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Medicinal mushrooms in prevention and control of diabetes mellitus

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Abstract Diabetes mellitus is a life-threatening chronic metabolic disease caused by lack of insulin and/or insulin dysfunction, characterized by high levels of glucose in the blood (hyperglycemia). Millions worldwide suffer from diabetes and its complications. Significantly, it has been recognized that type 2 diabetes is an important preventable disease and can be avoided or delayed by lifestyle intervention. Presently, there are many chemical and biochemical hypoglycemic agents (synthetic drugs), that are used in treating diabetes and are effective in controlling hyperglycemia. However, as they may have harmful side-effects and fail to significantly alter the course of diabetic complications, natural anti-diabetic drugs from medicinal plants have attracted a great deal of attention. Medicinal mushrooms have been valued as a traditional source of natural bioactive compounds over many centuries and have been targeted as potential hypoglycemic and anti-diabetic agents. Bioactive metabolites including polysaccharides, proteins, dietary fibres, and many other biomolecules isolated from medicinal mushrooms and their cultured mycelia have been shown to be successful in diabetes treatment as biological anti-hyperglycemic agents. In this review we discuss the biological nature of diabetes and, in particular, explore some promising mushrooms that have experimental anti-diabetic properties, preventing or reducing the development of diabetes mellitus. The importance of medicinal mushrooms as agents of medical nutrition therapy and how their metabolites can be used as supportive candidates for prevention and control of diabetes is explored. Future prospects for this field of study and the difficulties and constraints that might affect the development of rational drug products from medicinal mushrooms are discussed.

Keywords Medicinal mushrooms · Diabetes mellitus · Anti-diabetic agents · Anti-hyperglycemic agents · Bioactive metabolites · Mushroom supplementation · Diabetes prevention

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Introduction

Diabetes is a chronic disease causing several health problems to millions worldwide and has become a significant ailment in many countries (Wild et al. 2004; WHO 2011; Hagopian et al. 2011; Smith et al. 2012). Diabetes mellitus, or simply, diabetes, is a group of metabolic diseases characterized by high blood glucose levels that result from insulin imbalances. In one way this can be considered as a consequence of metabolic syndrome and gives rise to varied complications including high morbidity and mortality rates with increased risk of cardiovascular diseases and even cancers (Zimmet et al. 1997; Kaur et al. 2002; Laaksonen et al. 2004; Potenza and Mechanick 2009; Tourlouki et al. 2009; Cheng et al. 2012b; Dong et al. 2012; Hansen et al. 2012; Li 2012). The disease also contributes to complications, such as retinopathy, neuropathy and renal dysfunction through a series of pathological changes (Agardh et al. 2002; Thornalley 2002; Porta and Allione 2004; White et al. 2008; Sobngwi et al. 2012; Winkley et al. 2012).

According to the WHO (2011), diabetes mellitus accounts for 2.2 % of deaths in the world and is a one of the main causes of death among humans. The most recent data released by the Center for Disease Control and Prevention (CDC) reports that diabetes is the seventh leading cause of death in the United States; diabetes affects 25.8 million (8.3 %) of the US population (CDC 2011). One major tragedy of diabetes is that it can remain undiagnosed for long periods without serious symptoms and ends up with many untreatable complications such as coronary heart disease (Ved et al. 2010). Therefore early diagnosis and a healthy lifestyle are crucial to reducing risk (Vinicor 1998; Zhang and Ning 2011; Yates et al. 2012).

Epidemiological studies suggested that risk factors for diabetes and its complications include hypercholesterolemia and hyperglycemia, which are largely influenced by diet (Kaur et al. 2002; Tourlouki et al. 2009; Igel et al. 2012). It has been scientifically proven that a diet supplemented with fruits and vegetables has beneficial effects on diabetes and many cardiovascular diseases (Gallagher et al 2003; Bazzano et al. 2008; Mirmiran et al. 2009; Kanazawa 2011). A dietary pattern incorporating higher amounts of low-fat dairy products may lower the risk of type 2 diabetes and can be correlated with lessened hypertension, metabolic syndrome and cognitive function in the middle-aged (Choi et al. 2005; Liu et al. 2006; Crichton et al. 2012).

Medicinal mushrooms have been identified as remarkable therapeutic agents in traditional folk medicines and important as popular as culinary products all over the world (Ying et al. 1987; Rapior et al. 2000; Halpern 2010; Deepalakshmi and Mirunalini 2011; Dotan et al. 2011; Muszynska et al. 2011; Abdullah et al. 2012). Species of medicinal mushrooms have a long history of use for disease treatment in folk medicines, especially in countries such as China, India, Japan and Korea (Hobbs 1995, 2000, 2004, 2005; Chang 1999; Mizuno 1999a, b; Reshetnikov et al. 2001; Ajith and Janardhanan 2007; De Silva et al. 2012; Lee et al. 2012). Medicinal mushrooms have shown therapeutic action against the development of many diseases, primarily because they contain a number of biologically active compounds (Bao et al. 2001; Petrova et al. 2005; Moradali et al. 2007; Zhang et al. 2007; Lee and Hong 2011); they are also used in cosmetics because of their medicinal properties (Hyde et al. 2010). This includes mainly high molecular weight compounds such as polysaccharides, proteins and lipids as well as a number of low molecular weight metabolites such as lectins, lactones, terpenoids, alkaloids, sterols and phenolic substances (Kidd 2000; Alexandre et al. 2007; Zhong and Xiao 2009; Chung et al. 2010; Xiao et al. 2011). The polysaccharide (β-glucans) contained in mushrooms, in particular, can restore the functions of pancreatic tissues causing an increase in insulin output by the functional β-cells, thus lowering the blood glucose levels and has also been shown to improve the sensitivity of peripheral cells to circulating insulin (Misra et al. 2009; Qiang et al. 2009; Xiao et al. 2011). Health conscious diets can incorporate mushrooms as ideal low energy foods for diabetes patients as they contain very low amounts, or are lacking in fats and cholesterol, are low in carbohydrates, and high in proteins, vitamins and minerals (Mattila et al. 2002; Guillamón et al. 2010; Phillips et al. 2011a, b; Ulziijargal and Mau 2011; Smiderle et al. 2012).

The consumption of mushrooms markedly decreased the lipid levels including as total cholesterol, total triglyceride, and low-density lipoprotein cholesterol, and increased the level of high-density lipoprotein cholesterol (Kim et al. 2001c; Alarcon et al. 2003; Jeong et al. 2010; Wani et al. 2010; Chen et al. 2011, 2012). Besides containing macronutrients in a well-balanced proportion, mushrooms also have important micronutrients (vitamins) and non-nutrients (phenolics) with bioactive properties such as anti-oxidants (Ayaz et al. 2011; Reis et al. 2011; Wang et al. 2011a, b; Beluhan and Ranogajec 2011; Abdullah et al. 2012; Pereira et al. 2012; Liu et al. 2012). Mushrooms are also high in water and fibre content (Mattila et al. 2001; Colak et al. 2009). Moreover, they contain natural insulin-like compounds and enzymes which help break down sugar or starch in foods and improve insulin resistance (Kim et al. 2005, 2010a, b). Mushrooms are also known to contain certain compounds which help proper functioning of the liver (Wani et al. 2010), pancreas and other endocrinal glands, thereby promoting formation of insulin and related hormones which ensure healthy metabolic functioning (Wasser and Weiss 1999; Zhang and Lin 2004; Chen et al. 2012). Most medicinal mushrooms such as *Agaricus bisporus*, *A. subrufescens*, *Cordyceps sinensis, Coprinus comatus, Ganoderma lucidum, Inonotus obliquus, Phellinus linteus*, *Pleurotus* spp, *Poria cocos* and *Sparassis crispa* have been reported to have hypoglycemic effects on reducing blood glucose levels and anti-diabetic effects (Cha et al. 2006; Yang et al. 2008; Seto et al. 2009; Jeong et al. 2010; Kim et al. 2010a, b; Lu et al. 2010; Yamamoto and Kimura 2010; Lee et al. 2010; Li et al. 2011a, b).

Medicinal mushrooms and their constitutive active compounds have been described to have beneficial effects in reducing many diseases including cancer, hypertension, metabolic syndrome and cardiovascular diseases (Poucheret et al. 2006; Chen and Seviour 2007; Francia et al. 2007; Guillamón et al. 2011; Martin 2010; Jiangwei et al. 2011; Mujić et al. 2011; Wasser 2011; De Silva et al. 2012; Rathee et al. 2012). Many studies have focused on their immunomodulatory and anti-tumor effects because mushrooms may contain a diverse array of biologically active metabolites (β-D-glucans, immunomodulatory proteins, secondary metabolites) with well-known immune enhancing capabilities (Bao et al. 2001; Johnston 2005; Petrova et al. 2005; Moradali et al. 2007; Zhang et al. 2007; Reis et al. 2011; Wasser 2011; Wu et al. 2012).

Some chemical and biochemical hypoglycemic agents (anti-diabetes agents), such as insulin, metformin (Andujar-Plata et al. 2012; Greevy et al. 2011), tolbutamide, gliclazide (Avogaro 2012), phenformin, troglitazone and rosigitazone, exenatide are the mainstay in the treatment of diabetes and are effective in controlling hyperglycemia (Scheen 2011; Majithia et al. 2011; Liday 2011; Avogaro 2012; Colagiuri 2012). However, these anti-diabetes agents may have harmful side-effects, fail to significantly alter the course of diabetic complications and there is insufficient knowledge on the pharmacological management of the disease (Eurich et al. 2007; Anon 2008, 2009; Liday 2011; Seino et al. 2012). Therefore, natural anti-diabetic drugs from medicinal plants have attracted a great deal of attention (Yeh et al. 2003; Kirkham et al. 2009; Petersen et al. 2011; Poraj-Kobielska et al. 2011).

Admittedly, diabetes is a metabolic disorder which should be controlled or prevented with appropriate lifestyle adaptations including exercise, appropriate food and health-relevant environments (Ianculov et al. 2010; Chaufan et al. 2011; Jenkins and Hagberg 2011; Smith et al. 2012). Indeed healthy foods rich in various medicinal properties provide a means to good health (Milner 2000; de Mello et al. 2011). Edible and medicinal mushrooms are functional foods and thus a good solution to controlling diabetes and a potent source of biologically active compounds with anti-diabetic effects. Many mushroom species appear to be effective for both the control of blood glucose levels and the modification of the course of diabetic complications. Several examples of medicinal mushrooms and their putative anti-diabetic effects are shown in Table 1.

In this review we discuss the biological nature of diabetes and particularly explore some promising mushrooms that have demonstrated clinical and/or experimental anti-diabetic properties by preventing or lowering the development of diabetes mellitus. Even though current scientific /clinical evidence does not sufficiently demonstrate the direct hypoglycemic effects of mushrooms for use as commercial drugs or nutraceuticals, identification of their potential ability in preventing diabetes could be a useful investment in future drug discoveries.

What is diabetes?

The pathogenesis of diabetes is mainly due either to the pancreas not producing enough insulin or when the cells cannot respond effectively to the insulin it produces (Kuzuya et al. 2002; Kawasaki et al. 2004; Stadler et al. 2009; ADA 2011). Insulin is a hormone that is needed to convert sugar, starches and other food into energy needed for daily life and it is a hormone that regulates blood sugar. Low insulin levels and/or insulin resistance prevents the body from converting glucose into glycogen (mostly in the liver), which in turn makes it difficult or impossible to remove excess glucose from the blood (Chinner et al. 2005; ADA 2011). Hyperglycaemia, i.e., excessive levels of blood sugar, is a common effect of uncontrolled diabetes. This is generally a glucose level higher than 10 mmol/l (180 mg/dl), but symptoms may not start to become noticeable until even higher values such as 15–20 mmol/l (270–360 mg/dl) and over time leads to serious damage to many of the body's systems, especially the nerves and cardiovascular system (Capes et al. 2001; Anon 2011).

There are three main types of diabetes mellitus. Type 1 diabetes results from the body's failure to produce insulin. Type 1 diabetes mellitus is characterized by loss of the insulin-producing β-cells of the islets of Langerhans in the pancreas leading to insulin deficiency (also referred to as *insulin-dependent diabetes mellitus*, *IDDM*) (Kobayashi 1994; Kuzuya et al. 2002; Pozzilli et al. 2011). Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

Being the most common type of diabetes, type 2 diabetes results from a condition in which cells fail to use insulin properly (insulin resistance), sometimes combined with an absolute insulin deficiency (*non-insulin-dependent diabetes mellitus*, *NIDDM*) (Kitagawa et al. 1994; Beck-Nielsen et al. 1995; Horton 1995). The onset of type 2 diabetes has become most common in middle aged or later life, although it is being more frequently seen in adolescents and young adults due to an increase in child obesity and inactivity (Rosenbloom et al. 1999; Norris et al. 2002; Pozzilli and Guglielmi 2009). The increase in the number of children and young adolescents with a mixture of the two types of diabetes (i.e. persons who are obese and/or have basic features of insulin resistance as well as having antibodies in the blood which act against the insulin producing β-cells of the pancreas causing a decrease in the body's ability to produce insulin) has recently become topical. Under the current classification, it is difficult to define the type of diabetes which has elements of both type 1 diabetes and type 2 diabetes, and is referred to as "double diabetes" (or hybrid diabetes) (Pozzilli and Buzzetti 2007; Pozzilli and Guglielmi 2009). Prediabetes is a state in which the fasting

Table 1 Medicinal mushroom species with reported anti-diabetic effects

Mushroom species	Bioactive compound	Anti-diabetic effect	References
Agaricus bisporus	Dehydrated fruiting body extracts	Lowers blood glucose and cholesterol levels	Jeong et al. 2010
			Yamac et al. 2010
Agaricus campestris	Aqueous fruiting body extract	Anti-hyperglycemic, insulin-releasing and insulin like activity	Gray and Flatt 1998
Agaricus subrufescens (*A. blazei* Murril, *A. brasiliensis*)	β-glucans and enzymatically produced oligosaccharides	Improved insulin resistance in type 2 diabetes mellitus through increase in adiponectin concentrations	Kim et al. 2005
			Niwa et al. 2011
Agaricus sylvaticus	Aqueous fruiting body extract	Strong anti-oxidative effects with reduced cholesterol and triglyceride levels	Fortes and Carvalho Garbi Novaes 2011
			Orsine et al. 2012
Auricularia auricula-judae	Dried mycelia powder	Significant reduction of plasma glucose total cholesterol and triglyceride levels	Kim et al. 2007
Cerrena unicolor	Extracellular polysaccharide	Significant decrease in serum glucose level	Yamac et al. 2009
Coprinus comatus	4,5- Dihydroxy-2-methoxy-benzaldehyde (comatin)	Inhibiters of the non-enzymatic glycosylation (NEG) reaction Decreases concentrations of fructosamine, triglycerides and total cholesterol. Maintains a low level of blood glucose and improves glucose tolerance	Ding et al. 2010
Cordyceps militaris	Polysaccharide-enriched fraction of fruiting body	Insulin like and insulin release promoting activity	Yun et al. 2003
		Hypoglycemic effects with lower elevation rates of blood glucose levels	Zhang et al. 2006
Ophiocordyceps sinensis (*Cordyceps sinensis*)	Polysaccharide fraction CSP-1	Results in a significant drop in blood glucose levels. Increases blood insulin levels. Causes induced release of insulin from the residual pancreatic cells and/or reduced insulin metabolism in the body	Li et al. 2003, 2006
	Vanadium enriched fermented culture	Anti-depressant-like activity and hypoglycemic activities	Guo et al. 2010, 2011
Cordyceps takaomantana (*Paecilomyces tenuipes*)	Fruiting body extract containing 4- β- acetoxyscirpendiol (ASD)	Lowering blood sugar in the circulatory system as specific inhibitors of Na+/ glucose transporter-1 (SGLT-1)	Yoo and Lee 2006
			Yoo et al. 2005
Ganoderma lucidum sensu lato	(3β,24E)-lanosta-7,9(11),24-trien-3,26-diol (ganoderol B)	Strong α-glucosidase inhibition	Fatmawati et al. 2011
	Water extracts of polysaccharides from fruiting bodies	Dose-dependently increased nonenzymic and enzymic anti-oxidants, serum insulin levels and reduced lipid peroxidation and blood glucose	Jia et al. 2009
	Water extract of whole fruit body	Lowering the serum glucose levels through the suppression of the hepatic phosphoenolpyruvate carboxykinase (PEPCK) gene expression	Seto et al. 2009
Grifola frondosa	Mushroom extracts rich in vanadium	Decreases blood glucose HbA1c levels	Cui et al. 2009
	Glycoprotein extract (SX-fraction)	Improved glucose tolerance despite no elevation of circulating insulin concentrations and showed enhanced sensitivity to exogenous insulin.	Preuss et al. 2007
Hericium erinaceus	Methanol extract of the mushroom	Hypoglycemic effects with significantly lower elevation rates of blood glucose levels	Wang et al. 2005
Inonotus obliquus	Culture broth	Significant anti-hyperglycemic, anti-lipid peroxidative and antioxidant effects in alloxan-induced diabetic mice	Sun et al. 2008
			Xu et al. 2011
	Ethyl acetate fraction	Anti-hyperglycemic and anti-lipidperoxidative effects through decrease in blood glucose level.	Lu et al. 2010
	Terpenoid and sterol compounds	Decreased the total cholesterol level in serum, increased glutathione peroxidase activity. Decreased the levels of triglycerides and malondialdehyde, and increased the HDL cholesterol level in serum and the hepatic glycogen level	

Table 1 (continued)

Mushroom species	Bioactive compound	Anti-diabetic effect	References
Laetiporus sulphureus var. *miniatus*	Crude extracellular polysaccharides (EPS)	Increased the insulin antigenesity via proliferation or regeneration of diabetic islet β-cells	Hwang and Yun 2010
Lentinula edodes	Exo-polymer	Hypoglycemic effects with lower levels of blood glucose, decreased the levels of triglycerides and cholesterol. Increased insulin levels	Yang et al. 2002
Lentinus strigosus	Exopolysaccharides (EPS) from mycelial culture	Decreased plasma glucose level up to 21.1 % at the dose of 150 mg/kg bw. Induces regeneration of pancreatic islets and remediates destruction of microvascular pancreatic islets	Yamac et al. 2008
Phellinus baumii	Exopolysaccharides (heteropolysaccharides and proteoglycans)	Reduced fasting blood glucose levels by 52.3 % compare to control Amelioration of liver functions	Hwang et al. 2005
	Exopolysaccharides (EPS) by submerged mycelial culture	Reduced fasting blood glucose levels, improved glucose tolerance, and systemic insulin sensitivity Regulates through peroxisome profilerator-activated receptor (PPAR-γ) mediated lipid metabolism	Cho et al. 2007
Phellinus linteus	Polysaccharides	Inhibits the development of autoimmune diabetes by regulating cytokine expression	Kim et al. 2010a, b
	Submerged mycelial culture	Decreased the concentrations of triglycerides and blood glucose levels	Kim et al. 2001a, b
	Hispidin	Anti-diabetic property through preventing β-cells damage via hydrogen peroxide-induced apoptosis and increased insulin secretion	Jang et al. 2010
	Hispidin class of derivatives	Act as natural aldose reductase inhibitors, in preventing diabetic complications	Lee et al. 2008a, b
Phellinus merrillii	Ethanol extracts	Strong α-glucosidase and aldose reductase inhibitory activities	Huang et al. 2011
Phellinus ribis (Phylloporia ribis)	Polychlorinated compounds	Therapeutic effects through the enhance PPAR-γ agonistic activity	Lee et al. 2008a, b
Pleurotus eryngii	Diet rich with mushroom	Improved insulin sensitivity and exerts anti-hyperglycemic and anti-hyperlipidemic effects	Kim et al. 2010a, b
Pleurotus pulmonarius	Aqueous extract of the mushroom	Reduced the serum glucose level in alloxan-treated diabetic mice and increased glucose tolerance	Badole et al. 2006
Sparassis crispa	β-glucan component	An effective promoter of wound healing in patients with diabetes. Increase in the migration of macrophages and fibroblasts, and directly increases the synthesis of type I collagen	Kwon et al. 2008
	Freeze dried fruiting body samples	Increased plasma levels of adiponectine Decreases the concentrations of blood glucose levels, serum triglycerides and total cholesterol levels	Yamamoto and Kimura 2010
Tremella fuciformis	Exopolysaccharides (EPS) by submerged mycelial culture	Reduced fasting blood glucose levels, improved glucose tolerance, and systemic insulin sensitivity Regulates through peroxisome profilerator-activated receptor (PPAR-γ) mediated lipid metabolism	Cho et al. 2007
Tremella mesenterica	Fruiting body extract	Reduced fasting blood glucose levels in streptozocin-induced type 1 diabetic rats and pre-diabetic impaired glucose tolerant rats	Lo et al. 2006a
Tremella aurantia	Acidic polysaccharide	Reduced the serum glucose levels, total-cholesterol and triglyceride levels Significant decrease in plasma lipoperoxide level	Kiho et al. 2001
Wolfiporia extensa	Crude extract and triterpenes	Reduced postprandial blood glucose levels in db/db mice via enhanced insulin sensitivity irrespective of PPAR-γ	Li et al. 2011a, b

blood glucose level is elevated to above what is considered normal levels, but is not high enough to be classified as diabetes mellitus (Moutzouri et al. 2011). While in this range, patients are at risk for not only developing type 2 diabetes, but may be prone to increased risk of microvascular and macrovascular complications including cardiovascular diseases (Gossain and Aldasouqi 2010). Prediabetes has been reported as "America's largest healthcare epidemic," affecting more than 57 million Americans (ADA 2008). Prediabetes is also commonly termed as borderline diabetes, impaired glucose tolerance (IGT), and/or impaired fasting glucose (IFG) (Nichols et al. 2007; Moutzouri et al. 2011).

The third type, gestational diabetes develops in pregnant women who have never had diabetes before, and have a high blood glucose level during pregnancy (King 1998; Ben-Haroush et al. 2004; Zhang and Ning 2011). It may more similar to type 2 diabetes mellitus, and is fully treatable but requires careful medical supervision throughout the pregnancy.

The most recent research discussing the pathophysiology of type 2 diabetes correlates with the concept of activation of the innate immune system and is directly linked with insulin resistance and development of atherosclerosis (Fernández-Real and Pickup 2012). The human innate immune system is the body's first-line of defense against several foreign stimulations including microbial, chemical, physical and even psychological injuries, which ensures the homeostasis inside the body. When there is an imbalance between the response to the stimulus, or when the threat is frequent (e.g. continued over nutrition or inactivity), there is disease instead of repair (Stumvoll et al. 2003). Recent evidence indicates that innate immunity is closely linked to insulin resistance and this link may involve genetic and cellular factors that trigger the responses leading to diabetes and its complications (Pickup et al. 1997; Fernández-Real and Ricart 1999; Xie and Du 2011).

Although there may be a multiple causes for developing diabetes, factors can be broadly categorized as environmental and inherited (Prokopenko et al. 2008; Gupta et al. 2012). Type 1 diabetes mainly occurs due to inherited factors and type 2 diabetes is due primarily to lifestyle factors and genetics. Epidemiological studies reported a bi-directional relationship between diabetes and other disease types and their effects on incidence of diabetes. Metabolic disorders such as overweight, obesity and stress related disorders such as depression (Stuart and Baune 2012) are indirectly attributed to this and are also reported as risk indicators of cardiovascular disease (Lange and Piette 2005; Schneider et al 2011; Thyagarajan-Sahu et al. 2011; Osanai et al. 2012; Stuart and Baune 2012). Diabetes, is a chronic disease which cannot be fully cured, however, type 2 diabetes may be prevented or delayed by proper food intake (de Mello et al. 2011; Dodd et al. 2011; Wolden-Kirk et al. 2011) and several changes in lifestyle (Vinicor 1998; Hu et al. 2001; Goldberg 2006; Shawahna et al. 2012). Basically intake of food which is low in fat and high in fibre content, avoidance of excessive weight gain, regular physical exercise, and avoidance of aggravating factors such as smoking and a stressful lifestyle could be beneficial (Morrato et al. 2007; Kerr et al. 2011; Jenkins and Hagberg 2011; Wolden-Kirk et al. 2011; Brun et al. 2009, 2012; Smith et al. 2012).

It is interesting to note that diabetes care has improved with many technological advances in the field. From improvements in insulin pumps to the implementation of continuous glucose monitors, technology is helping deal with diabetes better than ever before (Cobelli et al. 2011; Farret et al 2012; Riveline et al. 2012).

Mushrooms as potent anti-diabetic agents

Agaricus bisporus (White button mushroom)

Agaricus bisporus is a popular edible mushroom worldwide. The mushroom has potential anti-inflammatory, hypoglycemic and hypocholesterolemic effects due to presence of high amounts of acidic polysaccharides, dietary fibre, and anti-oxidants, such as vitamins C, B_{12}, and D; folate, ergothioneine; and polyphenol (Fukushima et al. 2000; Mattila et al. 2001; Koyyalamudi et al. 2009a, b; Geosel et al. 2011). Literature also suggests that increased intake of white button mushrooms may promote innate immunity against tumors and viruses (Wu et al. 2007: Adotey et al. 2011; De Silva et al. 2012). High concentrations of blood cholesterol levels, hypercholesterolemia, can lead to a progression of hyperglycemia/type 2 diabetes in humans and animals (Mathe 1995; Kuller 2006). Cholesterol directly effects β-cell metabolism and opens a novel set of mechanisms that may contribute to β-cell dysfunction and the onset of diabetes (Hao et al. 2007). Epidemiological studies suggest that higher levels of dietary fibre intake play a significant protective role with respect to diabetes, in lowering the dietary glycemic load and shows potent hypocholesterolemic effects (Anderson et al. 2009).

Diabetic rats fed *A. bisporus* fruiting bodies exhibited significant anti-glycemic and anti-hypercholesterolemic effects (Jeong et al. 2010; Volman et al. 2010). Moreover, the mushrooms had a positive influence on lipid metabolism and liver function. Although soluble dietary fibre is the most likely candidate in lowering blood glucose levels and cholesterol levels, other constituents, such as anti-oxidants (polyphenols, vitamin C, and ergothioneine), proteins, and polysaccharides may also play an important role. Extracts from *A. bisporus* may result in decreased severity of streptozotocin-induced diabetes in rats with considerable protective effects on the pancreas and apparent repopulation of β-cells (Yamac et al. 2010). Serum glucose levels decreased by 29.68 % and insulin levels increased to 78.5 % with an oral administration of extract dose of 400 mg/kg body weight per day.

Agaricus campestris (Field mushroom or meadow mushroom)

Biologically active extracts of *A. campestris* have been considered as a traditional treatment for diabetes. Anti-hyperglycemic effects in administration of *A. campestris* in the diet or drinking water of streptozocin-induced diabetic mice have been demonstrated (Gray and Flatt 1998). In particular, 1 mg/ml of aqueous extract, significantly stimulated 2-deoxyglucose transport, glucose oxidation, and the incorporation of glucose into glycogen in the abdominal muscle of the mouse. In acute 20 minute tests, 0.25–1.0 mg/ml aqueous extract of *A. campestris* evoked a stepwise 3.5 to 4.6 fold stimulation of insulin secretion from the pancreatic β-cell line (Gray and Flatt 1998).

Activity of *A. campestris* extract was found to be heat stable, acetone soluble, and unaltered by exposure to alkali, but decreased with exposure to acid. The presence of both low and high molecular weight substances in *A. campestris* are responsible for the anti-hypertriglyceridemic, insulin releasing, and insulin like activities (Gray and Flatt 1998). A study conducted to assess the possible effects of plant products on glucose diffusion across the gastrointestinal tract showed the aqueous extracts of *A. campestris* and various other plants extracts significantly decreased the glucose movement, but were less effective than agrimony and avocado (Gallagher et al. 2003)

Agaricus subrufescens (Almond mushroom)

Agaricus subrufescens (also known as *Agaricus blazei* or *Agaricus brasiliensis*) is an edible mushroom, with a somewhat sweet taste and taste, and fragrance of almonds (Kerrigan 2005). *Agaricus subrufescens* has been valued as a medicinal mushroom having several biologically active metabolites including polyphenols, polysaccharides and glycoproteins which are thought to be responsible for its immunostimulatory and anti-tumor properties (Firenzuoli et al. 2008; Geosel et al. 2011; Lima et al. 2011; De Silva et al. 2012; Wisitrassameewong et al. 2012). *Agaricus subrufescens* is a common mushroom in South America and in Asia, and has been widely used in traditional medicine as a remedy for certain types of cancers and diabetes (Sorimachi and Koge 2008; Ishii et al. 2011).

β-Glucans and oligosaccharides of *A. subrufescens* showed anti-hyperglycemic, anti-hypertriglyceridemic, anti-hypercholesterolemic, and anti-arteriosclerotic activity indicating overall anti-diabetic activity in diabetic rats (Kim et al. 2005). Another study suggests that soluble β-glucan from the mushroom has glucose reducing properties and improves pancreatic β-cells in chemical-induced diabetic rats through the inhibition of intestinal α-glucosidase and enhancement of insulin secretion (Higaki et al. 2005).

A randomized, double-blinded, and placebo-controlled clinical trial conducted with *A. subrufescens* fruiting body extract in combination with metformin and gliclazide showed improved insulin resistance in type 2 diabetes patients. The increased adiponectin concentrations after taking fruiting body extract might be the mechanism that was responsible for the beneficial effects (Hsu et al. 2007). Apart from the hypoglycemic effect of β-glucans in *A. subrufescens*, recent studies were carried out to explore other possible constituents. A hot-water extract of the submerged-culture broth of *A. subrufescens* showed it to have potent hypoglycemic action, which could be useful in the treatment of diabetes mellitus. The hypoglycemic action might be attributed to isoflavonoids including genistein, genistin, daidzein, and daidzin and other substance derived from the culture media of soybean flakes of the extract (Oh et al. 2010).

There has been much recent attention given to the relationship between diabetes and oxidative stress, which suggests that oxidative stress is a mainstream effect of the metabolic mechanisms by which overfeeding leads to insulin resistance (Bisbal et al. 2010; Zhai et al. 2011). One study suggested that the anti-diabetic effects of *A. subrufescens* result from the suppression of oxidative stress and proinflammatory cytokine, TNF-α, and improvement in β-cells mass (Niwa et al. 2011). Diabetic patients with impaired metabolic control are more susceptible for pulmonary complications with micro- and macro vascular disorders (Davis et al. 2000; Kaparianos et al. 2008). A study demonstrated the beneficial effect of *A. subrufescens* aqueous extract on oxidative stress variables and pulmonary morphopathology in streptozotocin-induced diabetes (Cangeri Di Naso et al. 2010).

Agaricus sylvaticus (Sun Mushroom)

Agaricus sylvaticus, is a popular Brazilian mushroom species of major importance as a food product and contains substances with pharmacological and nutritional potential (Taveira et al. 2008; Fortes and Carvalho Garbi Novaes 2011; Orsine et al. 2012). Pharmacologically active substances present in the mushroom such as phenolic compounds, polyketides, terpenes and steroids are recognized as excellent anti-oxidants and have attracted considerable attention in clinical studies on immunosuppressed patients due to their potential in acting as “adjuvants” in cancer therapy (Taveira et al. 2008; Fortes and Carvalho Garbi Novaes 2011). The ability of these extracts in manipulating the metabolic parameters could be equally beneficial in diabetic treatments.

A randomized, double-blinded, placebo-controlled clinical trial was conducted to evaluate the metabolic and blood pressure effects on 56 patients with colorectal cancer who supplemented with *A. sylvaticus* (Fortes et al. 2008). The *A. sylvaticus* group presented a significant reduction of fasting plasma glucose (p=0.02), total cholesterol (p=0.01), creatinine (p=0.05), aspartate aminotransferase (p=0.05), alanine aminotransferase (p=0.04), systolic blood pressure (p=0.0001) and diastolic blood pressure (p=0.0001), while these alterations were not observed in the placebo group (Fortes et al. 2008, 2009; Fortes and Carvalho Garbi Novaes 2011). Higher levels of cholesterol and triglyceride lead to higher risk factors for diabetes, and a higher risk of developing cardiovascular disease (Schneider et al 2011; Thyagarajan-Sahu et al. 2011). Prevention of onset of atheroma plaques in hypercholesterolemic rabbits by water extracts of the mushroom *A. sylvaticus* containing strong anti-oxidants was also noted (Percario et al. 2008). Controlled levels of all these metabolic parameters may reduce the development of diabetes and related metabolic diseases.

Auricularia auricula-judae (Jew's Ear, Jelly Ear mushroom)

Auricularia auricula-judae, an edible mushroom which belongs to the family *Auriculariaceae* is widespread in China and many parts of the world. Modern pharmacological research indicates that this genus including *A. auricula-judae* and *A. polytricha* has several medicinal properties including antioxidant, antitumor, hypolipidemic and immunomodulatory activities (Luo et al. 2008; Song and Du 2010; Chen et al. 2011).

The hypoglycemic effect of water-soluble polysaccharides from fruiting bodies of *A. auricula-judae* was investigated on genetically diabetic mice and showed that mushroom supplementation had a significant effect in lowering plasma glucose, insulin, urinary glucose, and food intake. Most interestingly the study showed that reduced food consumption was not a major factor contributing to the hypoglycemic action of extract (Yuan et al. 1998). A further study also showed that hot-water extracts from *A. auricula-judae* had a reductive effect on food intake and blood glucose concentrations (Takeujchi et al. 2004). Administration of dried powder of *A. auricula* mycelia (AAM) (0.5 g/kg bw and 1.0 g/kg bw) caused a statistically significant reduction of plasma glucose (35 % and 39 %, respectively), total cholesterol (18 % and 22 %, respectively) and triglyceride (12 % and 13 %, respectively) levels with potential anti-diabetic effects (Kim et al. 2007). Another study indicated that polyphenolic compounds and polysaccharides found in *A. auricula*, prevented hypercholesterolemia with improving antioxidant status, decreasing the level of total cholesterol and the atherosclerosis index, and increasing the level of high-density lipoprotein cholesterol (Chen et al. 2011).

Coprinus comatus (Shaggy ink cap)

Another delicious and nutritious edible mushroom, *Coprinus comatus*, is highly valued for its medicinal properties. It has been reported to possess anti-diabetes, anti-oxidative, antitumor, and anti-mutagen properties, and to protect the liver from damage (Lee et al. 1999; Zaidman et al. 2008; Yu et al. 2009; Popović et al. 2010; Dotan et al. 2011).

Taking advantage of the ability of mushrooms to absorb trace elements, several studies were designed to evaluate the hypoglycemic effect of *C. comatus* enriched with vanadium. Vanadium compounds have the ability to imitate insulin and have shown anti-diabetic effects in several studies (Shechter 1990; Goldfine et al. 1995; Ma and Fu 2009). *C. comatus* enriched with vanadium had significant anti-hyperglycemic effects on mouse model tests and was confirmed as a hypoglycemic food or medicine (Han et al. 2006b; Han and Liu 2009; Lv et al. 2009; Yamac et al. 2009). Fermented *C. comatus* rich in vanadium (CCRV) produced significant decreases in blood glucose level, insulin secretion (p<0.05, p<0.01) and inhibited levels gluconeogenesis in hyperglycemic mice (p<0.01) (Zhou and Han 2008).

Despite previous anti-diabetes research on *C. comatus*, there are only few reports concerning anti-diabetic activity of 4,5-dihydroxy-2-methoxy-benzaldehyde (called comatin) found in *C. comatus*. Comatin is an inhibitor of the non-enzymatic glycosylation (NEG) reaction. It was revealed that the blood glucose concentration of normal rats treated with comatin at 80 mg/kg body weight was reduced from 5.14 mM to 4.28 mM in 3 h. Also, the concentrations of fructosamine, triglycerides and total cholesterol in induced-diabetic rats were significantly decreased. These results indicate that comatin could maintain a low level of blood glucose and improve glucose tolerance (Ding et al. 2010). Recently extracellular polysaccharides from *C. comatus* were produced using the submerged fermentation system (Ding et al. 2012) and these had high inhibitory effects on non-enzymatic glycosylation. These findings can be applied to improve the performance of *C. comatus* cultures in the production of bioactive metabolites on a bioreactor scale and provide the foundation for further investigation into medicinally active compounds derived from *C. comatus.*

Glucose lowering activities of five extracts (ethanol extract, water-soluble polysaccharide, alkali-soluble polysaccharide, protein and crude fibre) were prepared from the stipe and cap of *C. comatus*. The water-soluble polysaccharide of the cap powder (300 mg/kg *p.o.* daily) fed for 28 days to diabetic mice gave the best glucose lowering activity of the five extracts and almost decreased the blood glucose levels to that of normal mice. Thus, *C. comatus* can be developed as a potential oral hypoglycemic agent or functional food in the control of diabetes mellitus (Li et al. 2010).

Cordyceps spp

Cordyceps are ascomycetes and are one of the most valued fungi in traditional Chinese medicines. The medicine consists of the dried fungus growing on caterpillar larva (Chen and Jin 1992; Zhu et al. 1998a, b; Won and Park 2005; Yoo et al. 2005; Leung et al. 2009; Das et al. 2010). According to ancient descriptions, *Cordyceps* is believed to have important pharmacological activities in protecting lung and kidney functions and in promoting the essence and vital energy (Ying et al. 1987; Zhu et al. 1998a). Recent scientific evidence have shown that *Cordyceps* is capable of modulating immune responses, and inhibiting tumor growth (Zhang et al. 2006; Khan et al. 2010; Lee et al. 2011; Wong et al. 2010; De Silva et al. 2012; Yu et al. 2012), improving hyperlipidemia, and hyperglycemia, and sexual function (Kiho et al. 1996, 1999; Holliday et al. 2005; Shi et al. 2009).

Cordyceps militaris

Cordyceps militaris has traditionally been used as a tonic in folk medicine and its activity has been corroborated in recent research findings (Zhao-Long et al. 2000; Yu et al. 2004, 2007; Won and Park 2005; Das et al. 2010; Yu et al. 2012). Oral administration of hot water extracts of *C. militaris* fractionated by molecular weight showed mild hypoglycemic activity in streptozocin-induced diabetic rats (Yun et al. (2003).The anti-diabetic effect of various fractions of *C. militaris* was evaluated in streptozocin-induced diabetic mice. Results showed that seven-day administration of the ethanol soluble supernatant, cordycepin and acarbose, dramatically reduced blood glucose levels by 46.9, 48.4, and 37.5 %, respectively.

Water extracts of *C. militaris* (0.5 g/kg) ameliorated insulin resistance and improved insulin secretion in type 2 diabetic rats. Impaired intracellular insulin action of rats was induced by removal of 90 % of the pancreas and by feeding a high fat diet (10 g/kg). This study implicated significant reduction of fasting serum glucose levels, increased whole-body glucose disposal rates and glucose utilization in skeletal muscles in rats and it was concluded that *C. militaris* water extract contains a compound that acts as an insulin sensitizer.

Prior to the streptozocin treatment, oral administration of polysaccharide-enriched fractions significantly reduced glucose levels by 60–70 % in diabetic rats and suggests that *C. militaris* polysaccharides may be promising as a polyphyletic as it has protective action against streptozocin-induced diabetes. It is evident that *C. militaris* has both insulin-like and insulin release promoting activity and potential anti-diabetic activity (Zhang et al. 2006). Cordycepin isolated from *C. militaris* suppressed the diabetes regulating genes by activation in LPS-activated macrophages and inactivation of NF-kB dependent inflammatory responses and suggests that *C. militaris* will provide potential use as an immunomodulatory agent for treating diabetes (Shin et al. 2009). A recent study concerned the hypoglycemic mechanism of aqueous extracts of *C. militaris* tested with injection of atropine and hemicholinium-3 (HC-3) to normal Wistar rats, and a western blot was used to investigate insulin signaling. Research findings indicate that *C. militaris* can lower plasma glucose via the stimulation of insulin secretion and cholinergic activation and the extracts decreased the plasma glucose by 21 % and induced additional insulin secretion by 54.5 % after 30 minutes (Cheng et al. 2012a).

Cordyceps sinensis (Caterpillar fungus)

Fruiting bodies of *Cordyceps* attenuated diabetes induced weight loss, polydipsia and hyperglycemia, and these improvements suggest that the fruiting body of *Cordyceps* has a potential to be a functional food for diabetes patients (Lo et al. 2004, 2006b; Misra et al. 2009). Free-radical-induced lipid peroxidation is a common phenomenon which has been associated with several diseases, including diabetes mellitus (Feillet-Coudray et al. 1999). In type 1 diabetes islet cells may be damaged selectively due to the insufficient amounts of pancreatic anti-oxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) (Kakkar et al. 1998) and this can be prevented by use of an anti-oxidant which reduces the cell damage (Prasad 2000).

In one randomized trial, 95 % of patients treated with 3 g/day of *C. sinensis* showed a decrease in their blood sugar levels, while the control group showed only 54 % improvement with treatment by other methods (Guo and Zhang 1995). CSP-1, a polysaccharide with strong anti-oxidant activity was isolated from cultured *Cordyceps* mycelia with potent hypoglycemic effects. Administration of a CSP-1 dose of higher than 200 mg/kg body wt. daily for seven days, produced a significant drop in blood glucose levels and increased serum insulin levels in diabetic animals which suggests that CSP-1 may stimulate pancreatic release of insulin and/or reduce insulin metabolism (Li et al. 2003, 2006). The immunoregulatory activity of extracts of *C. sinensis* can be beneficially used to inhibit and regulate diabetes which is an autoimmune disease. Oral administration of *C. sinensis* resulted in reduction in the overall incidence of diabetes due to an increase in the ratio of Treg cells to Th17 in the spleen and pancreatic lymph nodes (Shi et al. 2009).

A new area of research focused on the prevalence of depression in diabetic patients. Diabetes mellitus is accompanied by hormonal and neurochemical changes that can be associated with anxiety and depression (Lustman et al. 1983; Musselman et al. 2003; Talbot and Nouwen 2000). Recent studies suggest a potential strategy for contemporary treatment of depression and diabetes through the co-effect of *C. sinensis* enriched with vanadium. *Cordyceps sinensis* has both anti-depressant-like activity and hypoglycemic activities (Nishizawa et al. 2007; Li et al. 2006); studies have also shown the hypoglycemic functions of vanadium by insulin mimicry (Shechter 1990; Goldfine et al. 1995). Co-effective interactions of both *C. sinensis* and vanadium together may provide a possible treatment strategy to depression associated with diabetes (Guo et al. 2010, 2011). CordyMax is a standardized mycelial fermentation product of *C. sinensis* which has been produced from a strain Cs-4. Much research has been conducted to evaluate the efficacy of the strain and it was found that CordyMax improves glucose metabolism and increases insulin sensitivity in normal rats (Zhu et al. 1998a, b). Another study concluded that CordyMax Cs-4 may have potentially beneficial effects on maintaining whole-body glucose disposal with a less pronounced effect on insulin secretion in carbohydrate metabolism (Balon et al. 2002). A recent study investigated the potential hypoglycemic and renoprotective effects of an extract from the solid-state fermented mycelium of *C. sinensis*. Extracts promote β-cell survival, increases renal NKA activity and decreases collagen deposition, and mesangial matrix accumulation suggests that *C. sinensis* might be a potential drug candidate for preserving β-cell function and offer renoprotection, which may afford a promising therapy for diabetes mellitus (Kan et al. 2012).

Ganoderma lucidum sensu lato (Lingzhi)

Ganoderma lucidum has been utilized for centuries in East Asia to prevent or treat various diseases and used in traditional Chinese medicine as a tonic in promoting good health, perpetual youth, vitality, and longevity (Ying et al. 1987; Hobbs 1995; Chang and Mshigeni 2000; Sanodiya et al. 2009; Deepalakshmi and Mirunalini 2011). In China, *G. lucidum* is called 'Lingzhi'. The Japanese name for the *Ganoderma* family is 'Reishi' (Wachtel-Galor et al. 2004). Scientific investigations have repeatedly confirmed the beneficial effects of *G. lucidum* to health and it is now frequently promoted as an effective agent against cancers due to its intrinsic immunomodulatory and anti-tumor properties (Liu et al. 2009; Shang et al. 2011; Ye et al. 2011). The primary bioactive compounds are commonly considered to be polysaccharides and triterpenoids (Hung et al. 2008; Cheng et al. 2010). Recent studies on *G. lucidum* have shown many interesting biological activities, including anti-tumor, anti-inflammatory, anti-oxidant and anti-diabetic effects (Paterson 2006; Meng et al. 2011; Ye et al. 2011; De Silva et al. 2012).

Anti-hyperglycemic and anti-hypercholestromic effects of *G. lucidum* have been extensively studied and have shown potential therapeutic activities. Hypoglycemic effects of *G. lucidum*-polysaccharides (*G. lucidum*-PS) are related to facilitation of Ca^{2+} influx into the pancreatic β-cells and thus insulin release (Zhang and Lin 2004; Bastami et al. 2007). Prevention of the progression of diabetic renal complications as well as a lowering of the increased serum glucose and triglyceride levels was reported in streptozotocin-induced diabetic mice (Zhang et al. 2003). It was found that *G. lucidum*-polysaccharides reversed the alloxan-induced viability loss of islets via an inhibition of NF-κB activation and the suppression of free radical formation.

The liver is an important organ in determining glucose homeostasis and cholesterol levels in blood and phosphoenolpyruvate carboxykinase is a hepatic enzyme which is involved in the regulation of gluconeogenesis (Saltiel and Kahn 2001). *G.lucidum* consumption can provide beneficial effects in treating type 2 diabetes mellitus by lowering the serum glucose levels through the suppression of the hepatic phosphoenolpyruvate carboxykinase gene expression (Seto et al. 2009).

Cellular oxidative damage is a well-established general mechanism for cell and tissue injury and is primarily caused by reactive oxygen species (ROS) (Agarwal and Sohal 1993; Adachi et al. 1998; Aksenova et al. 1998). An imbalance between the formation of active oxygen metabolites and the rate at which they are destroyed by enzymic and nonenzymic anti-oxidants is referred to as oxidative stress (Papas 1996). It has been suggested that cellular oxidative damage and oxidative stress plays an important role in some physiological conditions and in many diseases, including diabetes mellitus (DM) (Feillet-Coudray et al. 1999). Natural protective anti-oxidative enzymes found in cells (glucose-6- phosphate dehydrogenase, superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST) and reduced glutathione) are important in both preventing the production of free radicals and repairing oxidative damage (Chandra et al. 1994; Kakkar et al. 1998). In a randomized, placebo-controlled clinical study, Ganopoly (polysaccharide fractions extracted from *G. lucidum* by a patented technique) was given to 71 patients with confirmed type 2 diabetes mellitus and it showed efficacious and safe lowering of blood glucose concentrations (Gao et al. 2004).

A recent study demonstrated that polysaccharides isolated from *G. lucidum* significantly increased nonenzymic and enzymic anti-oxidants, and serum insulin levels, and reduced lipid peroxidation and blood glucose levels in streptozocin-diabetic rats (Jia et al. 2009; Rubel et al. 2011).

Suffering from diabetes for a long time may cause myocardial fibrosis, gradually leading to the development of a risk factor for cardiovascular disease (Asbun and Villarreal 2006). *G. lucidum*-polysccharides were used in the treatment of myocardial fibrosis found in diabetes (Meng et al. 2011). It was also shown that polysaccharides attenuated myocardial collagen cross-linking in diabetic rats, which was related to the decreased level of advanced glycation end products and augmented activities of antioxidant enzymes. Gl-PS accelerates refractory wound healing and improved wound angiogenesis in streptozotocin-induced type 1 diabetic mice, by suppression of cutaneous MnSOD nitration, p66Shc and mitochondrial oxidative stress (Tie et al. 2012).

Apart from the polysaccharide fraction, *G. lucidum* has terpenoid constituents which possess many biological activities (Sliva 2003; Cheng et al. 2010; Weng and Yen 2010; Grienke et al. 2011). Lanostane triterpenoid isolated from *G. lucidum*, namely ganoderol B[(3β,24E)-lanosta-7,9(11),24-trien-3,26-diol], had strong inhibitory activity on α-glucosidase (Fatmawati et al. 2011). Alpha-glucosidase, an enzyme located in the small intestine epithelium, catalyzes the cleavage of disaccharides and oligosaccharides to glucose. Any compound that inhibits the activity of α-glucosidase can be proposed as a treatment for diabetes mellitus type 2, since it works by preventing the digestion of carbohydrates. Ganoderol B shows high α-glucosidase inhibition with an IC_{50} of 48.5 μg/ml (119.8 μM) effect in *in vitro* studies.

Resistance to the hormones insulin and leptin are common metabolic conditions prevailing in type 2 diabetes mellitus patients and it is mainly associated with increased activity and expression of protein tyrosine phosphatase (PTP)1B. Therefore, inhibition of (PTP)1B activity or its expression should compensate the insulin and leptin resistance by providing a therapeutic approach to type 2 diabetes mellitus and obese patients (Popov 2011). Recently, a novel (PTP)1B activity inhibitor, named Fudan-Yueyang- *G. lucidum*, was identified from the fruiting bodies of *G. lucidum* and showed an efficient (PTP)1B inhibitory potency. Orally administered proteoglycan extract, Fudan-Yueyang- *G. lucidum* to streptozotocin-induced diabetic rats showed a significant decrease (IC_{50}=5.12±0.05 μg/mL) in plasma glucose levels (Teng et al. 2011) and the underlying mechanisms responsible for the anti-diabetic effect of *G. lucidum* were identified. It was suggested that the hypoglycemic effect of Fudan-Yueyang- *G. lucidum* is caused by inhibition of the (PTP)1B expression and activity. Further, regulation of the tyrosine phosphorylation level of the IR 13-subunit is also promising as an insulin sensitizer for the therapy of type 2 diabetes and accompanied dyslipidaemia (Teng et al. 2012; Wang et al. 2012). Furthermore, Fudan-Yueyang- *G. lucidum* significantly decreased the levels of free fatty acid, triglyceride, total cholesterol and low density lipoprotein-cholesterol as well as increased the level of high density lipoprotein-cholesterol accompanied with other metabolic disorders (Teng et al. 2011, 2012).

Grifola frondosa (Maitake)

Grifola frondosa is very popular in Korea, China and Japan and is thought to have many varied medicinal properties (Mori et al. 2008; Misra et al. 2009). Several experiments have found many beneficial activities attributable to *G. frondosa* and/or its extracts. Maitake lowers blood sugar because the mushroom naturally contains an α-glucosidase inhibitor. Alpha-glucosidase inhibitors are presently known to occur in aqueous methanol extracts of the seeds of *Momordica charantia* and the fruit bodies of *G. frondosa* (Matsuur et al. 2002). Researchers evaluated the anti-diabetic effect of an α-glucan (MT-α-glucan) from the fruit body of Maitake mushrooms on KK-Ay mice. Data suggest that MT-α-glucan has an anti-diabetic effect on KK-Ay mice, which might be related to its effect on insulin receptors (i.e., increasing insulin sensitivity and ameliorating insulin resistance of peripheral target tissues) (Hong et al. 2007).

Fermented *G. frondosa* rich in vanadium (GFRV) significantly induced decreases of the blood glucose levels in hyperglycemic mice (Cui et al. 2009). In addition, submerged culture mycelium and broth of *G. frondosa* improved glycemic responses in diabetic rats with significant decreases in postprandial blood glucose levels and serum triglyceride, fructosamine levels (Lo et al. 2008). Further studies with a few human trials have also shown that the anti-diabetic activity is present in the fruit body of *G. frondosa* (Horio and Ohtsuru 2001; Konno 2001; Manohar et al. 2002).

Hericium erinaceus (Lion's Mane Mushroom)

Hericium erinaceus is an edible mushroom in the tooth fungus group, native to North America which possesses significant medicinal properties. *H.erinaceus* is a rare food which contains components promoting NGF (nerve growth factor) synthesis and can be regarded as a useful food for the prevention of dementia and improving mild cognitive impairment without any adverse effects (Kawagishi et al. 1996; Mori et al. 2009). Recent studies have determined that *Hericium* spp may have important physiological functions in humans, including anti-oxidant activities, anti-tumor promoting activities and the regulation of blood lipid levels and blood glucose levels (Wang et al. 2005; Wong et al. 2009; Kim et al. 2011).

An extract of the mushroom has been demonstrated to be effective at lowering blood sugar and lipid levels in diabetic rats. The blood sugar levels of the rats fed with the extract decreased by 19–26 % and the serum lipids decreased by 20 % compared to that of the control diabetic rats (Wang et al. 2005). The biotransformation of *Ginkgo biloba* leaf extract by *H. erinaceus* showed regulated blood glucose effects through the increase of the serum superoxide dismutase activity (Zhang et al. 2008).

Inonotus obliquus (White rot fungus/ Chaga)

Inonotus obliquus belongs to the family *Hymenochaetaceae* of the basidiomycetes and is used as a folk health remedy in Russia and western Siberia (Mizuno et al. 1999; Dai 2010; Lee and Yun 2011). Many biologically active metabolites such as polyphenolic compounds, triterpenoids, and steroids have been identified from this mushroom, and these have shown various biological activities, including anti-viral (Ichimura et al. 1999), anti-fungal (Kahlos 1994), hepatoprotective (Wasser and Weiss 1999) anti-tumor (Mizuno et al. 1999; Kim et al. 2006) and hypoglycemic (Mizuno et al. 1999) effects. A study conducted to investigate the protective effects of Chaga mushroom supplement against diabetes, via the mitigation of oxidative stress and reduction of blood glucose in streptozotocin-induced diabetic rats, showed that the extracts may initially act on protecting endogenous DNA damage in the short-term by triggering high levels of total radical-trapping antioxidant potential (Cha et al. 2006; Park et al. 2009).

Alloxan-induced diabetic mice treated with dry matter culture broth of *I. obliquus* had significantly decreased serum contents of free fatty acids (FFA), total cholesterol (TC), triglyceride (TG) and low density lipoprotein-cholesterol (LDL-C) levels. Whereas *I. obliquus* culture broth demonstrate a significant anti-hyperglycemic and anti-lipidperoxidative effects by increased levels of high density lipoprotein-cholesterol (HDL-C), insulin and hepatic glycogen (Sun et al. 2008). An extracted polysaccharide fraction of *I. obliquus* administered to mice with diabetes mellitus resulted in significant increased concentrations of anti-oxidant enzymes which restored damaged pancreatic tissues (Xu et al. 2011). Crude polysaccharides from dry matter of culture broth of *I. obliquus* demonstrated a similar anti-oxidative effect with a significant anti-hyperglycemic activity and anti-lipidperoxidative properties (Xu et al. 2010a, b). Functional polysaccharides from *I. obliquus* showed anti-hyperglycemic effects and regulated lipid metabolism (Joo et al. 2010; Xin et al. 2010; Hu et al. 2012).

Another study conducted to evaluate the photochemical and hypoglycemic characteristics of the mushroom demonstrated that the ethyl acetate fraction from *I. obliquus* produced significant anti-hyperglycemic and anti-lipidperoxidative effects in alloxan-induced diabetic mice (Lu et al. 2010). Terpenoid and sterol compounds were the major active constituents including lanosterol (1), 3β-hydroxy-lanosta-8,24-diene-21-al (2), inotodiol (3), ergosterol peroxide (4) and trametenolic acid (5). Moreover, inotodiol and trametenolic acid showed an inhibitory effect on α-amylase activity and a scavenging effect on 1,1-diphenyl-2-picrylhydrazyl radicals.

Postprandial hyperglycemia is a key event in the development of type 2 diabetes mellitus and complications associated with the disease. An acid protein-bound polysaccharide IOPS, isolated from *I. obliquus* with a molecular weight of 1.7×10^4 Da exhibited an inhibitory activity against α-glucosidase with the IC_{50} value of 93.3 μg/ml. In addition, it produced inhibitory activity on hydroxyl radicals and on formation of thiobarbituric acid-reactive substances in Fe^{2+}/ascorbate-induced lipid peroxidation in rat liver tissues (Chen et al. 2010). The authors claimed that these research findings will benefit the investigation of effective and safe α-glucosidase inhibitors from natural materials and could be a good candidate for development as functional foods or lead compounds for use in anti-diabetes treatments (Chen et al. 2010).

Comparison of hypoglycemic activity of fermented *I. obliquus* rich in vanadium and wild-growing *I. obliquus* showed that mushrooms enriched with vanadium had high bioavailability and low toxicity to animals, and could be used as a means of vanadium supplementation, with an expectation of obtaining anti-hyperglycemic activity (Zhang et al. 2011b).

Lentinula edodes (Shiitake)

Lentinula edodes is widely consumed as a nutritional health food worldwide, and contains proteins, lipids, carbohydrates, fibre, minerals, vitamins B1, B2 and C, ergosterol, lectins and lentinan. It was the first medicinal mushroom to enter the realm of modern biotechnology and used in the treatment of several diseases (Cheung 2008; Zhang et al. 2011a). An exopolymer (200 mg/kg of the body weight) produced from submerged mycelia cultures of *L. edodes* reduced plasma glucose level by 21.5 % and increased plasma insulin by 22.1 % in streptozocin-induced diabetic rats as compared to normal rats. It also lowered plasma total cholesterol levels and triglyceride by 25.1 and 44.5 % respectively (Yang et al. 2002). A glycoprotein with a molecular weight of 52 kDa and containing 83.5 % carbohydrate and 16.5 % protein was the candidate bioactive compound. It is evident that *L. edodes* could alleviate the damage of pancreatic β-cells to some extent, promoting insulin synthesis and thus lower the plasma glucose levels (Yang et al. 2002). Supplementation of Shiitake mushroom with other potential medicinal plant extracts showed significant effects on plasma blood glucose levels and improved immunity (Guo et al. 2003).

Phellinus spp.

Phellinus is one of the largest of basidiomycete genera with many species recognized as having medicinal properties. Polysaccharides, proteoglycans and derivatives of polyphenols are the most cited medicinal metabolites from *Phellinus* species being reported to have promising anti-tumor activities (Han et al. 1999; 2006a; Dai et al. 2010; Lee et al. 2010). These metabolites have also been recognized as having anti-oxidant properties, and in treating diabetes as well as its complications.

The hypoglycemic effect of *Phellinus linteus* proved to have efficacy in lowering substantially the plasma glucose and total trilgyceride level in streptozotocin-induced diabetic rats (Kim et al. 2001a, b). Extracellular polysaccharides extracted from mycelia grown in submerged culture of *Phellinus linteus* showed hypoglycemic effects with decreased plasma glucose, total cholesterol and triacylglycerol concentrations by 49 %, 32 %, and 28 %, respectively (Kim et al. 2001b). Moreover, polysaccharides inhibit the development of autoimmune diabetes by regulating cytokine expression (Kim et al. 2010a, b). Hispidin from *P. linteus* exhibited quenching effects against reactive radicals in a dose-dependent manner. In addition, hispidin was shown to inhibit hydrogen peroxide-induced apoptosis and increased insulin secretion in hydrogen peroxide-treated cells. These combined results indicate that hispidin may act as an anti-diabetic through protecting β-cells from the toxic action of reactive oxygen species in diabetes (Jang et al. 2010). Hispidin also acts as natural aldose reductase inhibitors, in preventing diabetic complications (Lee et al. 2010)

Crude exopolysaccharides produced from submerged mycelial cultures of *Phellinus baumii* exhibited considerable hypoglycemic effect with substantially reduced plasma glucose levels (52.3 %) when fed to rats. The activities of alanine aminotransferase (ALT) and asparate aminotransferase (AST) were significantly decreased by administration of *P. baumii* exopolysaccharides, thereby exhibiting a remedial role in liver function (Hwang et al. 2005). The ethanol extracts of *Phellinus merrillii* (EPM) showed strong α-glucosidase and aldose reductase activities. Alpha-glucosidase and aldose reductase inhibitors were identified as hispidin, hispolon and inotilone (Huang et al. 2011). Unique polychlorinated compounds, named chlorophellins A-C, have been isolated from the methanolic extract of the fruiting body of the fungus *Phellinus ribis* and chlorophellin C exhibited the most potent PPAR-gamma agonistic effect for the therapy of type 2 diabetes compared to the other compounds (Lee et al. 2008a, b).

Pleurotus spp. (Oyster mushrooms)

Pleurotus species have been used by different cultures worldwide because of their nutritional value, medicinal properties and other beneficial effects. Oyster mushrooms are a good source of dietary fibre and other valuable nutrients. They also contain a number of biologically active compounds with therapeutic activities. *Pleurotus* species have been proven to be a good source of essential amino acids that have several medicinal properties and anti-oxidant activities (Mattila et al. 2001; Jayakumar et al. 2006; Badole et al 2006). Interestingly, Lovestatin, a cholesterol-lowering drug isolated from *Pleurotus* species and its derivatives were reported to be the best therapeutic agents for ameliorating hypercholesterolemia (Gunde–Cimerman and Plemenitas 2001; Mattila et al. 2001; Jayakumar et al. 2006).

Hypoglycemic activity of an aqueous extract of *P. pulmonarius* in alloxan-induced diabetic mice has been reported. Acute oral toxicity data showed no mortality in the normal mice up to 5,000 mg/kg, while oral administration of extracts reduced the serum glucose level in alloxan-treated diabetic mice at all the doses tested. The extract also showed increased glucose tolerance in both normal and diabetic mice (Badole et al. 2006). In a subsequent study, the interaction of an aqueous extract of *P. pulmonarius* with acarbose on serum glucose levels, and on an oral glucose-tolerance test in alloxan induced diabetic mice was studied. The anti-hyperglycemic effects of aqueous extract and acarbose alone were similar, but a combined treatment of *P. pulmonarius* extract with acarbose produced a greater synergistic anti-hyperglycemic effect than either agent alone (Badole and Bodhankar 2007).

Pleurotus species possess bioactive compounds, such as polysaccharides, mevinolin and other statins, with hypocholesterolemic activities (Gunde-Cimerman et al. 1993; Mattila et al. 2001; Jayakumar et al. 2006). It has recently been reported that *P. citrinopileatus* fruiting body extracts exerted anti-hyperlipidemic effects. Serum triglyceride and total cholesterol levels were lowered in hyperlipidemic rats supplemented with the extracts, while high-density lipoprotein levels were significantly increased (Hu et al. 2006a). Similar effects were noted when powdered *P. ostreatus* fruiting bodies or a water-soluble polysaccharide extracted from *P. citrinopileatus* fermentation broth were fed to hypercholesterolemic or diabetic rats, respectively (Hossain et al. 2003; Hu et al. 2006b). The fasting blood glucose levels of diabetic rats fed with polysaccharide extract were 44 % lower than the negative controls with minimum damage to the islets of Langerhans. A diet containing 4 % of *P. ostreatus* mushroom fed to rats with insulin-dependent diabetes (streptozotocin 45 mg/kg) for two months, had a significantly lower basal and postprandial glycaemia, with more than 40 % decrease in cholesterol concentrations (Chorváthová et al. 1993).

Another important species, the king oyster mushroom (*Pleurotus eryngii*) has been tested for insulin resistance, anti-hyperglycemic and anti-hyperlipidemic effects in mice. Dietary polysaccharides from the mushroom significantly reduced the total cholesterol, triglyceride levels, and increased high density lipoprotein cholesterol levels with improved insulin sensitivity (Kim et al. 2010a, b). The potential of *Pleurotus eous* in decreasing the hyperglycemic levels in alloxan induced diabetic male albino rats were also investigated (Raji et al. 2009). A novel polysaccharide-peptide complex with hypoglycemic activities was isolated and identified from the abalone mushroom *P. abalones* (Li et al. 2011a, b; Wang et al. 2011a). Diabetes mediated oxidative stress is responsible for damaging the nuclear component of the host cells and is known to be a vital cause for the mutation related somatic and germinal cell disorders (El-Rahim et al. 2010; Otton et al. 2004). A novel antioxidant polysaccharide-peptide complex LB-1b from the fruiting bodies of the edible abalone mushroom exhibited a high antioxidant activity with a significant hypoglycemic effect in drug-induced diabetic mice (Li et al. 2012).

Pleurotus ostreatus extracts (especially high level) were more effective in decreasing the genetic alterations and sperm abnormalities in diabetes conditions and could reduce the high blood glucose level in hyperglycemic rats (Ghaly et al. 2011). Recently a clinical study was conducted with participation of 120 diabetic patients to evaluate the efficacy of oyster mushroom (*Pleurotus* spp.) on glycemic control. The results included a significant association between mushroom supplementation and gradual reduction in hyperglycemia in type 2 diabetic subjects and demonstrate the potential use of oyster mushroom for better glycemic control, positive effects on lipid profiles and a better quality of life (Agrawal et al. 2010).

Tremella fuciformis (Snow fungus or Silver ear fungus)

Tremella fuciformis is a commonly found mushroom which is valued for its gelatinous texture as well as its supposed medicinal benefits (Guo et al. 2003). Glucuronoxylomannan (AC) from the fruiting bodies of *T. fuciformis* exhibited significant dose-dependent hypoglycemic activity in normal mice, and also showed a significant activity in streptozotocin-induced diabetic mice, when administered by intraperitoneal administration (administration into the peritoneal cavity) (Kiho et al. 1994). Anti-diabetic activities of exopolysaccharides produced in submerged *T. fuciformis* mycelial culture were investigated in mice (Cho et al. 2007). The exopolysaccharides exhibited considerable hypoglycemic effects and improved insulin sensitivity possibly through regulating PPAR-gamma-mediated lipid metabolism (Cho et al. 2007). These results indicate that *T. fuciformis* has potential oral hypoglycemic effects as a functional food for the management of diabetes mellitus.

Tremella mesenterica (Yellow brain mushroom)

The medicinal effects of the mushroom *T. mesenterica* is mainly brought about by their acidic heteropolysaccharide and several sugars including glucose contained in the fruit bodies (Reshetnikov et al. 2001). In a study using streptozocin-induced type 1 diabetic rats and nicotinamide and streptozocin-induced prediabetic impared glucose tolerant rats, it was demonstrated that fruiting bodies of *T. mesenterica* significantly reduced the elevated blood glucose levels (Lo et al. 2006a).

Wolfiporia extensa (*Poria cocos*) (Pine-tree rotting mushroom)

Poria cocos has long been used as Traditional Chinese Medicine and food (Jia et al. 2003; Li et al. 2004). *Poria cocos*, alone or in combination with other herbs is often used to treat diabetes as well as other disorders (Jia et al. 2003; Li et al. 2004). A mechanistic study on streptozocin treated mice showed that the crude extract dehydrotumulosic acid, dehydrotrametenolic acid and pachymic acid from *P. cocos* exhibited different levels of insulin sensitizer activity (Sato et al. 2002). The data suggested that the *P. cocos* extract and its triterpenes reduced postprandial blood glucose levels in db/db mice via enhanced insulin sensitivity irrespective of PPAR-γ (Li et al. 2011a, b).

Medicine, nutrition and supplementation in preventing diabetes

Diabetes is one of the world's most important causes of health expenditure, mortality, disability and lost economic growth. World treatment costs are growing rapidly with the larger costs of diabetes arising from disability and loss of life caused by its complications, including heart diseases, kidney, eye and foot disease (Wang et al. 2009a, b; Zhang et al. 2010a; Thyagarajan-Sahu et al. 2011). Therefore the disease imposes an increasing economic burden on national health care systems worldwide. According to the International Diabetes Federation, the global health expenditure on diabetes is expected to total at least USD $376 billion in 2010 and USD $490 billion in 2030. Globally, 12 % of the health expenditures and USD $1330 per person are anticipated to be spent on diabetes treatments in 2010 (Shaw et al. 2010; Zhang et al. 2010a). Finding cures for this disease has been a great challenge for scientists throughout this and the previous century.

Recent advances in medicine and developments in understanding the disease characteristics have given rise to novel therapies to fight diabetes and related complications (Lo and Wasser 2011; Sobngwi et al. 2012). However, few clinical drugs are available for diabetes, and those that are available usually have adverse side effects such as decreased efficacy over time and low cost-effectiveness (Howlett and Bailey 1999; Purnell 2008; Cheng and Fantus 2005). Thus, more efficacious and safer anti-hyperglycemic agents are needed. Therefore, research and development into novel drugs for diabetes has been in great demand (Krentz and Bailey 2005; Choi et al. 2011; Liday 2011; Scheen 2011; Avogaro 2012; Barra et al. 2012). Many therapeutic strategies from natural products with plant origins have been developed as supportive methods for preventing and controlling diabetes (Goyal et al. 2008; Karou et al. 2011; Ranjbar et al. 2011; Ghosh et al. 2012; Huseini et al. 2012). Currently, there is renewed interest in the plant based medicines and functional foods for modulating physiological effects and in the prevention and cure of diabetes. Today mushrooms are considered as a type of functional food which can ameliorate and prevent diabetes and its complications (Milner 2000; Perera and Li 2011).

Many of the curative and health promoting properties that have been attributed to mushrooms by traditional folk medicine have been validated by recent scientific research (Jia et al. 2009; Yamac et al. 2010; Lo and Wasser 2011; Huang et al. 2011). Extensive research, mostly in Japan, China, and Korea, where traditional medicines are still practiced and also in several European countries, led to the isolation of bioactive substances found in the fruiting bodies and the mycelium of fungi. This, in turn, resulted in the development of fungi-derived drugs and supplements effective against human ailments. Significantly, several novel investigations on active constituents isolated from mushrooms have been approved in several countries. Maitake-D-fraction (Maitake Products, Inc. of New Jersey), an over-the-counter immunostimulator compound derived from Maitake's β-(1→3)-D-glucans and β-(1→6)-D-glucans, was approved in 1998 by the Food and Drug Administration (FDA) for the application for Investigational New Drug (IND). This company also developed a new medicinal mushroom preparation from Maitake (SF-Fraction-Glycoprotein), which helps maintain healthy cardiovascular functions and a healthy circulatory system. It was patented in the USA (U.S. Patent # 5,773,426) (Shavit 2009). Some other examples of patented mushroom extracts investigated in recent years are shown in Table 2.

Examples of the available drug products and supplementary foods developed from medicinal mushrooms that claim to provide beneficial effects on reducing blood glucose levels and help in diabetes prevention are shown in Table 3 and Plate 1. There is growing evidence for the effectiveness of using medical nutrition therapy in preventing and managing chronic diseases such as diabetes (Pastors 2003; Anon 2010; Igel et al. 2012). Intake of foods enriched with medicinal properties is a cost effective means to achieve significant health benefits by preventing or altering the course of disease occurrence.

Furthermore, their intake may prevent or manage chronic disease by increasing medication effectiveness, maintaining nutritional status and preventing adverse complications (Milner 2000; Curll et al. 2010; Thielen et al. 2010; Arathuzik and Goebel-Fabbri 2011). It has also been accepted that medical nutrition therapy applications can be expanded and integrated with pharmacotherapy and can increase the effectiveness (Anon 2010).

As a general rule, prevention strategies are more efficient than treatments, and always more cost effective (Pastors et al 2002; Reimann et al. 2009; Costa et al. 2011; Andujar-Plata et al. 2012; Romain et al. 2011, 2012). What makes mushrooms most valuable as a medicinal/therapeutic food for curing diabetes is the fact that mushrooms can produce several bioactive metabolites that can directly act upon glucose metabolism and related biochemical pathways. On the other hand they are important as nutritional foods to provide complete defense against external, internal stressors and inflammatory processes, and indirectly help in prevention and amelioration of diabetes (Poucheret et al. 2006; Cui et al. 2009; Guo et al. 2011; Lo and Wasser 2011; Da Silva et al. 2012). Thus, incorporation of mushrooms as a daily food or as a supplement, containing many nutrients such as vanadium (Poucheret et al. 1998) and bioactive substances, can assist in maintaining more normal cellular and immune function which helps in normalizing blood glucose levels (Wachtel-Galor et al. 2004; Han et al. 2006a, b; Zhou and Han 2008; Han and Liu 2009; Cui et al. 2009; Guo et al. 2010, 2011; Zhang et al. 2011a; Brennan et al. 2012).

Conclusions and future prospective

Diabetes mellitus is a life-threatening chronic metabolic disease caused by lack of insulin and/or insulin dysfunction characterized by hyperglycemia. Over 220 million people worldwide suffer from diabetes and its complications, and this number is predicted to increase in future years (Morrato et al. 2007; Hagopian et al. 2011; Qi et al. 2011; Sattar 2012).

The growing impact of type 2 diabetes in the majority of the population requires the introduction of better and more secure treatments, but also requires the development of new prevention strategies to reduce the incidence and prevalence of the disease (Wang et al. 2009b; Narayan and Williamson 2010; Andujar-Plata et al. 2012). Significantly, type 2 diabetes is an important preventable disease and can be

Table 2 Examples of patented products of mushroom extracts with claimed anti-diabetic properties (Source: http://www.freepatentsonline.com)

Claimed product/extract name	Patent No	Inventers
Agent for preventing/ameliorating diabetes and functional food for preventing/ameliorating diabetes (*Agrocybe aegerita* (Brig.) Sing)	US 20070166320A1	Yamazaki K Nakagawa E (2007)
Crude exopolysaccharides produced from *Phellinus baumii* mycelium having hypoglycemic activity and preparation method thereof	US 20060270626A1	Hwang HJ, Kim W, Yun JW, Choi JW (2006)
Health Promoting Dairy and Food Products Containing Mushroom Glucan Produced Through Fermentation of *Grifola frondosa*	US 20080171104	Zhu Y, Sonnenberg ASM, Van Loo EN (2008)
Glycoprotein with antidiabetic, antihypertensive, antiobesity and antihyperlipidemic effects from *Grifola frondosa*, and a method for preparing same	US 7214778	Zhuang C, Kawagishi H, Preuss HG, (2007)
Method for processing chewing gum containing extracts of (*Grifola frondosa, Auricularia auricular*) traditional Chinese medicines for preventing and treating diabetes	CN 2010-10587474	Zheng, Gaoyu (2010)
Mushroom extracts from *Agaricus, Hericium erinaceum*, and *Hypsizigus marmoreus* as insulin secretion stimulators and health foods for prevention and therapy of diabetes mellitus	JP 2012077004A	Takeshi I, Hiroshi H, Satoshi I, Aya K (2012)

prevented or delayed by lifestyle intervention (Monnier et al. 2004). Many studies have been published on the efficacy of new preventive treatments for diabetes or its complications; however, there is still little information on its applicability.

Medicinal mushrooms present an exciting opportunity for the development of new types of therapeutics and have been valued for their potential healing properties for centuries. Mushrooms have been valued as remedies for disease and as natural health foods for thousands of years, and they are incredibly popular foods in numerous countries throughout the world (Lindequist et al. 2005; Ferreira et al. 2010; Guillamón et al. 2010; Pereira et al. 2012; Liu et al. 2012).

Biologically active metabolites and components derived from medicinal mushrooms have been demonstrated to have controlling effects on diabetes through the regulation of several pathophysiological pathways related to the onset of diabetes (Kim et al. 2005; Ding et al. 2010; Huang et al. 2011; Li et al. 2011a, b; Xiao et al. 2011). Some of the anti-hyperglycemic mechanisms of medicinal mushrooms have

Table 3 Examples of marketed products of mushroom extracts with claimed blood glucose lowering activity (The co-authors of the present paper have not confirmed these claims)

Product name	Product function claim	Fungus/extract present	Web page
Cordyceps sinensis capsules	Control blood glucose levels	*Cordyceps sinensis*	http://curingherbs.com
Dr. Myco San products DIMEMYKON	Optimally regulate blood sugar levels and keep diabetes mellitus under control	Mixed of several mushroom species	www.mykosan.com Jakopovich 2011
Ganoderma herbal antidiabetes capsules	Enhance human body's overall immunity, accelerate recovery of diabetes Increase the efficacy of medicinal treatments	Extract from young shoots of organic *Ganoderma lucidum* and cell-wall broken *G. lucidum* spore powder Triterpenes ≥ 8 % Polysaccharide ≥ 10 %	Fujian Xianzhilou Biological Science & Technology Co., Ltd.
GlucoSANO-Diabetes Health Formula	Specifically formulated for diabetic health, the nutrients promotes increased insulin sensitivity and balanced blood sugar levels	*Agaricus blazei*, ErgoD2™ (Enriched *Pleurotus eryngii*), White Beech, Brown Beech (*Hypsizygus tessellates*), *Cordyceps militaris*, Vitamin D2 (Ergocaliciferol)	http://www.totalnutraceutical.com/glucosano-diabetes-health-formula
ORIVEDA® *Agaricus blazei* Murill extract	Anti-hyperglycemic, anti-hypercholestromic and anti-lipidperoxidative effects. Great potential in normalizing blood glucose levels and help to prevent diabetes	Concentrated hot water *Agaricus blazei* Murill (ABM) extract (60 % of polysaccharides)	http://www.chaga.us.oriveda.com/agaricus.php
ReishiMax capsules	Inhibits adipocyte differentiation, stimulates glucose uptake and activates AMPK	Polysaccharides extracted from *Ganoderma lucidum*	Thyagarajan-Sahu et al. 2011
SX-Fraction®	Maintain healthy blood sugar levels and insulin sensitivity	Glycoprotein from Maitake mushroom	http://www.mushroomwisdom.com

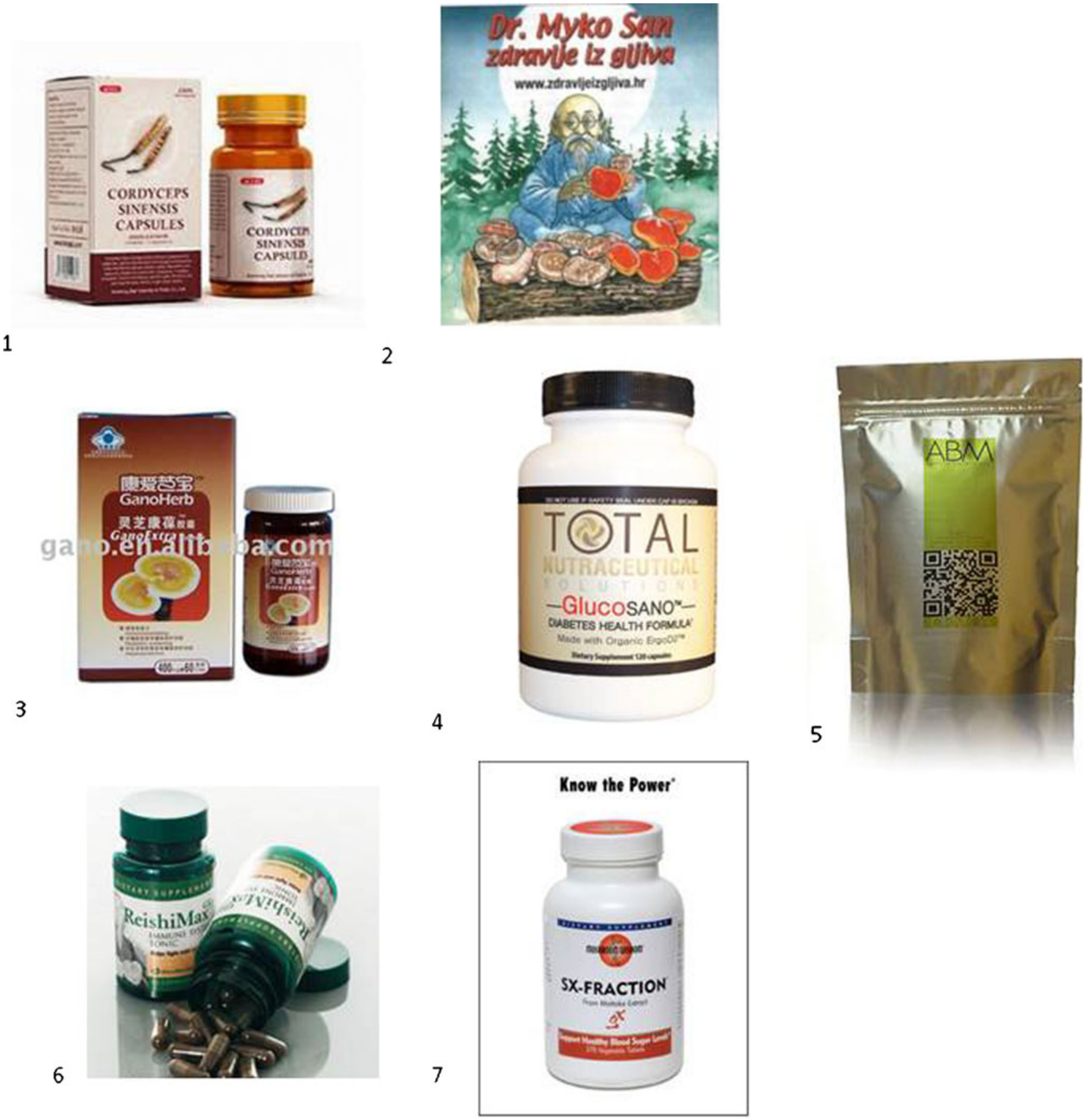

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Plate 1 Examples of products marketed with claimed anti-hyperglycemic properties containing mushrooms or their extracts* *1. Cordyceps sinensis capsules 2. Dr. Myco San products DIMEMYKON 3. Ganoderma herbal anti diabetes capsule 4. GlucoSANO-Diabetes Health Formula 5. ORIVEDA® Agaricus blazei Murill extract 6. ReishiMax capsules 7. SX-Fraction®.* * The co-authors of the present paper have not confirmed these claims

been investigated including β-cell improvement and insulin releasing activity, antioxidant defences, carbohydrate metabolism pathways, α-glucosidase and aldose reductase inhibitory activities, but more conclusive data is needed (Lo and Wasser 2011).

As there are many complicated signalling pathways and the involvement of a number of systems in regulating glucose homeostasis in the human body, the identification of the effect and activity of these metabolites is still uncertain. Specific recommendations and standards for the use of medicinal mushrooms in treating diabetes is lacking, which is mainly due to insufficient data concerning the efficacy of individual mushroom species and their products on diabetes. Currently, submerged culturing of basidiomycetes is preferred as the best technique for producing stable, safe mushroom biometabolites (Reshetnikov et al. 2001; Lee et al. 2004; Wasser and Akavia 2008; Kwon et al. 2009; Komura et al. 2010). Importantly, submerged culturing is less time consuming than mushroom cultivation and leads to the production of a consistent make up of mushroom metabolites in products as compared to fruiting bodies. The correct identification of metabolites with high quality specific constant compositions allows for the development of standard medicinal products with targeted activity (Abraham 2001; Shu et al. 2004; Zhong and Tang 2004; Lin and Liu 2006; Ferreira et al. 2010; Wasser 2011; Lo and Wasser 2011; De Silva et al. 2012). Most evidence regarding the beneficial effects of medicinal mushrooms has been obtained from *in vitro* and animal studies (Badole et al. 2006; Ding et al. 2010; Li et al. 2011a, b). Preliminary evidence from several medicinal mushrooms and their products suggest that further randomized controlled trials, especially for long term use, with large sample sizes may be warranted. Safety issues regarding the long term consumption of mushrooms, and inter-crossing or interactions with other drugs also needs further clarification. Therefore, future investigations directed towards these issues are necessary to rationalize the use of mushrooms and their products as potential drugs or nutriceuticals used in diabetes treatments.

There are still numerous countries and regions where mushroom diversity has not been well studied (Hyde 2001; Aly et al. 2010; Ge et al. 2010; Wu et al. 2010; Zhao et al. 2011; O'Hanlon and Harrington 2011, 2012; Sysouphanthong et al. 2010) and new taxa may contain biologically active metabolites with potential medicinal effects for controlling and preventing diabetes (Aly et al. 2010). Thus much research is needed on mushrooms, particularly in the tropics which is proving to support numerous undescribed mushroom species (Hawksworth 2001; Boonyanuphap and Hansawasdi 2010; Hyde et al. 2010; Zhang et al. 2010b; Welti and Courtecuisse 2010; Yang 2011; Zhao et al. 2010, 2011) and these need assaying for bioactive metabolites that can be used as possible remedies for diabetes treatments. Studies are needed to explore this un-tapped resource for the isolation and production of novel anti-diabetic compounds having medicinal and biochemical potential with therapeutic importance.

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