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Medicinal Mushroom *Cordyceps militaris* as a Potential Source of Anticancer Drug for Cancer Treatment

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ABSTRACT

The interest of people in complementary and alternative medicine systems is on the rise worldwide due to its wide applications in cancer prevention and treatment. *Cordyceps militaris* is an entomopathogenic fungus that is often used as a part of the traditional medicine system. Cordycepin (3′-deoxyadenosine) found in *Cordyceps* mushroom is one of the most common and important types of complementary and alternative medicine. Cancer is a group of diseases in the present time that have a significant mortality rate all over the world. The patient suffers several side effects while undergoing conventional anticancer treatments. In this review, we have reviewed recently published research on the cordycepin and its anticancer properties against several types of cancers. Many studies have suggested that the cordycepsin found in *Cordyceps militaris* induces apoptosis, cell cycle arrest, anti-metastatic and anti-proliferation effects in cancer cells. Therefore, *Cordyceps militaris* may serve as a source of natural anticancer drugs for the treatment of various types of cancers.

INTRODUCTION

Cancer is one of the most dangerous conditions which include broad groups of diseases with unregulated growth of cells. This disease is one of the leading causes of death throughout the world. In this disease, the uncontrolled cell divisions and growth of cells produce malignant tumors which have the potential to invade various organs and spread to the whole body [(1)]. The treatment of cancer includes surgery, chemotherapy, and radiotherapy and every option depends upon the type, size, and stage of tumors [(2)]. However, these treatments are very expensive and have various side effects on the patients which leads to the search for some novel anticancer compounds from natural sources. *Cordyceps militaris* is an entomopathogenic fungus that is often used in Asia as a traditional medicine developed from age-old wisdom. Presently, cordycepin and other bioactive compounds from *C. militaris* are of great interest in medicinal applications. This mushroom is regarded as an important medicinal mushroom that acts as an overall tonic to the body due to its vast health effects. Many studies demonstrate its efficacy in the stimulation of the immune system, faster recovery in bronchitis, respiratory problems, increase in stamina, and anticancer properties[(3)]. Cordyceps has been used as a medicinal food in China and many regions of South East Asia for many years [(4)].A number of studies suggested that the cordycepsin found in this mushroom various anticancer activities including induces apoptosis, cell cycle arrest, anti-metastatic and anti-proliferation effects in cancer cells. Therefore, *Cordyceps militaris* may serve as a source of natural anticancer drugs for the treatment of various types of cancers.

Medicinal mushrooms and their role as medicine

The medicinal mushrooms have a wide range of health benefits and have been used as a part of the traditional medicinal system for many years. Many researchers have studied the medicinal effects of the compounds found in medicinal mushrooms [(5)]. The various bioactive compounds which are produced as secondary metabolites by these mushrooms had been known for their health effects such as immune-modulatory, liver-protective, antifibrotic, anti-inflammatory, antidiabetic, antiviral, and antimicrobial activities. These fungi stimulate the immune system of the host by enhancing the maturation, differentiation, and proliferation of various immune cells [(6)]. One of the very first scientific reports published on the *in vivo* studies on the antitumor activity of fruiting bodies of medicinal mushrooms belonged to the family Polyporaceae (Aphyllophoromycetideae) which possessed host-mediated activity against grafted cancer [(7)].

Biometabolites of *Cordyceps militaris*

There is a global increase in people's interest in complementary and alternative medicine systems due to their wide applications in cancer prevention and treatment [8]. *Cordyceps* are the one of most known medicinal mushroom which produces several bioactive metabolites with health benefits. Cordycepsin found in these mushrooms is a nucleoside derivative and is the main bioactive metabolite of these fungi. This low molecular weight compound is known for its various medicinal properties such as anticancer, antitumor, antioxidant, anti-inflammatory, hypoglycemic, and immunomodulatory effects [4]. The fruiting bodies of *Cordyceps militaris* also contain a good amount of amino acids such as lysine, glutamic acid, proline and threonine. In a study conducted by Hur (2008), revealed that fruiting bodies of this mushroom were rich in various unsaturated fatty acids, which comprised about 70% of the total fatty acids. These workers demonstrated that linoleic acid was most abundant unsaturated acid found in these mushrooms besides adenosine and cordycepsin [9].

In this review, we have reviewed recently published research on the cordycepin and its anticancer properties against several types of cancers. It is a derivative of adenosine and has been widely used as an antitumor agent. It is also known to exert anti-angiogenic, anti-metastatic, and antiproliferative effects and induce apoptosis of cancer cells. However, the exact mechanism via which it exerts anti-tumour activity is not well known but it is known to regulate signaling pathways related to tumour growth and metastasis. Cordycepin is also known to inhibit tumour growth via up-regulating apoptosis of cancer cells, inducing cell cycle arrest, and targeting cancer stem cells (CSCs). Cordycepin also induces the antitumour effect via regulation of tumour microenvironment by suppressing tumour metastasis-related pathways. Therefore, cordycepsins may serve as potential food supplements or substitute medicine for cancer treatment [8].

Anticancer effects of *Cordyceps militaris*

Cordyceps militaris has been used as a part of the traditional medicine system in East Asia. Quan and co-workers (2020), determined whether extracts of *C. militaries* could induce immunogenic cell death (ICD) in breast cancer immunotherapy to improve the efficacy of immune checkpoint inhibitors. These workers tested human and mouse breast cancer cells were treated with various concentrations of this mushroom's extract for 72 h, and cytotoxicity was measured using the sulforhodamine B assay. This study revealed that the CFSE dilution assay confirmed that dendritic cells fed with the ethanolic extract-treated breast cancer cells

successfully. Additionally, the ethanolic extract also potentiated the cytotoxic activity of tumor-specific T cells. Therefore, the ethanolic extract can induce immunogenic and apoptotic cell death in breast cancer cells and proves it a good candidate for cancer immunotherapy [(10)]. *Cordyceps militaris* fraction (CMF) has shown inhibition effects on proliferation of chronic myeloid leukemia K562 cells, oral squamous carcinoma KB cells, and the metastasis of lung cancer cells. Li and co-workers (2020), has studied the anticancer effects of *Cordyceps militaris* extracts in HCC cells and these workers found encouraging results. The *Cordyceps militaris* fraction (CMF) has shown significant inhibition of the migration and invasion of SMMC-7721 cells and HUVECs. CMF has also significantly inhibited the tumor growth in mice xenografted with SMMC-7721 cells. Overall anticancer effects of CMF may be due to inhibition of angiogenesis of human cancer cells and the mechanism is linked with suppression of the VEGF/VEGFR2 signaling pathway [(11)]. We have cultivated *Cordyceps militaris* in our laboratory and received good growth of its fruiting bodies (Figure- 1 & 2).

(a) (b)

Figure No. 1a & b: Fruiting bodies of *Cordyceps militaris*

Eunbi and co-workers (2020), have evaluated the effects of *Cordyceps militaris* extract on apoptosis and proliferation of carboplatin- resistant SKOV-3 cells along with studies on the mechanisms responsible for overcoming carboplatin resistance in human ovarian cancer. These workers performed cell proliferation assay, cell morphological change assessment using transmission electron microscopy, apoptosis assay, and immunoblotting to measure the

protein expression of caspase-3 and -8, poly (ADP-ribose) polymerase (PARP)-1, B-cell lymphoma (Bcl)-2, and activating transcription factor 3 (ATF3)/TP53 signalling-related proteins. They suggest that *C. militaris* inhibits carboplatin-resistant SKOV-3 cell proliferation and induces programmed cell death through ATF3/TP53 signaling upregulation and CHOP/PUMA activation [(12)].

The angiogenesis process is essential for the development of tumors and metastasis. In some angiogenic factors, the vascular endothelial growth factor receptor (VEGF) is one of the important receptors for tumor-derived angiogenesis. This receptor is commonly over-expressed in solid tumors. Therefore, many antitumor strategies have been designed to target VEGF to inhibit cancer angiogenesis. However, several problems such as adverse effects on normal vascularity in clinical trials have been associated with these procedures. In these studies, *Cordyceps militaris* has shown anticancer as well as anti-angiogenic effects.

Ruma and co-workers (2014), worked on the demonstration of the biological role of *Cordyceps militaris* extract in human tumor cells particularly in regulating angiogenesis and tumor growth of a malignant melanoma cell line and found that *Cordyceps militaris* extract significantly suppress tumor growth via induction of apoptotic cell death in melanoma cells. The treatments of mushroom extracts in mouse model xenografted with human melanoma cells have demonstrated a good antitumor effect with downregulation of VEGF expression. This study suggests that the *Cordyceps militaris* extract could be a potential antitumor herbal drug for solid tumors[(13)].

Esophageal cancer is one most aggressive and metastatic malignancies with a significant death rate over the years. Cordyceps found in *Cordyceps* mushrooms has been known for its anti-cancer properties. Xu and co-workers (2019), have studied the anticancer effects of cordyceps targeting esophageal cancer. In various experiments, it is found that this compound has significantly suppressed the proliferation of esophageal cancer cells. It is also found that cordyceps has induced chromatin condensation in cancer cells and apoptosis through activation of caspase cascades, apoptotic signaling, and cell cycle assays showed that cordyceps altered cyclin-dependent kinase 1 and cyclin B1 expression which is responsible for blockage of G2/M phase in the cell cycle. These studies suggest that the cordyceps induced pro-apoptosis and anti-proliferation mechanisms in cancer cells and hence may be developed into a novel therapeutic drug for the treatment of cancer [(14)].

Figure No. 2: Cultivation of *Cordyceps militaris*

Yoon and co-workers (2018), also observed that the treatment of cancer cells with cordycepin, induce cell death and minimize the cancerous properties of the tumour cells. However, these workers did not describe the exact mechanism and pathways involved [15]. A number of studies suggest various mechanisms associated with anticancer effects of cordycepsin such as induction of apoptosis, cell cycle arrest, anti-metastatic and anti-proliferating effects as described in Table-1.

Table No.1: Possible anticancer effects of cordycepsin against various tumour types

Tumour type	**Mechanism of anticancer effect**	**References**
Liver cancer	Apoptotic induction	[16]
Colon cancer	Cell cycle arrest	[17]
Bladder cancer	Cell cycle arrest	[18]
Renal cancer	Apoptotic induction	[19,20]
Lung cancer	Apoptosis induction, Anti-proliferation, Anti-metastasis	[21]
Breast cancer	Anti-metastasis	[22]
Leukemia	Apoptosis induction, Cell cycle arrest	[23]

SUMMARY

Cancer is a group of diseases in the present time that have a significant mortality rate all over the world. In this condition, the uncontrolled cell divisions and growth of cells produce malignant tumours which can invade various organs of the body. The patient suffers several side effects while undergoing conventional anticancer treatments. *Cordyceps militaris* is an entomopathogenic fungus that is often used as a part of the traditional medicine system. Cordycepin and other bioactive compounds from *C. militaris* are of great interest in medicinal applications. This mushroom is regarded as an important medicinal mushroom that acts as an overall tonic to the body due to its vast health effects. Many studies demonstrated its efficacy in the stimulation of the immune system and anticancer properties. Many studies suggest that the cordycepsin found in this fungus induced apoptosis, cell cycle arrest, anti-metastasis and anti-proliferation effects and hence may serve as a natural therapeutic drug for the treatment of various types of cancers.

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