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Review Article

Hypoglycemic and glucose-lowering properties of *Cordyceps militaris*

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Abstract

Diabetes mellitus is a serious endocrine disease characterized by hyperglycemia. This disease has been regarded as a major global health issue. Although majority of the current therapeutic approaches are beneficial in treating diabetes, there are still unfavorable side effects. The Chinese traditional medicinal fungi, Cordyceps militaris, has been used in the treatment of diabetes mellitus for centuries. This study summarizes the chemical compounds in Cordyceps militaris and their corresponding hypoglycemic effect in the development of therapeutic agents for diabetes mellitus based on recent reports. Several studies using chemically induced diabetic rats and mice models have established the antidiabetic effect of Cordyceps militaris administered at various doses. This report reveals that Cordyceps militaris has a great deal of promise and should be taken into consideration for the development of novel antidiabetic therapies.

Keywords: *Cordyceps militaris, Diabetes mellitus, Anti-diabetes, Hypoglycemic activity*

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INTRODUCTION

Diabetes mellitus (DM) is a group of carbohydrate metabolic disorders characterized by chronic hyperglycemia (high blood glucose) due to insulin insufficiency, insulin resistance or both [1–4]. It is divided into two types viz: type 1 diabetes mellitus (T1DM) caused by the destruction of insulin-producing β-cells of the pancreas, leading to deficiency of insulin and type 2 diabetes mellitus (T2DM), also known as noninsulin-dependent diabetes mellitus, caused by insulin resistance. Other specific subtypes of DM include genetic defects in insulin action, genetic defects of β-cell function, endocrinopathies, diseases of the exocrine pancreas, uncommon forms of immune-mediated diabetes mellitus, and gestational diabetes mellitus [2].

Most of the current therapies for DM focus on the recovery of pancreatic islet function and normalization of blood glucose [5–7]. Various undesirable side effects, including dizziness, diarrhea, hypoglycemia, gastrointestinal disturbances, and insulin resistance, are reported in patients who receive long-term insulin treatment and commonly prescribed drugs such as metformin and pioglitazone [5,7,8]. There is a strong need to discover natural antidiabetic

medicines with fewer side effects as an alternative to pharmaceuticals for the treatment of the disease.

Recently, herbal fungal *Cordyceps*, the composite of entomopathogenic fungi that parasite the larva of insects, has being attracted increasing attention due to its medicinal value. More than 400 species of Cordyceps have been identified worldwide. They are distinguished by their cylindrical asci, thickened, ascus apices and filiform ascospores, which disarticulate into part-spores [9]. Within the genus of *Cordyceps*, *Cordyceps sinensis*, also known as *Dongchongxiacao*, has been recorded as a Chinese herbal drug in traditional Chinese medicine for more than 700 years [10].

Numerous *Cordyceps* species have been reported, for example, *Cordyceps militaris*, having medicinal and pharmaceutical properties. Besides *Cordyceps sinensis*, *Cordyceps militaris*, a well-known Chinese traditional herb, is one of the most typical and widely used *Cordyceps* species [11]. A 3'-Deoxyadenosine, also identified as Cordycepin, is one of the main bioactive metabolites in both *Cordyceps sinensis* and *Cordyceps militaris* [11,12]. Cordycepin has been postulated that its functions possess various medicinal and pharmaceutical activities, including anti-tumor, anti-diabetics, anti-hyperglycemic, anti-oxidant, anti-bacterial, and immunomodulatory effect [10–14]. The compound of Cordycepin was first isolated from cultured *Cordyceps militaris* in 1950. It is noteworthy that this compound is mostly found in small amounts in natural *Cordyceps sinensis* and has not been found in *Cordyceps sinensis* cultures [15,16]. For this reason, *Cordyceps militaris* has become a focus. Both the fruiting bodies and the mycelia of *Cordyceps militaris* have therapeutic bioactivities. Despite the widely accepted use of *Cordyceps militaris* as a food and health-supporting medicine, especially in the field of its application in DM treatment as well as hypoglycemic effect, there has been still no comprehensive review detailing its functions in this area. The chemical compounds of *Cordyceps militaris* and their corresponding bioactive effect have been shown in these studies to play important roles in the development of therapeutic agents for diabetes mellitus.

Adenosine and cordycepin, the major chemical constituents of *Cordyceps militaris*

Various bioactive compounds, including amino acids, fatty acids, polysaccharides, cordycepin and adenosine, have been identified in the fruiting body, corpus, and mycelia of *Cordyceps militaris* [7,17–20]. Cordycepin and adenosine are the major bioactive components [18].

Adenosine ($C_{10}H_{13}N_5O_4$) (Figure 1 A), a cellular energy transfer and signal transduction molecule, is the nucleoside which is major nucleoside in *Cordyceps* species, that has a wide spectrum of cytoprotection or prevents tissue/cell damage [10]. Furthermore, the bioactive effect of anti-inflammatory, antitumor, and antioxidant properties have been reported [21].

Cordycepin ($C_{10}H_{13}N_5O_3$, 3′-deoxyadenosine) is the adenosine analogue isolated from most *Cordyceps* species, which is an adenosine derivative differing from adenosine by the absence of oxygen in the 3' position of its ribose moiety (Figure 1 B) [15,18,22]. Cordycepin was first isolated from cultured *Cordyceps militaris* by Cunningham *et al* [23] in 1950, then, identified as 3'-deoxyadenosine in 1964. Compared to *Cordyceps militaris*, the low content of cordycepin exists in natural *Cordyceps sinensis*, and not in cultured ones [23]. It has been documented that cordycepin modulates cell proliferation, antinephritic, hypoglycemic, antitumor, anti-inflammatory, and antibacterial effect [10–14]. Therefore, *Cordyceps militaris* has become a valuable source of cordycepin.

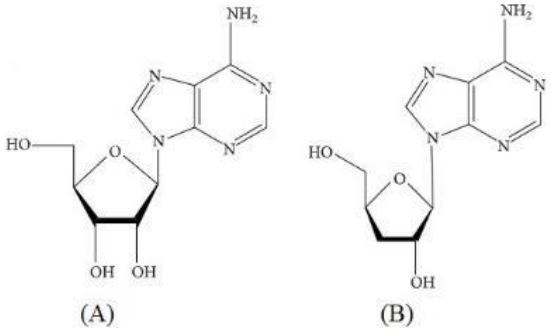

Figure 1: Chemical structures of Cordycepin (A); Adenosine (B)

Due to their therapeutic benefits, adenosine and its analogue, including Cordycepin, were considered to be of great interest in medical applications. Adenosine and Cordycepin were found in the fruiting body, corpus and mycelia. For example, the concentrations of Adenosine and cordycepin were 0.18 and 0.97 % in the fruiting body, and 0.06 and 0.36 % in the corpus of *Cordyceps militaris* [18]. Mat *et al* [11] concluded that Cordycepin from *Cordyceps militaris* could serve as a therapeutic agent for DM treatment. This conclusion was established based on the hypoglycemic effect of cordycepin on the regulation of glucose metabolism in the liver as well as the remarkable reduction of

plasma glucose in alloxan-induced diabetic mice [11]. The mechanism of hypoglycemic activity of cordycepin has been studied in RAW 264.7 cells. In their study, they verified the T2DM-inhibitory effect of cordycepin by assessing the mRNA levels of diabetes-regulating genes and the protein of cytokines using RT-PCR and western blot analysis, respectively. Cordycepin inhibited the levels of diabetes-regulating genes, including *11β-HSD1* and *PPARγ*, and the expression of co-stimulatory molecules such as ICAM-1 and B7-1/-2. Moreover, it has been documented that the inhibition of diabetic regulating genes in LPS-activated macrophages is mediated by the suppression of NO and pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α [24]. Accumulating evidence indicates that adenosine plays an important role in the regulation of insulin production and homeostasis of glucose via the activation of four G-protein-coupled adenosine receptors, i.e. A1, A2A, A2B and A3 [25,26]. Additionally, the adenosine receptor regulated the events of immunology and the reduction of oxidative stress observed in models of T2DM [26]. In light of this, it is thought that *Cordyceps militaris* emerges as a viable and different source of medicinal herbs for the advancement of diabetes treatment.

In vivo based studies

Because *Cordyceps militaris* has the ability to prevent diabetes, it has attracted a lot of interest from the pharmaceutical and medical industries. However, there is still not much *in vivo* data available on the anti-diabetic activity of *Cordyceps militaris*. The anti-diabetic bioactive of *Cordyceps militaris* has been studied in previous *in vivo* investigation. Table 1 summarizes previous studies related to bioactivity and anti-diabetic properties. *Cordyceps militaris* is known to contain many bioactive compounds, including adenosine, which help in the diabetics' recovery process. As shown in Table 1, various ethanolic, methanolic and water-soluble extracts of different parts of *Cordyceps militaris* administrated at different dosages showed the ability to reduce and stabilize blood glucose levels in the model of streptozotocin (STZ) or Alloxan-induced diabetic rats/mice. Moreover, data suggests that administering water or alcohol extract of *Cordyceps militaris* has been demonstrated to have hypoglycemic effect akin to that of metformin, the medication used to treat T2MD [5]. This could be explained that it may be partially associated with increasing absorption of glucose through enhancement of PK activity, a rate-limiting enzyme that facilitates the metabolism of sugar in the glycolytic pathway [27,28].

Diabetes mellitus has been reported to be related to oxidative stress caused by imbalance between antioxidant ability and levels of free radicals and/or reactive oxygen, subsequently, leading to reduction of the utilization of glucose [29]. Moreover, numerous studies indicated that the accepted mechanism is that insulin resistance in T2MD lead to disorder of lipid metabolism, resulting in dyslipidemia [7,29]. Therefore, studies on other bioactive effect of *Cordyces militaris*, such as its antioxidant and hypoglycemic properties, need to be conducted alongside the evaluation of hypoglycemic effect of *Cordyces militaris*. Tree. Liu *et al* reported that during long-term four weeks of oral administration of different doses of CM (*Cordyceps militaris* fruit body aqueous extract), the hypoglycemic effect as well as hypolipidemic activity of CM were reported in the studies of decreasing and normalization of plasma glucose, total cholesterol, triglycerides, HDL-, and LDL-cholesterol in the diet-STZ-induced rats [7]. Moreover, renal protective activities were also reported to have the ability to inhibit albuminuria, creatinine, urea nitrogen, and n-acetyl-*β*-d-glucosaminidase. They concluded that *Cordyceps miltatis* fruit body extract has promising potential as a development of new treatment for diabetic patients, especially those with nephritis [7].

Future perspective

The current review revealed that *C. militaris* has been explored for its noteworthy antidiabetic properties. The bio-constituents, including cordycepin, and adenosine, of this natural herbal mushroom offer opportunities for the design and development of some formulations and drugs for diabetic treatment. Further studies should be focused on the in-depth mechanisms of its antidiabetic properties as well as cultivation and isolating strategies for the commercialization of *C. militaris*.

CONCLUSION

Several complementary and alternative medicines are being developed for the treatment of human diseases, including diabetes mellitus. Known as a traditional Chinese herb, *Cordyceps militaris* appears prominent because it has a variety of bioactive constituents with a wide range of activities, including antidiabetic activity. The challenge is to provide a scientific explanation for its pharmacological and medicinal properties.

Table 1: Anti-diabetic effect of *Cordyceps militaris*

Model	*Cordyceps militaris*	Doses administration (mg/kg)	Negative Control	Results	References
STZ-induced diabetic mice	CCCA(1) CMESS Cordycepin	4 50 0.2	STZ	Both CMESS and cordycepin dramatically lowered blood glucose levels following a prolonged 7-day administration (Inhibition ratio: 46.9%, 48.4%, respectively)	[30]
STZ-induced diabetic rat	CM001-fe(2) CM001-pe CM001-me CM007-fe CM029B-fe CM029B-pf CM027-1-fe YN-A-fe	100 10 100 100 100 10 100 100	STZ	The hypoglycemic effect of *Cordyceps militaris* were recorded in STZ-induced diabetic rats. Protective effect of *Cordyceps militaris* against the diabetes-inducing action of STZ. It was noteworthy that the polysaccharide-enriched fraction reduced the level of blood glucose by 60-70%.	[31]
Diet-STZ-induced diabetic Sprague-Dawley rats	AE WE	5 and 200 5 and 200	STZ	The extracts of *Cordyceps militaris* showed a significant reduction of blood glucose levels in the model, which was similar to that of metformin the medicine to treat T2MD.	[5]
Alloxan-induced diabetic mice	Cordycepin	3600	Alloxan	Cordycepin from *Cordyceps militaris* reduces the level of blood glucose by 47%.	[11]
High-fat diet-induced T2MD mice	CmNo1(3)	360	DM	CmNo1 reduced the level of blood glucose by increasing insulin sensitivity.	[32]
Diet-STZ-induced diabetic Sprague Dawley rats	CM(4)	500, 1000 and 2000	STZ	CM at 1000 $mg.kg^{-1}$ showed a significant reduction in value AUC the area under the blood glucose curve). CM reduces blood glucose in diet-STZ-induced diabetic rats.	[7]
Type 2 diabetic nephropathy mice	CmNo1(3)	360	DN	The cmNo1-treated group showed a significant decrease in blood glucose levels. The value of AUC was significantly lower in the CmNo1-treated group than DN group.	[33]
STZ-induced diabetic mice	AE-PS(5)	100 and 400	STZ	AE-PS from C. militaris was possessed of potential activities, improved insulin resistance in T2DM mice	[20]

STZ: streptozotocin; (1)CCCA: crude cordycepin containing adenosine; CMESS: ethanol soluble supernatant. (2)Five strains of *Cordyceps militaris*, namely, CM001, CM007, CM029B, CM027-1 and YN-A; fe: fruiting body extract; pe: polysaccharide-enriched fraction; me: mycelial extract. (3)CmNo1: *Cordyceps militaris* Number 1 Crude Powder. (4)CM: *Cordyceps militaris* fruit body aqueous extract; (5)AE-PS: acidic-extractable polysaccharides from *Cordyceps militaris*

This review has summarized previous researches on *Cordyceps militaris* for treating diabetes. Altogether, by using diabetic rats/mice, the antidiabetic as well as hypoglycemic activities of *Cordyceps militaris* have been confirmed. It reveals that *Cordyceps militaris*, is safe for use and has a lot of promise as a new source for active pharmaceutical ingredients in diabetes treatment.

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Ethical approval

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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