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Original article

Therapeutic efficacy of water extract of Oyster Mushroom in streptozotocin induced diabetic Wistar rats

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Abstract. *Back ground and aim:* Currently, there are a lot of allopathic medications on the market that are very effective at controlling diabetes, but they eventually cause side effects. Plant derived products have proven to be effective and safe in the treatment of diabetes mellitus due to the presence of active bioactive compounds which have attracted scientists into the look insight of the natural products. Oyster mushroom is a low – calorie, fat free, fibre-rich food high in various vitamins and minerals such as copper, niacin and phosphorus. Hence, the present study was evaluated the potential effect of anti-hyperglycemic, anti-hyperlipidemic and anti-oxidative properties of oyster mushroom extract in streptozotocin induced diabetes. *Methods:* 32 rats (N=32) were given a standard diet and divided into four groups namely Group 1: normal control (NC), n=8, Group 2: Diabetic control (DC), n=8, Group 3: A dose of 200 mg/kg BW of oyster mushroom aqueous extract treatment for diabetic rats, n=8, Group 4: Glibenclamide treatment for diabetic rats or rats treated with allopathic drug, n=8. All the biochemical estimations were done at two different intervals, one after the induction of diabetes and second after completion of (21-day) therapy. *Result:* The present study was investigated for the quantitative analysis of phytochemicals, antioxidants, α-amylase inhibitory activity and antidiabetic properties of aqueous extract of oyster mushroom. Quantitative analysis of aqueous extract shows phenolics, flavonoids, tannins, alkaloids and saponins as bioactive compounds. Furthermore, using DPPH radical scavenging activity, hydrogen peroxide scavenging activity, total antioxidant capacity, and anti-haemolytic activity were found to be 54.41±1.18, 11.87±1.21, 29.23±3.12, and 14.42±4.89 (activity measured in % inhibition). In the next phase of our study, we evaluated the α-amylase inhibitory activity of the extract in a dose dependent manner and found the inhibition of (89.96±4.6 % at 1000 μg/ml). Finally, oyster mushroom extract was administered to diabetic rats (200 mg/kg) for 21 days to examine its anti-hyperglycemic, anti-hyperlipidemic and anti-oxidative properties. *Conclusion:* A significant reduction in triglyceride, total cholesterol, and low-density lipoprotein-cholesterol (LDL-C) was demonstrated by the extract. Furthermore, oyster mushroom aqueous extract improved high density lipoprotein- cholesterol (HDL-C) levels as well antioxidant enzymes.

Key words: Streptozotocin, Wistar rats, type -2 diabetes, Oyster Mushroom

Introduction

Lack of insulin and insulin dysfunction cause diabetes, a life-threatening disease characterized by elevated blood glucose levels (1). The treatment of diabetes mellitus, especially type-2 diabetes, is necessary to control blood sugar levels.; if not treated caused major complications like cardiovascular diseases, nephropathy and neuropathy which is the major threat of mortality and serious morbidity in the developing country (2, 3). Many allopathic drugs are available in the market which is excellently working

in the control of diabetes but ends with side effects after prolonged use (4-6). However, plant derived products have proven to be effective and safe in the treatment of diabetes mellitus due to presence of active bioactive compounds which have attracted scientists into the look insight of the natural products (7-10). The fungi are among the most popular natural resources due to their low calories content but their high content of proteins, carbohydrates, fibres, vitamins and minerals, as well as their essential bioactive compounds that are reported to aid in the prevention of diabetes mellitus and many more diseases (11-13). Mishra and Singh, 2010 (14), studied how an aged Swiss albino rat's lipid profile, lipid peroxidation, and liver function were affected by dried mushrooms and mushroom extract. Dried mushrooms and their extract can increase antioxidant status throughout aging and reduce the emergence of age-related illnesses caused by free radicals (14). A similar study in which rats fed 10% dried mushroom, 300 mg mushroom extract, and 300 and 600 mg L-carnitine had lower total lipids, including triglycerides, total cholesterol, low-density lipoprotein, and very low-density lipoprotein, as well as liver enzymes and lipid peroxidation. Furthermore, 10% dry mushroom and 300 mg L-carnitine supplementation improved rat liver tissues (15). The consumption of oyster mushrooms decreases total cholesterol, total triglycerides, and low-density lipoprotein, while increasing high-density lipoprotein levels (16). According to research by Alam et al., 2009 (17), feeding hypercholesterolemic rats 5% powdered oyster mushrooms *(Pleurotus ostreatus, P. sajor-caju, and P. florida)* decreased the plasma levels of triglycerides by 45%, 24%, and 14%, and total cholesterol by 37%, 21%, and 16%, respectively. Besides containing medicinal importance oyster mushrooms also have macronutrients, micronutrients (vitamins) and non-nutrients such as phenolics which is associated with anti-oxidants properties (18). Oyster mushroom are a low –calorie, fat free, fiber-rich food high in various vitamins and minerals such as copper, niacin and phosphorus (19-20). Hence, the present study was evaluated the potential effect of anti-hyperglycemic, anti-hyperlipidemic and anti-oxidative properties of oyster mushroom extract in streptozotocin induced diabetes.

Material and Methods

Experimental design

32 rats (N=32) were given a standard diet and divided into four groups namely Group 1: normal control (NC), n=8, Group 2: Diabetic control (DC), n=8, Group 3: Aqueous extract treatment for diabetic rats, n= 8, Group 4: Glibenaclamide treatment for diabetic rats or rats treated with allopathic drug, n=8. All the biochemical estimations were done at two different intervals, one after the induction of diabetes and second after completion of (21-day) therapy.

Preparation of water extract of mushroom and other analysis

Using the method described by Sze Han et al. 2015 (21). We prepared aqueous extracts of oyster mushrooms. A dose of 200 mg/kg BW of juice was administered daily to mice (22). The powder form of Oyster mushroom was obtained from the OMCAR India, Gwalior M.P. The Folin-Ciocalteu colorimetric method of Mallick and Singh 1980 (23) was used to estimate the total phenolic content (TPC) of the sample. Tannins were measured as tannic acid equivalents (24). Alkaloids and flavonoids were detected by methods described by Harborne, 1973 (25). Determinations of Saponins were performed by the methods of Brunner (1984) (26). α-amylase inhibitory activity was measured using the methods of Miller, 1959 (27). Various antioxidant parameters including scavenging of free-radicals DPPH, hydroxyl radicals; hydrogen peroxide scavenging, total antioxidant capacity; anti-lipid per-oxidation and anti-haemolytic activity was done according to the standard procedure of Shabbir et al., 2013 (28).

Induction of diabetes

To induce diabetes in overnight fasted rats (Brosky and Logothelopoulos, 1969 (29), a freshly prepared STZ solution in 0.1M citrate buffer, pH 4.5 was intraperitoneally injected. An ACCU-CHEK sensor glucometer was used at 72 hours following streptozotocin injection to confirm hyperglycemia or increased blood glucose level. For various biochemical analyses,

blood samples from experimental rats of each group were collected from bleeds of the retro-orbital plexus of the rats in each group.

Blood collection

All the biochemical estimations were done at two different intervals, one after the induction of diabetes i.e. in pre-treated animals (0-day estimation) and second after completion of 21 days of therapy i.e. in post treated animals (21 days estimation).

Biochemical analysis

Various lipid profiles were studied, such as the total cholesterol (TC) measured by Stockbridge et al., 1989 (30), the triglyceride (TG) concentration by Fossati and Prencipe (1982) (31), HDL-cholesterol calculated by Lopes-Virella et al., (1977) (32), and low density lipoprotein (LDL) and very low density lipoprotein (VLDL) dosed by Freidewald's Formula. A variety of kidney function tests were performed, such as serum creatinine calculated by Bowers and Wong (1980) (33), serum urea calculated by Fawcett and Scott (1960) (34) and serum uric acid calculated by Fossati et al., (1980) (35). The serum glutamic-pyruvic transaminase (SGPT) as well as serum glutamic-oxaloacetic transaminase (SGOT) were calculated by Reitman and Frankel (1957) (36), and the serum bilirubin was calculated by Fuehr (1964) (37). All these parameters were estimated by using kits manufactured by Crest Biosystems, Pvt. Ltd. India.

Oxidative stress markers in blood

Oxidative stress enzymes like GSH were calculated using Ellman 1959 (38), superoxide dismutase (SOD) was calculated using Winterbourn, 1975 (39). Thiobarbituric acid reacting substance (TBARS) was calculating using Ohkawa et al., 1979 (40), Catalase was calculated using Sinha 1972 (41), and protein concentration was estimated by the method of Lowry et al; 1951 (42).

Statistical analysis

An ANOVA with Tukey's post-hoc analysis of variance was performed using Sigma Stat 3.5. Statistical significance was determined at $p<0.05$ among eight animals in each group, with results expressed as mean ± SEM. A value of was considered significant and results are expressed as mean for eight animals in each group.

Results

Using streptozotocin inducement of diabetes, this study evaluated oyster mushroom extract for its anti-hyperglycemic, anti-hyperlipidemic, and antioxidative properties. Detailed results are presented below.

Screening of phytochemicals

The aqueous extract of mushroom was tested for the evaluation of phytochemicals showed (Table 1), in terms of phenols, tannins, flavonoids, saponins and alkaloids using Gallic acid standard. The major constituents found were phenols and flavonoids whereas tannins, glycosides and saponins were reported less in amount. All these phytochemicals are reported as potent antioxidant activity (43).

Antioxidant property of aqueous extract of Oyster mushroom

The antioxidant properties of aqueous extract of oyster mushroom are shown in the Table 2.

Table 1. Phytochemical constituents of Oyster mushroom.

	Phenolics (mg/gm)	Flavonoids (mg/gm)	Tannins (mg/gm)	Alkaloids (mg/gm)	Saponins (mg/gm)
Aqueous extract of oyster mushroom	0.84±0.03	0.69±0.01	0.29±0.04	0.04±0.03	0.002±0.02

All values are the average of three determinations. (Means± standard deviation SD). Significant at ($P \leq 0.05$).

Table 2. Antioxidant activities of Oyster mushroom.

S.No	DPPH (%Inhibition)	H2O2 (% Inhibition)	Total AO (%Inhibition n)	Egg Albumin (%Inhibition)	Goat Liver (%Inhibition)	Antihemolytic activity (% Inhibition)
Aqueous extract of oyster mushroom	54.41±1.18	11.87±1.21	29.23±3.12	32.58±2.54	46.78±0.08	14.42±4.89

All values are the average of three determinations. (Means± standard deviation SD) Significant at ($P \leq 0.05$).

Table 3. α-amylase inhibitory activity.

Sample concentration (µg/ml)	α-amylase inhibition activity (%)
100 µl	13.85±0.05
200 µl	18.12±0.03
300 µl	27.35±0.03
400 µl	33.87±0.02
500 µl	46.74±0.05
600 µl	58.69±0.02
700 µl	68.22±0.53
800 µl	72.63±0.04
900 µl	87.23±0.04
1000 µl	89.96±4.6

Table 4. Effect of 21 days therapy on fasting blood glucose levels.

Treatment Serum	Glucose Level	
	0-Day (mg/dl)	21-Day (mg/dl)
Normal control	86.64±1.76	79.32±0.03**
Diabetic control	475.75±6.54	465 ±3.28
Diabetic+Glibenclamide (0.5 mg)	446.23±3.58	144.75±1.95**
Diabetic+Mushroom extract (200 mg/kg) body weight	463.88±0.02	393.46±0.89**

Data was analysed by paired t-test. Value is statistically significant at $P<0.05$(*)

On analysing the different antioxidant properties of extract, it shows activity ranging from (14.42±4.89 to 54.41±1.18). The free radical activity was calculated using the DPPH hydroxyl radical-scavenging activity and found to be (54.41±1.18). The total antioxidant capacity (TAC) was found to be (29.23±3.12). The lipid per oxidation assay was analysed using the egg albumin and goat liver and found the inhibition of 32.58±2.54 and 46.78±0.08 respectively. Haemolytic activity was performed using the goat erythrocytes and found the inhibition of (14.42±4.89) (Table 2).

Evaluation of α-amylase inhibitory activity

α-amylase is an enzyme which helps in the breakdown of starch into free glucose, and absorbed by the small intestine. Nowadays, the inhibition of this enzyme is one of the most important approaches to treating type 2 diabetes mellitus. So, the food grains are tested for the α-amylase inhibitory activity and identified as staple food for the treatment of diabetes. In this research we also attempted to characterize the α-amylase inhibitory activity of the extract in a dose dependent manner and found the inhibition of (89.96±4.6 % at 1000 µg/ml) (Table 3).

Evaluation of anti-diabetic potential of aqueous extract of mushroom

On analysing the results, the streptozotocin induced diabetic rats exhibited significantly higher fasting blood glucose levels (475.75±6.54 mg/dl) as compared to those of normal rats (86.64±1.76 mg/dl) (Table 4). After 21- day therapy of mushroom extract, in diabetic Wistar rats, fasting blood glucose levels decreased by about 15.18% compared to pretreatment levels. The fasting blood glucose levels in diabetic rats treated with glibenclamide showed reduction of 67.56 % compared to pretreatment values.

Effect of water extract of mushroom on plasma insulin levels

Plasma insulin level was checked by the methods proposed by Baskaran et al., 1990 (44) (Table 5).

The plasma insulin levels increased from mean pretreatment value of 0.33±0.03 to 0.35±0.01 µg/L. The plasma insulin levels of glibenclamide treated group increased from 0.33±0.03 to 2.14±0.04 µg/L. The increase in plasma insulin level of glibenclamide treated groups was significant at (P<0.05).

Evaluation of anti-hyperlipidemic potential of mushroom extract

Compared with the normal control rats, diabetic rats showed significantly higher levels of total cholesterol (TC), TG, LDL, and VLDL, while HDL levels were significantly reduced (Table 6). The administration of aqueous extract of mushroom showed significantly reduction of TC, TG, LDL and VLDL as 20.84%, 29.81%, 35.54%, and 29.81% and increased of 29.05 % of HDL was obtained compared with diabetic control group (Table 6).

Effect of aqueous extract of mushroom on biomarkers of toxicity

On evaluating the results of kidney biomarkers showed the increased level of serum urea, uric acid and creatinine, in diabetic control groups of rats induced by STZ as compared with control group (Table 7).

The levels of urea, uric acid and creatinine were significantly increased by 60.65%, 69.87 % and 27.90% respectively. Interestingly, diabetic rats treated with mushroom extract for 21 days showed significant (P<0.05) reductions in urea, uric acid, and creatinine levels, respectively, by 5.23%, 33.99%, and 14.45% (Table 7).

Table 5. Effect of 21 days therapy on plasma insulin levels.

Group	Mean (µg/L)
Normal control	2.86±0.08
Diabetic control	0.33±0.03
Diabetic+Glibenclamide (0.5 mg)	2.14±0.04**
Diabetic+Mushroom extract (200 mg/kg) body weight	0.35±0.01

Table 6. Effect of 21 days therapy on Lipid Profile.

Group	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal control	50.15±3.58	34.10±0.4	23.93±1.1	19.4±0.05	6.82±0.02
Diabetic control	79.35±4.8	98.48±2.1	13.77±1.3	45.89±0.38	19.69±0.06
Diabetic+Glibenclamide (0.5 mg)	46.60±3.8**	59.79±3.2**	26.81±1.1**	7.84±0.64**	11.95±0.81**
Diabetic+Mushroom extract (200 mg/kg) body weight	62.81±1.2**	69.12±2.9**	19.41±1.4**	29.58±0.88**	13.82±0.67**

Data was analysed by one way ANOVA. Value is statically significant at P<0.05(*).

Table 7. Effect of 21 days therapy on Liver Profile.

Group	UREA (mg/dl)	URIC ACID (mg/dl)	CREATININE (mg/dl)
Normal control	34.46±0.08	2.39±0.03**	0.43±0.05*
Diabetic control	55.36±1.43	4.06±0.05*	0.55±0.04**
Diabetic+Glibenclamide (0.5 mg)	51.45±0.09	3.13±0.06	0.41±0.03***
Diabetic+Mushroom extract (200 mg/kg) body weight	52.7±2.38	2.68±0.02***	0.47±0.03***

Data was analysed by one way ANOVA. Value is statically significant at P<0.05(*).

Table 8. Effect of 21 days therapy on Antioxidant enzymes:

Group	GSH (mg/ml)	SOD (µm/min./mg protein)	CATALASE (µm/min./mg protein)	TBARS (n moles of MDA/ml of blood)
Normal control	3.88±0.03	73.26±5.2	4.56±0.04	387.56±8.65
Diabetic control	2.69±0.02	33.34±0.08	3.84±0.03	576.22±11.21
Diabetic+Glibenclamide (0.5 mg)	3.65±0.04**	55.87±0.05**	4.15±0.02**	464.76±7.87**
Diabetic+Mushroom extract (200 mg/kg) body weight	3.48±0.01**	50.65±0.06**	4.08±0.05**	387.55±9.25**

Data was analysed by one way ANOVA. Value is statistically significant at P<0.05(*).

Evaluation of anti-oxidant potential of Oyster mushroom aqueous extract

In normal control and diabetes control rats, oxidative stress markers such as GSH, SOD, Catalase, and TBARS were evaluated. Rats induced with STZ had decreased GSH, SOD, Catalase levels while TBARS levels were higher (Table 8). GSH, SOD, and Catalase levels increased significantly in diabetic rats after 21 days of treating aqueous extract and glibenclamide, while TBARS levels decreased significantly of 32.74%.

Discussion

The present study reveals that water extract of mushroom has many important phytochemicals such as phenolics, flavonoids, saponins and alkaloids which are reported as antidiabetic and antioxidant properties. In this study, administration of aqueous extract of oyster mushroom (200 mg/kg body weight) significantly decreases the elevated blood glucose level; compared to glibenclamide antidiabetic drugs, HDL-C was increased with TC, TG, LDL-C, and VLDL-C. Next, we evaluated the protective effect of mushroom extract against hepatic and renal damage caused by STZ and found the level of hepatic and renal markers near normal levels as compared to treatment with glibenclamide. The study results are in positive correlation with the findings of Prabu and Kumuthakalavalli, 2017 (45) that they found the inhibition of α-amylase with 94.93% reported by administrating the methanolic extract of (200 mg/kg bw) oyster mushroom *pleurotus florida*.

In diabetes, hyperglycemia persists, contributing to the production of free radicals, particularly reactive oxygen species (ROS), which are critical to the damage of the pancreas and insulin loss (46). There was a decrease in antioxidant enzyme expression (approx. half of the original value) in diabetes rats followed by an increase in TBARS (approx. twice the original value). Administration of aqueous extract in the diabetic rats, enhances the value of SOD, Catalase, GSH and reduces the levels of TBARS was recorded after the treatment of 21-day therapy. Similarly, Karim et al. 2020 (47), reported that methanol extract decreased blood sugar levels by 9.8% on the 30th day compared to day 0 and 48.71% (in 30-day) in diabetic mice (treated extract) compared with the respective diabetic control animal while ethyl acetate extract reduced blood sugar by 14.56% on 30th day compared with normal control group and a reduction of 50.85% (30-day) was observed in diabetic rats compared with respective diabetic control group (47). Alternatively, the STZ induces diabetes by increasing plasma cholesterol, triglycerides, LDL-C and lowering HDL levels (46). As a result of oral administration of mushroom extract, diabetic rats demonstrated significant decreases in TC, TG, and LDL-C levels and an increase in HDL-C levels.

An antioxidant is a natural substance which acts against the reactive species generated during the oxidation reactions in the human body. Antioxidant acts through the several mechanisms such as transfer of hydrogen atom, transfer of electrons and the ability to chelate the transition metals (48-49). Free radicals are generated during the metabolism of aerobic cells in the body which produces numerous oxidants which

are responsible for the various diseases (50). These oxidants are involved in the destruction of β-cell function and develop a type 2 diabetes (9). Vishwakarma et al., 2017 (51), studied the four species of oyster mushroom (*Pleurotus cystidiosus, Pleurotus flabellatus, Pleurotus florida, Pleurotus ostreatus*) and evaluated their antioxidant property such as free radical scavenging activity, β-carotene-linoleic acid assay and hydrogen peroxide reducing power activity. All the species have good property of antioxidant activity with the increasing concentration of extract. Our results are in agreement with the findings of Vishwakarma et al., (2017); that on analysing the aqueous extract of oyster mushroom it shows considerable amount of phytochemicals such as phenolics, flavonoids, saponins and alkaloids which are considered as natural antioxidants reported in literature (52). Plasma insulin levels were measured in the present study. Compared to normal control rats, STZ-induced diabetic rats showed a significant decline in plasma insulin levels. Treatment of aqueous extract at 200 mg/kg body weight does not increase the levels of plasma insulin as compared with the allopathic drugs glibenclamide (52), found that metformin at a dose of 150 mg/kg could not make a significant difference in plasma insulin levels in diabetic rats, however, 800 mg/kg of petroleum ether extract of Reishi mushroom increased plasma insulin levels by 78.34% so, in future, administration of higher doses of aqueous extract should be checked. The main approach for treating the type 2 diabetes is to control the blood glucose level. This can be achieved by decreasing the breakdown of glucose through the inhibition of enzyme found in small intestine of the human called α-amylase and α-glucosidase (53-54). These enzymes breakdown the oligosaccharides; disaccharides into monosaccharides and resealed glucose is utilized by the body (55). To evaluate the inhibitory activity against the α-amylase enzyme the aqueous extract of oyster mushroom was tested. In this study we found a dose dependent inhibition of α-amylase with 89.96 % inhibition.

Conclusion

Mushrooms are rich sources of nutrients, fibres and proteins with low amount of lipid and calorific value which are used by human beings since time immemorial. From the above discussion, Oyster mushroom can be useful in treating the diabetes mellitus and a better option for new therapeutic agents against harmful allopathic drugs. Phytochemicals like flavonoids, saponins, phenolics and alkaloids found in this mushroom reduce free radicals generated in the body as well as oxidative stress. The oral administration of aqueous extract of mushroom produces significant hypoglycemic, antidyslipidemic and antioxidant enzymes which lower the glucose level and total cholesterol level in the experimental animal. However, more critical investigations are required to explore the therapeutic potentials of mushroom with effects on insulin level.

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Conflicts of Interest: None.

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