Research Article

Interactions Between Adenosine Receptors and Cordycepin (3'-Deoxyadenosine) from Cordyceps Militaris: Possible Pharmacological Mechanisms for Protection of the Brain and the Amelioration of Covid-19 Pneumonia

Jing Du[1,2*], Weijing Kan[1], Hongkun Bao[2], Yue Jia[2], Jian Yang[1], Hongxiao Jia[1]

[1]The National Clinical Research Center for Mental Disorders and Department of Chinese Traditional Medicine, Beijing Anding Hospital, and Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, 100088, China

[2]Yunnan University, School of Medicine, 2 Cuihu North Road, Kunming, Yunnan, 650091, China

*Corresponding Author: Jing Du, The National Clinical Research Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, 100088, China.

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Abstract

At present, the novel Covid-19 pneumonia is prevalent, affecting millions of people. Here, we summarized the pharmacological basis of adenosine, adenosine receptors, adenosine agonist cordycepin (3'-deoxyadenosine), and Cordyceps product in the brain protection and amelioration of pneumonia to provide useful information to cope with the global pandemic of novel coronavirus (COVID-19). Adenosine, a mediator of innate immunity, is abundantly secreted by the injured lung tissues during inflammation. Through the activation of adenosine receptors A1,

A2A, A2B and A3, adenosine plays an important role in protecting against acute lung injury and brain injury. Cordycepin (3'-deoxyadenosine) is an activator of adenosine receptors. It can enhance human immunity, promote anti-inflammatory processes, inhibit RNA virus reproduction, protect against brain, lung, liver, heart, and kidney damage, and ameliorate lung-fibrosis in clinical and animal models. Cordyceps and cordycepin products could be used as a potential medicinal adenosine receptor agonist that can play a beneficial role in the amelioration of Covid-19 pneumonia and protection of brain.

Keywords: Adenosine receptor; Brain protection; Covid-19; Cordycepin; pneumonia

Abbreviations: ARDS- Acute respiratory distress syndrome; ATP- Adenosine triphosphate; AMP-Adenosine monophosphate; Aβ- Beta amyloid protein; ALI- Acute lung injury; A1R- Receptor; A2AR- A2A receptor; AD- Alzheimer's disease; ADA- Adenosine deaminase; AMPA- Aminomethyl phosphonic acid; Akt/PKB- Protein Kinase B; BLM-bleomycin; Covid-19- Coronavirus disease 2019; CAMP- Cyclic Adenosine monophosphate; COX-2- Cyclooxygenase-2; CCL2- Chemokine (C-C motif) ligand 2; CNS- Central nervous system; DNA-Deoxyribonucleic acid; DA- Dopamine; GSH-Pox- glutathione peroxidase; IL-1β- Interleukine-1 beta; IL-6- Interleukin-6; IFN-γ- γ-Interferon; IL-2-Interleukin-2;IL-4- Interleukin-4; IL-6- Interleukin-6; IL-8- Interleukin-8; IL-10- Interleukin-10; IL-12-Interleukin-12; IL-13- Interleukin-13; IgA-Immunoglobulin A; IgM- Immunoglobulin M; IgG-Immunoglobulin G; IBO- Ibotenic acid; INOS-Inducible nitric oxide synthase; LPS-Lipopolysaccharides; mRNA- Messenger RNA; MIP-1α-Macrophage inflammatory protein-1α; MIP-2- Macrophage inflammatory protein-2; MDD- Major depression disease; MCP-1- Monocyte chemotactic protein 1; MPTP- Methyl 4-phenyl 1- 2- 5-6 tetrahydropyridine; NF-κB- Nuclear factor kappa-B; NK- Natural killer; 6-OHDA- 6-Hydroxydopamine Hydrobromide; PI3K- Phosphatidylinositol 3-kinase; PD- Parkinson's disease; p-Tau- protein Tau; PI-Proliferation index; PD- Parkinson's Disease; RNA-Ribonucleic acid; SOD- Superoxide dismutase; SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2;TNF-β- Tumor Necrosis Factor-β; TLR- Toll-like receptors; TGF-β- Transforming growth factor-β; Th1- T helper cell 1; TNF-α- Tumor necrosis factor α; TAA- Thioacetamide.

1. Introduction

At present, there exists a global urgency in identifying supportive medication for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the disease caused by Covid-19. This review discusses the adenosine receptor-mediated pharmacological effects of Cordyceps and cordycepin on acute and chronic pneumonia and the subsequent organ damage.

Adenosine is produced in injured lung tissues and plays multiple roles in the regulation of inflammation and tissue remodeling. Adenosine acts as an anti-inflammatory molecule through suppressing the production of cytokine storm, protecting against organ damage, and repairing damaged tissue from acute lung diseases. The activation of adenosine receptors A1, A2A, A2B, and A3 benefits the recovery of lung diseases and is of great significance for the amelioration of pneumonia [1]. Cordycepin (3'-

deoxyadenosine), the most important active ingredient in Cordyceps militaris or Cordyceps sinensis, is proposed as an agonist of adenosine receptors. The "Pharmacopoeia of the People's Republic of China" notes the ability of Cordyceps as an herb "to nourish the lungs and kidney, stop bleeding, and reduce phlegm" [2]. Cordyceps as a family of eatable mushroom have been found mainly in North America, Europe, and Asia [3], and have a history of medicinal use spanning millennia in Asia [4]. However, exploitation of Cordyceps has significantly reduced its wild occurrence [5], the manufacturers make efforts to artificially cultivate this mushroom by surface and submerged fermentation techniques.

In this article, we give a detailed and objective review of research on Cordyceps and cordycepin and on their interactions with adenosine receptors for the prevention and amelioration of acute and chronic pneumonia, such as that observed in Covid-19. We

discuss cordycepin's ability to 1) enhance human immunity in the lung; 2) inhibit virus replication; 3) exert anti-inflammatory, reparative, and regenerative effects; 4) inhibit cytokine storm; 5) protect the brain, lung, liver, heart, and kidney; and 6) protect against pulmonary fibrosis.

2. Efficacy and chemical structure of cordycepin

Cordycepin's chemical name is 3'-deoxyadenosine (Figure 1). It has a molecular weight of 251.24kD and is soluble in water and ethanol. The rotation of natural cordycepin is unique and determines its efficacy. Most of the bioactive cordycepin products on the market are produced biosynthetically from Cordyceps militaris. Cordycepin is higher in Cordyceps militaris, up to approximately 0.12% [6]. Cordycepin in Cordyceps militaris that is artificially cultivated by some manufacturers can reach up to 1-3%.
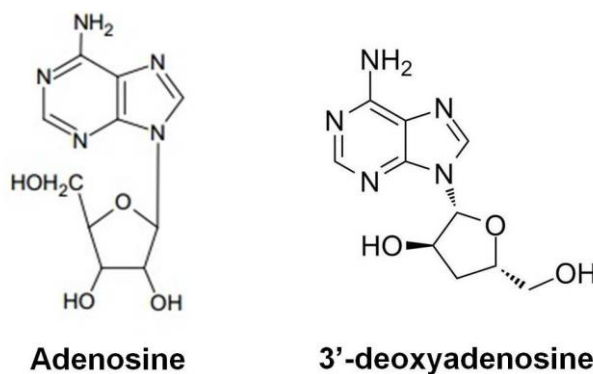

Figure 1: Adenosine and 3'-deoxyadenosine.

2.1. Cordycepin is a specific activator of adenosine receptors

Adenosine acts in anti-bacterial, anti-viral, anti-neoplastic, and immune repair and recovery

mechanisms [7]. The family of adenosine receptors includes four members: adenosine receptors A1, A2A, A2B, and A3 [7]. Adenosine is a metabolite of the energy metabolism pathway of ATP and is an

important marker of the body's energy exhaustion. Adenosine activates sleep, immune system, tissue repair, and energy regeneration. Currently, there are reports that cordycepin and adenosine receptor subtypes such as A1, A2A, A2B, and A3 can interact to promote anti-inflammatory effects and cell repair, as well as to protect the lung, liver, kidney, heart, and brain [8-10]. Adenosine has high affinity for adenosine receptor subtypes A1 and A2A and a low affinity for A2B and A3 [1]. Cordycepin, however, has good affinity for all four subtypes [8-10].

A growing body of studies showed that the interaction of cordycepin with four types of adenosine receptors was shown in various organs and cell lines. Cordycepin could induce apoptotic cell death in a couple of tumor cell lines, including a mouse Leydig tumor cell line MA-10 and a follicular thyroid carcinoma cell line CGTH W-2. In both tumor cell lines the specific antagonists to four AR subtypes A1AR, A2AAR, A2BAR, and A3AR, all blocked cordycepin-induced apoptosis to different degrees [11, 12]. Cordycepin also stimulated mouse Leydig cell testosterone production, regulated the mRNA expression of the A1, A2A, A2B, and A3 adenosine receptors, and that antagonists of A1, A2A, and A3 suppressed 20-50% testosterone production in the mouse Leydig cells [13]. In the CNS, cordycepin reduced sleep-wake cycles and increased non-rapid eye movement (NREM) sleep, and the protein levels of AR subtypes (A1, A2A, and A2B) were increased after the administration of cordycepin in the rat hypothalamus [8]. In addition, cordycepin remarkably alleviated LTP impairment and protected pyramidal cell of hippocampal CA1 region against cerebral ischemia and excitotoxicity, and the effect was blocked by A1 specific antagonist DPCPX (8-

cyclopentyl-1, 3-dipropylxanthine) [14]. Several additional studies also showed that cordycepin exerts neuroprotective effect through activation of A1, and the neuroprotective effects of cordycepin were blocked by DPCPX [15, 16]. Furthermore, it has been shown that the anti-tumor, anti-inflammation, and anti-fibrosis effects of cordycepin were mediated through A3 receptors [9, 17-19].

Adenosine receptor A1 is widely expressed throughout the body, but its highest level of expression is in the brain, especially at the excitatory nerve endings. This receptor regulates the activity of neurons and reduces the firing rate by blocking the release of neurotransmitters, protecting the brain, regulating sleep, and protecting the heart muscle when the blood oxygen concentration decreases and during myocardial ischemia [7].

The A2A subtype is expressed in many organs and cells, such as the striatum, spleen, thymus, heart, lung, blood, white blood cells, and platelets. A2A receptors play a regulatory role in peripheral tissues, in brain during exercise, mental behavior, sleep, and others, and in controlling inflammation, myocardial oxygen consumption, coronary blood flow, and angiogenesis in cancer and other diseases [7].

The adenosine receptor A2B subtype is widely expressed in vivo and is found in almost all organs, but its expression level is low. Under the condition of elevated adenosine levels, such as in hypoxia and ischemia, it has a certain protective effect on organs and tissues. Therefore, the tissue can survive without oxygen [7].

In normal tissues, the adenosine receptor A3 subtypes

are mainly distributed in the brain, lung, liver, aorta, testis, and heart. After activation of the adenosine receptor A3 subtype, it mainly plays a protective role in the tissues in which it resides [7, 20-23].

The expression level of the adenosine receptor A3 subtypes in cancer tissues and inflammatory tissues is extraordinarily high. A large number of adenosine receptor A3 subtypes are activated by cordycepin in inflammatory tissues and have a good effect on eliminating inflammation, including cytokine storm. It is worth noting that cordycepin, with its high affinity for the adenosine receptor A3 subtypes, plays an important role in the anti-inflammatory protection of organs [24, 25]. A large number of adenosine receptors A3 can cause cancer cell apoptosis after cancer cell activation, which is one of the main drug mechanisms of cordycepin's anti-inflammatory and anti-tumor properties [9, 10, 26].

2.2. Cordycepin is a strong antioxidant

Studies have shown that a low concentration of cordycepin can effectively inhibit the oxidation reaction of free radicals. During the process of viral pneumonia, super-oxidative free radicals can damage mitochondrial functions and cause mitochondrial dysfunction. This results in damage to lung cells during acute respiratory failure, which are important causes of lung dysfunction [27]. Therefore, cordycepin has a scavenging effect on free radicals and can delay, inhibit, and block the oxidative damage of active oxygen/oxygen-free radicals to protect mitochondrial function and cells and tissues from oxidative damage [16, 28, 29].

2.3. Cordycepin can selectively inhibit the

formation of messenger RNA polynucleotide A chains

Cordycepin, which is also named 3'-deoxyadenosine, can be phosphorylated to generate 3'-deoxytriphosphateadenosine. This molecule can interact with RNA polymerase to stop the synthesis of polyadenylated RNA strands, which is important for inhibiting RNA viruses (Figure. 2).

Cumulative studies have confirmed that cordycepin effectively inhibited the replication and reproduction of a variety of RNA and DNA viruses. Such RNA viruses include influenza virus [30], poliovirus [31], rhinovirus [32], Epstein-Barr virus [33], hepatitis C virus (HCV) [34], Hantaan virus [35], picornavirus [36], type-c RNA tumor viruses [37], Semliki Forest virus [38], western equine encephalitis virus [39] and others. Cordycepin can also inhibit the proliferation of DNA viruses, such as herpes simplex virus [40], vaccinia virus [41] and others. The effect of cordycepin on the virus that causes Covid-19 has not yet been reported. However, since cordycepin has an inhibitory effect on the reproduction of many RNA viruses, it is likely to also to effectively inhibit this new virus, as the replication and reproduction mechanisms of RNA viruses in humans are nearly the same for all viruses.

Cordycepin blocks the reproduction of RNA viruses because the RNA replication of many viruses requires a polyadenylated (poly A) tail. Cordycepin, or 3'-deoxyadenosine, lacks a hydroxyl group in the 3' position, which allows it to interfere with the elongation of the poly A tail of the RNA [31, 36, 38] to block RNA virus replication. The Covid-19 coronavirus is a positive, single-stranded RNA virus with a polyadenylic acid tail, similar to poliovirus,

which experiments have shown that its reproduction can be inhibited by cordycepin [31]. Cordycepin inhibits virus replication and synthesis, which is of

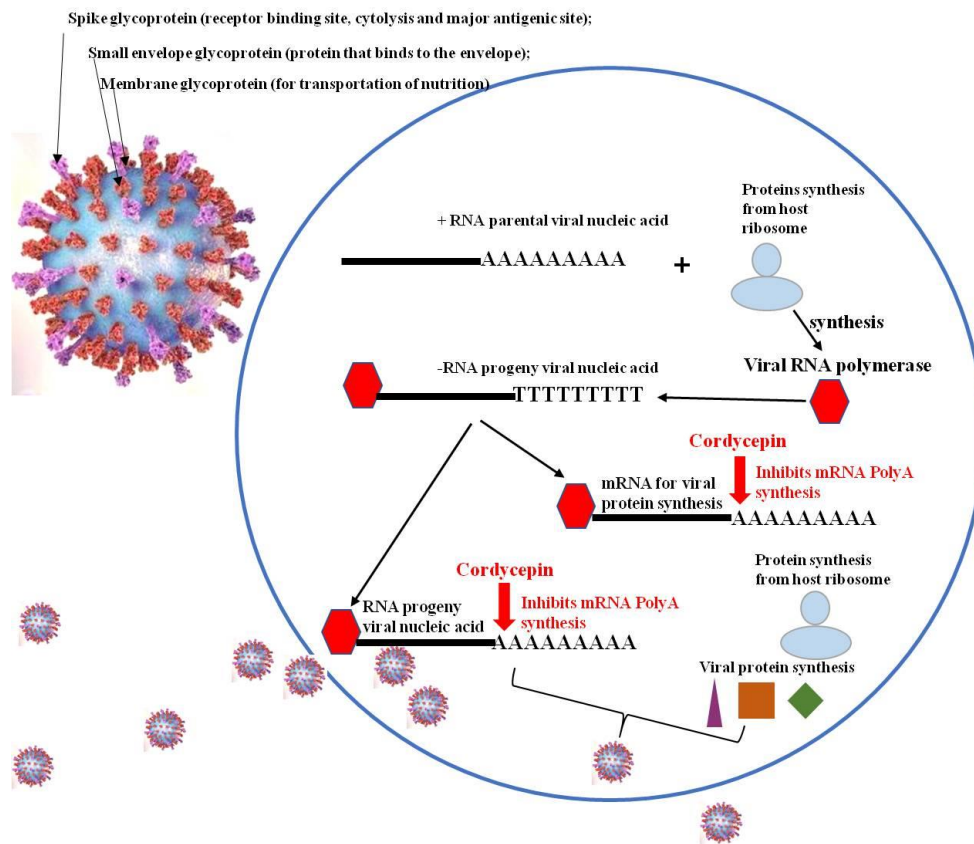great significance for the amelioration of viral pneumonia (Figure. 2).

Figure 2: Coronavirus Covid-19 reproduction and how cordycepin may inhibit the poly-A tail formation as a mechanism to block Covid-19 virus synthesis.

3. Adenosine receptors and Cordyceps enhance the functioning of the human immune system

3.1 Adenosine increase is an important natural mechanism to relieve lung inflammation

In patients with lung disease and in animal models of lung injury, adenosine levels in the lungs increase significantly [42-46]. During the progression of acute lung injury, adenosine elevation in injured lung tissue plays an important anti-inflammatory role. Both lung

tissue and epithelial cells express adenosine receptors that activate G-proteins that cause changes in the intracellular cAMP and Ca^{2+} levels [47-49]. The key immune cells associated with lung disease include lymphocytes, neutrophils, dendritic cells, and macrophages. These cells all express adenosine receptors and are involved in regulating various aspects of the innate and adaptive immunity [50, 51].

Elevated adenosine levels during acute tissue injury often have anti-inflammatory and tissue-protective

effects. Under normal circumstances, the concentration of adenosine in extracellular fluid varies from 40-600 nM [52]. It is noteworthy that in acute pathological conditions, such as sepsis or ischemia, patients can have adenosine concentrations as high as 10 μM [53]. In chronic diseases such as arthritis [54], asthma, and chronic obstructive pulmonary disease [43], concentrations of adenosine reach 100 μM. In the case of tissue damage, the main source of extracellular adenosine comes from the breakdown of released adenine nucleotides [46, 55] or from infiltrating inflammatory cells such as mast cells [56], eosinophils [57], neutrophils [58] and others. These nucleotides are subsequently dephosphorylated to AMP by exonucleoside triphosphate diphosphate hydrolase CD39 [59], and AMP is subsequently dephosphorylated to adenosine by exonucleoside 5'-nucleotidase CD73 [60]. Increases in CD39 and CD73are often observed in inflammatory states [61].

3.2 Cordyceps or cordycepin enhances the immune cell function of lymphocytes and monocytes

An increasing number of studies have shown that cordycepin can enhance immunity [62-67]. Studies have shown that cordycepin can enhance the proliferation and secretion of T and B lymphocytes. Cordycepin can enhance the function of T lymphocytes, regulate effect of T cells, and release immune-active lymphokines: interleukins, interferon, and others [68, 69]. Lymphokines mostly exert their immune effect by strengthening the action of various related cells. Cordycepin directly induced a proliferation response in B lymphocytes or amplify and regulate the response of B lymphocytes. Cordycepin also promoted the secretion of γ-interferon (IFN-γ), which is a highly effective anti-viral substance with extensive immune-regulatory

effects [70], the enhancement and enlargement of B lymphocytes, and the strengthening of the body's resistance to bacteria, viruses, and other harmful substances.

Cordycepin enhanced the activity of natural killer (NK) cells and the phagocytic index of monocytes [68, 69, 71-73]. NK cells synthesize and secrete a variety of cytokines, exerting a role in regulating immune functions, and directly killing target cells [68, 71]. Cordycepin also increased the NK activity and IL-2 secretion in mouse spleen cells and can enhance the secretion of Tumor Necrosis Factor-β (TNF-β) by human tonsil-activated T cells [74]. In macrophages, cordycepin transformed their pro-inflammatory M1 status into an anti-inflammatory M2 status, which plays a role in cell protection and repair [75].

Kang et al. evaluated the effect and safety of Cordyceps militaris on the cellular immune function of 79 healthy adult men [64]. These subjects took equal amounts of Cordyceps militaris or placebo capsules for 4 consecutive weeks. After treatment, NK cell activity, the lymphocyte proliferation index (PI), and T helper cell 1 (Th1) cytokines (including IFN-γ, interleukin-12, interleukin-2, and tumor necrosis factor α) were measured at weeks 0, 2, and 4. Compared with the placebo, NK cell activity (P=0.0010), lymphocyte PI (P ≤ 0.0001), IL-2 (P=0.0096), and IFN-γ (P=0.0126) increased significantly in the Cordyceps militaris-treated group. Thus, Cordyceps militaris enhanced NK cell activity and lymphocyte proliferation, partially increased Th1 cytokine secretion, and was safe and effective for improving cellular immunity in healthy adult males [64].

4. Role of adenosine receptor and Cordyceps in acute lung injury

4.1 Protective role of activated adenosine receptors A2A and A2B in acute lung injury

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) may be caused by pneumonia (including viral pneumonia), acid inhalation, severe trauma, or prolonged mechanical ventilation [76]. Experimental and clinical studies have shown that the pathogenesis of ALI and ARDS is characterized by the massive production of inflammatory cytokines and the transport of inflammatory neutrophils into the lung [77].

Extracellular adenosine has an important anti-inflammatory effect in acute lung injury. Pharmacological and genetic studies have shown that the adenosine receptor A2A is the major signaling pathway that mediates the anti-inflammatory properties of adenosine in LPS-induced lung injury [78]. Up-regulation of A2A may improve the healing process after acute LPS-induced lung injury [79]. A2A also down-regulated the expression of IL-12 [80], which in turn promoted the development of an anti-inflammatory cytokine environment that stimulates repair. A recent study showed that inhalation of the selective adenosine receptor A2A agonist ATL202 reduced LPS-induced neutrophil migration, microvascular permeability, and chemokine release, making it a possible clinical amelioration for acute lung injury amelioration [81].

Studies have also shown that the adenosine receptor A2B mediates adenosine protection in acute lung injury models and that A2B agonists can reduce lung injury. Measurements of alveolar fluid clearance indicated that the activation of adenosine A2B receptors enhanced alveolar fluid transport clearance after hypoxia, suggesting that A2B agonist amelioration was accomplished by promoting fluid clearance in the lung and protecting the lung barrier [61, 82, 83]. It has also been reported that A2B receptor activation had a tissue protective effect on ischemic lung injury [84]. Taken together, these studies indicate that adenosine signaling via A2B plays important roles in decreasing inflammation, clearing alveolar fluid, and protecting lung tissue in ALI. Clinically, doctors recommend inhaled A2B agonists for the amelioration of acute lung injury [85].

It is noteworthy that althoughA2BAR signaling serves important anti-inflammatory functions in acute lung injury [83], however, in chronic lung diseases multiple studies demonstrated the ability of A2BAR engagement to promote the expression of pro-inflammatory mediators from various cell types [86]. Moreover, increases in A2BAR have been described as a feature of individuals with accelerated pulmonary fibrosis, suggesting A2BAR antagonists may have utility in the treatment of chronic lung diseases where fibrosis was a major component [87]. Therefore, the timing of A2BAR agonist or antagonist treatment is very important.

In short, the anti-inflammatory effect of the adenosine receptor A2A and the effect of the A2B receptor on the clearance of alveolar fluid and protection of the lung barrier are very beneficial for acute lung injury. Cordycepin, as an activator of both these receptors, may also have a beneficial effect on acute lung injury. Currently, clinical trials targeting these receptors have

entered the second phase.

4.2 Activation of the adenosine receptor A3 resists the formation of cytokine storm

Acute inflammation is triggered when virus-infected cells are apoptotic or necrotic, which is characterized by directing plasma and leukocytes to the site of injury outside the blood vessel and activating pro-inflammatory cytokines or chemokines [88, 89]. These cytokine and chemokine signals led to the accumulation of inflammatory cells, increased expression of inflammatory, antiviral, and apoptotic genes, and immune cell infiltration and tissue damage [90, 91]. At the same time, the regeneration process and the recovery of the injury began. In most cases, this repair process completely restored lung function [80, 88, 89]. However, when cytokine storms occur, severe pathological changes can be observed, such as diffuse alveolar injury, transparent membrane formation, fibrin exudation, and fibrotic healing.

Cytokine storm has the potential to result in multi-organ dysfunction. The release of inflammatory cytokines enhances the immune response, activates immune cell proliferation, and further secretes inflammatory cytokines. This series of events leads to a cycle between inflammatory cytokines and immune cells, which can potentiate a cytokine storm [88]. A severe cytokine storm has significantly higher levels of pro-inflammatory cytokines, especially tumor necrosis factor-alpha (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6). Studies have shown that cytokine storms are at least partially IL-6-mediated [92-94].

A3 activation effectively inhibited the production of IL-6 and IL-8 [95, 96]. It also led to the inhibition of PI3K/Aktto cause powerful anti-inflammatory effects [97]. The use of A3 adenosine receptor agonists for lung injury significantly reduced the levels of TNF-α, IL-1β, IL-6, and IL-12, as well as immune cell infiltration [98]. This may play an important role in the regulation of cytokine secretion. Phase I and II clinical data showed that the highly selective A3AR agonists namodenoson and piclidenoson have good safety and pharmacokinetics profiles [99-101]. This suggests that they may possibly replace hormones and become candidates for the amelioration of inflammatory factor storms. Moreover, the A3R plays complex roles in inflammation, with both pro- and anti-inflammatory functions being described in multiple cellular and animal models with varying roles being dictated largely by species differences [86]. It is likely that the usefulness of A3AR agonists and antagonists in the treatment of acute lung diseases will only be revealed following appropriate clinical trials with such compounds [1].

4.3 Cordycepin as an adenosine receptor agonist improves respiratory tract inflammation

The protective effect of Cordyceps sinensis extract on experimental LPS-induced acute lung injury mice was studied by Fu and colleagues. This study demonstrated that giving Cordyceps sinensis extract (10, 30, 60 mg/kg) to mice 4-6 hours after LPS injection significantly reduced the number of total cells, neutrophils, and macrophages in bronchoalveolar lavage fluid ($P < 0.05$). Additionally, Cordyceps could significantly reduce the increase of TNF-α, IL-1β, IL-6 and NO levels after LPS in bronchoalveolar lavage fluid ($P < 0.05$). Cordyceps sinensis extract also

significantly reduced the protein and mRNA levels of iNOS and COX-2 and the NF-κBp65 DNA-binding ability in the LPS group ($P < 0.05$) [102].

Cordycepin, as an A3 adenosine receptor agonist, achieves its anti-inflammatory effects by inhibiting the expression of pro-inflammatory cytokines. Studies have shown that cordycepin inhibited the production of NO and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in macrophages from LPS-induced animals [75]. Cordycepin also increased the expression of the anti-inflammatory interleukin-10 (IL-10) in human peripheral blood mononuclear cells to play an anti-inflammatory repair role [69]. Cordycepin inhibited NF-κB function, thereby attenuating tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-12, and macrophage inflammatory protein-1α (MIP-1α). Cordycepin enhanced the expression of MIP-2, which has the effect of inhibiting autoimmune inflammation [78, 81].

Zheng and colleagues studied the clinical effect of Cordyceps sinensis in preventing and treating respiratory infections in elderly patients. Eighty patients were randomly divided into three groups: 30 in the Cordyceps sinensis decoction group (stewed twice a week, 10g/dose), 26 in the Cordyceps powder group (1.5g/dose, 2 times/day), and 24 in the levamisole control group. The groups received their respective ameliorations for 2 months. The statistical analysis of the immunoglobulin levels of the Cordyceps sinensis group showed that levels of immunoglobulin IgG, IgA, and IgM were better than the control group [103]. These studies have laid the foundation for the possible application of Cordyceps or cordycepin in acute lung injury.

5. Adenosine receptors and cordycepin from Cordyceps showed a brain-protection efficacy

5.1 The role of adenosine receptors in brain protection

Studies have shown that adenosine is an essential neuro-modulatory molecule in the brain and plays an important role in multiple physiological and pathophysiological processes [104, 105]. Adenosine exerts its effects throughout the brain through a family of four G protein-coupled adenosine receptors, A1, A2A, A2B, and A3 [106]. These receptors can affect crucial processes such as normal neuronal signaling [107, 108], astrocytic function [109-111], learning and memory [107, 112-114], motor function [115], feeding [116], control of sleep [117], and normal aging processes [114, 118, 119]. Of the four adenosine receptors, the A1 receptor and A2A receptor are both highly expressed throughout the brain, and their effects in the brain have been extensively studied [112, 120].

A1 receptors, which have high affinity for adenosine, are distributed both pre- and postsynaptically in the brain. When presynaptically localized, they specifically inhibited the release of excitatory and/or inhibitory neurotransmitters, e.g., glutamate, dopamine, serotonin, and acetylcholine [105]. When situated postsynaptically, A1 receptors inhibited neuronal signaling by hyperpolarization and reduced excitability via the regulation of potassium channels. The potential role of A1receptor in protecting against brain damage from ischemia was investigated in terms of its ability to control calcium, glutamate release, membrane potential, and metabolism after ischemic damage [121-124]. Cumulative studies have shown that A1receptor was enriched in excitatory synapses,

where it inhibited glutamate release and decreased glutamatergic responsiveness and the hyperpolarization of neurons to reduce the hyperexcitability associated with epilepsy [125, 126].

A2A receptors are highly expressed on striato-pallidal neurons, with a lower presence in other parts of the brain such as the cortex and the hippocampus. These receptors can form heteromers with A1 receptors [127-129] and with dopamine D2 receptors [130], which enabled adaptive responses in the regulation of synaptic plasticity [131]. Adenosine A2B and A3receptors may play a protective role in brain ischemia [132] and excitotoxicity [133]. Extracellular adenosine concentrations in the brain are determined by the hydrolysis of ATP released from neurons or astrocytes and by transport through equilibrative nucleoside transporters [134]. Under neuropathological conditions (e.g., ischemia, trauma, excitotoxicity, neurodegeneration, neuro-inflammation, and epilepsy), the extracellular concentration of adenosine in the brain can rise rapidly from nanomolar to micromolar levels, which can have both beneficial and detrimental effects on the course of the illness [104, 135, 136].

5.2 The neuroprotective role of cordycepin from Cordyceps in diseases of the central nervous system

Cordycepin showed neuroprotective effects on cerebral ischemia-reperfusion injury during inflammation, which included improving the behaviors in mice, reducing the area of cerebral infarction, inhibiting the expression of the pro-inflammatory factors IL-1β and TNF-α, and increasing the expression of the inflammatory factors IL-10 and TGF-β1[137, 138]. Our previous studies also found that cordycepin significantly ameliorated cuprizone-

induced motor dysfunction, demyelination, glial cell activation and pro-inflammatory cytokine (IL-1β and IL-6) expression in the corpus callosum and hippocampus in a mouse model of demyelination [139], which demonstrated that cordycepin may protect against demyelination via suppression of neuroinflammation.

Covid-19 pneumonia may provoke systemic inflammation [140], leading to psychiatric problems, including anxiety, depression, guilt, stigma, and anger. Cordycepin also plays an important role in the amelioration of the psychiatric disorders, including major depression disease (MDD) and anxiety disorder. Studies on depression showed that an injection of cordycepin led to a rapid and robust antidepressant effect, which may be modulated at multiple beneficial mechanisms, particularly in regulating the prefrontal AMPA receptor signaling pathway [141]. Our previous studies also found that cordycepin exhibited a stronger and faster anxiolytic effect in behavioral tests and that IL-4 expression showed a strong positive correlation with reduced anxiety behaviors. RIL-4Rα (an IL-4 specific inhibitor) can completely block the anxiolytic effects induced by cordycepin, providing a novel and common anxiolytic IL-4 signaling pathway and an innovative drug with a novel neuroimmune mechanism for the amelioration of anxiety disorder [142].

Cordycepin also showed neuroprotective properties in other neurotoxicity disease models, such as Alzheimer's disease (AD) and Parkinson's disease (PD). Studies on Aβ-induced toxicity in primary hippocampal cultured neurons showed that cordycepin significantly inhibited Aβ-induced apoptosis and decreased the upregulated p-Tau expression in

hippocampal neurons [15]. Studies in an Aβ plus ibotenic acid (IBO)-induced injury model of cultured hippocampal neurons showed that cordycepin significantly delayed Aβ plus IBO-induced excessive neuronal membrane depolarization. Furthermore, the suppressive effect of cordycepin against Aβ plus IBO-induced excessive neuronal membrane depolarization was blocked by an antagonist of adenosine A1 receptor [143]. Moreover, cordycepin protected PC12 cells against 6-OHDA-induced neurotoxicity through its potent antioxidant activity, including inhibition of 6-OHDA-induced cell apoptosis, mitochondrial dysfunction, and enhancement of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Pox) [144]. Studies in a rotenone-induced PD rat model showed that cordycepin significantly protected dopamine neurons against rotenone-induced apoptosis by improving mitochondrial dysfunction [145]. In addition, cordycepin effectively alleviated motor dysfunction, the loss of DA neurons, and the activation of the TLR/NF-κB signaling pathway in an MPTP-induced PD model [146]. In summary, cordycepin protected neuronal functions and cell apoptosis in many different neurotoxic animal models, which may be relevant to the psychiatric disorders during Covid-19 infection.

6. Adenosine receptor and cordycepin from Cordyceps protect important organs such as the heart, liver, and kidney during hypoxemia

6.1 Elevated adenosine in hypoxemia or bacteremia activates adenosine receptors to protect the functions of multiple organs

Adenosine is a signaling molecule produced after injury, which promotes wound healing and tissue protection. It exerts significant effect on the regulation of angiogenesis, stromal formation, and inflammation [147]. Studies have shown that in the case of ischemia [148] and sepsis [149], the extracellular adenosine concentration rises and then sends a signal through the adenosine receptor on the tissue's cells to provide systemic protection and avoid causing host tissue damage. Activation of the adenosine receptor A2A has also been shown to provide extensive organ protection against ischemic damage, including for the heart [150], lung [151], liver [152], kidney [153], and spinal cord [154]. The A2A adenosine receptor agonist has a good anti-inflammatory effect, especially for lung ischemia-reperfusion injury. A2A agonists significantly reduced ischemia-reperfusion injury and block neutrophil-mediated inflammatory responses in lung transplantation models [101, 151, 155, 156]. A mouse model of LPS-induced injury also exhibited the A2AR-mediated protection of lung tissue [157].

At the same time, it was discovered that adenosine receptor A2B can maintain tissue functional integrity in the heart [61] and kidney [158]. In addition, gene knockout or antagonism of the adenosine A1 and A3 receptors increased cecal ligation-induced systemic inflammation and mortality [159, 160]. A3 receptors activated anti-inflammatory pathways in lung ischemia-reperfusion injury [161], while A3 receptor agonists protected against reperfusion lung injury and reduce apoptosis [161, 162]. It is noteworthy that activation of the A1 receptors mediated the protective properties of ischemic preconditioning and adenosine preconditioning against pulmonary ischemia-reperfusion injury [163].

6.2 Cordyceps and cordycepin protect the lung, liver, and kidney in hypoxemia or inflammation

When the human body is attacked by germs, viruses, or pathogens, it shows an inflammatory pattern that the activities of pro-inflammatory cytokine (IL-1β, IL-6, TNF-α) and chemokine (CCL2) increased, causing functional cell death, and eventually leading to tissue fibrosis [74, 164]. At this time, cordycepin can transform the human immune inflammatory status (M1) into an immune repair and regeneration status(M2) to stimulate immune cells to release anti-inflammatory cytokines (IL-4, IL-10, IL-13) and to increase the phagocytosis of macrophages. The phagocytosis of necrotic tissue and the secretion of cytotropic factors promote tissue repair [69, 75, 165].

Cordycepin's mechanism of action involves its role in protecting organs and tissues, including against pulmonary fibrosis, liver fibrosis, and renal fibrosis. First, cordyceps and cordycepin can prevent pulmonary fibrosis [166-169]. Studies have shown that the continuous intragastric feeding of Cordyceps sinensis for 14 days improved the intratracheal injection of bleomycin, which results in an increased lung coefficient (lung weight/body weight) in rats, a reduced weight-bearing swimming time, and decreased arterial oxygen pressure, and lung tissue fibrotic lesions [166]. When using cordycepin to treat bleomycin (BLM)-induced pulmonary fibrosis in rats, it was found that cordycepin reduced the infiltration of inflammatory cells, fibroblast deposition, and prevented pulmonary fibrosis [168]. Clinical experiments have shown that Cordyceps sinensis dilated the bronchi, worked as an expectorant, and moderated asthma [170-172]. Zhang and colleagues treated 20 patients with pulmonary interstitial disease with Cordyceps sinensis capsules and found that the beneficial effect was significant [173].

Cordyceps can reduce myocardial oxygen consumption, increase myocardial nutritional blood flow, improve myocardial oxygen supply, and demand balance, and support the improvement of the pathophysiological status of myocardial ischemia and hypoxia. A Cordyceps water extract (2.5 g/kg) was able to enhance the ability of mice to withstand hypoxia at normal pressure. In addition, intraperitoneal injection and intragastric administration of cordycepin to mice significantly reduced myocardial oxygen consumption, counteracted the effect of isoproterenol on increasing myocardial oxygen consumption, improved hypoxia tolerance, and extended the survival time of hypoxic mice [174, 175].

Cordycepin also protects against liver fibrosis. Studies have shown that cordycepin and adenosine have anti-fibrotic effects in mice with hepatic fibrosis induced by intraperitoneal injection of thioacetamide (TAA) [176]. It was also found that 200 μ mol/L cordycepin amelioration significantly inhibited the increase in mRNA and protein expression of MCP-1 in cells under LPS stimulation in order to reduce the inflammatory phenotype and fibrosis response [177].

Cordycepin showed good protection in kidney diseases. Cordycepin inhibited high glucose-induced renal tubular epithelial-mesenchymal transition in rats. The mechanism may be achieved by down-regulating transforming growth factor-β (TGF-β) [178]. Cordycepin can protect the kidney by inhibiting renal tubular epithelial cell apoptosis [17, 179]. Studies have found that the mechanism by which cordycepin worked on membranous nephropathy was to protect

the foot processes and cytoskeleton structures of the podocyte and to suppress complement-mediated signaling pathways, and to protect complement-mediated podocyte damage [180]. This also has related clinical findings. Shen and colleagues showed that clinical observation of 31 cases of acute renal failure with the addition of Cordyceps sinensis demonstrated that urine osmotic pressure increased after the addition of Cordyceps sinensis compared with the control group. Glucosidase decreased significantly, confirming that Cordyceps sinensis had a good effect on renal tubular epithelial cell repair in patients with acute renal failure [181]. Two other related studies have also found that Cordyceps sinensis was effective in treating acute renal damage due to epidemic hemorrhagic fever [182, 183].

7. Conclusions and Remarks

For a long time, the western medical community has been working on the development of adenosine

receptor-selective agonists and antagonists [100]. Selective adenosine receptor A1 agonists may have some clinical effects in patients with heart failure and patients with renal failure [184, 185]. Medical institutions are developing clinical applications and continuing research on A2A activators for the amelioration of lung disease and Parkinson's disease [186, 187]. A2B and A3 selective agonists have also been studied in clinical trials of inflammatory and autoimmune excitatory diseases, respectively [51, 100]. It is noteworthy that adenosine receptors have also been studied as potential therapeutic targets for acute respiratory stress syndrome and acute lung injury [188, 189]. For example, the protective effect of A2B signaling can prevent ischemic lung injury [84]. A3 activation also has protective effects in reducing reperfusion-induced lung injury [161]. In addition, adenosine kinase inhibition can also reduce acute lung injury [190].

Disease	Treatment & Clinical Trail & design	Participants & Interventions	Outcomes	Conclusion
Lung diseases	Cordyceps Militaris (capsule) Double-blind, randomized, treatment control Zhu et al. 2017. [191]	180 patients with idiopathic pulmonary interstitial fibrosis.Oral Cordyceps powder, One gram per time, three times per day.	The Cordyceps powder group was significantly improved in the levels of PO_2, PCO_2, TLC (total lung capacity), VC (vital capacity) and DLCO (carbon monoxide diffusing capacity) , compared to the control group.	The combination of tetrandrine and cordyceps sinensis powder or thymosin in treatment of idiopathic pulmonary interstitial fibrosis was better than that of tetrandrine alone.

Dongchong-xiacao (DCXC, Cordyceps Sinensis) capsule Randomized, controlled trail. Wang et al. 2007. [192]	60 patients with moderate persistent asthma. Inhaled corticosteroid and beta-agonist as control group; this plus DCXC capsule as treatment group.	The serum level of IgE, sICAM-1, IL-4 and MMP-9 of the treatment group was lowered to a greater degree than that of the control group ($P < 0.05$ or $P < 0.01$).	DCXC capsule can reduce the serum markers of airway inflammation, which suggests this therapy bares the anti-inflammation effects.
Cordyceps Sinensis Prospective trial. Zhang et al. 2000. [173]	20 patients with pulmonary interstitial disease. Cordyceps Sinensis treatment, dose for 3 months or 2 years.	Patients with early stage of the disease showed significant recovery. For the patients in the middle and late stage of the disease, symptoms were improved.	Cordyceps sinensis has a beneficial therapeutic effect on lung interstitial disease.
Cordyceps sinensis Double-blind randomized, levamisole – controlled trail. Zheng et al. 1999. [103]	80 patients with respiratory tract infections. 30 in the Cordyceps sinensis decoction group (twice a week, 10g/dose), 26 in the Cordyceps powder group (1.5g/dose, 2 times/day), and 24 in the levamisole control group for 2 months.	The Cordyceps sinensis group showed that serum levels of immunoglobulin IgG, IgA, and IgM were higher than the control group.	Cordyceps sinensis provided a simple, effective and side-effect-free treatment for the prevention and treatment of recurrent respiratory tract infections in the elderly.

Renal Diseases	Cordyceps militaris Randomized, placebo-controlled trail. Sun et al. 2019 [193]	98 chronic kidney disease patients Cordyceps militaris (COG, 100 mg daily) and placebo (CG) groups.	Cordyceps militaris reduced the levels of urinal protein, blood urea nitrogen (BUN), and creatinine ($P < 0$ 05); and the serum levels of TG, TC, and LDL-C; and increased the HDL-C level (P < 0 05). The serum levels of cystatin-C (Cys-C), myeloperoxidase (MPO), and malondialdehyde (MDA) were reduced while nitric oxide (NO) and superoxide dismutase (SOD) were increased in the COG group ($P < 0.05$).	Cordyceps militaris protected against CKD progression.
	Cordyceps Randomized, placebo-controlled trail. Zhao et al.2013. [194]	103 stable angina pectoris (SAP) inpatients. Corbrin capsules (3g; t.d.s.) were used 3 days before angioplasty and 3 days after angioplasty).	The post-procedure mean peak of Scr, post-procedure increased in Scr levels from baseline, and urine levels of KIM-1, NGAL and IL18 after the procedure in the Dongchongxiacao (Cordyceps) treatment group were significantly lower than those in the basic treatment group *(P < 0.05)*.	Prophylactic treatment with Dongchongxiacao (Cordyceps) in SAP patients who undergo coronary angiography or coronary intervention could prevent contrast-induced renal impairment.
	Cordyceps sinensis (DCXC) Double-blind, randomized,	120 patients with type 2 diabetes. Basic treatment group (n = 41), standard DCXC	The prevalence of contrast- induced nephropathy (CIN) was lower in the DCXC	DCXC treatment may protect against CIN in patients with type 2 diabetes and renal

controlled trail. Kai et al. 2015. [195]	therapy group (n = 39, 2-g corbrin capsules, 3 times/d, 3 days before and after angiography), and intensive DCXC therapy group (n = 40, 3-g corbrin capsules, 3 times/d, 3 days before and after angiography)	treatment groups than in the basic treatment group ($P < 0.05$), with a more significant decrease in the intensive DCXC therapy group ($P < 0.01$). Urine levels of KIM-1, NGAL and IL-18 in patients in the intensive DCXC therapy group were lower ($P < 0.05$).	insufficiency under-going coronary angiography, with intensive DCXC therapy being more effective.
Cordyceps and ginkgo leaf tablet. Randomized, controlled trail. Huang et al. 2008. [196]	65 patients undergoing long-term maintenance hemodialysis. Patients in both groups underwent hemodialysis regularly, meanwhile, 3 capsules of Jinshuibao (each capsule containing hypha cordyceps 0.33 g) and 1 tablet of ginkgo leaf tablet (0.23 g/tablet) were additionally given to the patients in the treated group orally, 3 times per day, and 3 months as 1 treatment course.	Compared with the normal control group, the serum levels of hs-CRP (4.94±2.21 mg/L), IL-6 (0.472± 0.220 microg/L) and TNF-alpha (1.748±0.724 microg/L) in the treated group were higher before treatment, these indexes decreased markedly after treatment (3.28±1.28 mg/L, 0.379±0.163 microg/L, and 1.330±0.458 microg/L, respectively, all $P < 0.01$), but without significant change in the control group.	Micro-inflammation reaction exists popularly in patients undergoing maintenance hemodialysis, and the combined therapy with hypha cordyceps and ginkgo leaf tablet could effectively improve this kind of micro-inflammation reaction.
Cordyceps Sinensis Randomized, controlled trail. Gong et al. 2001 [183]	150 patients with hemorrhagic fever and renal syndrome treat-ment group were with basic treatment and added with 2g	Reduced the incidence of acute renal failure and kidney injury and promoted kidney function recovery.	Cordyceps sinensis has a beneficial effect on the prevention and treatment of acute renal failure caused by hemorrhagic fever with renal syndrome.

	Cordyceps Sinensis, three times per day.		
Cordyceps sinensis and artemisinin Randomized, controlled trail. Lan et al. 2002 [197]	61 lupus nephritis (LN) patients. The 31 cases in the treated group were given Cordyceps powder 2-4 g/d before meal and artemisinin 0.6 g/d after meal in three portions orally taken for 3 years. The 30 patients in the control group were treated with tripterygiitotorum and/or Baoshenkang tablet.	The therapeutic effect showed markedly effective in 26 cases (83.9%), effective in 4 (12.9%) and ineffective in 1 (3.2%) in the treated group, while in the control group, the corresponding numbers were 15 (50.0%), 8 (26.7%) and 7 (23.3%), the difference between the two groups in markedly effective rate was significant ($P < 0.01$).	Cordyceps and artemisinin could prevent the recurrence of LN and protect kidney function.
Cordyceps Sinensis Randomized, placebo-controlled trail. Zheng et al. 1995 [182].	58 patients with epidemic hemorrhagic fever. For Cordyceps Sinensis treatment group 2g per time, 3 times per day; in placebo treatment group, give the placebo starch powder.	There were significant declines in serum creatinine after 15 days of Cordyceps Sinensis treatment in either severe or moderate cases.	Cordyceps Sinensis treatment shortens the period of oliguria, reduces the need for dialysis, and accelerates the recovery of renal function in patients with EHF renal damage.

Renal transplant	Cordyceps sinensis Randomized, placebo-controlled trail. Ding et al. 2011 [198]	182 renal transplant recipients Maintenance immuno- suppression was Cyclosporine A in combination with Mycophenolate mofetil and steroids. Recipients in the treatment group were plus oral Cordyceps sinensis (CS) at a dosage of 1.0 g 3 times a day as an additional immuno-regulator.	With the exception of those showing acute rejection, the incidence of complications was significantly lower in the CS treatment group compared with that in the control group. Furthermore, the dosage and the concentration trough of CsA in whole blood were significantly lower in the treatment than control group.	These data demonstrated that CS may be used in combination with a low dose of CsA in the long-term treatment of kidney transplant patients.
	BLC, a dry powder preparation of Cordyceps sinensis mycelia Controlled trail. Ding et al.2009 [199]	67 recipients of renal homo-allograft. The 42 cases in the control group were treated with mycophenolate mofetil (MMF) plus cyclosporine A (CsA), or tacrolimus (FK506) plus prednisone (Pred); the 25 in the treated group treated with the chemotherapy the same as in the control group plus BLC.	Levels of urinary erythrocytes and leucocytes, blood alanine transaminase, aspartate amino transferase, uric acid, total bilirubin, direct bilirubin, as well as the incidence of infection were significantly lower, and serum total protein and albumin were significantly higher in the treated group (all $P < 0.01$); moreover, counts of erythrocyte and leukocyte from 12 to 48 weeks, T-lymphocyte from 4 to 48 weeks after transplantation were significantly higher in the treated group ($P < 0.05$ and $P < 0.01$).	BLC could effectively protect liver and kidney, stimulate hemopoietic function, improve hypo- proteinemia, as well as reduce the incidence of infection and the dosage of CsA and FK506 used, etc. Therefore, it is a useful drug for immuno- regulation after organ transplantation.

| Cordyceps sinensis Randomized, controlled trail. Li et al.2009 [200] | 202 patients (164 men/38 women) who underwent renal transplantations. Patients in the treatment group were treated with Cordyceps sinensis (CS) 1.0 g 3 times a day in addition to the immunosuppressive regimen given to the control group. | Serum uric acid (UA) and 24-hour urinary total protein (24-hour UTP) were significantly lower in the treatment group than in the control group ($P<0.05$). The incidences (11.83% vs 15.60%) and times to patients receiving thymoglobulin anti-rejection therapy (3 cases) were fewer in the heated versus control group (13 cases; $P=0.014$). The incidences of hepatotoxicity and nephrotoxicity in the treated group were 12.90% and 19.35%, significantly lower than 24.77% and 33.94% in the control group, respectively ($P<0.05$). | The use of CS may allow decreased dosages and concentrations of CsA causing fewer side effects without an increased risk of acute rejection. In addition, CS with reduced dose CsA may decrease proteinuria and retard CAN progression. |
| BLC (a dry powder preparation of Cordyceps sinensis mycelia) Randomized, controlled trail. Sun et al.2004 [201] | 121 recipients of renal homo- allograft. The 64 cases in Group A were treated with cyclosporin A (Cs A) + prednisone (pred) + azathioprine (Aza), the 57 in Group B treated with Cs A + pred + BLC. | As compared with Group A, in Group B, levels of urinary erythrocytes and leucocytes, blood alanine transaminase (ALT), aspartate aminotransferase (AST), total cholesterol, uric acid as well as the incidence of infection | BLC could effectively prevent the reject response after renal transplantation, protect renal and liver function, stimulate hemopoietic function, improve hypoproteinemia and |

		were significantly lower, and blood high density lipoprotein, serum total protein, albumin, RBC and WBC count were significantly higher.	hyperlipidemia, etc., therefore, it is an ideal immunosuppressor after organ transplantation.
Liver disease	Cordyceps militaris （Xinganbao）Randomized, treatment controlled, prospective trial. Wang et al.2012 [202]	60 patients with chronic hepatitis B.The trail group (40 cases) was treated with Xinganbao Capsule, 8 capsules each time, three times a day. The control group was given HeluoShugan Tablet, 5 pills each time, thrice daily. Six months consisted of one therapeutic course.	After treated with Xinganbao Capsule, 81% patients (17/21) had decreased liver inflammation, 52% patients (11/21) had decreased fibrosis staging one or more, and 33% (7/21) patients had no change in fibrosis. Xinganbao Capsule could reduce serum ALT and AST levels, serum HA, PC-III and LN levels (all $P<0.05$).	Xinganbao Capsule could improve the liver function, reduce liver inflammation, and fight against hepatic fibrosis.
General Health	Cordyceps militaris Double-blind, randomized, placebo-controlled trail. Kang et.al. 2015 [185]	79 healthy male adults. Given 1.5 g/day of ethanol. extracted Cordyceps Militaris in capsules or given placebo capsules for 4 weeks.	The C. militaris group showed a statistically significant greater increase in NK200 ($P = .0010$), lymphocyte PI ($P \leq .0001$), IL-2 ($P = .0096$), and IFN-γ ($P = .0126$), compared with the basal level, than the placebo group.	Cordyceps militaris is safe and effective for enhancing cell-mediated immunity of healthy male adults.
	Mycelium extract of Cordyceps 8 weeks, randomized, double blind, and placebo controlled clinical	80 healthy adults. Healthy adults were divided into the intervention group (n = 39), who were given	The CBG-CS-2 group showed a significant 38.8 ± 17.6% enhancement from the baseline of NK cell cytotoxic activity	The immune system functions were well with CBG-CS-2 supplementation. Thus, CBG-CS-2 is

	trial. Jung et.al. 2019 [203]	1.68 g/day of CBG-CS-2 in capsules, and the control group (n = 40) for 8 weeks.	relative to the placebo group after the administration of the capsules for 8 wks. ($P < 0.019$).	safe and effective for enhancing cell-mediated immunity in healthy adults.
	Cordyceps sinensis Double-Blind, Placebo-Controlled prospective trial. Chen et al.2010 [204]	20 healthy elderly (age 50–75 years) subjects. The subjects were taking either Cordyceps sinensis-4 333 mg or placebo capsules 3 times a day for 12 weeks.	After receiving Cs-4 for 12 weeks, the metabolic threshold increased by 10.5% from 0.83±0.06 to 0.93±0.08 L=min ($p<0.02$) and the ventilatory threshold increased by 8.5% from 1.25±0.11 to 1.36±0.15 L=min. Significant changes were not seen for the placebo group after 12 weeks.	Supplementation with Cs-4 (Cordyceps sinensis) improves exercise performance and might contribute to wellness in healthy older subjects
	Rhodiolacr-enulata (R) and Cordyceps sinensis. Double-blind and placebo-controlled trial. Chen et al. 2014 [205]	18 male long-distance track and field athletes. Placebo (n=9) and R/C supplementation (RC, n=9). Both groups received either RC (R: 1400 mg+C: 600 mg per day) or the placebo during a 2-week training period at an altitude of 2200 m.	Compared with Placebo group, the exhaustive run time was markedly longer (Placebo: +2.2% vs. RC: +5.7%; $p<0.05$) and the decline of parasympathetic (PNS) activity was significantly prevented in RC group (Placebo: −51% vs. RC:−41%; $p<0.05$).	The provision of an RC supplement during altitude training provides greater training benefits in improving aerobic performance.

Table 1: The beneficial effects of the Cordyceps products in clinical studies.

Cordyceps militaris can activate the adenosine receptors A1, A2A, A2B, A3, and its affinity for these receptors is very similar [8-10, 26]. Studies have shown that it has the effects of enhancing human immunity, inhibiting virus reproduction, reducing inflammation, inhibiting the generation of cytokine storms, protecting the lungs, liver, heart, and kidney, and resisting pulmonary fibrosis [206]. Cordyceps

militaris and cordycepin are also very safe. We summarized the clinical trials which used Cordycepin or Cordyceps for the treatment of various diseases (Table 1). Cordyceps is a new food resource approved by the Chinese government. There are almost no significant side effects. Only approximately 0.5% of people may have a fungal allergic reaction. Although there is no clear research on its use in pregnant women and children, it is recommended for safety reasons to not be used in these populations. With all its beneficial properties, why hasn't cordycepin been developed as a medicine?

In fact, cordycepin has been approved as a new drug for leukemia in the United States [207]. With the application of an artificially purified monomer cordycepin, it is extremely easy to lose activity in the human body due to adenosine deaminase (ADA) activity. The pharmacokinetic reports suggest that the presence of ADA in the human body causes cordycepin into be rapidly deaminated to form a non-bioactive metabolite, 3'-deoxyhypoxanthine, and only a small portion of which is phosphorylated to the effective cordycepin triphosphate (the bioactive ingredient). To delay the metabolism time of cordycepin in the body, it must be used in combination with anti-deamination ADA inhibitors (such as pentostatin); however, this is more costly and has limited the widespread use of cordycepin [207].

Since ancient times, people have been treating and curing diseases with unrefined Cordyceps powder. Wang's team recently found the molecular mechanism of the concomitant biosynthesis of cordycepin and pentostatin (ADA inhibitor) in Cordyceps militaris, in which cordycepin and the ADA inhibitor pentostatin

could be simultaneously synthesized from the same gene cluster in Cordyceps militaris [207]. This finding reveals the mystery of why the Cordyceps can be utilized by the human body to produce a medicinal effect, since when taking the cordycepin in the original Cordyceps, the adenosine deaminase (ADA) inhibitor pentostatin, which prevents the deamination of cordycepin, is also present [207]. Cordycepin in Cordyceps militaris is very stable, easily absorbed, and utilized by the human body. Therefore, Cordyceps militaris with high cordycepin (> 1%) can be used as an activator of the adenosine receptors A1, A2A, A2B, and A3. It is safe and reliable and comes with a protective agent, pentostatin. Now, some pharmaceutical companies can produce Cordyceps powder with a high cordycepin content, up to 0.5-3%. The cultivated Cordyceps militaris can be made into tablets or granules and can play its important role for the prevention, adjuvant amelioration and rehabilitation of viral pneumonia.

The role of cordycepin in preventing cytokine storms and protecting alveolar tissue in COVID-19 pneumonia is worth exploring to overcome the devastating disease and to save lives. Because Cordyceps militaris is ideal to use as a food supplement to build up the immune system, and its anti-viral properties may prevent the infections from becoming severe or critical cases. It can be used as an adjunctive therapy to ameliorate the lung inflammation and cytokine storm, to clear alveolar fluid, and to protect the lung tissue. In the long run, it may be able to protect against lung fibrosis and repair lung tissue. A clinical trial for the cordycepin from Cordyceps militaris in the amelioration of COVID-19 pneumonia is warranted.

Acknowledgments

Conflict of Interest

The authors have no conflicts of interest to disclose, financial or otherwise.

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