Antihyperglycemic activity of *Ophiocordyceps sinensis*: A Review

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**ABSTRACT**

Diabetes mellitus, one of the non-communicable diseases, is still the seriously problem due to leading the causes of death in the developed countries. Therefore it is important to identify novel nutraceuticals or drugs for curing or preventing diabetes because the existing synthetic drugs have several limitations. Traditional medicinal plants and medicinal mushrooms are used in the treatment of diabetes mellitus more than century, but only a few of these have proved their safe and efficacy. Aim of this review article is focused *Ophiocordyceps sinensis* one of the edible and medicinal mushrooms used for therapeutic effects and antioxidant activities. It contains several kinds of polysaccharides, proteins, nitrogen compounds, fatty acids, phenolic acids, and isoflavones. Many researches have evaluated that these phytochemical substances have the major impact on diabetes mellitus. This review focuses on the antihyperglycemic activity of this mushroom and clears that it has the potential to be considered as a candidate for preparing the new treatment of diabetes mellitus.

**Key words:** Antihyperglycemia, Diabetes mellitus, Mushroom, *Ophiocordyceps*, Polysaccharide, *Sinensis*.

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The medical cost for specific diabetes-related complications and long-term effects is greater than that of other diseases (Jonsson, 2002; Ashton *et al*., 2003; Zhuo *et al*., 2014). There are the ethnobotanical and ethnomycological studies of medicinal plants and medicinal mushrooms used in the management of diabetes mellitus in many countries due to their costs and effective. Many Asian countries use traditionally wild edible mushrooms as delicious and nutritional foods and medicines (Saiqa *et al*., 2008; Perea and Li, 2011). Edible mushrooms have higher protein contents, nitrogen compounds, minerals and contain less fat but are rich in vitamins (Wani *et al*., 2010). *Hericium erinaceus* is named for its shape, and is literally interpreted as “monkey head mushroom” (Wang *et al*., 2005) and *Pleurotus ferulae* with nicknamed the “beef-liver mushroom of the prairie” (Wang *et al*., 2014) are the wild strain of mushrooms with delicious taste and several nutrients that were studied the antihyperglycemic activities of exopolysaccharides in Taiwan. *Inonotus obliquus* or chaga mushroom grows on birch trees in colder climates and has been used as a folk medicine in Russia and western Siberia. Researches exposed that dry matter of culture broth of chaga mushroom possesses significant antihyperglycemic, antihiperlipic and antioxidant effects in alloxan induced diabetic rats (Rajeswari and Krishnakumari 2013). *Ophiocordyceps sinensis*, one of the medicinal mushrooms has been in ethnomycological use of medicine in China, Tibet, Nepal, Bhutan, and India (Chen *et al*., 2010). Its synonym with *Sphaeria sinensis* and *Cordyceps sinensis*. It has been widely used as “Traditional Medicinal Mushrooms and Fungi” to relief symptoms of various diseases (Vaidya and Lamrood, 2000). It is commonly known as caterpillar fungus, cordyceps mushroom. Its taxonomy is in Fungi (Kingdom), Ascomycota (Phylum), Sordariomycetes (Class), Hypocreales (Order), Ophiocordyciptraceae (Family), Ophiocordyceps (Genus). There are around 140 widespread species belonging to the genus Ophiocordyceps, first described scientifically by British mycologist Tom Petch (1870-1948) (Xing and Guo, 2008).

**Nomenclature**

The name *Cordyceps* comes from Latin words meaning *Cordi*- ‘club, *ceps*- ‘head’ and *sinensis* - ‘Chinese’ (Panda, 2010; Panda and Swain, 2011). *Cordyceps sinensis*...
was discovered about 2000 years ago as exotic medicinal mushroom described in traditional Chinese and Tibetan medicine. The British mycologist Miles Joseph Berkeley (1803-1889) first described it in 1843 as *Sphaeria sinensis* Berk. Later in 1878, Italian mycologist Pier Andrea Saccardo (1845-1920) renamed it as *Cordyceps sinensis* (Berk) sacc (Winkler, 2008). Based on molecular phylogenetic study, Sung et al. (2007) separated the megagenus *Cordyceps* into four genera, *Cordyceps*, *Ophiocordyceps*, *Metacordyceps* and *Elaphocordyceps*, and also shown that *C. sinensis* is part of a clade based on the concept of *Ophiocordyceps* Petch and the correct name for it now is *Ophiocordyceps sinensis* (Berk.) G.H. Sung, J.M. Sung, Hywel-Jones & Spatafora. The vernacular name of *O. sinensis* is “dòng chóng xià cao meaning winter-worm, summer-plant or summer-grass, winter-insect” in Chinese. The other names are in bubble (Bhutanese), ruspenderoo (Dutch), kiananloisikka (Finnish), ghaas fafoond (Hindi), to chu kaso (Japanese), dong chug ha cho (Korean), jeevan buti, keeda ghass, chyou kira, sanjeevani bhooti, keera jhar (Nepali), dbyar rtswa dgun bu or yartsa gunbu (Tibetan), and chong cao (Thai) (Panda and Swain, 2011; Shrestha et al., 2010; 2012).

**Morphological Characters**

*O. sinensis* is the composite of a genus of fungus that grows on the larvae of insects. To date, more than 350 related species have been found worldwide based on fungus and insect host. The fungus parasitizes larvae of ghost moths belonging to the order *Lepidoptera*, especially *Thitarodes* that formerly classified as *Hepialus* (Wang and Yao, 2011). The infected larva is converted into a sclerotium covered by the intact exoskeleton of the insect to withstand the winter, which is regarded as “winter worm”. In the late spring or summer of the next year, a clavate stroma of the fungus grows from the sclerotium and emerged from the ground appearing as an herb, which is regarded as “summer grass” (Pegler et al., 1994). *Hepialus armoricans* Oberthur is the host insect species of *O. sinensis*. It consists of two parts, the fruiting body (fungus) and the worm (caterpillar). Caterpillar is invaded by *O. sinensis* mycelia and thus the two parts show similar constituents and pharmacological functions (Li et al., 2002).

**Phytochemical Substances**

Major phytochemical constituents of *O. sinensis* are

(i) Proteins: cadaverine, spermidine, spermine, putrescine, flazin, perlyrolupe, methylpyrimidine, carbole, cordymin, tryptophan (Zhang et al., 1991; Qian et al., 2012; Wang et al., 2012); (ii) Nitrogenous compounds: uracil, adenine, guanine, hypoxanthine, adenosine, cordycepin, dideoxyadenosine, inosine, guanosine, thymine, thymidine, uridine, cordyceamides, cordysinin (Zhu et al., 1998a, Huang et al., 2004, Jia et al., 2009); (iii) Sterols: ergosterol, sitisterol, daucosterol, stigmasterol, cholesterol, campesterol (Bok et al., 1999); (iv) Fatty acids: palmitic acid, lauric acid, myristic acid, pentadecanoic acid, palmitolate acid, linoleic acid, oleic acid, stearic acid, docosanoic acid, lignoceric acid, succinic acid (Yang et al., 2009); (v) Phenolic acids: hydroxybenzoic acid, vanillic acid, syringic acid, protocatechuic acid, acetovanillone, salicylic acid (Yang et al., 2011); (vi) Isoflavones: genistein, daidzein, orobol, genistein (Yang et al., 2011); (vii) Polysaccharides and sugar derivatives: glucan, corydinosin, mannoglucon, mannotol (Wu et al., 2007; Zhong et al., 2009; Yang et al., 2011); (viii) vitamins, inorganics and volatile compounds (Zhu et al., 1998a and 1998b; Yu et al., 2012).

**Traditional uses**

*O. sinensis* is traditionally used (Wang and Shiao, 2000; Seth et al., 2014) for anti-inflammation (Yang et al., 2011; Wang et al., 2012), antimicrobial activity (Negi et al., 2014; Mentha Mehratra et al., 2015), anti-diabetic (Kihoe et al., 1999; Balon et al., 2002; Lo et al., 2004; Li et al., 2006; Zhang et al., 2006; Shi et al., 2009; El Ashry et al., 2012), antitumor activity (Bok et al., 1999; Zhang et al., 2004), antimitastatic (Nakamura et al., 1999), immunomodulatory (Gong et al., 1990), hypocholesterolemia (Koh et al., 2003), and antioxidant activities (Yamaguchi et al., 2000; Li et al., 2002; Dong and Yao, 2007; Wang et al., 2009), and associated diseases such as hepatic diseases (Liu and Shen, 2003) and chronic kidney diseases (Zhang et al., 2014). Meena et al. (2013) reported that laboratory cultured mycelia powder of *O. sinensis* is safe and non-toxic up to 2g/kg body weight dose. Oral administration of laboratory cultured mycelia powder of *O. sinensis* did not show any sign of toxicity as no significant change was observed in organ weight and serological parameters in rats. However, there was a significant increase in food intake, body weight gain and hematological parameters like white and red blood cells, hemoglobin and lymphocytes in treated groups. Histopathology of vital organs also supported the non-toxic effect of *O. sinensis*.

**Antihyperglycemic Activity**

Medicinal mushrooms have gained huge interests from researches around the world because of their positive bioactivity effects (Perera and Li, 2011). However, there are still not many data available about the antihyperglycemic activity of this medical mushroom. Kiho et al. (1993) studied the crude polysaccharide of *O. sinensis* in normal mice and streptozotocin induced diabetic mice. It significantly lowered the glucose level by oral administration in mice. These crude hypoglycemic polysaccharides obtained from a hot-water extract and alkaline extracts were found to be composed of galactose, glucose, and mannose in a ratio of 62:28:10 with a MW 45 kDa. More additional, Kiho et al. (1996) evaluated a polysaccharide named CS-F30 obtained from the cultural mycelium of *O. sinensis* showed potent hypoglycemic activity in genetic diabetic mice after intraperitoneal administration, and the plasma glucose level was quickly
reduced in normal and streptozotocin induced diabetic mice after intravenous administration. Lo et al. (2004) investigated the effects 28 days treated with 1 g/kg fruiting body of *O. sinensis* on streptozotocin induced diabetic rats. The results showed *O. sinensis* significantly decreased the levels of serum glucose and fructosamine. Further, Li et al. (2006) revealed that isolated polysaccharide from *O. sinensis*, named CSP-1 with MW 210 kDa which composed of glucose, mannose, and galactose in the ratio of 1:0.6:0.75 and was shown to have strong antioxidant activity and the abilities to decrease blood glucose and insulin secretion in diabetic animals. It suggested that CSP-1 may stimulate pancreatic release of insulin and reduce insulin metabolism. Another research, El Ashry et al. (2012) designed the experiment using streptozotocin induced diabetic rats and treated with 100 mg/kg of *O. sinensis* for 21 days. The results showed *O. sinensis* significantly decreased the levels of serum glucose, fructosamine, total cholesterol, triglycerides, insulin resistance index and pancreatic malondialdehyde content. It also showed significantly increased serum insulin, HDL-cholesterol, total antioxidant capacity levels, a cell function percent, and pancreatic reduced glutathione content.

The antidiabetic effect of *O. sinensis* may be due to the induced insulin release from the residual pancreatic cells and reduced insulin metabolism in the body by a polysaccharide called CSP-1 (Li et al., 2006). Another polysaccharide, CS-F30, had a potent effect on glucose metabolism in the liver of diabetic mice as it significantly increased the activities of hepatic glucokinase, hexokinase and glucose-6-phosphate dehydrogenase (Kiho et al., 1996).

The antioxidant properties of *O. sinensis* are partly due to its polysaccharides (Li et al., 2001; Chen et al., 2006). Yan et al. (2009) reported the antioxidant polysaccharides designated EPS-1 with an average MW of 38 kDa was hydrolyzed in diluted sulfuric acid solution at pH 1 and 90°C to yield two major MW fractions: 3.0 kDa and 30 kDa possessed high about 30-80% of antioxidant and radical-scavenging activities. Wang et al. (2009) also reported the antioxidant polysaccharide was found to be a glucomannogalactan with a monosaccharide composed of glucose, mannose, and galactose in a ratio of 2.8:2.9:1, and its total carbohydrate content and average MW were 99.0% and 8.1 kDa, respectively. The antioxidant efficiency of *O. sinensis* in protecting lipid, protein, and low density lipoprotein against oxidative damage was reported (Hui et al., 2006). The strong antioxidant property of *O. sinensis* is mainly due to its activity against superoxide radicals and hydrogen peroxide-induced cytotoxicity (Li et al., 2003; Zhang et al., 2003; Wu et al., 2005). Leung et al. (2009) indicated that polysaccharides obtained from *O. sinensis* with MW ranging from 5 to 210 kDa has antioxidant and hypoglycemic activities. From review literatures that regarding the bioactive ingredients and bioactivities in antidiabetic and antioxidant effects of *O. sinensis* are shown in Table 1.

### Table 1: Bioactive ingredients and bioactivities in antidiabetic and antioxidant effects of *Ophiocordyceps sinensis*

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<tr>
<th>Bioactive Ingredient</th>
<th>References</th>
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<td>Antioxidant Polysaccharides</td>
<td>Chen et al., 2006; Chen et al., 2008; Hui et al., 2006; Li et al., 2001; Li et al., 2003; Wang et al., 2009; Wu et al., 2005; Yan et al., 2009; Zhang et al., 2003; Zhong et al., 2009</td>
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<tr>
<td>Hypoglycemic Polysaccharides</td>
<td>Balon et al., 2002; El Ashry et al., 2012; Guo et al., 2010; Guo et al., 2011; Huang et al., 2002; Kan et al., 2012; Kiho et al., 1993; Li et al., 2006; Lo et al., 2004; Lo et al., 2006; Wang et al., 2003; Zhong et al., 2009</td>
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*O. sinensis* is relatively considered to be a non-toxic medicinal mushroom (Tuli et al., 2014). No human toxicity report was found and even animal models were failed to determine median lethal dose (Tuli et al., 2014). *Cordyceps* dose in patients suffering from long-term renal failure was demonstrated up to 3-6 g/day (Zhu et al., 1998b). In clinical studies involving lung cancer, chemotherapy was carried out with the combination of *Cordyceps* (Hollliday and Cleaver, 2008). Mizuno (1999) demonstrated that 3-4.5 g/day of *Cordyceps* was sufficient in patient suffering from severe liver disease. Kai et al. (2014) reported the preventive effects of *C. sinensis* against contrast induced nephropathy in a total of 210 patients with type 2 diabetes. Luo et al. (2015) reviewed existing evidence on the effectiveness of *O. sinensis* for the treatment of diabetic kidney disease. They identified 60 trials involving 4288 participants. The meta-analysis suggested that use of *O. sinensis* combined with angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) may have a more beneficial effect on the proteinuria, inflammatory, dyslipidemia status as compared to ACEI/ARB alone in diabetic kidney disease. III-IV stage patients.

Many researchers reviewed the most phytochemical substances with anti-diabetes activity as following flavonoids (Zou et al., 2014), quercin (Vessal et al., 2003), metformin (Nasri et al., 2013), quinolizidine, anthocyanin, catechin, flavone (Nayak et al., 2014), phenylpropanoids, lipoic acid (Konrad et al., 1999) and coumarin (Pari et al., 2009). Apart from the conventional medicines, traditional or alternative therapy plays a significant role in treating diabetes mellitus. It needs to know how to use and what the phytochemical constituents are. This review article has attempted to compile the new medicinal mushroom, *O. sinensis*, to be the one of choice in the treatment. All of this information will help researchers to explore its scientific evidence.
In conclusion, it has been suggested that mushrooms with polysaccharides appear to be effective for both the control of blood glucose and the modification of the course of diabetic complications without side-effects. This review particularly explores the *O. sinensis* that has demonstrated clinical and experimental antihyperglycemic property by preventing or lowering down the development of diabetes mellitus.

REFERENCES


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