CORDYCEPIN AND DERIVATIVES IN PRE-CLINICAL AND CLINICAL TRIALS

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Abstract

Cordycepin (also known as 3'-deoxyadenosine) is insoluble in water, the organic compound from the group of nucleosides. This compound is produced by entomopathogenic mushrooms: Cordyceps spp. The structure of cordycepin and its potential modifications, aimed at improving pharmacokinetic and pharmacodynamic parameters as well as safety profiles, is an area for further research. It was found that cordycepin shows numerous biological activities and most of them have been demonstrated in in vitro and in vivo studies. Until now, clinical studies (or experiments involving volunteers) have confirmed, that cordycepin or its derivatives presented anti–tumor, immunostimulatory activity and symptomatic relief in multiple sclerosis.

Keywords: cordyceps spp., edible mushrooms, neuroregenerative activity, cordycepin

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1. Introduction

Cordycepin (also known as 3'-deoxyadenosine Fig.1.) is insoluble in water, the organic compound from the group of nucleosides. Structure of nucleosides are composed as nucleobases (nitrogenous bases) with an attached saccharide group. The molecule of cordycepin is created by adenine (purine) with attached a sugar unit – ribose so cordycepin is a structural analog of adenosine (nucleoside) [1; 2].

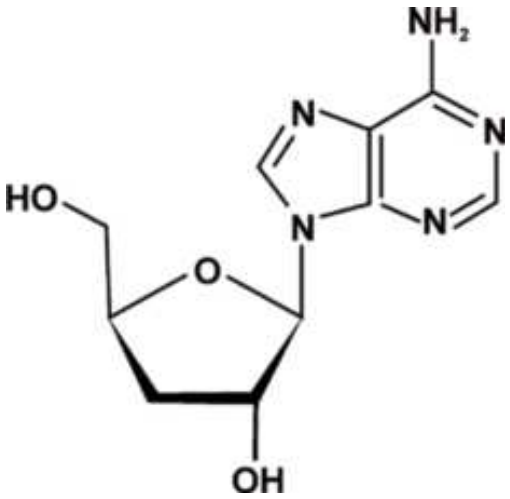

Fig.1. Cordycepin

Cordycepin is a natural biometabolite produced by entomopathogenic fungi *Cordyceps spp*., which parasitize of selected species of moths larvae. Cordycepin was isolated from *Cordyceps militaris* fruiting bodies (Photo. 1.) in 1950 for the first time [3; 4].

Fig. 1. *Cordyceps militaris* (author: Piotr Zięba)

In analytical research, cordycepin has also been confirmed in other *Cordyceps spp.* such as *Cordyceps sinensis*. So far, it has been proven that the highest concentration of cordycepin, corresponds to species *Cordyceps militaris.* Depending on the growing/breeding conditions, different values of cordycepin concentration in fruiting bodies and mycelium of *Cordyceps militaris* were obtained [5; 6].

In research of Zhou et al. 2009 content of cordycepin in fruiting bodies of *Cordyceps militaris* was estimated at 2.65 mg/g dry weight (d.w.). In mycelium *Cordyceps militaris* was obtained a lower concentration of cordycepin on the level 0.9 mg/g d.w. [5].

In 2008 analytical studies of *Cordyceps militaris* fruiting bodies and mycelium, indicate the concentration of cordycepin amounted 0.97% and 0.36%, respectively [7]. In other studies, it was found that the content of cordycepin in fruiting bodies of *Cordyceps militaris* was 1.10 mg/g d.w. , while in the mycelium of this species was estimated 1.82 mg/g d.w. [8].

Concentration of cordycepin was estimated in 2014 on the level at range 8.37 mg/g in ethanol extract, 5.28 mg/g in water extract and 1.74 mg/g in mycelial biomass of *Cordyceps militaris* [6].

In pre–clinical studies, *in vitro* and *in vivo* experiments, cordycepin has been proven to exhibit numerous biological activities, such as: immunostimulating, anti–tumor, antiviral, anti–inflammatory, ergogenic. For cordycepin was obtained also regulating activity of the endocrine system (steroidogenesis and spermatogenesis), coagulation and platelet process. For this compound was also presented its ability to inhibit adipogenesis, lipid deposition, and to improve bone structure [1].

2. Pre–clinical trials

Immunostimulating activity

An experiment conducted *in vivo* (rodents) provides evidence that cordycepin from *Cordyceps militaris* stimulated cellular and humoral immunity. The study showed an increase in the concentration of interleukins: IL-4, IL-10, IL-12. It was also confirmed the decrease in the concentration of IL-2, transforming growth factor β (TGF-β), and an effect on the level of T lymphocytes [9; 10]. An animal model was proved that *Cordyceps militaris* (enriched cordycepin) reverses immunosuppression induced by cyclophosphamide in mice [11].

Antitumor activity

In simplified terms, the main target points of cordycepin antitumor action should be mentioned: disrupting or arrest of the cell cycle, inhibiting proliferation and stimulating apoptosis of neoplastic cells. The above-mentioned effects in cell lines correlate with the biological activity of cordycepin as antimetabolite and inhibition of purine biosynthesis, disturbance in DNA or RNA biosynthesis, interaction with mTOR signal pathway, 5'AMP-activated protein kinase (AMPK), cyclin-dependent kinases (CDK), cell death such as Bcl-2 [1; 12].

Cytotoxic activity of cordycepin against neoplastic cells such as bladder, colon and stomach, has been demonstrated [13; 14].

In research from 2020, it was confirmed that cordycepin suppressed growth of human liver cancer cells. The mechanism of activity correlated with decrease in expression of CxCR4 chemokine. CxCR4 chemokine is considered as promoter invasiveness and migration of liver neoplastic cells [15].

Antiviral activity

Antiviral activity of cordycepin has been confirmed an *in vitro* experiment against various types of viruses, including influenza, Epstein-Barr (EBV) and HIV. The mechanism of action has not been fully understood, but actually research indicated that the antiviral activity of cordycepin and its derivatives is related to the inhibition of reverse transcriptase and RNA polymerase of the virus [16; 17].

In the United States in 2020 Food and Drug

Administration (FDA) approved cordycepin as a molecule with antiviral activity and the potential against coronavirus was researched in India, opening new possibilities in therapy COVID-19 [18].

Anti-inflammatory activity

An *in vitro* experiment on mouse microglia proved that cordycepin acts as an inhibitor of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) enzymes and decrease concentration of inflammatory mediators: nitric oxide (NO), TNF-α, prostaglandin E2 (PGE2), IL-1β. Cordycepin has also been found to inhibit the activity of NF-κB and to inhibit the phosphorylation of mitogen-activated protein kinase (MAPK) [19].

On *in vitro* and *in vivo* experiments *Cordyceps militaris* with cordycepin reduced the ischemic area, reduced brain swelling, and limited damage of the blood-brain barrier [20]. These research results confirmed the neuroprotective activity of cordycepin and provide opportunities for further research and therapy of neurodegenerative diseases.

Ergogenic activity

Cordycepin ergogenic activity is related to its function as a precursor of ATP. It has been proven in numerous scientific evidence that precursors of ATP, such as creatine support exercise performance in human [21; 22]. Furthermore, EFSA approved health claim for creatine supplementation in daily intake of 3 g such as ergogenic aid – increases physical performance in successive bursts of short-term, high intensity exercise [23].

An animal model, confirmed the improvement of exercise capacity (grip strength test) in mice fed 12-weeks diet with the extract of *Cordyceps militaris* (concentration of cordycepin 2.33 mg/g). Intensification of ATP production, correlated with the increase concentration of markers such as AMPK, PPAR-γ, and phosphocreatine [24].

Endocrine system

In experimental rats implemented for 6 weeks a diet containing mycelium of *Cordyceps militaris* (18.92 mg/g cordycepin), demonstrated an increase motility of sperm and effect on the concentration of hormones. Confirmed increase in testosterone and estradiol levels in experimental animals. Also, an increase in concentration of cordycepin in serum of experimental rats has been noted [25].

In rats with age-related testicular dysfunction, it has been shown that the administered cordycepin, improvement of sperm quality, increased sperm motility, increased activity of antioxidant enzymes such as glutathione peroxidase (GPx4), glutathione S-transferase mu 5 (GSTm5), and peroxiredoxin (PRx4) [26].

In another scientific work was confirmed in animal models of hypogonadism, late onset (LOH) and benign prostate hyperplasia (BPH), and in vitro cell lines of the prostate, that the extract from fruiting bodies of *Cordyceps militaris* (comprising cordycepin) increased the secretion of androgens or inhibition the catabolism of androgens – testosterone and dihydrotestosterone (DHT). It was proved that the symptoms of BPH were alleviated, and hyperplasia and cells proliferation of the prostate was reduced [27].

Respiratory system

Cordycepin has been shown to reduce airway hyperresponsiveness and inflammation in murine model of asthma. Confirmed decrease in the concentration of IgE, eosinophils, as well as IL-4, IL-5 and IL-13, NF-κB [28].

In scientific work [29] in relation to cordycepin showed reduction of airway remodeling in a rat model of asthma. As in the previous cited publication, at this point has also been demonstrated decrease in IgE, eosinophil and neutrophil level, and decrease of expression TNF-α, TGF-β1, IL-5, IL-13.

Locomotor system

In vitro experiments confirmed that cordycepin inhibits osteoclast differentiation. It is associated with inhibition of the NF-κB ligand receptor activator (RANKL). In murine model of osteoporosis (induced LPS), for cordycepin

has been proven to limited bone loss [30]. An animal model of osteoarthritis in rats, cordycepin has been demonstrated to reduce pain and inflammation in the synovium. Cordycepin acts as an inhibitor of polyadenylation [31].

3. Clinical trials

On the website clinical trials.gov for the phrase "cordycepin", we can find only 23 results for this molecule. Two studies as intervention used a combination of cordycepin and pentostatin (also known as deoxycoformycin) applied in the form of intravenous (IV) infusion. Pentostatin is an inhibitor of enzyme adenosine deaminase (ADA), which is responsible for the degradation of cordycepin [32].

In the first research, phase I clinical trial, attended 14 participants with refractory acute lymphocytic or chronic myelogenous leukemia [33]. On second Interventional Open Label Clinical Trial which covered I and II phase, participate 44 patients with refractory TdT-positive leukemia [34]. Anti–tumor or cytotoxic activity of cordycepin has been confirmed in pre-clinical studies, but similar results have not been achieved on abovementioned clinical trials. As the main cause it is lability of cordycepin and susceptibility to enzymatic degradation by enzyme ADA.

Only one clinical trial (Phase I), which include 94 participants suffering from advanced solid tumours or lymphoma, given IV new phosphoramidate analogue of cordycepin signed as NUC-7738. The addition of phosphoramidate group to the cordycepin molecule is responsible for resistance and limiting the enzymatic degradation this molecule by ADA [35; 36].

Also one item study concerns of the influence, 8-weeks oral supplementation the mushroom beverage (contain mushroom extract *Cordyceps militaris*), on emotions regulation and explore of the antidepressant effect in humans. In this Interventional and triple-blind, randomized-controlled trial, qualified 80 participants. Volunteers received mushroom beverage with extract of *Cordyceps militaris* provides three different bioactive compounds: cordycepin, polysaccharides and mannitol. So far, not reported any research results [37].

The remaining 19 studies related to structurally similar but 2-chloro-2-deoxyadenosine – Cladribine, in combination with other drugs. In one of the studies, attended 37 participants, with secondary acute myeloid leukemia. As a chemotherapeutic intervention, it was used IV: Cladribine, Cytarabine (as antimetabolite) and Uproleselan (as glycomimetic and novel E-selectin antagonist, interferes with activation of the survival cells, enhances the response to chemotherapy and protects against the toxicity) [38]. Studies have been undertaken in patients with mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), or B cell non-Hodgkin's lymphoma. As chemotherapy interventions, a combination Vorinostat, Cladribine, and Rituximab, was used in patients [39; 40].

The European Medicines Agency (EMA) has approved active substance - cladribine as a neurological medicine, in tablet formulation, intended for oral administration at dose 10 mg, with indication for pharmacotherapy relapsing forms of multiple sclerosis [41; 42; 43].

Some study on human subjects have been conducted in Asia. Most studies have verified the consumption of *Cordyceps sinensis* or *Cordyceps militaris.* In three example studies, the active ingredient is specified as cordycepin. In some scientific works, the major active ingredient were not specified, or they were a combination (or one listed) of active ingredients, such as: adenosine, polysaccharides or mannitol (also known as cordycepic acid).

In patients with mild liver dysfunction, it was proved that 8-weeks supplementation of 1.5 g/day *Cordyceps militaris* (cordycepin 1.9 mg/g) contributes to support protection of the liver against lipids accumulation [44].

In group of healthy adults' males who sup-

plemented 1.5 g/day of *Cordyceps militaris* (1.9 mg/g cordycepin) for 4 weeks, immunostimulatory activity was demonstrated, which resulted from an increase expression of: IL-2, IL-12, NK, TNF-α, IFN-γ [45].

Another study in a group of 100 patients (20–70 years) analyzed the effect of 12-weeks supplementation of *Cordyceps militaris* (cordycepin 1.9 mg/g) on upper respiratory tract infection and immune response. It was confirmed that consumption of *Cordyceps militaris* had no significant effect on the frequency and symptoms of cold. However, have been demonstrated an increase IgA concentration and stimulation NK cell activity, which are indicated immunostimulating activity [46].

4. Conclusions

It was found that cordycepin presented numerous biological activities. Most of them have been demonstrated an *in vitro* and in *vivo research.* Until now, clinical studies (or experiments involving on volunteers) have confirmed, that cordycepin or its derivatives as anti–tumor, immunostimulatory activity and symptomatic relief in multiple sclerosis. Proven immunostimulatory activity and *in vitro* antiviral activity, including against RNA viruses, made cordycepin a potential structure for the prevention and/or treatment of COVID-19 in the "era" of the coronavirus pandemic. Ergogenic activity perhaps correlates with a strengthening the physical condition of the body, which is important in the period of convalescence, recovery after traumatic injuries or in devastating diseases, in the terminal stages. Modifications of the structure cordycepin, recognition of the structure-activity relationship (SAR) and the use of additional substances that will increase the effectiveness of therapy with cordycepin or its derivatives require further research in science.

Resumo

Kordicepino (ankaŭ konata kiel 3'-deoksiadenosino) estas nesolvebla en akvo, organika komponaĵo el la grupo de nukleozidoj. Ĉi tiu kemiaĵo estas produktita de entomopatogenaj fungoj: Cordyceps spp. La strukturo de kordicepino kaj ĝiaj eblaj modifoj, celantaj plibonigi farmakokinetikajn kaj farmakodinamikajn parametrojn kaj ankaŭ sekurecajn profilojn estas areo por plua esplorado. Oni trovis, ke kordicepino montras multajn biologiajn efikojn kaj plej multaj el ili estis pruvitaj en in vitro kaj en in vivo. Ĝis nun klinikaj studoj (aŭ eksperimentoj pri volontuloj) konfirmis, ke kordicepino aŭ ĝiaj derivaĵoj prezentis kontraŭtumoran, imunostimuligan efikon kaj trankviliĝantajn simptomojn en multloka sklerozo.

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