

## Cordycepin: pharmacological properties and their relevant mechanisms

Baoyan Fan, Haibo Zhu\*

State Key Laboratory of Bioactive Substances and Functions of Natural Medicines & Ministry of Health Key Laboratory of Biosynthesis of Natural Products, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China

### ABSTRACT

Cordycepin, a nucleoside derivative, was extracted from *Cordyceps sinensis*, and then proved to be a bioactive compound present in traditional Chinese medicine Cordyceps. Early investigations revealed cordycepin possessed anti-microbial activity mainly by inhibiting nucleic acid synthesis. Although cordycepin is not used as antibacterial agents in clinic, its other pharmacological effects and possible mechanisms have gradually been deeply studied. This review serves to summarize the research progress of cordycepin.

**Keywords** cordycepin, pharmacological properties, mechanism

### INTRODUCTION

Cordycepin is a nucleoside derivative (analogue of adenosine) extracted from *Cordyceps sinensis* (Cunningham et al., 1950) and showed inhibitory action on 43 strains of *Bacillus subtilis*. Cordycepin was later found to be a main component of Cordyceps. The earliest information about Cordyceps can be traced back as early as 1694, in a Chinese medicine book “Ben Cao Bei Yao”, Cordyceps was recorded to possess pharmacological actions such as reinforcing deficiency, eliminating phlegm, maintaining hemostasis, etc. Modern investigation revealed the extract of Cordyceps contains cordycepin, cordycepic acid, cordycepin polysaccharide and other compositions. The analysis of cordycepin agreed with the formula  $C_{10}H_{13}O_3N_5$ , its aqueous solution is neutral (pH 7.1) and it exhibits a maximum ultra-violet absorption at 2600Å. In 1964, the structural formula of cordycepin was identified as 3'-deoxyadenosine (3'-dA, Fig. 1), and following studies proved the molecular weight of cordycepin is 251, and the melting point is between 230 - 231°C. Cordycepin can be dissolved in water, hot ethanol and methanol, but not in benzene, ether or chloroform (Kaczka et al., 1964).

Since 1970s, increasing number of studies has focused on the bioactivity of cordycepin, and its inhibitory effects on nucleic acid synthesis (especially polyadenylation inhibition) are widely reported (Aravindan et al., 1991; Arslan et al., 1998; Astrom et al., 1991; Brattin et al., 1978; Duncan et al., 1995; Kuznetsov et al., 1990; Mathew et al., 1989; Hecker et al., 1977). Until now, some investigators still refer cordycepin as a polyadenylation inhibitor. In the meantime, other groups have reported cordycepin could inhibit virus protein synthesis (Weiss et al., 1975), and depress methylation of nuclear RNA (Glazer et al., 1978).

In 1990s, scientists made a breakthrough in discovering other pharmacological properties afforded by cordycepin and potential underlying mechanisms. In 1997, the combination of

cordycepin and deoxycoformycin (dCF) entered clinical trials to treat leukemia in several medical centers in the United States. Moreover, such pharmacological activities as anti-tumor, anti-inflammatory and anti-platelet effects were discovered subsequently. In our laboratory, cordycepin was recently found to regulate the glucose and lipid metabolism through AMP-activated protein kinase (AMPK) signal pathway (Wong et al., 2010; Guo et al., 2010). One possible mechanism is that cordycepin might convert into cordycepin monophosphate, and the latter acted as an AMP analog to activate AMPK (Wang et al., 2010).

### Anti-microbial activity

In 1950s, Chinese researchers had proved that cordycepin could inhibit the growth of different types of pathogenic bacterium such as *Streptococcus*, *Bacillus mallei*, *Bacillus anthracis*, *Bacillus bipolaris septicus* and *Staphylococcus* (Zheng et al., 1952). In 1970s, antiviral activities of cordycepin had been reported on rhinovirus (Nair et al., 1976), poliovirus (Nair et al., 1976), murine sarcoma virus (Richardson et al., 1975), and western equine encephalitis virus (Hashimoto et al., 1976). In 1990s, the sensitivity of *Saccharomyces cerevisiae* to the antibiotic property of cordycepin was found to be decreased by the addition of thiamin to the growth medium (Iwashima et al., 1992). The antifungal activity of cordycepin was tested in a murine invasive candidiasis model. In this study, cordycepin exerted antifungal effect with two different *Candida* isolates; the result suggested that cordycepin may offer new options for the treatment of fungal infections (Sugar et al., 1998). Moreover, cordycepin core trimer and its 5'-monophosphate derivative, have shown to display pronounced anti-human immunodeficiency virus type 1 (HIV-1) activity *in vitro* via strongly inhibiting HIV-1 reverse transcriptase (Müller et al., 1991). Ahn et al. (2000) published their study about potent growth-inhibiting activity of cordycepin toward *Clostridium paraputrificum* and *Clostridium perfringens*, implicating that cordycepin could be useful as a new preventive agent against various diseases caused by *clostridia*. In other studies, cordycepin showed direct insecticidal activities on *Culex pipie* L, *Aedes aegypt* L, the fresh pupae of *A. atropalpus*L and *Plutella xylostella* L (Kim et al., 2002). Intraperitoneal injection of the cordycepin, together with adenosine deaminase

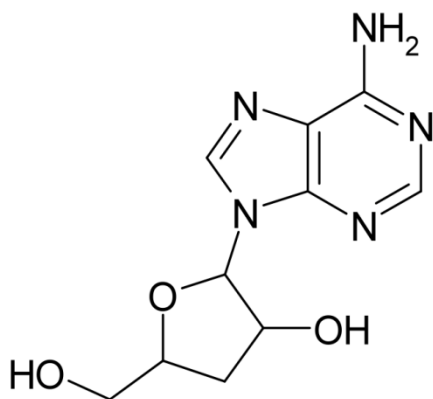
\*Correspondence: Haibo Zhu  
E-mail: zhuhaibo@imm.ac.cn

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**Fig.1.** cordycepin (3'-deoxyadenosine)

(ADA) inhibitor, cured *Trypanosoma brucei brucei* infection in mice (Rottenberg et al., 2005).

### Anti-tumor effects

Anti-tumor is the most broadly studied bioactivity of cordycepin. It is well known that imbalance between cell cycle progression and apoptosis might lead to tumor genesis and development (Evan et al., 1998). Most anticancer drugs were design to exert antiproliferative activity and/or induce apoptosis. Evidence has suggested that cordycepin possesses both of these anti-tumor properties. In 1990s, cordycepin was tested to be specifically cytotoxic for terminal deoxynucleotidyl transferase-positive (TdT<sup>+</sup>) leukemia cells (Koç et al., 1996), and this compound was considered as a therapeutic agent for TdT<sup>+</sup> leukemia. TdT<sup>+</sup> leukemia cells treated with cordycepin underwent the classic changes associated with apoptosis. The investigators proposed that cordycepin monophosphate in TdT<sup>+</sup> cells might be able to activate protein kinase A (PK-A), and the later may phosphorylate TdT, the activity of recombinant TdT might be an apoptotic endonuclease (Wyllie, 1980). Kodama et al. (2000) reported that blockade of ADA-mediated deamination of cordycepin was necessary for its antileukemic activity.

Lallas et al. (2004) reported that the combination of cordycepin with either 5-fluorouracil or interferon-alpha sensitized chemoresistant K562 cells to apoptosis, which was followed by distinct polyadenylate polymerase (PAP) modulations before and after the appearance of characteristic apoptosis pointers. PAP modulations appeared to be essential for K562 sensitization. Thomadaki et al. (2005) reported, in two epithelial cancer cell lines (HeLa and MCF-7), PAP changed very early in response to cordycepin treatment. Apoptosis induced by cordycepin could be observed by endonucleosomal DNA cleavage, 4', 6-diamidino-2-phenylindol (DAPI) staining and caspase-6 activity assay. Other researchers reported similar results, treatment of Molt-4 cell line (Thomadaki et al., 2008b), HeLa cells (Thomadaki et al., 2008a), BEL-7402 cells (Shi et al., 2008) and OEC-M1 cell line (Wu et al., 2007) with cordycepin led to cell accumulation at the G1 phase of cell cycle and apoptosis. The authors thought, this phenomenon might be associate with an increase of PAP activity which was caused by cordycepin treatment (Thomadaki et al., 2008a; Shi et al., 2008; Wu et al., 2007). The underlying mechanism of PAP activity modulation and apoptosis induction is not yet clearly understood.

Lui et al. (2007) reported cordycepin induced eryptosis (an apoptosis-like process in enucleated erythrocytes) via a calcium-dependent pathway in the absence of mitochondria and caspase-3 activation. Ding et al. (2008) showed cordycepin

inhibits the proliferation of HepG2 cells and induces apoptosis, which may be associated with down-regulation of the expression of NF-KBp65 and decreased activity of telomerase. In human leukemia cells, cordycepin significantly inhibited cell growth by inducing apoptosis through a signaling cascade involving a reactive oxygen species (ROS) -mediated caspase pathway (Jeong et al., 2011). Jen et al. (2009) reported, cordycepin induced apoptosis in MA-10 mouse Leydig tumor cells through a caspase-9 and -3 and -7 dependent pathway. Last year, Kitamura et al. (2011) reported cordycepin blocked endoplasmic reticulum (ER) stress-induced apoptosis in rat renal tubular epithelial cell line NRK-52E and the human bronchial epithelial cell line BEAS-2B. Cordycepin was indicated to inhibit inositol-requiring enzyme 1 (IRE1) - c-Jun N-terminal kinase (JNK) pro-apoptotic pathway and also reinforce pro-survival eukaryotic translation initiation factor 2 $\alpha$  (eIF2 $\alpha$ ) signaling. This effect is through A3 adenosine receptor without affecting PKR-like ER kinase (PERK) activity.

Nakamura and his colleagues tested the effects of cordycepin, as an adenosine analogue, on adenosine receptors (Nakamura et al., 2006). Their results showed cordycepin functioned as a selective adenosine A3 receptor agonist, through which it exerted remarkable inhibitory effects on the growth curves of B16-BL6 melanoma and Lewis lung carcinoma cell lines *in vitro* (Nakamura et al., 2006). In 2007, their research group published another article; demonstrating cordycepin suppressed the growth of HL60 cells by stimulating adenosine A3 receptors, followed by activation of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) in the Wnt signaling pathway (Yoshikawa et al., 2007).

Furthermore, cordycepin exhibited anti-metastatic action in melanoma cells and in human bladder cancer cells (Nakamura et al., 2005; Lee et al., 2010). In addition, Cordycepin suppresses tumor necrosis factor (TNF)- $\alpha$ -mediated matrix metalloproteinase (MMP)-9 expression by decreasing nuclear factor- $\kappa$ B (NF- $\kappa$ B) or activator protein-1 binding activity, which may account for its inhibitory activity on the invasion and migration of cancer cells (Lee et al., 2010).

### Anti-inflammation actions

Inflammation is a common etiological factor of a majority of multifactorial diseases, such as atherosclerosis (Rose, 2005), neurodegenerative diseases (Khandelwal et al., 2011), metabolic disorders (Wellen et al., 2005, Hotamisligil et al., 2006), and cancer (Mantovani et al., 2008). In 2006, the observations began to focus on anti-inflammation effect of cordycepin. In lipopolysaccharide-stimulated macrophages, cordycepin inhibited nitric oxide (NO) production by down-regulation of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 expression and TNF- $\alpha$  gene expression via suppressing NF- $\kappa$ B activation, Akt and p38 phosphorylation (Kim et al., 2006). In 2009, the phenotypic of macrophages switched via a decrease in the expression of pro-inflammatory cytokines and chemokines (Interleukin-1 $\beta$ , Interleukin-6, TNF- $\alpha$ , RANTES, CX3CL1), and an induction of anti-inflammatory cytokine (Interleukin-1ra, Interleukin-10, Tumor Growth Factor- $\beta$ ) (Shin et al., 2009). These results strongly supported that cordycepin might be a potential agent to improve inflammatory diseases. In 2010, the findings on inflammatory reactions in ischemia-reperfusion revealed cordycepin was able to attenuated the release of inflammatory mediators (NO, prostaglandin E2, TNF- $\alpha$ , and Interleukin-1 $\beta$ ) via the prevention of NF- $\kappa$ B activation and by the inhibition of I $\kappa$ B- $\alpha$  degradation, which provided cordycepin an effective treatment for a great number of neurodegenerative diseases (Jeong et al., 2010). Cheng et al. (2011) reported that

cordycepin inhibited MMP-3 expression and exerted a potent neuroprotective function *in vivo* and *in vitro*. Noh et al. (2009) suggested that cordycepin was a potent inhibitor of Interleukin-1 $\beta$ -induced chemokine production and MMP expression and strongly blocks the ability of activator protein-1 and p38/JNK signaling pathway in rheumatoid arthritis synovial fibroblasts (RASf). Therefore, cordycepin was considered to be a potential candidate to prevent inflammation of rheumatic arthritis.

#### Immunoregulation

Kuo et al. (1996) announced immunosuppressive ingredients were contained in *Cordyceps sinensis*. Zhou et al. (2002) discovered that cordycepin extracted from *Cordyceps sinensis* might exert immunoregulative effects. According to Zhou's results, cordycepin upregulated Interleukin-10 production, inhibited phytohaemagglutinin -induced Interleukin-2 production and proliferation of peripheral blood mononuclear cells simultaneously. Their further study revealed cordycepin also up-regulated Interleukin-1 $\beta$ , Interleukin-6, Interleukin-8 and suppressed production of Interleukin-4, Interleukin-5, Interferon- $\gamma$  and Interleukin-12. Besides, a higher binding activity of SP1 and SP3 was observed in cordycepin treated cells compared to the control. Thus, they concluded cordycepin pleiotropically affected the actions of immune cells and cytokine network (Zhou et al., 2008). In 2009, another research group reported that cordycepin suppressed the production of NO and pro-inflammatory cytokines such as Interleukin-1 $\beta$ , Interleukin-6, and TNF- $\alpha$  in lipopolysaccharide-activated macrophages via suppressing protein expression of pro-inflammatory mediators (Shin et al., 2009).

#### Neuroprotective effects

Hwang et al. (2008) reported that treatment with cordycepin in gerbils reduced 4-hydroxy-2-nonenal, a marker of lipid peroxidation, immunoreactivity and levels in the ischemic CA1 region. Glial fibrillary acidic protein immunoreactive astrocytes and ionized calcium-binding adapter molecule 1 immunoreactive microglia in the vehicle-treated ischemic group were activated in the CA1 region 4 days after ischemia/reperfusion, whereas in the cordycepin-treated ischemic group, their activation was significantly decreased. Repeated treatment with cordycepin protected against neuronal damage from ischemia/reperfusion by reducing oxidative damage. Cheng et al. (2011) investigated that cordycepin was able to prevent mice post-ischemic neuronal degeneration and brain slice injury. In ischemia/reperfusion mice, excitatory amino acids such as glutamate and aspartate were increased in brain homogenized supernatant. Cordycepin was able to decrease the extracellular level of glutamate and aspartate significantly. Moreover, cordycepin was able to increase the activity of superoxide dismutase (SOD) and decrease the level of malondialdehyde (MDA), ameliorating the extent of oxidation. Furthermore, MMP-3 expression was inhibited sufficiently.

#### Anti-platelet aggregations

In 1977, cordycepin was originally reported to be able to inhibit adenylatecyclase activity in platelets (Londos et al., 1977; Haslam et al., 1978). Depressed adenylatecyclase resulted in a decrease of cAMP content and an acceleration of platelet aggregation. However, Cho and his colleagues published a series of articles, demonstrating the inhibitory action of cordycepin on human platelet aggregation induced by U46619 (a Thromboxane A<sub>2</sub> analogue) (Cho et al., 2006), thapsigargin (Cho et al., 2007) and collagen (Cho et al., 2007). Cho et al. (2006) first reported Cordycepin completely inhibited

U46619-induced platelet aggregation and reduced intracellular Ca<sup>2+</sup> ([Ca<sup>2+</sup>]<sub>i</sub>), which is an aggregation-stimulating molecule. U46619-stimulated phosphorylation of Ca<sup>2+</sup>-dependent proteins was also strongly inhibited by cordycepin. These results suggest that cordycepin may have a beneficial effect on Thromboxane A<sub>2</sub>-mediated thrombotic diseases. Their other study showed that in thapsigargin-treated platelet, cordycepin suppressed the levels of [Ca<sup>2+</sup>]<sub>i</sub> through the [Ca<sup>2+</sup>]<sub>i</sub>-regulating system such as cGMP (Cho et al., 2007). Similar result was observed when using collagen to induce platelet aggregation (Cho et al., 2007). Cordycepin at 500  $\mu$ M could block the up-regulation of [Ca<sup>2+</sup>]<sub>i</sub> by 74%, suppress the Thromboxane A<sub>2</sub> production by 46%, and cause the Ca<sup>2+</sup>-dependent phosphorylation of both 47-kDa and 20-kDa proteins in collagen-treated platelets to greatly diminish. However, upstream pathways for producing these two proteins, such as the activation of phospholipase C- $\gamma$ 2 (PLC- $\gamma$ 2) and the formation of Inositol 1, 4, 5-trisphosphate (IP<sub>3</sub>), were not altered by cordycepin.

#### Glucose and lipid metabolism

In recent years, anti-hyperglycemic and anti-hyperlipidemia activity of cordycepin and the corresponding mechanism have attracted more and more attention. In streptozotocin (STZ) induced diabetic mice, administration of cordycepin (0.2 mg/kg) was reported to reduce blood glucose level by 37.5%. The proliferation of splenocytes and peritoneal macrophages were evaluated. T-lymphocyte level was significantly decreased; while NO production was increased more than two fold against STZ control in the cordycepin-administered group. Serum enzyme levels of glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were higher. Accordingly, it was concluded that cordycepin might be a useful tool in the control of blood glucose level in diabetes and promising new drug as an anti-hyperglycemic agent without defects of immune responses and other side effects (Yun et al., 2003). Our laboratory was the first to provide evidence for the hypolipidemic effects of cordycepin by lowering serum total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-c). Further investigation suggested an increase in lipoprotein lipase (LPL) and hepatic lipase (HL) activity afforded by cordycepin was considered to contribute to the regulation on lipid profiles (Gao et al., 2010). Our data from *in vivo* and *in vitro* studies indicated that cordycepin stimulated robust concentration- and time-dependent AMPK activation that correlated with the activation of Acetyl CoA carboxylase (ACC) and the suppression of lipid biosynthesis (Guo et al., 2010). The possible mechanism is that cordycepin converted into cordycepin monophosphate *in vivo*, and the latter bound to AMPK and functioned as an AMP mimic to activate AMP-activated protein kinase (Wang et al., 2010). Another study explored the effects of cordycepin on lipid metabolic disorder induced by a high-fat-diet in C57BL/6 mice. These mice had an obese body, lipid metabolic disorder and insulin resistance and were treated orally with 100 mg/kg/day cordycepin, 15 mg/kg/day rosiglitazone and 150 mg/kg/day fenofibrate, respectively. Compared to the control model mice, the body weight gain in cordycepin -treated mice were decreased by 66.5%, serum triglyceride and total cholesterol levels were decreased by 20.7% and 16.7%, respectively, and the triglyceride content in the skeletal muscle was reduced by 41.2% (Niu et al., 2010). Interestingly, this treatment also had a significant effect on insulin resistance. In cordycepin -treated mice, the serum insulin levels and homeostasis model assessment of the insulin resistance index were decreased by 30% and 46%, respectively, and the areas under the glucose-time

**Table 1.** Pharmacological effects and underlying mechanisms afforded by cordycepin

Pharmacological Properties	Mechanisms
Anti-Microbial activity	Inhibit nucleic acid synthesis (Sugar et al., 1998)
Anti-tumor effects	Activate A3 receptor (Yoshikawa et al., 2007) and PAP (Thomadaki et al., 2008a; Shi et al., 2008; Wu et al., 2007)
Anti-inflammation	Decrease expression of pro-inflammatory cytokines and chemokines (Kim et al., 2006; Shin et al., 2009; Jeong et al., 2010), inhibit MMP-3 expression (Cheng et al., 2010)
Immunoregulation	Affect the actions of immune cells and cytokine network (Zhou et al., 2008)
Neuroprotective effects	Reducing oxidative damage (Hwang et al., 2008), inhibit MMP-3 expression (Cheng et al., 2011)
Anti-platelet aggregation	suppress $[Ca^{2+}]_i$ (Cho et al., 2006; Cho et al., 2007)
Regulation of glucose and lipid metabolism	Activate AMPK (Guo et al., 2010)

curve were decreased by 18% in the insulin tolerance test and by 21.5% in the oral glucose tolerance test (Niu et al., 2010). Finally, the value of glucose infusion rates and insulin induced-glucose uptake into the skeletal muscle in the hyperinsulinemic-euglycemic clamp test were increased by 18% and 41%, respectively, compared to those in the control mice (Niu et al., 2010). This data suggests that the effects of cordycepin on lipid metabolic disorder induced by a high-fat-diet may be linked to its improvement on insulin resistance, especially concerning the increase of insulin sensitivity in the skeletal muscle.

## CONCLUSION

The compilation of scientific publications in the past half a century has shown that there is a gradual increase of interest in the beneficial pharmacological property of cordycepin. Characterization of cordycepin has progressed from its initial known function in polyadenylation inhibition to the expanding field of therapeutic research; including its properties in anti-microbial, anti-tumor, anti-inflammatory, and anti-platelet aggregation. Furthermore, the roles of cordycepin in immunoregulation, neural protection, and glucose and lipid metabolism merit additional research. The medical value of cordycepin has been recognized by its use in clinical trials. With further investigation of the mechanism of action of cordycepin, there are great potential to improve its pharmacological applications. For example, early research has demonstrated, cordycepin was quickly delaminated by ADA in vivo and metabolized to an inactive metabolite (Adamson et al., 1977). Combined application of cordycepin and dCF was proved to be able to enhance the activity of cordycepin, but dCF might lead to cytotoxicity. In 2007, development on co-drugs of cordycepin to eliminate the need for the toxic dCF has received promising results (Wehbe-Janek et al., 2007). The pharmacological effects and mechanisms of cordycepin have not been thoroughly studied yet, but its potential clinical significance in humans is great, and should warrant further research, particularly in human/ patient studies.

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