IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
May 2021 Vol.:18, Issue:3
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The Possible Treatment Strategies, Therapeutic Potential of Medicinal Mushroom *Cordyceps militaris* against COVID-19

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

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Submitted: 27 April 2021
Accepted: 03 May 2021
Published: 30 May 2021

HUMAN JOURNALS
www.ijsrm.humanjournals.com

Keywords: antiviral, COVID-19, mushroom, cordycepsin, treatment

ABSTRACT

The novel corona virus, SARS-CoV-2 has caused significant mortality all over the world. The poor understanding of the pathophysiology of this virus and lack of suitable treatment therapy has made this disease very challenging and difficult for the health care personnel. Recently, the interest of people towards complementary and alternative medicine systems is on the rise worldwide. *Cordyceps militaris* is an entomopathogenic fungus that is often used as a part of the traditional medicine system in several parts of the world. The present review attempted to highlight the possible treatment strategies and therapeutic potentials of medicinal mushroom *Cordyceps militaris* in the treatment of COVID-19. Based on recent data, it is indicated that the bioactive compounds from the *Cordyceps militaris* have great therapeutic potential against COVID-19 viral infection. Therefore, this mushroom can serve as a potential source for the development of antiviral drugs against SARS-CoV-2 infection. However, more studies are still required for clinical validation of compounds from these mushrooms which could help in the development of novel antiviral drugs.

INTRODUCTION

In December 2019, a novel coronavirus (2019-nCoV) strain, also known as severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), was first detected in China. This virus causes COVID-19 disease which is highly contagious with mild to severe symptoms such as weakness, headache, dizziness, fever, cough, and dyspnea to severe hypoxia with acute respiratory distress syndrome and multiorgan failure [1]. Coronavirus is very small in size with 65-125 nm in diameter and has a single-stranded RNA as a genetic material of 26 to32 kbs in dimension. The structure of this virus contains crown-like spikes on the external surface. SARS-CoV is the major causative agent of acute lung injury and acute respiratory distress syndrome (ARDS) which may cause pulmonary distress and death [2]. This virus belonged to the group of corona viruses which was named SARS-CoV- 2 by the International Committee on Taxonomy of Viruses (ICTV). SARS-CoV infected a huge number of individuals with a mortality rate of more than 9% in about 26 countries globally [3, 4]. *Cordyceps militaris* is a medicinal mushroom that is often used in many Asian countries as a part of the traditional medicine system. Cordycepin and other bio-metabolites from this mushroom have tremendous use in medicinal applications [5]. This review aims to discuss whether medicinal mushroom *C. militaris* can be used as a potential source of the development of drugs for the treatment of COVID-19. We have discussed the possible treatment strategies and potential therapeutic efficacy of this mushroom in the treatment of COVID-19.

Covid 19- potential treatment strategies

Viruses are not as easy to treat as bacteria because viruses are very diverse with unique characteristics. Bacteria can be targeted using broad-spectrum drugs like antibiotics. Viruses use host cell machinery to create proteins that help in its replication, therefore, targeting the virus without damaging host cells is very challenging and difficult. All the possible potential treatment strategies for COVID-19 have been summarized in Table-1.

Blocking of viral critical enzymes

The identification of viral proteins which help in replication and then blocking them can be a useful step. Wu and co-workers (2020), systematically analyzed all the proteins encoded by SARS-CoV-2 genes and compared the gene sequences with proteins of other coronaviruses. These workers screened a total of twenty-one drug targets against compound libraries. They

discussed the structure and screening results of virus target sites such as 3-chymotrypsin-like protease (3CLpro), Spike, RNA-dependent RNA polymerase (RdRp), and papain-like protease (PLpro) [6].

Monoclonal antibodies drug therapy

Monoclonal antibodies (mAb or moAb) are antibodies that are made by identical immune cells that are all clones of a unique parent cell. Viral components derived from the immune system can be used to produce monoclonal antibodies especially from the patient who recovered from the disease. The diseased person's finely tuned immune system already had a way to clear the virus. The therapeutic applications of monoclonal antibodies have been assumed by researchers since the production of them in 1975. Monoclonal antibodies produced in murine models may cause an immunogenic response in human patients, therefore decreasing their therapeutic potential. However, chimeric and humanized antibodies have been developed that generate a low level of immune response in human patients as compared to murine-derived antibodies. Today monoclonal antibodies may have several therapeutic applications in the treatment of various diseases such as asthma, autoimmune diseases, cancer, poisoning, septicemia, substance abuse, and viral infections [7]. Many workers are trying to develop a treatment for coronavirus infection based on antibodies that can block and/or neutralize the virus. Researchers have also published several reports of the development of specific monoclonal antibodies against COVID-19 and very hopeful for the efficacy of these in the treatment of the disease [8].

Inhibition of viral replication

Antiviral drugs can be designed to target viral replication. The proteins which help in the viral replications can be cut into non-functional proteins which no longer will remain helpful for the virus. However, the search for the replication inhibitors will depend on the understanding of molecular events taking place during the infection [9]. Aftab and co-workers (2020), proposed RNA-dependent RNA polymerase (RdRp), which regulates viral replication, as a potential treatment option for the inhibition of viral infection. These workers suggested that targeting RdRp active sites, ASP760 and ASP761 through antiviral drugs may be a potential therapeutic strategy for inhibition of replication of coronavirus [10].

RNA interference

RNA interference is a biological process in which RNA molecules inhibit gene expression or translation, by neutralizing targeted mRNA molecules. Uludag and co-workers (2020), revealed that this mechanism can be used to develop front-line drugs against the virus as this strategy allows specific binding and silencing of viral targets using short interfering RNA (siRNA) and short hairpin RNA (shRNA) molecules. These workers have summarized the feasibility of the application of promising drug therapies through inhalational route with a belief that this route may provide the most effective way to stop viral spread [11]. It has been observed that the natural compounds which have antioxidant, antiviral activities, and RNA interference agents may play an important role in the prevention and treatment of coronavirus infection by suppressing critical viral genes. Kalhori and co-workers (2021), also demonstrated the genetic and morphological structure of coronavirus and determined the role of miRNAs, siRNAs, chemical drugs, and natural compounds in boosting the immune response, inhibiting structural and essential genes of SARS-CoV-2 virus replication [12].

Gene silencing techniques and Interferons

Selective gene silencing technologies such as RNA interference (RNAi) have shown significant therapeutic potential for the treatment of viral infections. In these techniques, the key enzyme required for the virus **is** turned off [13]. Human cells release some molecules which serve as an alarm to another cell to prepare them for the infection, they are not specific to a single virus and respond to all viruses at all stages of their replications. Interferons (IFNs) are the approved therapeutic agents and are clinically in use [14].

Blocking of viral binding sites on the host cell

It is inspiring to see the quickness and seriousness of the scientific community towards the development of therapeutic strategies against the current corona crisis. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) contains a spike protein that helps in the entry of the virus into the host's cells through binding of cell surface receptor known as angiotensin-converting enzyme 2 (ACE2) [15]. Identification of receptor molecule and designing complementary receptor molecules similar to viral binding components. Identification of virus

binding sites on the human cell surface to which viruses bind and blocking them may help to develop an antiviral drug against the SARS-CoV-2.

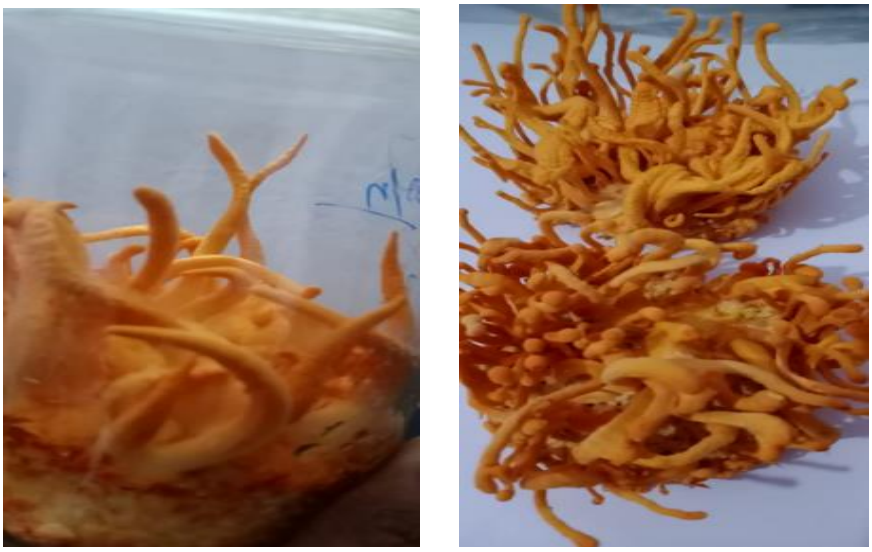
Table No. 1: Possible potential treatment strategies against SARS-CoV-2

Sr. No.	Treatment Strategy	Mechanism of action	References
1	Blocking of viral critical enzymes	Blocking of 3CLpro, RdRp, and PLpro.	[6]
2	Monoclonal antibodies drug therapy	Blocking and neutralization of the virus.	[7,8]
3	Inhibition of viral replication	Conversion of The viral useful proteins into non-functional proteins Targeting RdRp active sites which regulate viral replication	[9] [10]
4	RNA interference	Specific binding and silencing of viral targets using siRNA) and shRNA molecules. Inhibiting structural and essential genes	[11] [12]
5	Gene silencing techniques	The selective gene silencing	[13]
6	Interferons	Targeting virus at all stages of replication.	[14]
7	Blocking of viral binding sites on the host cell	Blocking the binding of cell surface receptor angiotensin-converting enzyme 2 (ACE2)	[15]

Cordyceps militaris

Recently, there is an increase in the use of traditional medicines derived from natural compounds [16]. *Cordyceps militaris* is regarded as an important medicinal mushroom that acts as an overall tonic to the body due to its number of health effects (Fig-1 a&b). Many studies

demonstrate its efficacy in the stimulation of the immune system, faster recovery in bronchitis, respiratory problems, increase in stamina, and anticancer properties [5]. *Cordyceps* has been used as a medicinal food in China and many countries of southeast Asia for many years. *Cordyceps* are the one of most known medicinal mushroom which contains several bioactive compounds which have many health benefits. The major component of these mushrooms is cordycepin found which is a low molecular weight compound and is known for its number of medicinal properties such as anticancer, antitumor, antioxidant, anti-inflammatory, hypoglycemic, and immunomodulatory effects [17].



(a) **(b)**

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

***Cordyceps* as medicine**

Medicinal mushroom *Cordyceps sinensis* is used as traditional Chinese medicine and have been clinically tested for its efficacy in the treatment of several diseases such as diabetic kidney disease, and lung fibrosis. Wang and co-workers (2016), investigated the effectiveness of this mushroom against the moderate-to-severe cases of persistent asthma. These workers concluded that the formulation of this mushroom improved the asthma symptoms, lung function, and inflammation in the patients with moderate-to-severe asthma [18]. Cultured mycelia and fruiting bodies of *Cordyceps* have been widely used in the commercial health food formulations. Many studies and experiments have demonstrated antitumor, immunomodulatory, antioxidant, sexual

function enhancement, hypoglycemic, and antifatigue effects of biometabolites found in these mushrooms. The cultured mycelia are as effective in medicinal effects as natural *Cordyceps* [19]. The chemical effects of *C. militaris* are very similar to natural *Cordyceps* and this species is being studied in detail as an alternative to *O. sinensis*. A number of researches have been conducted on its genetic resources, nutritional and environmental requirements, mating behaviour along with biochemical and pharmacological properties and genome of this fungus has recently been sequenced [20]. *Cordyceps militaris* has been regarded as oldest source of useful bioactive components and now the compounds found in this mushroom has been extensively used in modern medicine system [21]. Ueda and co-workers (2014), also evaluated formulations of oral health supplements prepared from *Cordyceps militaris* for anti-HCV effects. These workers found that the capsules made from this mushroom have demonstrated moderate anti-HCV activity as compared to liquid formulation. They also suggested that this mushroom would be useful as an oral anti-HCV agent when combined with interferon-α or ribavirin [22].

Antiviral effects of mushrooms

The number of approved antiviral agents has increased recently. However, these are not always effective in treatment as the emergence of drug-resistant virus strains is rapidly increasing. Therefore, there is a great need to continuously search for new antiviral agents from natural sources. Many polysaccharides from mushrooms have been approved as medicines [23]. Mushrooms are used as a food supplement and food additive in their natural form. These contain several bioactive compounds such as polysaccharides, carbohydrate-binding protein, peptides, proteins, enzymes, polyphenols, triterpenes, and triterpenoids which are beneficial for human health. These bioactive compounds have antiviral activity against DNA and RNA viruses targeting the entry of virus, genome replication, and viral protein synthesis [24]. The published research suggests that various mushroom species such as *Calvatia gigantia, Cordyceps militaris, Cortinarius caperatus, Fomes fomentarius, Ganoderma lucidum, Grifola frondosa, Hericium erinaceus, Inonotus hispidus, Inonotus obliquus, Lentinula edodes, Omphalotus illudens, Ophiocordyceps sinensis, Phellinus ignarius, Pleurotus citrinopileatus, Pleurotus eryngii. Pleurotus ostreatus, Polyporus umbellatus,* and *Trametes versicolor* have medicinal, antiviral, and antibacterial properties [25].

Lee and co-workers (2014), investigated the immune-modulatory and anti-influenza effects of *Cordyceps* mushroom extract using a DBA/2 mouse model. These workers used three different concentrations of extracts and administered them orally to mice for seven days. The mice were intranasally infected with influenza H1N1 virus which was pandemic in 2009 and observed for changes in body weight and survival. These workers found that *Cordyceps* extract has shown the anti-influenza effect which was associated with stable body weight and decreased mortality. The anti-viral effect of *Cordyceps* extract against influenza viral infection was mainly due to the increased expression of IL-12 and the number of Natural Killer cells [26]. He and his co-workers (2020), reviewed the information about the antiviral polysaccharides from medicinal plants and mushrooms. These workers observed that these polysaccharides can inhibit viral infections via interrupting the virus life cycle or improving the host immune response. Several efforts have been made to develop novel antiviral polysaccharides from medicinal plants and mushrooms [23].

Ohta and co-workers (2007), isolated an acidic polysaccharide (APS) from the *Cordyceps militaris* extract and studied its antiviral effects. These workers observed that after administration of polysaccharide in mice infected with the influenza virus, there was a decrease in virus titers and bronchoalveolar lavage fluids in the mice's lungs. Also, the APS increased the levels of TNF-α and INF-γ in the infected mice along with enhancement of nitric oxide production, protein expression in macrophage cells, IL-1 β, IL-6, IL-10, and TNF- α. Their studies indicated the potential benefits of *Cordyceps militaris* in the treatment of influenza virus infection [27].

Effectiveness of *Cordyceps militaris* in COVID -19

The COVID -19 pandemic was caused by a novel coronavirus, has few effective vaccines or treatment options which made it a global health emergency. The data suggests that some nutraceuticals such as omega-3 fats, beta-glucans, amino acids, probiotics, minerals, and other herbal compounds have the potential to treat this disease. However, there is less clinical data available in support of this. The natural compounds from different sources may not only boost the immunity of susceptible individuals but may also help in the development of new drugs for the treatment of COVID-19. Some clinical and experimental studies are still required to confirm their efficacy [28].

Kaymaci and Metin, (2020), revealed that the pathophysiology of this virus is unclear and the lack of targeted treatment therapy has made this disease very challenging and difficult for the health care personnel. Entomopathogenic fungi such as *Cordyceps sinensis* and *Cordyceps militaris* are known for their anti-inflammatory, immunomodulatory, lung improving, and antiviral effects in traditional Chinese medicine systems [1].

Verma (2020), has demonstrated that spike protein and several other proteases of the SARS-CoV-2 virus may be potential therapeutic targets for the antiviral drugs as inhibition of these targets may restrict the viral entry and replication in the host cells. The experiments were conducted to evaluate the binding affinity of cordycepin compound found in *Cordyceps militaris* with viral target proteins and to study protein interactions along with associated pathways based on computational and pharmacological studies. Since cordycepin has structural similarity with adenosine; but it lacks a 3' hydroxyl group in its ribose moiety which makes this compound poly (A) polymerase inhibitor to terminate premature protein synthesis. It is known that the functional RNAs of the SARS-CoV-2 genome are highly 3'-polyadenylated and required in the synthesis of all viral proteins. Cordycepin has shown a strong binding affinity with SARS-CoV-2 spike protein and main proteases which significantly strengthen its therapeutic potential against COVID-19 [29]. If cordycepin can destabilize SARS-CoV-2 RNAs through inhibition of polyadenylation step which may not only lead to inhibition of viral replication but also its multiplication inside the host cells.

Lee and co-workers (2020), have summarized the immunomodulatory effects of *C. militaris* polysaccharides and cordycepin extracts. These workers observed that the total water or ethanolic extracts and polysaccharides from *C. militaris* were found to boost type 1 immunity, and cordycepin obtained from *C. militaris* were able to promote type 2 immune response. Their work provides comprehensive knowledge about the immunomodulatory effects of precious folk medicine and guidance on its use for both healthy people and those with immunodeficiency [30].

It has been observed that the majority of individuals infected with SARS-CoV-2 have mild-to-moderate COVID-19 disease. Therefore, convalescence results from this mild-to-moderate (MtoM) condition may be supported using integrative medicines which may help in recovery. The patients may adopt an anti-inflammatory diet, food supplements containing vitamin D,

glutathione, melatonin, *Cordyceps*, Astragalus, and garlic. Also, osteopathic manipulation, breathing, and aerobic exercises may help in pulmonary recovery [31].

The demand for immunity boosters to fight virus has increased as the pandemic began to spread. Centre for Cellular and Molecular Biology (CCMB) Hyderabad, incubated and validated 'CoronAid', which is a novel nutraceutical that help to boost body's immunity against COVID-19. This product has been developed by Clone Deals, a Hyderabad-based startup in collaboration with CCMB. This formulation contains *Cordyceps militaris* and curcumin from turmeric, evaluated for its immune boosting and antioxidant properties. The product was launched in October 2020 [32].

Polyadenylation is a very important process for all the viruses as this increase the half life of the polyadenylated RNA transcripts by protecting RNA degradation by exonuclease enzymes [33]. Polyadenylation at the 3′ end in SARS-CoV-2 virus plays major role in its pathogenesis and multiplication [34,35]. Cordycepin (3′-deoxyadenosine), which is a bioactive compound found in *Cordyceps militaris* is believed to control replication of SARS-CoV-2. This compound possesses structural similarity with adenosine but lacks a 3′ hydroxyl group in its ribose moiety and some enzymes fails to differentiate between these two. Therefore, this compound can participate in some biochemical reactions such as inhibition of poly (A) polymerase and purine synthesis, shortening of poly (A) tails, destabilization of mRNAs, and also may be responsible for premature polypeptide chain termination [36,37]. Cordycepin has great potential to inhibit virus entry and replication into the host cells. Besides this, due to many other clinical benefits of cordycepin in various health issues, this mushroom may also be beneficial in the later phase of SARS-CoV-2 infection [29].

The potential therapeutic efficacy of medicinal mushroom *Cordyceps militaris* in the treatment of COVID-19 has been summarized in Table-2.

Table No. 2: Potential therapeutic efficacy of *Cordyceps militaris* in treatment of COVID-19.

Sr. No.	Mechanism of action	References
1	Anti-inflammatory, immunomodulatory, lung improving, and antiviral effects	[1]
2	Destabilization of SARS-CoV-2 RNAs through inhibition of polyadenylation by cordycepin Binding of cordycepin with SARS-CoV-2 spike protein and main proteases	[29]
3	Boosting of type-1 and type-2 immune response by polysaccharide and cordycepin extracts	[30]
4	Increased in the levels of TNF-α, INF-γ, IL-1 β, IL-6, IL-10, and TNF- α. By APS	[27]
5	Polysaccharide mediated inhibition of the viral infections Boosting host immune response.	[23]

HUMAN

SUMMARY

The present review attempted to highlight the possible treatment strategies and potential therapeutic efficacy of medicinal mushroom *Cordyceps militaris* in the treatment of COVID-19. Recently, there is an increase in the use of traditional medicines derived from natural compounds. *Cordyceps* has been used as a part of traditional medicines in China and many countries of South East Asia for many years. The pathophysiology of this virus is still unclear and the lack of appropriate treatment therapy has made this disease very challenging and difficult for the health care personnel. In this review, the therapeutic potential of the bioactive compounds from the *Cordyceps militaris* against the ongoing COVID-19 pandemic has been discussed as per the recent literature which indicates that this mushroom can serve as a potential source for the development of antiviral drugs against SARS-CoV-2. However, more studies are required for clinical validation of compounds from these mushrooms which could help in the development of new antiviral drugs and help to combat COVID-19 infection.

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