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The effect of aqueous extract of some wild edible macrofungi on *in vitro* diffusion of glucose

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ABSTRACT

Edible fungi are used as antidiabetics since ancient times. In the present studies aqueous extract of some edible macrofungi viz., *Calocybe indica* Purkay. & A. Chandra, *Cantharellus subalbidus* Smith & Morse, *Macrolepiota procera* (Scop.) Singer, *Pleurotus florida* (Mont.) Singer, *P. ostreatus* (Jacq.) P. Kumm., *Termitomyces heimii* K. Natarajan and *Tuber aestivum* Vitt. were analyzed for their *in vitro* antidiabetic activity. Tested macrofungi exerted a significant inhibitory effect on glucose movement out of dialysis membrane. This effect was found to be concentration and time dependent. Higher the concentration of aqueous extract higher its activity was. Most effective concentration in present studies was found to be 50g/L. Aqueous extract of *P. ostreatus* was able to inhibit glucose movement out of dialysis bags at all concentrations tested when compared with other macrofungal extracts. The result clearly suggests that these macrofungi can be used as an alternative therapy for diabetes treatment.

Keywords: Diabetes, Dialysis membrane, Diffusion, Glucose, *in vitro* studies, Macrofungi

INTRODUCTION

The word diabetes was coined by a Greek physician Aeretaeus in the first century A.D. Diabetes mellitus is known since ages and has been mentioned in Ayurveda by Sushruta (Wadkar *et al.,* 2008). Diabetes mellitus is a chronic and metabolic disease characterized by elevated plasma glucose concentration in fasting and or postprandial state or insulin resistance (Oluba *et al.,* 2010). About 1.3% of population of world suffers from diabetes and the number is increasing by 6% per year. Approximately 300,000 deaths/year are attributed to diabetes. Its prevalence increases with age from about 0.2% in persons with less than 17 years of age to about 10% in persons aged 65 years and over (Patil *et al.,* 2010). Currently treatment of diabetes mellitus involves exercise, diet therapy, insulin therapy and oral antidiabetic agents such as sulphonylureas, biquanides, thiazolidinediones and α-glucosidase inhibitor. Despite of their effectiveness in reducing hyperglycemia, the use of these drugs is associated with non-desirable side effects (Adam *et al.,* 2011). Hence herbal medicine can be used as an alternative therapy for treatment of diabetes.

The present studies try to explore the effect of aqueous extract of some wild edible macrofungi available in North Eastern part of Uttar Pradesh, India on diffusion of glucose across dialysis membrane. In India rate of diabetes mellitus is increasing and it is necessary to monitor up on it. In the present studies herbal remedies are considered convenient for the management of diabetes type 2. Herbal medicines are easily available, have low costs and less side effects and more important traditionally acceptable.

MATERIALS AND METHODS

i) Macrofungi collection and identification: Macrofungi (*C. indica, C. subalbidus, M. procera, P. florida, P. ostreatus, T. heimii* and *T.aestivum*) were collected from forest regions of Gorakhpur during the years 2011-14. These were identified on the basis of their macro and microscopic characterization following several authors (Asef and Muradov, 2012; Atri *et al.*, 2012, Castellano *et al.*, 2003; Jordan, 1995; Ruhul *et al.*, 2010, Wei *et al.,* 2006) and confirmed by mycokeys (www.mushroomexpert.com and www.mycokeys.com).

ii) Preparation of aqueous extract of macrofungi: Macrofungal samples were dried under shade and grounded to fine powder with the help of grinder and stored in opaque screw top jar at room temperature. Aqueous extract of macrofungal samples were prepared by the method of infusion. One gram of macrofungal powder was mixed in 40 mL of boiling distilled water and allowed to infuse for 15 min, it was then filtered by Whatman no. 1 filter paper and volume was readjusted to 40 mL(Gallagher *et al.*, 2003).

iii) *In vitro* antidiabetic activity of macrofungal extract on glucose movement: A simple model system as described by Edward *et al.* (1988) with slight modification was used to evaluate the effect of macrofungal extracts on glucose movement. This method involved the use of sealed dialysis tube into which 15 mL of a solution of D glucose (0.22 M) and Sodium chloride (0.15 N) was introduced and the appearance of glucose in the external solution was measured. The model used in the present experiment consists of dialysis bag (6 cm X 15 mm) into which 1 mL of macrofungal extract and 1 mL each of NaCl and D glucose was added. The dialysis bags were sealed at each end, placed in centrifuge tube containing 45 ml of 0.15 N NaCl and placed on an orbital shaker. The movement of glucose into the external solution was monitored at set interval of times (30 min, 1h, 2h, 3h, 4h, 5h, 6h, 7h and 24h). All tests were carried out in triplicate and compared with control that had everything except macrofungal extract. The concentration of glucose within the dialysis bags at the end of experiment was also evaluated. Amount of glucose was measured by using anthrone method (Thimmaiah, 1999).

iv) Concentration dependent studies of various macrofungal extract on glucose diffusion: To study the effect of different concentration of macrofungi on diffusion of glucose out of dialysis bags, four concentrations of macrofungal extract viz., 6.25, 12.5, 25 and 50 g/L were taken and variation in inhibitory effect of macrofungal extract on glucose movement into the external solution was evaluated using the above described method.

v) Statistical Analysis: Experimental values are given as mean ± standard deviation (SD). Statistical significance was determined by one way variance analysis (ANOVA). Difference at $p<0.05$ were considered to be significant.

RESULTS

Each dialysis bag used in the present studies is a semi-permeable membrane which allows only small molecules to pass through it by the process of diffusion. It shows similarity with small intestine and hence used for *in vitro* studies. These dialysis bags are similar to the small intestine in the presence of fluid outside the membrane and having low concentration of food molecules while dialysis membrane differs from actual intestine in the presence of folding which increase surface area of actual intestine and presence of blood vessels and active transport system.

All macrofungal spp. extracts tested exhibited concentration dependent inhibitory effect on glucose movement out of dialysis bags (**Table 1-7**). *Pleurotus ostreatus* inhibited glucose diffusion at each tested concentration (6.25, 12.5, 25 and 50 g/L) of extract (**Table 5**) at very high rate as compared to other samples tested. The external glucose concentration after 24 h were greater at 6.25 g/L compared to 50 g/L (99.38±3.87 mg/dl versus 38.47±2.85 mg/dl). A similar concentration dependent decrease in glucose movement was also observed with other tested macrofungal samples. The most effective concentration (50 g/L) of various macrofungal species was compared with standard antidiabetic drug i.e. Metformin solution, prepared by dissolving 500 mg of metformin in 10 mL of distilled water, at different time intervals.

It is evident from **Table 8** that, after 24 h of study, glucose movement out of dialysis bag in case of metformin was 34.61±2.15 mg/dl. *P. ostreatus* and *T. aestivum* extract were the most potent inhibitor of glucose movement in the model system in comparison to other macrofungal spp. tested. Concentration of glucose inside the dialysis bags after 24 h incubation period in the absence or presence of macrofungal extracts were inversely related to the glucose concentration in the external solution (**Table 9**). *P. ostreatus* and *T. aestivum* increased glucose concentration inside the dialysis bags when compared to control (97.902±3.50 and 95.540±1.64 versus 27.972±0.98 mg/dl). Similarly *T. heimii*, *C. subalbidus*, *C. indica*, *M. procera* and *P. florida* extract decreased glucose level in the bags in increasing order when compared to control. There was 79.54% reduction of glucose out of dialysis bag in case of metformin while *P. ostreatus* and *T. aestivum* was found to be next to it (76.09% and 73.60%, respectively) showing its high effect comparable to potent antidiabetic drug.

Table 1. Dose dependent effects of aqueous extracts of *Calocybe indica* on the movement of glucose out of dialysis bags.

Time	Amount of glucose (mg/dl) in external solution (0.15 N NaCl)				
	Control	Concentration of macrofungal species (*C. indica*)			
		6.25g/L	12.5g/L	25g/L	50g/L
30 min	64.96±1.8	50.42±3.24	45.45±1.65	17.48±3.65	13.99±1.11
1h	70.42±2.09	55.94±3.68	53.94±3.94	27.97±3.42	17.48±3.27
2h	83.92±1.67	66.47±2.47	59.45±3.43	31.46±2.27	27.97±3.96
3h	90.92±1.3	76.93±3.92	69.93±3.75	38.47±4.21	31.46±2.75
4h	97.9±1.58	83.93±1.35	80.42±2.95	41.96±3.67	34.97±1.67
5h	101.39±2.33	87.43±1.99	84.65±2.64	45.47±2.75	38.45±2.92
6h	111.88±2.57	90.92±2.36	89.92±3.42	52.45±2.52	41.96±3.75
7h	118.89±2.8	94.41±3.64	91.41±1.96	66.44±1.98	55.94±1.07
24h	122.38±1.59	101.41±1.95	97.9±2.75	73.87±2.75	55.94±3.88
Values are means ± SEM for groups of 3 observations with their standard errors					

Table 2. Dose dependent effects of aqueous extracts of *Cantharellus subalbidus* on the movement of glucose out of dialysis bags

Time	Glucose (mg/dl) in external solution (0.15 N NaCl)				
	Control	Concentration of macrofungal species (*C. subalbidus*)			
		6.25g/L	12.5g/L	25g/L	50g/L
30 min	64.96±1.8	69.93±2.37	55.94±3.27	20.97±3.29	25.96±3.24
1h	70.42±2.09	83.93±2.45	62.93±3.78	55.94±1.75	31.46±3.62
2h	83.92±1.67	83.93±3.34	69.93±2.46	62.93±3.36	34.95±1.95
3h	90.92±1.3	90.92±2.85	76.91±3.17	62.95±2.97	34.96±3.76
4h	97.9±1.58	97.90±2.49	83.92±2.72	66.44±1.34	38.46±3.59
5h	101.39±2.33	104.95±3.57	83.92±1.86	73.42±2.57	40.46±2.85
6h	111.88±2.57	111.87±1.30	90.92±2.73	76.93±2.82	45.47±3.74
7h	118.89±2.8	125.89±3.63	104.90±3.92	80.40±3.54	52.45±3.65
24h	122.38±1.59	125.89±3.47	111.88±4.71	87.41±1.36	62.94±2.85
Values are means ± SEM for groups of 3 observations with theirstandard errors					

Table 3. Dose dependent effects of aqueous extracts of *Macrolepiota procera* on the movement of glucose out of dialysis bags

Time	Glucose (mg/dl) in external solution (0.15 N NaCl)				
	Control	Concentration of macrofungal species (*M. procera*)			
		6.25g/L	12.5g/L	25g/L	50g/L
30 min	64.96±1.8	41.96±1.22	20.97±2.64	17.49±2.23	20.97±1.54
1h	70.42±2.09	69.93±2.31	55.94±3.55	27.97±2.16	27.97±2.33
2h	83.92±1.67	73.42±2.90	69.93±2.15	38.47±1.49	30.46±1.89
3h	90.92±1.3	76.91±3.32	74.91±2.79	41.96±2.33	31.46±1.30
4h	97.9±1.58	83.72±1.21	76.91±1.64	48.84±1.43	33.87±3.01
5h	101.39±2.33	90.92±1.67	80.42±2.31	55.99±2.40	34.95±2.19
6h	111.88±2.57	95.85±2.59	82.48±2.55	62.73±1.44	38.47±2.01
7h	118.89±2.8	97.13±2.65	85.65±1.62	69.54±1.90	41.96±1.33
24h	122.38±1.59	104.90±1.23	101.39±4.54	83.93±2.85	48.94±2.98
Values are means ± SEM for groups of 3 observations with their standard errors					

Table 4. Dose dependent effects of aqueous extracts of *Pleurotus florida* on the movement of glucose out of dialysis bags

Time	Glucose (mg/dl) in external solution (0.15 N NaCl)				
	Control	Concentration of macrofungal species (*P. florida*)			
		6.25g/L	12.5g/L	25g/L	50g/L
30 min	64.96±1.8	66.44±2.27	34.97±3.47	17.48±2.74	10.49±2.10
1h	70.42±2.09	73.42±3.92	41.96±3.65	38.47±3.65	13.99±3.45
2h	83.92±1.67	83.93±4.31	48.94±1.84	41.96±3.42	17.48±3.51
3h	90.92±1.3	87.43±2.95	55.81±3.61	45.63±2.62	31.46±2.95
4h	97.9±1.58	90.92±2.28	55.98±2.17	49.44±3.54	31.47±2.37
5h	101.39±2.33	94.48±1.64	62.45±4.28	52.95±2.62	34.98±2.42
6h	111.88±2.57	99.41±3.69	87.91±2.35	62.82±3.50	34.77±3.68
7h	118.89±2.8	101.93±1.95	95.15±2.95	69.53±2.98	38.42±2.94
24h	122.38±1.59	125.87±3.45	101.41±3.38	83.92±3.45	52.65±2.73
Values are means ± SEM for groups of 3 observations with their standard errors					

Table 5. Dose dependent effects of aqueous extracts of *Pleurotus ostreatus* on the movement of glucose out of dialysis bags

Time	Glucose (mg/dl) in external solution (0.15 N NaCl)				
	Control	Concentration of macrofungal species (*P. ostreatus*)			
		6.25g/L	12.5g/L	25g/L	50g/L
30 min	64.96±1.8	20.97±3.45	17.48±1.98	13.99±3.67	10.43±2.84
1h	70.42±2.09	45.45±3.67	38.45±2.34	20.97±3.55	13.99±1.87
2h	83.92±1.67	48.94±2.98	41.96±2.39	24.46±2.75	17.48±3.65
3h	90.92±1.3	52.93±3.75	48.94±1.37	27.97±4.78	20.97±4.67
4h	97.9±1.58	56.44±2.47	50.94±3.17	31.46±3.61	20.99±2.57
5h	101.39±2.33	69.93±3.66	62.93±4.35	31.46±2.73	24.46±3.44
6h	111.88±2.57	89.9±3.78	77.9±1.38	34.96±4.21	27.97±2.37
7h	118.89±2.8	95.89±1.95	80.39±3.67	41.96±2.70	31.48±1.79
24h	122.38±1.59	99.38±3.87	83.87±3.87	54.41±2.66	38.47±2.85
Values are means ± SEM for groups of 3 observations with their standard errors					

DISCUSSION

Present day treatment of diabetes mellitus involves exercise, diet therapy, insulin therapy and oral antidiabetic agents. Despite of their effectiveness in reducing hyperglycemia, the use of these drugs is associated with non-desirable side effects (Adam *et al.*, 2011). Hence herbal medicines can be used as an alternative therapy for treatment of diabetes. These herbal medicines reduce the complications of drugs and help in maintaining normal glucose level without any complication (Pullaiah and Naidu, 2003). Mushrooms are important food sources and represent a vast, untapped source of natural pharmaceutical products (Rushita *et al.*, 2013). In the present studies, a simple *in vitro* dialysis based model was used to investigate various aqueous extract of macrofungi for their antidiabetic properties. Dialysis bags mimic the small intestine of living form which employed simple diffusion of

Table 6. Dose dependent effects of aqueous extracts of *Termitomyces heimii* on the movement of glucose out of dialysis bags

Time	Glucose (mg/dl) in external solution (0.15 N NaCl)				
	Control	Concentration of macrofungal species (*T. heimii*)			
		6.25g/L	12.5g/L	25g/L	50g/L
30 min	64.96±1.8	45.45±1.15	41.96±3.22	13.99±1.22	10.49±3.73
1h	70.42±2.09	52.45±2.48	48.94±3.87	45.45±3.42	31.46±2.90
2h	83.92±1.67	69.93±1.37	55.94±2.97	48.94±2.73	34.96±2.77
3h	90.92±1.3	76.91±3.24	55.94±3.89	52.45±3.27	38.47±1.73
4h	97.9±1.58	90.92±1.27	66.44±3.48	55.94±3.59	45.45±2.92
5h	101.39±2.33	94.41±1.88	80.42±2.54	62.93±2.73	45.45±3.79
6h	111.88±2.57	96.9±1.57	87.41±2.48	62.93±2.86	52.45±3.92
7h	118.89±2.8	98.9±2.96	87.41±1.97	66.44±2.79	60.74±3.28
24h	122.38±1.59	101.39±1.97	97.9±3.81	73.42±2.82	69.34±2.23
Values are means ± SEM for groups of 3 observations with their standard errors					

Table 7. Dose dependent effects of aqueous extracts of *Tuber aestivum* on the movement of glucose out of dialysis bags

Time	Glucose (mg/dl) in external solution (0.15 N NaCl)				
	Control	Concentration of macrofungal species (*T. aestivum*)			
		6.25g/L	12.5g/L	25g/L	50g/L
30 min	64.96±1.8	32.45±2.24	23.99±2.77	10.49±3.75	6.98±3.23
1h	70.42±2.09	49.45±3.27	35.94±3.27	19.46±3.27	13.48±1.94
2h	83.92±1.67	61.45±3.97	47.94±3.58	27.94±2.48	17.59±3.88
3h	90.92±1.3	69.93±4.27	59.45±3.78	31.46±1.59	20.99±2.09
4h	97.9±1.58	73.42±1.84	62.93±2.45	34.97±3.87	23.97±2.75
5h	101.39±2.33	76.93±2.73	66.44±4.33	38.47±1.45	27.85±3.82
6h	111.88±2.57	79.93±2.35	69.93±2.73	41.96±3.42	31.46±2.38
7h	118.89±2.8	83.93±3.33	73.33±3.71	48.94±1.89	39.96±1.86
24h	122.38±1.59	97.9±1.37	76.93±1.98	52.45±3.79	45.45±3.90
Values are means ± SEM for groups of 3 observations with their standard errors					

glucose into external solution through semi permeable membrane. In small intestine glucose is co-transported with sodium ions into the epithelium cells of the villi by facilitated diffusion. From villi it moves to capillaries where it dissolves into blood plasma. With the help of blood glucose moves to hepatic portal vein and enters into liver. In liver excess of glucose is absorbed and stored in the form of glycogen (Nelson and Cox, 2004). The model system employed constant agitation to mimic gastrointestinal convection; the model may be limited in that the time for glucose to completely diffuse out from dialysis bags which is not directly comparable with the timing of cellular mechanisms of glucose absorption within the gut (Gallagher *et al.*, 2003; Sattar *et al.*, 2012).

In the present studies, aqueous extracts of *T. heimii*, *C. subalbidus*, *C. indica*, *M. procera*, *P. florida*, *T. aestivum* and *P. ostreatus* exerted a significant inhibitory effect on glucose movement in increasing order. This effect was found to be concentration dependent. Higher the concentration of aqueous extract higher its activity was. Most effective concentration was found to be 50g/L. Aqueous extract of *P. ostreatus* was able to inhibit glucose movement out of dialysis bags at all concentrations tested when compared with other macrofungal extracts and results in 76.09% reduction on glucose movement out of dialysis bags. *T. aestivum* was also very much effective in comparison to other extracts but its effect was little lower than *P. ostreatus.* Gallagher *et al.* (2003) clearly stated that mushroom extract significantly decrease glucose diffusion up to 27% when compared to

Table 8. Comparative efficacy of macrofungal species with standard antidiabetic drug

Treatment / Time	Metformin	*C. indica*	*C. subalbidus*	*M. procera*	*P. florida*	*P. ostreatus*	*T. heimii*	*T. aestivum*
30 min	4.81±1.98	13.99±1.11	25.96±3.24	20.97±1.54	10.49±2.10	10.43±2.84	10.49±3.73	6.98±3.23
1h	10.55±2.07	17.48±3.27	31.46±3.62	27.97±2.33	13.99±3.45	13.99±1.87	31.46±2.90	13.48±1.94
2h	12.67±1.33	27.97±3.96	34.95±1.95	30.46±1.89	17.48±3.51	17.48±3.65	34.96±2.77	17.59±3.88
3h	17.68±1.79	31.46±2.75	34.96±3.76	31.46±1.30	31.46±2.95	20.97±4.67	38.47±1.73	20.99±2.09
4h	19.85±2.66	34.97±1.67	38.46±3.59	33.87±3.01	31.47±2.37	20.99±2.57	45.45±2.92	23.97±2.75
5h	22.92±2.8	38.45±2.92	38.46±2.85	34.95±2.19	34.97±2.42	24.46±3.44	45.45±3.79	27.85±3.82
6h	24.57±2.97	41.96±3.75	45.47±3.74	38.47±2.01	34.97±3.68	27.97±2.37	52.45±3.92	31.46±2.38
7h	28.82±2.71	55.94±1.07	52.45±3.65	41.96±1.33	38.47±2.94	31.48±1.79	60.74±3.28	39.96±1.86
24h	34.61±2.15	55.94±3.88	62.94±2.85	48.94±2.98	52.45±2.73	38.47±2.85	69.34±2.23	45.45±3.90
Values are means ± SEM for groups of 3 observations with their standard errors								

Table 9. Effect of aqueous macrofungal extract (50g/L) on the movement of glucose out of dialysis bags over 24 h incubation periods

Test	Glucose in external solution		
	AUC*(mmol/L per 24 h) Mean±SEM	Decrease of movement** (%)	Glucose inside membrane
Control (In absence of extract)	2754.52±2.30	-	27.972±3.54
Metformin	211.9±1.75	79.54	99.822±2.47
C.indica	642.4±0.98	63.11	62.928±1.98
C.subalbidus	794.60±2.37	57.44	55.98±2.57
M. procera	679.95±2.54	64.17	66.582±3.69
P.florida	755.37±3.78	69.20	80.496±2.66
P.ostreatus	459.70±3.55	76.09	97.902±3.50
T.heimii	1203.6±3.12	54.93	41.958±3.85
T.aestivum	630.96±2.58	73.60	95.540±1.64

Values are means (SEM) for group of 3 observation
* AUC (area under curve) was calculated according to Gallagher *et al.* (2003) using total glucose diffusion over 24 h incubation period as described in the methods section and expressed as mg/dl per 24 h.
** Percentage decre ase in movement of glucose into the external solution in comparison to control.

control during *in vitro* study. Previous studies have demonstrated that some macrofungal extracts increased pancreatic insulin secretion and insulin dependent glucose uptake and metabolism *in vitro* (Gray and Flatt, 1998).

Edible mushrooms have been recognized as the ideal food for prevention of hyperglycemia as they have high content of fibre, protein and a low fat content (Yang *et al.*, 2008). Many mushroom species appear to be effective for both the control of blood glucose levels and the modification of the course of diabetic complications. 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 (reduction of blood glucose levels) and antihyperglycemic effects. Mushrooms are known to contain compounds which help in proper functioning of the liver, pancreas and other endocrinal glands, thereby promoting formation of insulin and related hormones which ensure healthy metabolic functioning (Silva *et al.*, 2012).

Polysaccharides, such as β glucans contained in mushrooms have the ability to restore the function of pancreatic tissues by causing increased insulin output by β-cells, which leads to lowering of blood glucose levels. It has also been shown to improve the sensitivity of peripheral tissues to insulin. Consumption of mushrooms markedly decreases the lipid levels including total cholesterol, total triglyceride and low-density lipoproteins and increases the level of high-density lipoproteins (Kaur *et al.*, 2015).

CONCLUSION

Macrofungi are widely available in nature and show wide range of therapeutic activities. Present work clearly confirms that aqueous extract of macrofungi showed a significant inhibitory effect on glucose diffusion out of dialysis bags in *in vitro* condition thus validating the effect of macrofungi against diabetes. In particular macrofungi can be used as an alternative drug for diabetic treatment which helps in controlling blood glucose as well as to overcome various complications because of it.

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