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Mushroom extracts in the management of Diabetes: A systematic review with special reference to Oyster Mushrooms

Review Article

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Abstract

A multifactorial metabolic illness with a significant risk of death called diabetes mellitus is defined by elevated blood glucose levels. The quality of life, the health care system, and the economics of nations are all significantly impacted by diabetes and its persistent problems. There are numerous commercial medications available today that are successful in treating hyperglycemia but have several substantial side effects and are unable to appreciably modify the course of diabetes complications. Mushrooms and their bioactive constituents like polysaccharides and terpenoids, are useful in the cure of diabetes mellitus. This systematic review aims to provide an overview of the effects of mushrooms on diabetes. Details on relevant studies were examined using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) norms. Although the mechanism of Pleurotus mushrooms in treating diabetes is still unknown, the anti-diabetic properties of many other species of oyster mushrooms have not been thoroughly researched. More research on edible medicinal mushrooms is required to close the research gap and use their clinical potential to prevent metabolic diseases.

Keywords: *Diabetes, Diabetes management, Oyster mushroom, Pleurotus species, Mushroom extract, Anti-diabetic properties.*

Introduction

Diabetes is a global health concern with increasing prevalence. It is a chronic disease in which the body is unable to properly regulate glucose (sugar), resulting in the abnormally high level of blood glucose (1). Diabetes comes in two main forms: type 1 and type 2. Type 1 diabetes occurs due to a lack of insulin secretion, often from an autoimmune attack on insulin-producing cells in the pancreas (2). Treatment typically involves insulin injections or an insulin pump (3). Type 2 diabetes, on the other hand, arises from insulin resistance in cells or inadequate insulin production by the pancreas. Figure 1 illustrates the role of insulin receptors and glucose transportation in healthy individuals versus those with Type I and Type II Diabetes.

Synthetic anti-diabetic drugs such as biguanides, sulfonylureas, tolbutamide, glinides, phenformin, repaglinide troglitazone and rosiglitazone have been extensively used to treat diabetes, but they cause various side effects when used for long-term (4). It is necessary to pursue natural and harmless method to prevent and treat diabetes. As a result, the focus has recently turned to the identification of safe natural antidiabetic agents derived from edible materials. (5).

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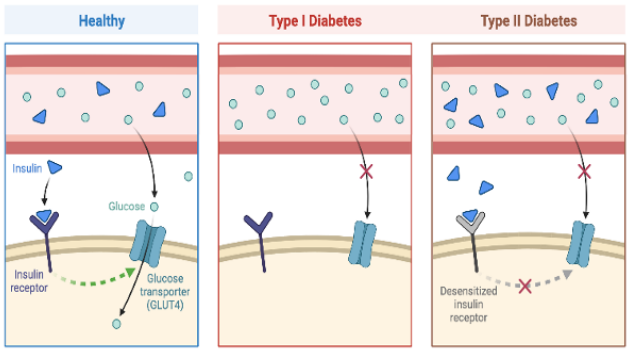
Figure 1: Type I and Type II diabetes mechanism



Several researches are going on to find out an alternative therapeutic strategy for diabetes treatment, according to recent reports (6). Mushrooms are gaining popularity due to their numerous pharmacological benefits (7). According to some research, water-soluble polysaccharides of mushroom have hypoglycemic activity (8) (9). There are several species of mushrooms that have anti-diabetic properties, and certain mushroom extracts, including oyster mushrooms, may have potential benefits for diabetes management.

The presence of β-glucans polysaccharide in the oyster mushroom has been confirmed through high-performance liquid chromatography (HPLC) analysis and Fourier transform infrared spectroscopy (FTIR) results (10). The bioactive components found in oyster mushroom extracts, such as polysaccharides and ergothioneine, have been shown to have anti-diabetic characteristics by enhancing insulin sensitivity,

decreasing insulin resistance, and decreasing oxidative stress (11). Mushroom polysaccharides, recognized for their antihyperglycemic properties, offer a natural alternative for diabetes management by reducing insulin resistance (12). Extracts from Pleurotus species regulate glycogen synthase, GLUT4 (glucose transporter 4), and GSK-3β (glycogen synthase kinase) gene expressions. (13)

Among the bioactive compounds found in mushrooms, terpenes, phenols, and polysaccharides have shown potential in diabetes management. Terpenes such as ursolic acid, particularly those sourced from fermented sources of mushrooms like *Pleurotus eryngii*, could be helpful in the treatment of diabetes as natural medicinal agents by enhancing their positive health benefits. It works by lowering triglycerides and cholesterol, lowering oxidative stress on the pancreas. (14), (15)

Ergosterol, a bioactive compound in edible mushrooms like Pleurotus ostreatus, has been demonstrated to lower blood glucose levels in type 2 diabetic mice by enhancing GLUT4 translocation via the PI3K/Akt and PKC pathways. Additionally, ergosterol improves biochemical markers, reduces diabetic nephropathy, decreases inflammation, and enhances glucose uptake in muscle cells (16),(17),(18)

Phytochemical screening of *Pleurotus florida* extracts reveals a high phenolic content, measured at 61.85 mg catechol equivalents per gram. These phenolic compounds, known for their strong antioxidant properties, may help reduce oxidative stress, which is closely linked to diabetes management. By lowering oxidative stress, these phenols could potentially improve insulin sensitivity and contribute to better blood sugar control, making *Pleurotus florida* a promising dietary option for those managing diabetes. (19)

Polysaccharides, complex carbohydrates made of connected monosaccharide units, are categorized into two types: homopolysaccharides and heteropolysaccharides. They can have either linear or branching structures. Polysaccharides prevent autoimmune diabetes by regulating the gut immune system. Changes in gut microbiota can disrupt immune cell communication, leading to an excessive immune response and autoimmune diabetes. Polysaccharide administration increases the growth of short-chain fatty acid-producing bacteria, thereby elevating short-chain fatty acid levels. This helps maintain the balance of diabetogenic and regulatory T cells in the colon and pancreas, reducing diabetes prevalence. (20)

Mushroom β-glucans are non-starch polysaccharides characterized by a glucose polymer chain core with beta-(1-3) linkages in the main chain and additional beta-(1-6) branch points. Their effectiveness varies based on the molecular weight and structural complexity of the glucan. Mushroom polysaccharides have already been isolated and characterized like pleuran from *Pleurotus* species, lentinan and erothionine in *L. edodes*, ganoderan from *Ganoderma lucidium* and agaritine from *Agaricus* and calocyban from *Calocybe indica.*(21)

Data from in vivo and in vitro experiments showed that treatment with mushroom polysaccharides had an anti-hyperglycemic impact by enhancing insulin-signaling pathways, decreasing the efficiency of glucose absorption, and raising pancreatic beta-cell mass.(22) Mushroom polysaccharides, also known as fungal glycans, are heterogeneous collections of macromolecule carbohydrate polymers composed of monosaccharide units linked by O-glycosidic linkages. Mushroom glycans have been the subject of extensive research and reviews.(23)

Polysaccharides may reduce diabetes by inhibiting glucose absorption efficacy and postprandial glycemia via gastrointestinal viscosity mechanisms. Water-soluble dietary fibres and polysaccharides increase the viscosity of gastrointestinal content, slowing gastric emptying and delaying carbohydrate digestion and absorption. Aside from improving hyperglycemia, -glucan administration under diabetic conditions has been shown to promote a systemic improvement, which can increase the organism's resistance to the onset of diabetic complications.(22) Mushroom polysaccharides (β-glucans) restore pancreatic tissue function, increasing β-cell insulin production and reducing blood glucose. (24)

Furthermore, immune system activation induced by water-soluble polysaccharide administration may repair a partially damaged pancreas or prevent it from worsening in diabetic rats with autoimmune damage, resulting in increased insulin secretion. Studies have found that water-soluble polysaccharides boosted insulin secretion and inhibited increased blood glucose levels in STZ-induced diabetic rats (25)

This systematic review aims to provide an overview of the effects of Oyster mushrooms on diabetes. Details on relevant studies were examined using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) norms. By summarizing current knowledge, this review highlights potential mechanisms of action and identifies areas requiring further investigation, contributing to the broader understanding of natural alternatives for diabetes management.

Materials and methods

Literature search strategy

A systematic review of the PubMed and Google Scholar database was performed that examined the impact of mushroom extract on diabetes management. The keywords were used for the literature search were “Diabetes management” OR “Diabetes” OR “Blood sugar levels”) AND (“*Pleurotus* mushroom” OR “Oyster mushroom” OR “*Pleurotus* mushroom extract” OR “Oyster mushroom extract”. One filter was applied: English language. Non-English, non-relevant articles were removed during data retrieval. The papers that featured research on oyster mushrooms with potential as antidiabetic agents were the only ones. The database check, which was completed by one evaluator, was completed on August 31, 2022. Eligible papers released up to that point in time are included only. Furthermore, we have combed through the papers referenced in the

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included articles to find the other articles related to our inclusion criteria that had not been in PubMed and Google Scholar.

Inclusion criteria

This review concentrated on studies that looked into the effectiveness of *Pleurotus* mushroom extract on diabetic animal model or cell lines. Studies that are considered for inclusion if they address:

(1) The impact of *Pleurotus species* extracts on diabetes,

(2) Glucose metabolism measures. (glucose, insulin, HbA1c).

Exclusion criteria

Studies that are excluded because of the following reasons:

(1) Treatment with mushrooms other than *Pleurotus* species;

(2) Not being a clinical study; and

(3) Treating illnesses other than diabetes. (e.g., anticarcinogenic effects, cardiovascular, hepatoprotective etc)

(4) Treatment with other medicinal plants.

Selection of the study and data extraction

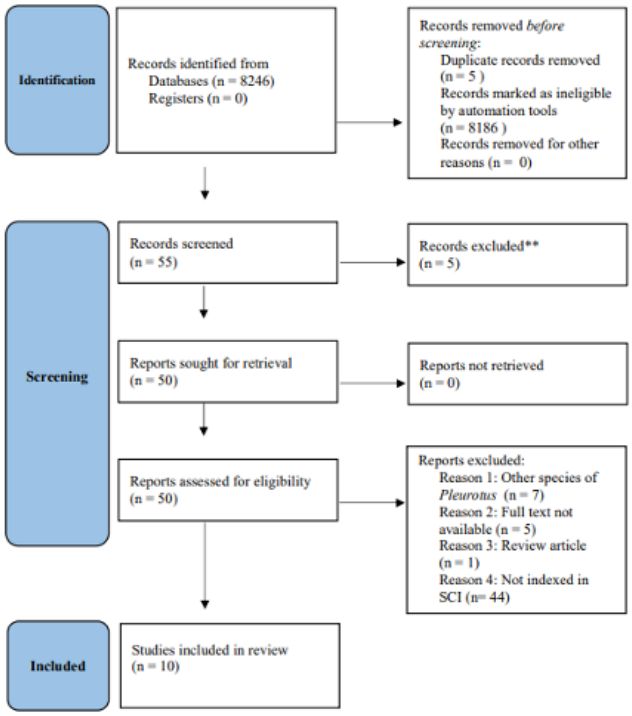
All the papers were first screened by title and then by perusing the abstract, to eliminate those studies that met exclusion criteria. Following that, by reading the full-text paper, all eligible studies were selected and finally, the selected eligible studies were included in this systematic review. These criteria were checked by a self-created Excel sheet (Mushroom species, method of extraction, bioactive compound, and animal model, dose of extract, standard drug used, biochemical tests, and statistical tools) for each study.

Results

Study characteristics and selection

By searching the relevant papers through keywords 36 research papers were obtained from PubMed and 8210 publications from Google scholar. From those 8186 records were removed by reading titles and abstracts, and then 50 records were remained after removing all the duplicates and studies coming under exclusion criteria (studies of other mushrooms than *Pleurotus species*). Full text of some papers was not available so those were also excluded. Review articles were excluded. One other paper that used a different *Pleurotus spp.* for therapy was omitted after reviewing the full-text publications. After excluding the papers not coming under indexed journal, there are ten studies which are presented in this review. Figure 1 depicts a flow diagram of study identification and selection.

Figure 2: This diagram depicts the development of a systematic literature search. The identification, screening, eligibility, and inclusion procedures for the systematic literature search are thorough and follow the Preferred Reporting Items for Systematic Reviews (PRISMA) flow chart.



Effect of oyster mushroom in diabetes management

Various species of oyster mushrooms including *Pleurotus sajor-caju, Pleurotus ferulae, Pleurotus pulmonarius, Pleurotus ostreatus Pleurotus eryngii, P. cystidiosus and Pleurotus albidus* have shown promising effects in the management of diabetes mellitus, with diverse bioactive compounds contributing to their therapeutic potential. These findings underscore the potential of oyster mushrooms as functional foods or sources of therapeutic agents for diabetes management, although further research is needed to elucidate their mechanisms of action and optimise their clinical application.

Table 1: Outcome of various studies on effect of oyster mushroom in treating diabetes

Oyster mushroom species	Bioactive compound	Experimental model	Outcome	Reference
Pleurotus sajor-caju (hot-aqueous extract)	b-glucan-rich polysaccharides	3T3-L1 cells	• Stimulation of lipolysis and lipogenesis in 3T3-L1 cells • Attenuated protein carbonyl and lipid hydroperoxide levels • Elevated GLUT-4 gene expression	(26)
Pleurotus ferulae	Exopolysaccharide	Sprague Dawley rats	• The insulin level increased	(8)

P. pulmonarius (basidiocarps)	Proteins (ammonium sulphate precipitated protein fractions)	-	• Antidiabetic-related proteins identified: Glyceraldehyde-3-phosphate dehydrogenase-like protein, catalase-like protein, profilin-like protein, and trehalose phosphorylase-like protein.	(27)
Pleurotus sajor caju aqueous extract	-	Male Sprague-Dawley rats	• Beneficial effects in reducing glucose intolerance and the severity of diabetes.	(28)
Pleurotus djamor	Mycelium zinc polysaccharides (Including acidic-, alkalic-, and enzymatic-MZPS)	Kunming strain mice	• En-MZPS had significant potential antioxidant benefits in the liver at high doses (800 mg/kg), but not in the kidney at low doses (200 mg/kg).	(29)
Pleurotus eryngii	Polysaccharide	Kunming mice (KKAy mice)	• Helped to lower the blood glucose level	(30)
Pleurotus tuberregium Sclerotia	Phenolic acids and organic acids	New Zealand white rabbits	• Phenolic acids (Chlorogenic acid (11.08%), caffeic acid (80.24%), ferulic acid (0.34%) piperic acid (6.11%), and sinapinic acid (2.14%), and Organic acids (protocatechuic acid, p-hydroxybenzoic acid, Syringic acid, gallic acid, vanillic acid, gentisic acid, and salicylic acid) were found. • Alloxan-induced hepatotoxicity and renal toxicity were prevented in the rabbits	(31)
Oyster mushroom (Powder)			• In mushroom-treated diabetic model, Western blot analyses revealed higher band intensity of AMPK and p-CREB.	(32)
Pleurotus eryngii	polysaccharide (enzymatic, alkalic and acidic)	Kunming strain mice	• Polysaccharides examined have the ability to improve lipid metabolism and defend against oxidative stress-induced tissue damage by reducing lipid peroxidase.	(4)
Pleurotus albidus	Phenol, flavanoid. Ergothrionine	e EA.hy926 human vascular endothelial cell line	• Prevented an increase in complex I activity of the electron transport chain • Reduced ROS generation caused by hyperglycemia • Reduced oxidative damage to lipids and proteins, and lowered hyperglycemia-induced nitric oxide levels.	(33)

The b-glucan-rich polysaccharides of *Pleurotus sajor-caju* are found to be a novel AMPK activator that may help in the prevention and treatment of diabetes mellitus (26). Large polysaccharide fractions (>105 Da) of *P.ferulae* have antihyperglycemic activity as suggested in a study in STZ-induced diabetic rats at a dose of 250 mg/kg daily of the extract helped in improving hyperglycemia and regulating blood lipid profiles (8). The study by (Ng et al. 2015) also discusses the usefulness of polysaccharides as an alternative medicine in the treatment of diabetes. *P. pulmonarius* basidiocarps have the potential to reduce insulin resistance, blood glucose levels, and vascular complications. Although the precise mechanism of action for these proteins is unknown, additional in-depth studies may offer an explanation and support for it. (27). Zinc polysaccharides had strong antioxidant properties to treat diabetes and its complications caused by STZ(29). In KKAy mice, *Pleurotus eryngii* polysaccharides demonstrated significant hypoglycemic and hypolipidemic activity. It can be a promising hypoglycemic and hypolipidaemic medicine (30). The aqueous preparation of *Pleurotus tuberregium* sclerotia prevented the rabbits from alloxan induced hepatotoxicity and renal toxicity. The substance also had a beneficial effect on plasma electrolytes (31). The anti-hyperglycemic properties of oyster mushrooms explained by (32) by increased AMPK expression and CREB activation. Polysaccharides extracted from *P. eryngii* mushroom, particularly those with low molecular weight, have shown potent antioxidant and organ-protective effects in diabetic mice induced by STZ. This suggests that utilizing polysaccharides from *P. eryngii* could offer potential benefits in preventing and treating diabetes and its complications (4).

Phenol and ergothioneine compounds of *P. albidus*, inhibit the decline in complex I of the electron transport chain activity and reduces the oxidative damage induced by hyperglycaemia, according to Gambato *et al*. While cell culture findings may not directly apply to human clinical settings, this discovery holds promise for developing novel therapeutic drugs to mitigate the adverse effects of hyperglycemia (33).

Variability in Mushroom Extract Extraction Techniques: A Comparative Analysis

The extraction technique for mushrooms is modified to the desired end result, and as such, it varies across studies depending on specific research objectives. Various methods have been employed to

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extract mushroom constituents, each selected for its efficacy in isolating desired bioactive compounds. These techniques, outlined in detail within the accompanying table, reflect the diversity of approaches utilized in scientific inquiry to obtain mushroom extracts.

Table 2: Mushroom extracts used in the treatment of diabetes

Mushroom	Extract	Reference
Pleurotus ferulae	Extraction and purification of a water-soluble exopolysaccharide from GPY broth which includes filtration, precipitation with ethyl alcohol, deproteination using trichloroacetic acid, ultra filtration to recover large molecules, and freeze-drying of the obtained molecules.	(8)
Pleurotus pulmonarius	Aqueous extract	(27)
Pleurotus sajor-caju	Aqueous extract	(28)
Pleurotus djamor	Liquid fermentation technique to create MZPS.	(29)
Pleurotus tuberregium	Aqueous extract	(31)

Figure 3: Mushroom extract

Safety Profile of Oyster Mushroom Extract in Experimental Models

In all trials reviewed, the administration of oyster mushroom extract did not yield any discernible negative side effects. Notably, there were no adverse impacts observed on the kidney and liver functions of the experimental models following mushroom treatment. This absence of adverse effects underscores the potential safety profile of oyster mushroom extract, suggesting its suitability for further investigation and potential therapeutic applications in managing diabetes mellitus.

Table 3: Safe dose of mushroom extract for the animals models in different studies

Mushroom	Animal model	Dose of Streptozotocin/alloxan	Age of Animal	Weight of the animal	Safe dose of mushroom	Reference
Pleurotus ferulae	Sprague–Dawley rats	STZ 65 mg/kg body weight	5 weeks old	150± 10 g	250 mg/kg body weight.	(8)
Pleurotus sajor-caju	Male Sprague-			250–300 g	750 mg/kg	(28)
Pleurotus djamor	Kunming strain mice	STZ 120 mg/Kg	4 weeks old	20 ± 2 g	800 mg/Kg effective for liver, mg/Kg	(29)
Pleurotus eryngii	Kunming mice (KKAy				10% (w/w)	(30)

Biochemical Assessment Techniques for Evaluating the Efficacy of Oyster Mushroom Extracts in Diabetes Management

The methodologies of biochemical tests used in the included studies to scrutinize the potential efficacy of mushroom extracts, with a particular focus on diabetes management:- Protein Carbonyl Content Assay assay served as a reliable marker for evaluating oxidative damage to proteins, indicative of the presence of reactive oxygen species. Lipid Hydroperoxide Assay has been used for the measurement of lipid hydroperoxides provided insights into lipid peroxidation and oxidative stress levels within the biological systems under study. LCMS (Liquid Chromatography-Mass Spectrometry) technique facilitated the identification and quantification of various chemical compounds, offering a nuanced understanding of the chemical composition of mushroom extracts. Gene expression analysis through RT-PCR elucidated the molecular mechanisms influenced by mushroom extracts, shedding light on potential therapeutic pathways. Phenol Sulfuric Acid Method has been used for the determination of polysaccharide content, a pivotal parameter in assessing the anti-diabetic properties of mushroom extracts. Thin-layer chromatography and Gas-Liquid chromatography methods were instrumental in delineating the composition of polysaccharides, revealing the specific sugar components present in the mushroom extracts. High-Performance Gel-Permeation Chromatography applied to ascertain the molecular weight of polysaccharides, providing crucial insights into their structural characteristics. Integral for the estimation of protein content, facilitating a comprehensive assessment of the proteinaceous constituents within mushroom extracts Protein Assay Kit was used. Ammonium Sulphate Precipitation Method enabled the fractionation of proteins, allowing for the isolation of specific protein fractions for subsequent analysis. Inhibition Assay for α-Glucosidase Activity used for assessing the inhibitory effects on α-glucosidase, a pivotal enzyme in carbohydrate metabolism. Reversed Phase-High-Performance Liquid Chromatography (RP-HPLC) was employed for the purification and analysis of active protein fractions

within the extracts. MALDI-TOF/TOF Mass Spectrometry was utilized for the identification and characterization of proteins present in mushroom extracts, offering a detailed insight into their composition. FBG (Fasting Blood Glucose) and OGTT (Oral Glucose Tolerance Test) tests gauged glucose levels and tolerance, pivotal parameters in the context of diabetes research. LD50 experiment discerned the lethal dose causing mortality, providing critical information on the toxicity profile of the mushroom extracts. Assessment of Serum Parameters has been performed for the evaluation involving diverse parameters such as body weight, blood glucose levels, liver and kidney indices, and lipid profiles, contributing to a holistic understanding of the physiological impact. GC (Gas Chromatography) deployed for the phytochemical profiling of mushroom extracts, revealing detailed insights into their chemical composition. Determination of Plasma Electrolytes contributed to the evaluation of overall physiological balance by assessing the levels of essential electrolytes in the blood. Western Blot and Immuno-Precipitation Techniques applied for the identification and quantification of specific proteins (e.g., AMPK and CREB) involved in cellular signaling pathways. Assessment of Mitochondrial Respiratory Chain Activity: This evaluation provided insights into the functioning of mitochondrial complexes, shedding light on cellular energy metabolism. In Vitro Antioxidant Activity Tests These assays, including DPPH· and ABTS·+ methods, measured the antioxidant capacity of mushroom extracts by assessing their ability to scavenge free radicals.

This comprehensive set of tests, as used across several researches, considerably improves our understanding of the biochemical effects of mushroom extracts, with possible implications for diabetes treatment and other health applications.

Exploration of Oyster Mushroom Species with Potential Anti-Diabetic Activity: Insights from other Relevant Studies

There were other similar studies according to our inclusion criteria but those were excluded just because they were not in the SCI journal, so data might or might not be authentic, but in this section, we have mentioned those studies also, to see the species of oyster mushroom on which some work has been done and in future more research can be performed on them. Oyster mushroom acts as an anti-hyperglycemic via phosphorylating AMPK and increasing GLUT4 expression, in type 2 diabetes model rats (13) and also possess alpha-amylase inhibitor**s** in the mycelium (34). Other species of oyster mushroom which possess anti diabetic activity are *Pleurotus ostreatus* (35) (36) (37), *Moringa oleifera and*
Pleurotus ostreatus (38), *Pleurotus tuber-regium* (39) (40), *Pleurotus tuberregium Sclerotia* (41), *Pleurotus florida* (42) (43), *Pleurotus fossulatus* (44), *Pleurotus pulmonarius* (45). More specific studies can be further performed on these species of oyster mushroom.

Future Directions and Conclusion

Future research should focus on identifying the molecular pathways involved in the management of diabetic complications by mushroom extracts, along with exploring their impact on other metabolic pathways to understand their relation to diabetes and other risk factors. Such research would be pioneering in elucidating the underexplored molecular mechanisms that contribute to the therapeutic effects of mushrooms, potentially identifying novel biomarkers for diabetes treatment.

Additionally, further investigation into various species of oyster mushrooms could broaden the options for diabetes treatment through mushroom therapy. Despite the limitations in the current systematic review, it underscores the potential of oyster mushrooms as a functional food source, particularly their polysaccharides such as β-glucans, which may aid in repairing pancreatic tissue function and improving glucose metabolism. This aspect of oyster mushrooms as a functional food source is still underexplored, making it a fertile ground for innovation.

While studies have shown positive effects of *Pleurotus* mushroom extract on diabetic experimental models, further research is required to determine optimal dosages, treatment duration, and safety for diabetes management in humans.

Also further studies are needed to compare the effects of oyster mushroom extracts with other antidiabetic treatments, both synthetic and natural, to contextualize their effectiveness within the broader landscape of diabetes management options. Future studies should investigate the long-term effects and sustainability of using oyster mushroom extracts.

Overall, oyster mushrooms contain diverse bioactive compounds that hold promise for future development of new medications for diabetes treatment. Medications as well as some value added products for diabetics and prediabetics can be prepared from mushroom extracts. It will take more investigation and clinical testing to completely understand the therapeutic potential and create standardized products that can be used widely.

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