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Review

Medicinal mushrooms as potential therapeutic agents in the treatment of diabetes mellitus: a review with focusing on in vivo and clinical studies

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Abstract
Diabetes is a metabolic disorder that affects 1 in 11 people. More than 1.5 million deaths worldwide each year are related to the disease. Many medications are used for diabetes, but these medications only prevent the disease from progressing and its symptoms. Medicinal mushrooms have been used to treat diabetes since 2,000 years ago in the traditional medicine of different countries. This study reviews the research conducted on the anti-diabetic effect of several medicinal mushrooms reducing blood sugar level by various mechanisms. Mushrooms affect carbohydrate metabolism by inhibiting α-amylase and α-glycosidase enzymes, affect cellular pathways involved in fat metabolism, insulin secretion, and cellular apoptosis. The antioxidant activity of mushrooms prevents oxidative damage to pancreatic beta cells, reduce blood sugar, cholesterol, and triglycerides and normalize liver enzymes levels. The anti-diabetic activity of medicinal mushrooms has been proven by in vitro and in vivo experiments, as well as by clinical trials. They were suggested as dietary food supplement in the treatment of diabetes.

Keywords
Medicinal mushrooms, antidiabetic, antioxidant, in vitro, in vivo, clinical trials

1. Introduction

Diabetes is a set of metabolic disorders that cause high blood sugar levels. In this disease, pancreatic cells cannot produce enough insulin, or the body's cells do not respond to the insulin produced (Veiseh et al., 2015; Chaudhury et al., 2017; Morikawa et al., 2021). In type 1 diabetes, insulin production is inadequate, and in type 2 diabetes, the cells are resistant to insulin absorption, plus inadequate insulin production. Gestational diabetes is the third type of this disease that increases blood sugar levels in pregnant women without a history of diabetes (Patel et al., 2012; Friedman, 2016; Wang et al., 2016). According to the World Health Organization (WHO), about 422 million people worldwide have diabetes and 1.6 million deaths are directly attributed to diabetes each year (Prabu and Kumuthakalavalli, 2017; Jia et al., 2009). Due to hyperglycemic conditions, eight types of

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pathophysiological mechanisms occur singly or in combination with each other. These conditions include: 1) insulin secretion from pancreatic β-cells is reduced, 2) glucagon secretion from pancreatic α cells is increased, 3) glucose production increases in the liver, 4) neurotransmitters are inadequate in transmitting nerve messages and insulin resistance in the brain, 5) lipolysis increased, 6) glucose reabsorption increased in the kidneys 7) incretin hormones is reduced in the small intestine, 8) glucose uptake is reduced in peripheral tissues (Chaudhury et al., 2017; Sarmah and Roy, 2022).

Several drugs such as biguanides, sulfonylureas, meglitinides, thiazolidinediones, and α-glucosidase inhibitors are used to control diabetes with different mechanisms of action. Due to these drugs side effect, the focus has shifted from chemical to natural drugs derived from herbs and medicinal mushrooms (De Silva et al., 2012; Chaudhury et al., 2017; Baker and Sardari, 2021; Deveci et al., 2021). These products contain flavonoids, terpenoids, alkaloids, polyphenols, saponins, quinones, and glycosides with antidiabetic effects. One of the antihyperglycemic effects of these compounds is associated with the inhibition of α-amylase and α-glycosidase. Also, plant and medicinal mushrooms products improve pancreatic function and increase insulin secretion (Alam et al., 2018; Afsharnezhad et al., 2021).

The use of medicinal mushrooms to treat diseases has been common in traditional medicine in different countries. The upward trend of studies in the field of medicinal mushrooms shows their importance and application in the prevention and treatment of diseases (Fig. 1). Commercial products of many medicinal mushrooms are also used as supplements or medicines in different countries (De Silva et al., 2012). Medicinal mushrooms and their metabolites have antioxidant, antidiabetic, and immune-enhancement properties (Alvandi et al., 2020a, b; Huang et al., 2020; Yasrebi et al., 2020). The antidiabetic effect of fruiting bodies, mycelium, and mushrooms polysaccharides have been studied in vitro, in vivo and clinical trials. Various mechanisms have been proposed to explain the antidiabetic effect of medicinal mushrooms (Li et al., 2011). This review studied the hypoglycemic effect of the most known medicinal mushrooms focusing on in vitro, in vivo and clinical studies (Table 1).

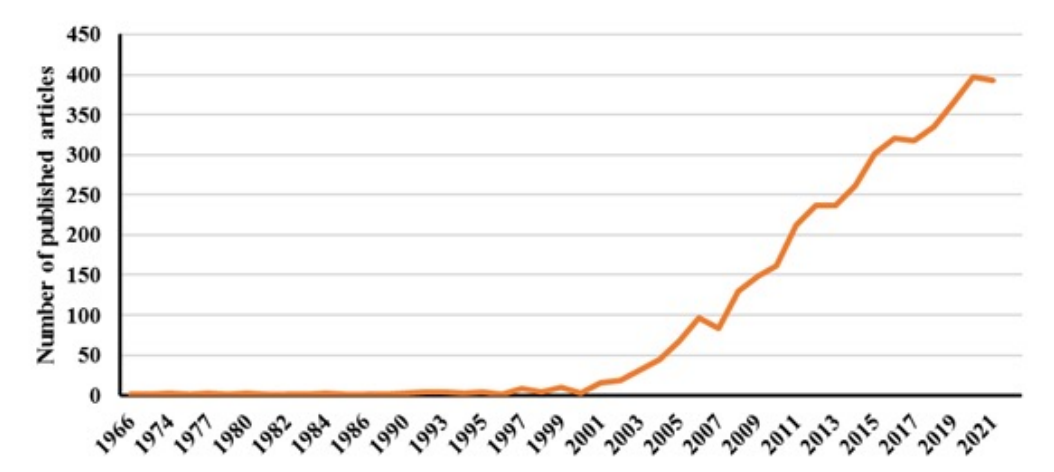

Fig. 1 - Documents published as medicinal mushrooms in Scopus for the last 50 years.

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Table 1 - Medicinal mushroom species with anti-diabetic effects.

Species	**Antidiabetic effects**	**Commercial products***	**References**
Agaricus bisporus (White button mushroom)	Decrease TBARS, cholesterol, TG, LDL, MDA; increase antioxidants; increase liver and body weight; repaire pancreatic tissue damage	FB	Abou Zaid et al. 2017; Jeong et al. 2010; Liu et al. 2013; Mircea et al. 2018
Agaricus subrufescens (*A. blazei*, *A. brasiliensis*)	Increase insulin resistance; increase adiponectin concentrations	FB & E	Kim et al. 2005
Agaricus sylvaticus (Sun mushroom)	Decrease TC, TG; increase AOA	FB	Fortes 2011
Auricularia auricula-judae (Jew's Ear, Jelly Ear mushroom)	Decrease TC, TG, and plasma glucose concentrations	FB & E	Kim et al. 2007
Coprinus comatus (Shaggy ink cap)	Decrease cholesterol, TC, TG, MDA, and plasma glucose concentrations; increase HDL concentration and antioxidants in liver and kidney	FB & E	Yu et al. 2009
Ganoderma lucidum (Lingzhi)	Decrease blood glucose level, lipid peroxidation, HbAlc; increase AOA; regulate liver enzymes; alter gut microbiota	E	De Silva et al. 2012; Ma et al. 2015; Rašeta et al. 2020
Grifola frondosa (Maitake)	Decrease blood glucose level, HbAlc; decrease biomarkers of nephropathy (BUN, SCr, UA, NAG); alter gut microbiota	FB & E	De Silva et al. 2012; Jiang et al. 2020a; Kou et al. 2019
Hericium erinaceus (Lion's Mane mushroom)	Decrease serum glucose level; increase serum insulin level and antioxidants	E	Liang et al. 2013
Inonotus obliquus (White rot fungus/ Chaga)	Decrease blood glucose level, cholesterol, TG, LDL, MDA; increase antioxidants activity; increase PI3K-p85, p-Akt (ser473), GLUT expression	E	Lu et al. 2010; Wang et al. 2017
Lentinus edodes (Shiitake)	Decrease blood glucose levels; increase glucose metabolism; decrease insulin resistance; modulation of the gut microbiome	FB & E	Afiati et al. 2019; Hata 2021; Yang et al. 2018
Phellinus spp.	Decrease blood glucose and TG levels; regulate lipid metabolism;	E	De Silva et al. 2012; Kim et al. 2010
Pleurotus spp. (Oyster mushrooms)	Decrease blood sugar; increase Catalase activity; repairs the pancreas, liver, and kidney tissues; inhibition of α-amylase and α-glucosidase activity	FB	Balaji et al. 2020; Omale et al. 2020; Prabu and Kumuthakalavalli 2017
Schizophyllum commune	Decrease blood glucose and MDA levels; increase the length of small intestine; restoration of renal parameters; improved liver enzymes levels	E	Ekowati et al. 2018; Muthuramalingam et al. 2019; Sharma et al. 2021
Tremella fuciformis (Snow fungus)	Decrease blood glucose; increase glucose tolerance	E	De Silva et al. 2012
Tremella mesenterica (Yellow brain mushroom)	Decrease blood glucose, TC, TG; increase glucose tolerance	Unknown	De Silva et al. 2012
Trametes versicolor	Decrease blood glucose, TC, TG, and LDL levels; decrease destruction of liver tissue; increase HDL concentration; increase bone strength	E	Alvandi et al. 2020a; Chen et al. 2015a; Shokrzadeh et al. 2017

*FB = Fruiting bodies; E = Extracts

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2. *Agaricus bisporus* (J.E. Lange)

Agaricus bisporus (white button mushroom) with high amounts of dietary fiber, vitamins C, D, B_{12} and folate have the highest production globally (Atila et al., 2021). In most studies, the antidiabetic properties of *A. bisporus* are associated with its antioxidant activity (AOA). The function of antioxidant enzymes in type 2 diabetes is significantly reduced. Also, reactive oxygen species (ROSs) increase as the disease progresses (Holy and Ngoye, 2016). The polysaccharides of this fungus with high phenolic and flavonoid content significantly increased the activity of antioxidant enzymes in mice's serum, liver, and heart (Liu et al., 2013; Srivastava et al., 2017). Furthermore, intracellular ROS production decreased with *A. bisporus* treatment (Vishvakarma and Mishra, 2020). *Agarics bisporus* flavonoids prevented the oxidation of pancreatic β-cells DNA by reducing ROS production. In this way it regulated pancreatic β-cells functions and improved insulin secretion. *Agaricus bisporus* polysaccharide is a lectin-like molecule, which can stimulate insulin secretion by interaction with pancreatic β-cells. This polysaccharide also appears to stimulate the uptake of Ca^{2+} in pancreatic β-cells, which ultimately increases insulin production by affecting cell pathways (Abou Zaid et al., 2017; Ekowati et al., 2018). The AOA of this fungus has also been studied clinically. Treatment of 37 pre-diabetics adults with 100 g *A. bisporus* significantly reduced oxidative stress factors in serum after 16 weeks (Calvo et al., 2016). *Agaricus bisporus* also affects blood factors by regulationg carbohydrates and lipids metabolism. *Agaricus bisporus* stimulated glucose uptake by fat cells similar to the rosiglitazone and caused insulin-sensitizing in the presence of insulin (Mayasa et al., 2016; Vishvakarma and Mishra, 2020). Treatment of diabetic rats with 200 mg kg^{-1} of *A. bisporus* lowered blood glucose, cholesterol, and triglyceride (TG) levels after 21 days. High cholesterol in diabetics causes damage to pancreatic β-cells; by reducing cholesterol, this fungus prevented this damage and improved the function of pancreatic β-cells (De Silva et al., 2012; Abou Zaid et al., 2017). Treatment with 500 mg kg^{-1} of *A. bisporus* extract also reduced glucose and fructose absorption from the intestine in diabetic rats by inhibiting glucose transporter 2 (GLUT2), a glucose transporter in the liver, pancreas, and intestine (Abou Zaid et al., 2017; Ekowati et al., 2018). Figure 2 shows the mechanism of action of mushrooms polysaccharide on diabetes.

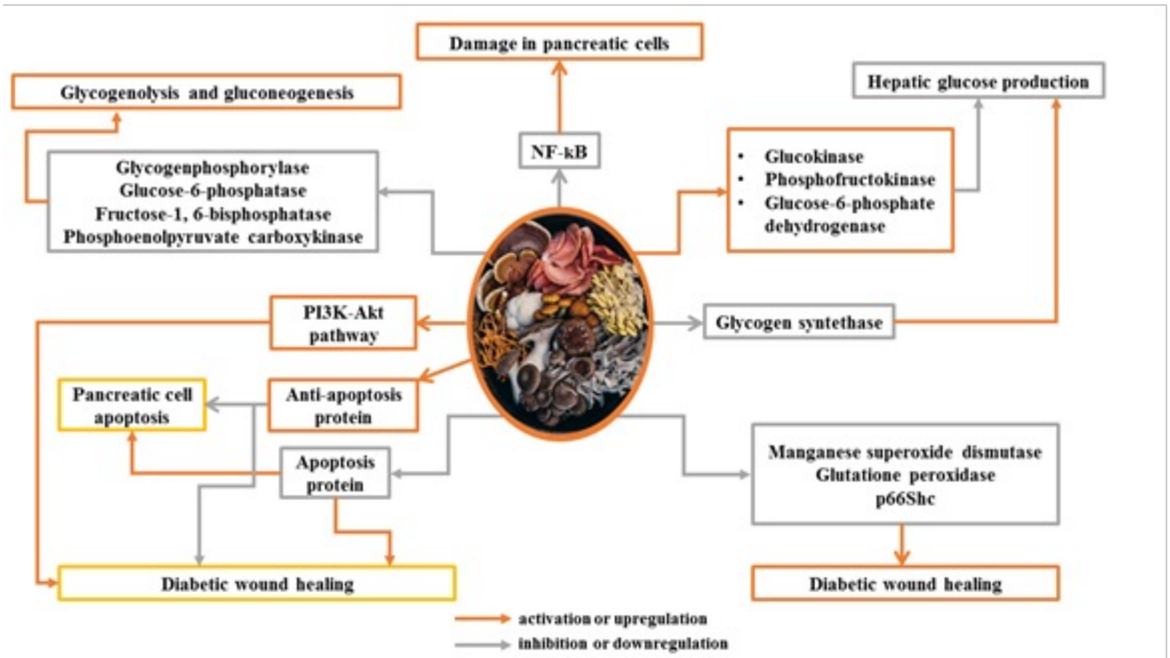

Fig. 2 - Possible cellular mechanisms of antidiabetic effect of medicinal mushrooms.

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3. *Ganoderma lucidum* (Fr.) Karst.

Ganoderma lucidum, known as "Lingzhi" in China and "Reishi" in Japan, is the most famous fungus in traditional East Asian medicine. The antidiabetic properties of *G. lucidum* have been investigated in many studies. This effect is associate with β-glucan, α-β glucan, protein and glucuronic acid compounds in the fruit body, mycelium and polysaccharides of *G. lucidum* (Bach et al., 2018; Kalantari-Dehaghi et al., 2019; Heydarian et al., 2021; Ahmad et al., 2022). *Ganoderma lucidum* extract inhibit the activity of the α-glucosidase enzyme, which is involve in starch and disaccharides hydrolyzes. Cho et al. (2021) found that the extraction conditions could affect this activity. Under optimal conditions (65-70 °C for time 2.8-3 h) the α-glucosidase inhibitory activity was 39% (Cho et al., 2021). *Ganoderma lucidum* triterpenoids are also α-glucosidase inhibitors (Ma et al., 2015).

Consumption of *G. lucidum* polysaccharides reduced blood glucose in different animal models such as Wistar rats, SD rats, pregnant rats, and Kunming species mouse (Zeng et al., 2018). Consumption up to 5,000 mg kg^{-1} of *G. lucidum* polysaccharides was non-toxic in mice (Li et al., 2011). *Ganoderma lucidum* polysaccharides increased plasma insulin levels and prevented high blood sugar by inhibiting glycogen synthetase activity and reducing hepatic glucose production (Xiao et al., 2012; Singh et al., 2016; Bach et al., 2018). In a study, diabetic mice were treated with *G. lucidum* polysaccharides (400 mg kg^{-1}) for 8 weeks. Fasting blood sugar and glycosylated hemoglobin (HbAlc) concentrations in the groups treated with polysaccharides were significantly lower than the control group. Also, these polysaccharides lowered fasting blood glucose concentration in mice more than metformin (Pan et al., 2021). *Ganoderma lucidum* polysaccharides significantly reduced the concentrations of alanine aminotransferase (ALT), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr) and blood urea nitrogen (BUN) in the serum of diabetic mice compared to the control group. It also increased the concentration of high-density lipoprotein cholesterol (HDL-C) in the serum of diabetic mice. Uric acid (UA), uric creatinine (Ucr) and urine microalbumin (U-LAB) levels were also significantly lower in the urine of polysaccharide-treated mice (Pan et al., 2021). In a clinical study, fasting blood glucose reduced significantly in type 2 diabetes patients treated with *G. lucidum* polysaccharides after 12 weeks (three times daily, 1,800 mg) (Gao et al., 2004).

Ganoderma lucidum also alters the cellular pathways involved in diabetes. Lee et al. (2020) investigated the effect of *G. lucidum* extract in different doses for 12 weeks on C57BL/6 mice. Treatment with *G. lucidum* improved glucose uptake, insulin receptor (IR), IR substrate 1 (IRS1) and AKT serine/threonine kinase 1 (AKT1) phosphorylation. As a result, it increased the level of glucose transporter types 4 and 1 (GLUT4 and GLUT1) and also activated AKT1 at phosphorylation sites T308 and S473. *Ganoderma lucidum* supplementation attenuated the expression of lipogenesis-related genes such as FAS, SCD1 and SREBP1c (Lee et al., 2020) and stimulated PI 3-kinase and AMPK and increased glucose uptake into L6 skeletal muscle cells (Jung et al., 2006). *Ganoderma lucidum* polysaccharides increased insulin secretion by facilitating Ca^{2+} influx in pancreatic β-cells (Zhang and Lin, 2004). *Ganoderna lucidum* low molecular weight polysaccharides regulated Bcl-2 (anti-apoptotic protein) expression and reduced apoptosis in pancreatic β-cells (Ma et al., 2015). They also prevented the pancreatic islets from damage by increasing superoxide dismutase and glutathione peroxidase activities in the plasma and liver of diabetic rats (Jia et al., 2009). The polysaccharides of this fungus reduced NOX expression and ROS production in vascular endothelial cells (Zeng et al., 2018).

As mentioned, in addition to polysaccharides, other compounds of this fungus also have antidiabetic activity. Liang et al. (2020) found that the *G. lucidum* proteoglycan (200 mg mL^{-1}) reduced apoptosis in rat islet β cells (INS-1 cells) and intracellular ROS accumulation and NO release. *Ganoderma lucidum* proteoglycan ultimately improved insulin secretion by deactivating NF-κB, JNK, and p38 MAPK signaling pathways in streptozotocin (STZ)-induced INS-1 cells (Liang et al.,

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2020). In another study, the effect of 20 mg kg^{-1} ganoderic acid on streptozotocin-induced diabetic rats was evaluated for two weeks. Treatment with ganoderic acid reduced blood glucose levels in a dose-dependent manner. It also improved body weight and serum insulin levels. Other results included a decrease of HbAlc levels, free fatty acids in adipose tissue, aspartate transaminase (AST) and ALT (alanine transaminase) levels. Ganoderic acid also increased the size of β-cells, repaired tissue and increased the volume of the pancreas (Ren, 2019).

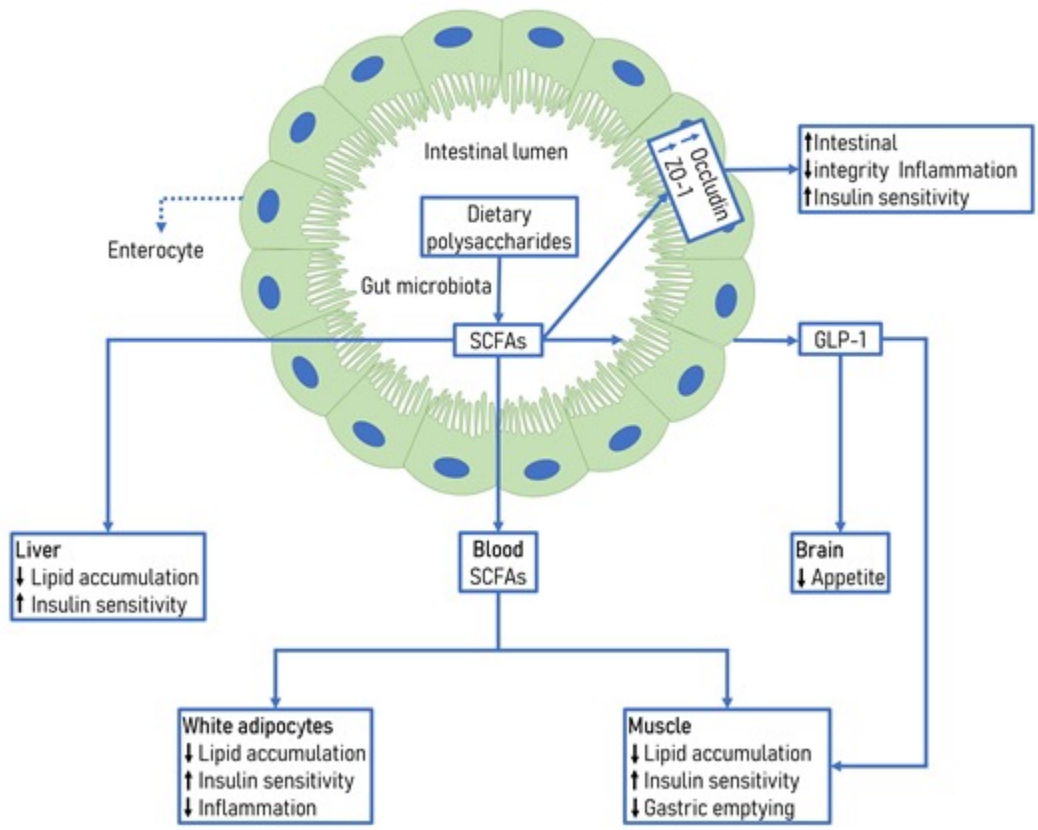

Fig. 3 - Medicinal mushrooms polysaccharides have antidiabetic effect via the gut microbiota. The duodenal environment is not suitable for the digestion of dietary polysaccharides. Dietary polysaccharides are digested into short-chain fatty acid (SCFAs) by microbiota after entering the large intestine. SCFAs stimulate intestinal cells to secrete glucagon-like peptide 1 (GLP-1). SCFAs and GLP-1 have direct and indirect anti-diabetic effects after entering the bloodstream. SCFAs and GLP-1 prevent lipid accumulation. Fungal polysaccharides induce occludin and zonula occludens protein 1 (ZO-1) expression in intestinal cells, helping to maintain intestinal integrity and preventing the secretion of bacterial endotoxins into the bloodstream. Modified with permission from (Martel et al., 2017).

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One of the most important mechanisms of action of fungal polysaccharides on diabetes is the effect on intestinal bacteria. Studies show that disturbances in these bacteria cause diseases such as intestinal syndrome, inflammatory bowel disease, obesity, depression, diabetes, anxiety and neurodevelopmental disorders like autism and Parkinson's disease (Marvasti et al., 2020; Mehrabadi and Sadr, 2020; Mirmazloum et al., 2021; Zhang et al., 2022). The high molecular weight (> 300 kDa) polysaccharides of *G. lucidum* are not digested in the stomach or small intestine. Digestion of these polysaccharides by bacteria in the large intestine short-chain fatty acids (SCFAs) produced which stimulate the secretion of glucagon-like peptide-1 by intestinal cells, regulated liver function and induced β-cell proliferation (Martel et al., 2017) (Fig. 3). Consumption of *G. lucidum* changes the gut bacterial population over time, reduce blood sugar level in diabetic rats by reducing harmful bacteria such as *Aerococcus* spp., *Ruminococcus* spp., *Corynebacterium* spp. and *Proteus* spp. (Chen et al., 2020), increase the levels of *Blautia* spp., *Halobacterium* spp., *Parabacteroides* spp., and *Bacteroides* spp. and improve the metabolism of carbohydrates and fats in diabetic rats (Martel et al., 2017; Chen et al., 2020).

4. *Grifola frondosa* (Dicks.) Gray

Grifola frondosa or Maitake mushroom, is one of China's most popular edible mushrooms (Ma et al., 2014; Chen et al., 2019). This polypore possesses antioxidant and anti-hyperlipidemic properties (Jiang et al., 2020a) and contains oleic acid, which inhibits α-glucosidase activity and prolongs carbohydrates' digestion in the intestine (Su et al., 2013). *Grifola frondosa* polysaccharides have antidiabetic effects by acting on cellular pathways. These polysaccharides stimulated intracellular glycogen synthesis via the Akt/GSK-3 pathway (Wu et al., 2020; Xiao et al., 2021). Polysaccharides from the fruiting bodies increased glucose uptake in a hepatocellular carcinoma cell line (HepG2) by improving mRNA and protein expression of IRS1 and phosphatidylinositol-3-kinase (P13K), which are involved in the insulin signaling pathways. These polysaccharides also affect the expression levels of GLUT-4, IRS1, P13K and c-Jun N-terminal Kinase (JNK1). IRS1 activates P13K by binding to it, which is a key kinase in glucose uptake and insulin-induced glucose transport. P13K also inhibits JNK activity and affects glucose metabolism. GLUT-4 also facilitates the penetration of glucose into muscle cells (Chen et al., 2018).

Consumption of 900 mg kg^{-1} *G. frondosa* polysaccharides decreased TG and LDL-C levels and increased hepatic glycogen levels ($p < 0.05$) (Guo et al., 2020). After four weeks, treatment of diabetic mice with 150 mg kg^{-1} body weight polysaccharides significantly reduced hemoglobin A1c (HbA1c). Jiang et al. (2020) investigated the inhibitory effect of *G. frondosa* polysaccharides on the progression of renal fibrosis in rats with diabetic nephropathy. Consumption of 500 mg kg^{-1} polysaccharides of this fungus caused a significant reduction in blood sugar after 60 days ($p < 0.05$), and helped to recover the weight of diabetic rats. *Grifola frondosa* polysaccharides improved glomerular filtration capacity and glomerular blood flow by reducing the biomarkers of nephropathy such as BUN, SCr, UA, and urinary N-acetyl-beta-D glucosaminidase (NAG). These polysaccharides improved nephropathy by regulating IL-2, interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), interferon α (IFN-α) levels. At the same time, they repaired the epithelial cells in the proximal convoluted tubule and kidney tissue (Jiang et al., 2020a; Kou et al., 2019). Consumption of *G. frondosa* polysaccharides with a molecular weight fewer than 5,000 Da reduced fasting serum glucose, liver enzymes AST and ALT, and total serum cholesterol. Lipid accumulation in the liver, which is caused by diabetes, was also reduced (Xiao et al., 2021). Studies have shown that *G. frondosa* α-glucan has an antidiabetic effect in mice by improving immune function and preventing pancreatic β-cells damage (Friedman, 2016). Chromium (III) is one of the important trace minerals that is useful for improving type 2 diabetes. This element is one of the components of glucose tolerance factor and plays an important role in

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regulating blood glucose levels and insulin resistance. *Grifola frondosa* polysaccharides contain single electron pairs such as C=O, C-O-C, C-O-H, which can be suitable for ligand-binding with Cr (III). Oral administration of 900 mg kg^{-1} day of *G. frondosa* polysaccharide-Cr (III) complex returned liver glycogen levels to normal in diabetic Kunming mice. It also lowered fasting blood sugar and lipid accumulation in these mice (Guo et al., 2019).

Grifola frondosa polysaccharides regulated blood glucose by altering the gut microflora and significantly increasing the population of Bacteroidetes (Chen et al., 2019) and increased *Firmicutes/Bacteroidetes* in diabetic rats. The *Firmicutes/Bacteroidetes* ratio is a biomarker in diabetes that is negatively correlated with plasma glucose (Magne et al., 2020; Xiao et al., 2021). The polysaccharides of this fungus caused a significant increase in *Porphyromonas gingivalis*, which affected glycemic levels in diabetes (Chen et al., 2019). *Grifola frondosa* also increased *Alistipes* spp. population, which play an important role in the glucose and fat metabolism (Guo et al., 2020). *Grifola frondosa* polysaccharides also increased the population of *Turicibacter* spp. in diabetic rats. These bacteria improved insulin sensitivity by increasing intestinal butyric acid (Zhong et al., 2015; Xiao et al., 2021).

5. *Lentinus edodes* (Berk.) Singer

One of the most important mushrooms in traditional Asian medicine is *L. edodes* (Shiitake), widely used today due to its good taste and hypoglycemic effect (Sheng et al., 2021; Hatamian Zarmi et al., 2022). The *L. edodes* extract inhibited glucose transfer up to 37.2% in Caco-2 cells and reduced adipose tissue accumulation in the intestine (Nisar et al., 2017; Hata, 2021). *Lentinus edodes* mycelium extract with AOA reduced the degree of INS-1 cells damage and Bax expression was reduced in cells treated with this fungus. *Lentinus edodes* also affected the expression of cleaved caspase 3, cleaved caspase 1 and the NF-κB signaling pathway and prevented cell damage (Cao et al., 2019). The polysacchride lentinan (400-800 kDa) has AOA and reduced apoptosis of pancreatic β-cells (Jiang et al., 2020b).

Consumption of *L. edodes* polysaccharides (50 mg kg^{-1} body weight) could significantly ($p < 0.05$) reduced blood glucose, TG and cholesterol levels in streptozotocin-induced diabetic rats after 7 days (Kim et al., 2001). *Lentinus edodes* is a good source of β-glucans, which lowers blood glucose levels by 55.87% in diabetic mice. β-Glucans also reduced cholesterol absorption in the stomach and intestines (Afiati et al., 2019). Due to effect of the *L. edodes* polysaccharides on fat and carbohydrate metabolism, its consumption alters the intestinal bacterial population (Martel et al., 2017).

Gestational diabetes is a glucose intolerance and insulin resistance seen during pregnancy. There is currently no specific treatment that affects the mother and fetus, increasing the risk of preterm birth, birth defects, miscarriage, and the risk of developing type 2 diabetes in the future. Laurino et al. (2019) examined the use of Shiitake (100 mg kg^{-1}) in two forms of gestational diabetic rats: 1) exposure to *L. edodes* from days 1 to 19 of pregnancy (before fetal implantation) and 2) exposure to *L. edodes* from days 9 to 19 of pregnancy (after fetus implantation). The fungus did not reduce hyperglycemia in the mother, but improved maternal glucose tolerance in amniotic fluid and placenta and increased insulin levels. It also lowered cholesterol and TG levels and reduced liver damage (Laurino et al., 2019).

6. Oyster mushrooms (*Pleurotus* spp.)

Pleurotus spp. are also known as oyster mushrooms, which are widely used as food and prebiotics due to their high fiber contant (Elkhateeb and Daba, 2021). These mushrooms are beneficial for human health due to its antioxidant, anti-inflammatory, anti-tumor, and antidiabetic activities. One thousand μg per mL fruiting body of oyster mushroom reduced glucose uptake by inhibiting α-amylase and α-glucosidase enzymes by 94.93% and 84.90%, respectively. *Pleurotus* spp. also significantly reduced cholesterol, TG, and LDL levels in diabetic rats (Friedman, 2016; Prabu and Kumuthakalavalli, 2017).

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More than 200 species of this genus have been identified that have antidiabetic effects by different mechanisms. One of the most important species is *Pleurotus ostreatus* (Jacq.) P. Kumm. Agunloye and Oboh (2021) studied the diet of *P. ostreatus* on the blood sugar of diabetic rats. After 14 days, fasting blood sugar decreased in diabetic rats. Also, the activity of superoxide dismutase and catalase in rats treated with this fungus was significantly increased. Studies show that in diabetic rats, the activity of the angiotensin-1 converting enzyme (ACE) and arginase increases, which is associated with high blood pressure. The results showed that treatment with *P. ostreatus* reduced their activity (Agunloye and Oboh, 2021). *Pleurotus ostreatus* extract at 5.0 mg mL^{-1} inhibited 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals by more than 80%. Also, 100 mg mL^{-1} of extract inhibited α-amylase activity by more than 70% (Shamtsyan and Pogačnik, 2020). In one study, diabetic rats were treated with bread containing 5%, 10% and 20% of *P. ostreatus*. Fasting blood sugar in the group treated with bread containing 20% *P. ostreatus* was significantly reduced to 91 mg dl^{-1}. Total cholesterol, HDL, LDL and TG levels decreased after 28 days and rats lost weight from 149 to 122 g. This significant weight loss in diabetic and obese rats indicated that this mushroom bread would be effective in managing metabolic syndrome, as well as possibly cardiovascular disease (Okobiebi and Okhuoya, 2019).

The antidiabetic effect of oyster mushrooms and other mushrooms or herbs, has been investigated. Nnadiukwu et al. investigated the effect of the combination of ethanolic extract of *Moringa oleifera* Lam. and *P. ostreatus* on the liver enzymes of alloxan-induced diabetic rats. The oral LD_{50} value of *M. oleifera* and *P. ostreatus* was 5,000 mg kg^{-1} body weight. Increased liver enzyme activity in diabetic rats is a sign of liver tissue damage. The combination of *P. ostreatus* and *M. oleifera* (3:2 w/w) significantly ($p < 0.05$) reduced ALT, AST, alkaline phosphatase (ALP), total bilirubin and uric acid in diabetic rats (Nnadiukwu et al., 2017). Supplements of *A. bisponus* and *P. ostreatus* also reduced blood sugar in diabetic rats after 30 days. The effect of these mushrooms was associated with the presence of four proteins (profilin-like protein, glyceraldehyde-3-phosphate dehydrogenase-like protein, trehalose phosphorylase-like protein and catalase-like protein), which affected the metabolism of carbohydrates. This fungal supplement also modified the levels of AST, ALT and ALP (Nweze et al., 2020). In clinical studies, a mixture of *P. ostreatus* and *Pleurotus cystidiosus* (50 mg kg^{-1}) significantly reduced fasting blood glucose levels (Jayasuriya et al., 2015). Table 2 summarizes the clinical studies on the antidiabetic effect of mushrooms and Figure 4 shows this effect on human organs.

Table 2. Clinical trials of medicinal mushrooms for antidiabetic activity.

Species	Clinical trial	Results	References
Agaricus bisporus (fruiting body)	37 pre-diabetics (100 g, 16 daily weeks)	Increase antioxidant enzymes and anti-inflammatory hormones; decrease oxidative stress factors, carboxymethyl lysine, and methylglyoxal in serum	Calvo et al. 2016
Agaricus blazei (fruiting body)	536 diabetic patients (1,500 mg daily, 12 weeks)	Decrease HOMA IR index; increase plasma adiponectin concentration and insulin resistance	Hsu et al. 2007
Ganoderma lucidum (polysaccharides)	71 diabetic patients (1,800 mg three times daily, 12 weeks)	Decrease HbA1c and fasting blood glucose	Gao et al. 2004
Agaricus sylvaticus	56 patients with colorectal cancer (30 mg kg^{-1}, 6 months)	Decrease fasting blood glucose, TG, cholesterol	Fortes et al. 2008
Pleurotus ostreatus & *P. cystidiosus* (fruiting body)	28 diabetic patients (50 mg kg^{-1} body weight)	Decrease blood sugar levels; increase glucokinase and insulin secretion	Jayasuriya et al. 2015

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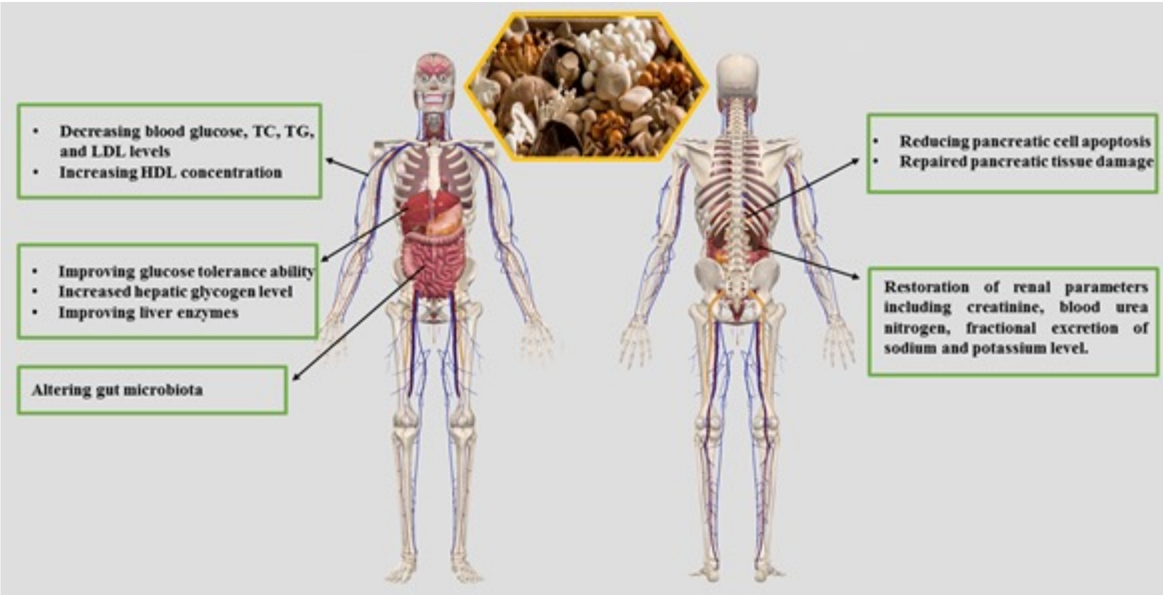

Fig. 4 - Possible effects of medicinal mushrooms on the function of various human organs that improve diabetes.

The antidiabetic effects of other species of this genus have also been studied. Oral administration of *Pleurotus tuber-regium* (Fr.) Singer polysaccharides (20 mg kg^{-1} for 8 weeks) had hypoglycemic effects by increasing peroxisome proliferator-activated receptor (PPAR)-α mRNA expression in the diabetic rats liver. These polysaccharides increased lipid metabolism; as a result, they reduced TG and prevented obesity in diabetic rats (Friedman, 2016). Consumption of 5,000 mg kg^{-1} *Pleurotus pulmonarius* sensu auct. extract with acarbose had a significant anti-hyperglycemic effect (Badole and Bodhankar, 2007). *Pleurotus pulmonarius* significantly repaired the pancreas, liver and kidney tissues in diabetic Wistar albino rats (Balaji et al., 2020). *Pleurotus nebrodensis* (*Pleurotus fossulatus* (Cooke) Sacc.) extract regulated liver enzymes function and reduced blood glucose levels by more than 50% in diabetic albino Wistar rats (Dubey et al., 2020). Consumption of *Pleurotus eryngii* (DC.) Quĕl extract (200 mg kg^{-1}) significantly reduced blood glucose and HbA1c levels and increased insulin secretion in alloxan-induced hyperglycemic mice after 5 weeks. Studies showed *P. eryngii* and *Pleurotus citrinopileatus* Singer also recover damaged β-cells with their antioxidant properties (Hu et al., 2006; Li et al., 2014). *Pleurotus cystidiosus* increased insulin expression and decreased circulating glucose levels (Chen et al., 2015b). Studies showed that GLUT 4 expression was increased in L6 cells treated with oyster mushrooms (Khursheed et al., 2020).

7. Other agaricoid and polyporoid medicinal mushrooms

Agrocybe spp. mushrooms has a wide range of growth in Europe, Asia, and North America (Yong et al., 2018). The antidiabetic properties of *Agrocybe chaxingu* N.L. Huang in diabetic mice have been studied (Lee et al., 2010). The results showed that the polysaccharide isolated from this mushroom significantly prevents STZ damage to pancreatic β-cells (Lee et al., 2010). Antidiabetic and antioxidant properties and α-glycosidase inhibitory effect were found in *Agrocybe aegerita* (V.Brig.) Singer (Wu and Xu, 2015).

Agaricus blazei Murrill can lower blood glucose by containing isoflavonoids such as genistein, genistin, and daidzein (De Silva et al., 2012). Ethyl extract of *A. blazei* had significant glucose-lowering activity on HepG2 cells, comparable to metformin (Wei et al., 2020). The mixture of *A. blazei* and *G. lucidum* could reduce blood sugar and HbA1c concentration in diabetic rats after 14

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days (Vitak et al., 2015).

Auricularia auricula-judae (L.) Undrew mushroom has been used in traditional Chinese medicine (TCM) for over 1,000 years. Recent clinical studies have been conducted on the therapeutic effects of this mushroom and its polysaccharides. Treating diabetic Wistar rats with the polysaccharides of this mushroom for four weeks improved their lipid metabolism and weight (Lu et al., 2018).

Coprinus comatus (O.F. Müll.) Pers., the shaggy ink cap, regulates the immune system, lowers blood sugar and lipids, and has anti-tumor and antibacterial activities. *C. comatus* extracts inhibit α-amylase and α-glucosidase activity (Ding et al., 2010; Stojkovic et al., 2019). Yu et al. investigated the antidiabetic effect of selenium-containing polysaccharides of this fungus. In addition to lowering blood glucose, Se-polysaccharides significantly reduce malondialdehyde (MDA) levels and increase the activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) in the liver and kidneys of all diabetic mice (Yu et al., 2009).

Fomes fomentarius (L.) Fr. has been used for thousands of years to treat gastrointestinal disorders, liver cirrhosis, inflammation and various cancers (Alvandi et al., 2020b). Keshavarz-Rezaei et al. (2022) observed that polysaccharide and selenium polysaccharide of *F. fomentarius* improve insulin secretion and decrease HbA1c level in diabetic rats .

Hericium erinaceus (Bull.) Pres. has antidiabetic properties in diabetic rats. After 28 days of treatment (100 and 200 mg kg^{-1} BW), *H. erinaceus* extraction significantly increases insulin levels and enzyme activity (AT, SOD, GSH-Px, and GSH level) (Liang et al., 2013). *Hericium erinaceus* polysaccharides reduce fasting blood glucose, increase glucose tolerance, improve lipid metabolism and inhibit lipid peroxidation. They also activate PI3K/Akt signaling pathway (Cai et al., 2020).

Inonotus obliquus (Fr.) Pilăt has been used to treat heart disease and diabetes in Europe and Russia since the 16^{th} century (Cui et al., 2005). This fungus extract inhibited the activity of α-glucosidase (IC_{50} = 220.31 μg mL^{-1}) (Stojkovic et al., 2019). Treatment of alloxan-induced diabetic mice with ethyl acetate extract of *I. obliquus* significantly ($p < 0.05$) reduced their water and food intake. *Inonotus obliquus* lowered blood sugar, TG, and MDA and increased HDL and hepatic glycogen levels (Lu et al., 2010).

Phellinus linteus (Berkeley & M. A. Curtis) Teng has been used to treat diabetes and obesity in traditional Japanese, Chinese, and Korean medicine (Khursheed et al., 2020). The *P. linteus* polysaccharides also suppress inflammatory cytokines (such as TNF-α) production (Kim et al., 2010). Oral administration of *P. linteus* (100 mg kg^{-1} body weight per day) reduces blood glucose by up to 35% in diabetic mice ($p < 0.05$) (Friedman, 2016).

Schizophyllum commune Fr. is an edible fungus used in TCM to treat inflammation, obesity, and weakness (Kamalebo et al., 2018; Sharma et al., 2021). *Schizophyllum commune* inhibit the α-glucosidase activity more than 90% and decrease blood glucose levels (Sharma et al., 2021). The hot water, methanol, and ethanol extract of *S. commune* had DPPH free radical scavenging properties higher than that of ascorbic acid. *Schizophyllum commune* β-glucan also lowers cholesterol and controls diabetes mellitus (Chandrawanshi et al., 2017; Muthuramalingam et al., 2019).

Tremella spp. are also known as jelly fungi with more than 100 known species. *Tremella fuciformis* Berk. and *Tremella aurantialba* (*Naematelia aurantialba* Bandoni & M. Zang) are cultivated commercially for food and medicine (Du et al., 2010). Low molecular weight *T. aurantialba* polysaccharides improved glucose metabolism and increased insulin secretion in type 1 and 2 diabetes. This fungus (50 mg kg^{-1}) decreased plasma glucose and TG in genetic type 2 diabetic KK-A^y mice after 10 weeks (Lo and Wasser, 2011). Zhang et al. (2009), showed that *T. aurantialba* mushroom extract contains saponins. These compounds can reduce cholesterol and triglyceride in alloxan-induced diabetic rats (Zhang et al., 2009).

Trametes versicolor (L.) Lloyd. is one of the most important medicinal fungi whose

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polysaccharides are commercially produced. Krestin is the most important secondary metabolite of this fungus, used as a supplement in many countries (Price et al., 2010). Alvandi et al. (2020) observed that exopolysaccharides of *T. versicolor* reduced blood sugar, TG, and cholesterol in diabetic rats by 50%, 89% and 20%, respectively (Alvandi et al., 2020a). Methanolic extract of this fungus (1,500 mg kg^{-1}) reduced serum blood glucose, TG, and ALT enzyme in male mice. Histopathological studies showed *T. versicolor* extract improved liver tissue damage (Shokrzadeh et al., 2017).

8. Conclusions

The prevalence of diabetes is increasing dramatically worldwide and is the fifth leading cause of death in the world. Complications of this disease include retinopathy, nephropathy, neuropathy, and cardiovascular diseases (De Silva et al., 2012; Alvandi et al., 2020a). Medicinal mushrooms have long been used in traditional medicine in Asian countries to treat diabetes. Various studies have shown the effects of hypoglycemia, antioxidants and strengthening the immune system of fungi in vitro, in vivo and clinically. These fungi protect and repair the tissue of the liver and pancreas. This effect appears to be by lowering cholesterol, triglycerides, improving fat metabolism, improving enzyme function, and reducing oxidative stress. Fungi also have anti-inflammatory effects by regulating the production of cytokine (Yun et al., 2003; Friedman, 2016; Martel et al., 2017; Jiang et al., 2020b).

Studies show that several factors can affect the production and properties of fungal metabolites and their molecular weight (Alvandi et al., 2020c). Culture medium conditions (e.g. temperature, pH and aeration), chemical compounds (e.g. Selenium and Zinc) or the use of elicitors can affect the production and properties of these polysaccharides (Nojoki et al., 2016; Nojoki et al., 2017; Kalantari-Dehaghi et al., 2019; Alvandi et al., 2021). Low molecular weight polysaccharides often have antiproliferative and antioxidant properties, while metabolites with a molecular weight of more than 100,000 Da stimulate macrophages to strengthen immune function. Therefore, the use of purification methods in polysaccharides is of particular importance (Wasser, 2011).

In recent years, the use of drug delivery nanosystems for loading fungal polysaccharides has received much attention from researchers (Othman et al., 2021). In addition to solving the solubility problem, these nanocarriers also allow polysaccharides to be targeted. Thus, low molecular weight polysaccharides can purposefully target the pancreas and repair damaged islets of Langerhans (Xu et al., 2011; Hu and Jiang, 2012). Although studies in this area are still ongoing, it seems that the combination of fungal polysaccharides and nanotechnology can make a huge difference in the treatment of diabetes.

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Conflict of Interest

The authors report no conflicts of interest.

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