

Hypothesis

A Contemporary Treatment Approach to Both Diabetes and Depression by *Cordyceps sinensis*, Rich in Vanadium

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Diabetes mellitus is accompanied by hormonal and neurochemical changes that can be associated with anxiety and depression. Both diabetes and depression negatively interact, in that depression leads to poor metabolic control and hyperglycemia exacerbates depression. We hypothesize one novel vanadium complex of vanadium-enriched *Cordyceps sinensis* (VECS), which is beneficial in preventing depression in diabetes, and influences the long-term course of glycemic control. Vanadium compounds have the ability to imitate the action of insulin, and this mimicry may have further favorable effects on the level of treatment satisfaction and mood. *C. sinensis* has an antidepressant-like activity, and attenuates the diabetes-induced increase in blood glucose concentrations. We suggest that the VECS may be a potential strategy for contemporary treatment of depression and diabetes through the co-effect of *C. sinensis* and vanadium. The validity of the hypothesis can most simply be tested by examining blood glucose levels, and swimming and climbing behavior in streptozotocin-induced hyperglycemic rats.

Keywords: antidepressants – vanadium enriched *Cordyceps sinensis* – diabetes – depression – high blood sugar-diabetes

Introduction

Diabetes mellitus is accompanied by hormonal and neurochemical changes that can be associated with anxiety and depression (1, 2). The prevalence of depression is ~18% higher in diabetic patients than in the general population, and only 33% of depression cases among diabetic patients are diagnosed and treated (3, 4). These associations may be related to the increased risk of depressive symptoms in individuals with diabetes, increased risk of Type 2 diabetes in individuals with depressive symptoms or both. Growing evidence from clinical studies indicate that diabetic patients with major depression demonstrate poor adherence to antidiabetic regimens,

have poor glycemic control, and are at an increased risk for retinopathy (5) and macrovascular complications (6).

The two processes, diabetes and depression, negatively interact, in that depression leads to poor metabolic control and hyperglycemia exacerbates depression. A contemporary treatment approach advocates an aggressive stance toward both diabetes and depression management to optimize global outcome. However, to our knowledge, an algorithm incorporating the management of both has not been discovered or reported in the literature to date. It is worthwhile to investigate one potential strategy of contemporary treatment toward both diabetes and depression. We hypothesize one novel vanadium complex of vanadium-enriched *Cordyceps sinensis* (VECS), which will be beneficial in preventing depression in diabetes and also influence the long-term course of glycemic control.

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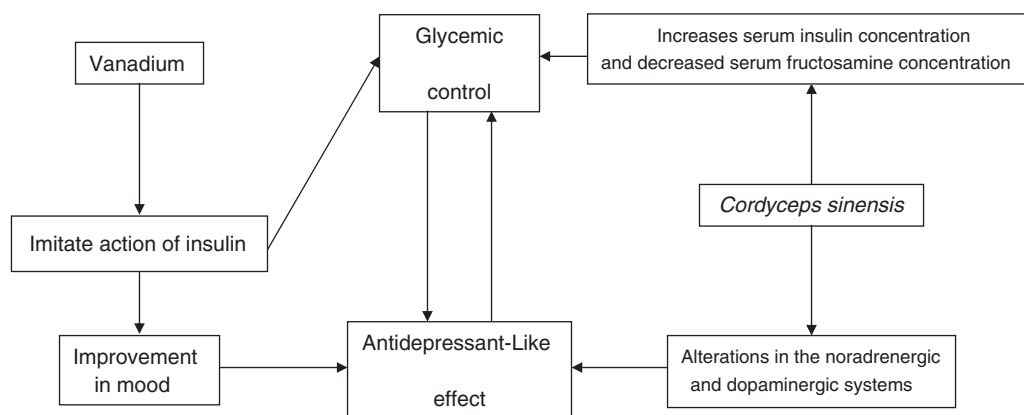


Figure 1. Diagram illustrating processing scheme of contemporary treatment approach of Vanadium and *C. sinensis* toward both diabetes and depression.

Vanadium, glycemic control and depression management

Vanadium, element number 23, atomic weight 50.94, is normally present in very low concentrations ($<10^{-8}$ M) in virtually all the cells in plants and animals. As a potential therapeutic agent, in recent times, it is attracting increasing attention. Vanadium compounds have the ability to imitate the action of insulin (7, 8). Oral administration of inorganic vanadium salts has shown antidiabetic activity *in vitro* (9), *in vivo* (10) and even in patients (11). The improved metabolic control can improve the mood and the insulin mimicry may have further favorable effects on the level of treatment satisfaction and mood (12). Some evidence suggests that patients with adequate glycemic control will have an improved sense of well-being (13, 14).

Cordyceps sinensis, depression management and glycemic control

Mushrooms and primarily basidiomycetous fungi are a popular and valuable food, low in calories and high in minerals, essential amino acids, vitamins and fibers (15, 16). Some of them produce substances, which have potential medical effects, and are called medicinal mushrooms (17–20).

Mushrooms are a low-calorie food with minimal fat and are highly suitable for obese persons. With no starch and low sugars, mushrooms might be considered the ‘delight of diabetics’ (21). *Cordyceps sinensis* is a fungus, and has been known as a traditional medicine in China. Many studies have shown that *C. sinensis* possesses hypoglycemic (22, 23) and vasorelaxant activities (24). *Cordyceps sinensis* has an antidepressant-like activity and some of its constituents might act as adrenoceptor and dopamine D2 receptor agonists or noradrenaline/dopamine reuptake inhibitors (25). Fermented *C. sinensis* improved the diabetes-induced decrease in serum insulin

concentration, and attenuated the diabetes-induced increases in blood glucose concentrations (26).

Vanadium enriched *Cordyceps sinensis*

Using trace elements at lower doses, in combination with fungus have been ascribed as one of the potent ways to reduce trace elements-associated toxicity and maintain their effect (27, 28). An important property of fungus is the ability to take up and accumulate trace metals such as cadmium, lead, arsenic, copper, nickel, silver, chromium, and mercury in the body or mycelium of the fungus (29–31). Taken together, these data suggest that fermented fungus of *C. sinensis* rich in vanadium may be beneficial in preventing depression in diabetes (Fig. 1).

Testing the hypothesis

The validity of the hypothesis can most simply be tested by examining blood glucose levels and the swimming and climbing behavior in streptozotocin-induced hyperglycemic rats following VECS treatment. Streptozotocin inhibits insulin secretion and causes a state of insulin-dependent diabetes mellitus (32). The streptozotocin-induced diabetic rats prematurely and repeatedly present more intense immobility in the forced swimming test, demonstrating their susceptibility to behavioral alterations in this animal model (33).

Conclusions

In this article, we suggest that the VECS may be a potential strategy for contemporary treatment of depression and diabetes through the co-effect of *C. sinensis* and vanadium (Fig. 1). This hypothesis represents a completely novel area of study, which will lead to valuable treatments for psychological disorders as well as physical diseases.

If the hypothesis is supported by further experimentation, it may improve people's quality of life and reduce the medical cost of our healthcare system.

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References

- Bellush LL, Rowland NE. Stress and behavior in streptozotocin diabetic rats: Biochemical correlates of passive avoidance learning. *Behav Neurosci* 1989;103:144–50.
- Lustman PJ, Amado H, Wetzel RD. Depression in diabetics: a critical appraisal. *Comp Psychiatry* 1983;24:65–74.
- Gavard JA, Lustman PJ, Clouse RE. Prevalence of depression in adults with diabetes. *Diabetes Care* 1993;16:1167–78.
- Lustman PJ, Griffith LS, Gavard JA, Clouse RE. Depression in adults with diabetes. *Diabetes Care* 1992;15:1631–9.
- Kovacs M, Mukerji P, Drash A, Iyengar, S. Biomedical and psychiatric risk factors for retinopathy among children with IDDM. *Diabetes Care* 1995;18:1592–9.
- Lloyd CE, Matthews KA, Wing RR, Orchard TJ. Psychosocial factors and complications of IDDM. The Pittsburgh Epidemiology of Diabetes Complications Study VIII. *Diabetes Care* 1992;15:166–72.
- Gil J, Miralpeix M, Carreras J, Bartrons R. Insulin-like effects of vanadate on glucokinase activity and fructose 2,6-bisphosphate levels in the liver of diabetic rats. *J Biol Chem* 1988;263:1868–71.
- Han C, Cui B, Wang Y. Vanadium uptake by biomass of *Coprinus comatus* and their effect on hyperglycemic mice. *Biol Trace Elem Res* 2008;124:35–9.
- Tolman EL, Barris E, Burns M, Pansini A, Partridge R. Effects of vanadium on glucose metabolism in vitro. *Life Sci* 1979;25:1159–64.
- Meeks MJ, Landolt RR, Kessler WV. Effect of vanadium on metabolism of glucose in the rat. *J Pharm Sci* 1971;60:482–3.
- Goldfine AB, Simonson DC, Folli F, Patti ME, Kahn CR. In vivo and in vitro studies of vanadate in human and rodent diabetes mellitus. *Mol Cell Biochem* 1995;153:217–31.
- Reza M, Taylor CD, Towse K, Ward JD, Hendra TJ. Insulin improves well-being for selected elderly type 2 diabetic subjects. *Diabetes Res Clin Pract* 2002;55:201–7.
- Lustman PJ, Clouse RE. Identifying depression in adults with diabetes. *Clin Diabetes* 1997;15:78–81.
- Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* 1998;280:1490–6.
- Firenzuoli F, Gori L, Lombardo G. The medicinal mushroom *Agaricus blazei* Murrill: review of literature and pharmacotoxicological problems. *Evid Based Complement Alternat Med* 2008;5:3–15.
- Lindequist U, Niedermeyer TH, Jülich WD. The pharmacological potential of mushrooms. *Evid Based Complement Alternat Med* 2005;2:285–99.
- Cooper EL. The immune system and complementary and alternative medicine. *Evid Based Complement Alternat Med* 2007;4:5–8.
- Madamanchi G, Tzeng Y-M. Review of pharmacological effects of *Antrodia camphorata* and its bioactive compounds. *Evid Based Complement Alternat Med* 2009 (Advance Access published on August 17); doi:10.1093/ecam/nep108.
- Hsu JW, Huang HC, Chen ST, Wong CH, Juan HF. Ganoderma lucidum polysaccharides induce macrophage-like differentiation in human leukemia THP-1 cells via caspase and p53 activation. *Evid Based Complement Alternat Med* 2009 (Advance Access published on August 20); doi:10.1093/ecam/nep107.
- Al-Fatimi MA, Jülich WD, Jansen R, Lindequist U. Bioactive components of the traditionally used mushroom *Podaxis pistillaris*. *Evid Based Complement Alternat Med* 2006;3:87–92.
- Cooper EL. Ayurveda and eCAM: a closer connection. *Evid Based Complement Alternat Med* 2008;5:121–2.
- Wu Y, Sun H, Qin F, Pan Y, Sun C. Effect of various extracts and a polysaccharide from the edible mycelia of *Cordyceps sinensis* on cellular and humoral immune response against ovalbumin in mice. *Phytother Res* 2006;20:646–52.
- Zhang G, Huang Y, Bian Y, Wong JH, Ng TB, Wang H. Hypoglycemic activity of the fungi *Cordyceps militaris*, *Cordyceps sinensis*, *Tricholoma mongolicum*, and *Omphalia lapidescens* in streptozotocin-induced diabetic rats. *Appl Microbiol Biotechnol* 2006;72:1152–6.
- Balon TW, Jasman AP, Zhu JS. A fermentation product of *Cordyceps sinensis* increases whole-body insulin sensitivity in rats. *Altern J Complement Med* 2002;8:315–23.
- Nishizawa K, Torii K, Kawasaki A. Antidepressant-like effect of *Cordyceps sinensis* in the mouse tail suspension test. *Biol Pharm Bull* 2007;30:1758–62.
- Lo HC, Hsu TH, Tu ST, Lin KC. Anti-hyperglycemic activity of natural and fermented *Cordyceps sinensis* in rats with diabetes induced by nicotinamide and streptozotocin. *Am J Chin Med* 2006;34:819–32.
- Han C, Yuan J, Wang Y. Hypoglycemic activity of fermented mushroom of *Coprinus comatus* rich in vanadium. *J Trace Elem Med Biol* 2006;20:191–6.
- Han C, Liu T. A comparison of hypoglycemic activity of three species of basidiomycetes rich in vanadium. *Biol Trace Elem Res* 2009;127:177–82.
- Kalac P, Niznamska M, Bevilacqua D, Staskova I. Concentrations of mercury, copper, cadmium and lead in fruiting bodies of edible mushrooms in the vicinity of a mercury smelter and a copper smelter. *Sci Total Environ* 1996;177:251–8.
- Kalac P, Svoboda L. A review of trace element concentrations in edible mushrooms. *Food Chem* 2000;69:273–81.
- Malinowska E, Szefer P, Falandaysz J. Metals bioaccumulation by bay bolete, *Xerocomus badius*, from selected sites in Poland. *Food Chem* 2004;84:405–16.
- Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia* 2008;51:216–26.
- Gomez R, Barros H. Ethopharmacology of the antidepressant effect of Clonazepam in diabetic rats. *Pharmacol Biochem Behav* 2000;66:329–35.

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