Cordyceps militaris*, and its physical and chemical properties and antioxidation. *Journal of Microbiol.* **17**:13-17.

Ma, L., Chen, H., Zhang, Y., Zhang, N. and Fu, L. 2012. Chemical modification and antioxidant activities of polysaccharide from mushroom *Inonotus obliquus*. *Carbohydrate Polymers*. **89** (2):371-378.

Ma, L., Zhang, S. and Du, M. 2015. Cordycepin from *Cordyceps militaris* prevents hyperglycemia in alloxan-induced diabetic mice. *J.Nutres*. **35** (5): 431-439.

Malviya, N., Jain, S. and Malviya, S. 2010. Antidiabetic potential of medicinal plants. *Acta Poloniae Pharmaceutica* **67** (2):113-118.

Mizuno, T., Zhuang, C., Abe, K., Okamoto, H., Kiho, T. and Ukai, S. 1999. Antitumor and hypoglycemic activities of polysaccharides from the sclerotia and mycelia of *Inonotus obliquus* (Pers.:Fr.) Pil. (*Aphyllophoromycetideae*). *International J. Medical Mushrooms*. **1** (4): 301-316.

Morsy, M.A. and Fouad, A.A. 2008. Mechanisms of gastroprotective effect of eugenol in indomethacin-induced ulcer in rats. *Phytotherapy Research*. **22** (10):1361-1366.

Nam, B., Jo, W.S., Choi, Y.J., Lee, J.Y., Kang, E.Y., Jeong, M.N. and Lee, J.D. 2010. Inhibitory effects of melanin secretion on B16 melanoma cell of *Cordyceps militaris* water extract. *Kor. J. Mycol*. **38**

(2):167-171.

Nathan, C. 2002. Points of control in inflammation. *Nature* **420** (6917) 846-852.

Park, B.T., Na, K.H., Jung, E.C., Park, J.W. and Kim, H. 2009. Antifungal and anticancer activities of a protein from the mushroom *Cordyceps militaris. The Korean Journal of Physiology & Pharmacology* **1**: 49-54.

Patel, K.J. and Ingalhalli, R.S .2013. *Cordyceps militaris* An important medicinal mushroom. *Journal of Pharmacognosy and Phytochemistry* **2**(1):315-319.

Rodrigo, R. and Bosco, C. 2006. Oxidative stress and protective effects of polyphenols: comparative studies in human and rodent kidney. A review. *Comp. Biochem. Physiol. Part C Toxicol. Pharmacol*. **142**: 317-327.

Shi, B., Wang, Z., Jin, H., Chen, Y.W., Wang, Q. and Qian, Y. 2009. Immunoregulatory *Cordyceps sinensis* increases regulatory T cells to Th17 cell ratio and delays diabetes in NOD mice. *Int. Immunopharmacol.* **9**: 582-586.

Shimoda, N., Mutou, Y., Shimura, N., Tsukimoto, M., Awaya, A. and Kojima, S. 2010. Effect of heterocyclic pyrimidine compounds on UVB-induced cell damage in human keratinocytes and on melanogenesis in mouse B16 cells. *Biol. Pharm. Bull*. **33**: 862-868.

Sharma, S. K., Gautam, N. and Atri, N. S. 2015a. Optimization, composition and antioxidant activities of exo and intracellular polysaccharides from submerged culture of *Cordyceps gracilis* (Grev.) Durieu & Mont. *Evid. Based Complement. Altern. Med.* 2015: Article ID 462864, 8 pages.

Sharma, S. K., Gautam, N and Atri, N. S. 2015b. Evaluation of mycelial nutrients, bioactive compounds and antioxidants of five Himalayan entomopathogenic ascomycetous fungi from India. *Int. J. Med. Mushrooms* **17** : 661-669.

Sharma, Sapan Kumar, Gautam Nandini, Atri, Narender Singh and Dhancholia, Subhash 2016. Taxonomical establishment and compositional studies of a new *Cordyceps* (*Ascomycetes*) species from Northwest Himalayas (India). *Int. J. Med. Mushrooms* **18** (12) : 1121-1130.

Silva, D.D., Rapior, R. Hyde, K. and Bahkali, A. 2012. Medicinal mushroom in prevention and control of Diabeties mellitus. *Oncol. Rep*. **56**:1-29.

Singh, K.S., Rai, P.K., Jaiswal, D. and Watal, G. 2008. Evidence-based critical evaluation of glycemic potential of *Cynodon dactylon*. *Evid. Based Complement. Altern. Med.* **5** (4): 415-420.

Tenover, C.F. 2006. Mechanism of antimicrobial resistance in Bacteria. *Am. J. Med.* **119** (6A): S3-S10.

Ueshima, S. and Matsuo, O. 2006. Development of new fibrinolytic agents. *Curr. Pharm. Des*. 12: 849-857.

Villares, A., Lafuente, A.G., Guillamón, E. and Ramos, A. 2012. Identification and quantification of ergosterol and phenolic compounds occurring in Tuber spp. truffles. *Journal of Food Composition and Analysis* **261**(2): 177-182.

Wang, H.J., Pan, M.C., Chang, C.K., Chang, S.W. and Hsieh, C.W. 2014. Optimization of ultrasonic-assisted extraction of cordycepin from *Cordyceps militaris* using orthogonal experimental design. *Molecules* **19**: 20808-20820

Wol, S.J., Choi, Y.J., Kim, H.J., Lee, J.Y., Nam, B.H., Lee, J.D., Lee, S.W., Seo, S.Y. and Jeong, M.H.2010. The anti-inflammatory effects of water extract from *Cordyceps militaris* in murine macrophage. *Mycobiology* **38** (1): 46-51.

Wong, J.H., Ng, T.B., Sze, S.C., Zhang, K.Y., Li, Q. and Lu, X. 2011. Cordymin, an antifungal peptide from the medicinal fungus *Cordyceps militaris*. *Phytomedicine* **18** (5):387-92.

Zaidi, K.U., Ali, A.S. and Ali, S.A. 2015a. Comparative evaluation of purified and characterized tyrosinases from two edible mushrooms, *Agaricus bisporus* and *Pleurotus ostreatus* and their clinical potential. Biosci. *Biotech. Res. Comm.* **8** (2): 161-170.

Zaidi, K.U., Ali, A.S., Ali, S.A. and Naaz, I. 2014a. Microbial tyrosinase: promising enzymes for pharmaceutical, food bioprocessing, and environmental industry. *Biochem. Res. Int*. **2014**:1-16.

Zaidi, K.U., Ali, A.S. and Ali, S.A. 2014b. Purification and characterization of melanogenic enzyme tyrosinase from button mushroom. *Enzyme Res.* **2014**: 1-6.

Zaidi, K.U., Ali, A.S. and Ali, S.A. 2015b. Purification and characterization of high potential tyrosinase from macrofungi and its appliance in food engineering. *J. Microbiol. Biotech. Food Sci.* **5** (3): 203-206.

Zhan, Y., Dong, C. and Yao, Y. 2006. Antioxidant activities of aqueous extract from cultivated fruit-bodies of *Cordyceps militaris. Journal Integer. Plant Biol.* **48** (11), 1365-1370.

Zhang, Al. L. U. J., Zhang, N., Zhang, D., Zhang, G. and Teng, L. 2010. Extraction, purification and anti-tumour activity of polysaccharide from mycelium of mutant *Cordyceps militaris*. *J. Pharmaceu.* **26** (5): 798−802.

Zhang, G., Huang, Y., Bian ,Y., Wong, J.H., Ng, T.B. and Wang H. 2006. Hypoglycemic activity of the fungi *Cordyceps militaris*, *Cordyceps sinensis*, *Tricholoma mongolicum* and *Omphalia lapidescens* in streptozotocin-induced diabetic rats. *Appl. Microbiol. Biotechnol*. **72:** 11521-156.