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ORIGINAL ARTICLE

Interaction of aqueous extract of *Pleurotus pulmonarius* (Fr.) Quel.-Champ with acarbose in alloxan induced diabetic mice

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Summary
Mushrooms are a low calorie food with very little fat and are highly suitable for obese persons. The objective of the present investigation was to study the interaction of aqueous extract of *P. pulmonarius* (called PP-aqu) with acarbose on serum glucose levels, and on the oral glucose tolerance test (OGTT) in alloxan induced diabetic mice. PP-aqu (500 mg/kg), acarbose (50 mg/kg) and their combination were administered orally in alloxan (70 mg/kg i.v.) induced diabetic mice. In the acute study, the serum glucose level was estimated at 0, 2, 4, 6 and 24 h after drug administration. The subacute study involved repeated administration of the drugs for 28 days, a serum glucose level estimation at 7, 14, 21 and 28 days and recording of the body weights of the mice. In the OGTT, D-glucose (2.5 g/kg) was administered in diabetic mice half an hour after pre-treatment with PP-aqu (500 mg/kg), acarbose (50 mg/kg) and their combination. Serum glucose levels were estimated 30 min prior to glucose administration and at 0, 30, 60 and 120 min after glucose loading. The antihyperglycaemic effects of PP-aqu and acarbose alone were similar; i.e. the onset was 2 h, the peak effect was 6 h but the effect waned at 24 h. The effect of the combination of PP-aqu with acarbose was however different, as serum glucose was lower at 24 h. In the subacute study, repeated administration (once a day for 28 days) of the acarbose, PP-aqu and combination caused a significant ($P<0.001$) reduction in the serum glucose level as compared to the vehicle treated group. Combination treatment prevented a decrease in the body weight of the diabetic mice. In the OGTT test, the combination of PP-aqu with acarbose increased the glucose threshold at 120 min after the administration of glucose. The combination treatment of PP-aqu with acarbose produced a more synergistic antihyperglycaemic effect than either drug alone.

Keywords: P. pulmonarius – acarbose – alloxan diabetes – serum glucose – OGTT

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INTRODUCTION

Mushrooms are a group of fleshy macroscopic fungi, which until recently, along with other fungi, were included in the plant kingdom because of their cell wall and spores. Mushrooms have been valued throughout the world as both food and medicine for thousands of years (Tribe and Tosco 1973, Wright 2004, Lindequist et al. 2005).

There are many varieties of mushrooms species one of which – *Pleurotus* - is characterized

by a white spore print, attached to gills, often with an eccentric stip, or no stip at all. It is commonly known as the "oyster mushroom" (Miles and Chang 1997).

Mushrooms are highly nutritive as they contain good quality proteins, vitamins and minerals (Flegg and Maw 1976, Khanna and Garcha 1984). Mushrooms are a low calorie food with very little fat and are highly suitable for obese persons. With no starch and very low sugars, they are the "delight of the diabetics" (Bano 1976). In adequate quantities they can serve as medicinal food for diabetes. Earlier studies have reported insulin release and insulin- like activity of other mushroom species such as *Agaricus campestris* (Swanston-Flatt et al.1989, Gray and Flatt 1998, Talpur et al. 2002). Badole et al. (2006a) reported the hypoglycaemic activity of *P. pulmonarius* in diabetic mice.

The increasing use by patients of herbal medicinal products along with prescription medicines, suggests that adverse herb-drug interactions may be of significant public health consequence (Coxeter et al. 2004). Geriatric patients often add herbal medicines to medications prescribed by their physicians, yet do not always inform the physician (Bressler 2005). Whereas most herbal remedies, when used as directed and under the supervision of knowledgeable individuals, are safe, the potential for adverse effects or intoxications certainly exists. In addition, because nearly all herbal remedies contain multiple, biologically active constituents, interaction with conventional drugs is a concern (Fugh-Berman and Ernst 2001, Poppenga 2002, Woodward 2005). Hence, the likelihood of herb-drug interactions is theoretically higher than drug-drug interactions (Izzo 2005).

On the other hand, the combination of herbal drugs (or isolated phytochemicals) is found to be beneficial in certain diseases when given along with conventional drugs (Kelly 2004, Samane et al. 2006, Zeng et al. 2006). Herbal agents when given in combination with prescription medication may favourably alter the pharmacokinetics (Singh et al. 2005) as well as the pharmacodynamics of prescription medications (Awang et al. 2002, Kelly 2004, Lin et al. 2004). However, to date, there is less evidence relating to the herb-drug interaction in the case of antidiabetic medicines and understanding of the mechanisms involved is also far from complete (Izzo 2005). Studies of their interaction with rosiglitazone (Badole et al. 2006b) and glyburide (Badole et al. 2007) have been reported.

The objective of the present investigation is to study the interaction of aqueous extract of *P. pulmonarius* with acarbose on serum glucose levels and on the oral glucose tolerance test (OGTT) in alloxan induced diabetic mice.

MATERIALS AND METHODS

Drugs and chemicals

The mushroom of *Pleurotus pulmonarius* (Fr.) Quel.-Champ (Lentinaceae) was provided to us as a gift sample from Bajaj Orchard, Pvt. Ltd., Mumbai, India. It was authenticated by Dr. A. M. Mujumdar, Department of Botany, at Agharkar Research Institute, Pune and a voucher specimen was deposited at that Institute. Acarbose (Glenmark Pharma. Ltd., Mumbai, India), alloxan monohydrate (Spectrochem, India), glucose estimation kit (Accurex Biomedical Pvt. Ltd., India) and D-glucose (S.D. Fine-Chem. Ltd, India) were purchased from the respective companies.

Experimental animals

Swiss albino mice (25-30 g) of either sex were purchased from the National Toxicology Centre, Pune, India. They were maintained at a temperature of 25 ± 1 °C and relative humidity of 45 to 55% under 12-h light : 12-h dark cycle. The animals had free access to food pellets (Chakan Oil Mills, Pune, India) and water *ad libitum*. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Poona College of Pharmacy, Pune.

Preparation of aqueous extract of P. pulmonarius (PP-aqu)

A weighed quantity of powdered air-dried *Pleurotus pulmonarius* was added to distilled water (1:15), boiled for 20 min in a water bath, cooled to room temperature and filtered. The filtrate was dried on a tray dryer at 70 ºC. (yield 24% w/w). The dry extract powder was dissolved in distilled water to prepare the drug solution in a concentration of 100 mg/ml which was used for the pharmacological studies.

Induction of experimental diabetes

Diabetes was induced in mice by a single intravenous injection of aqueous alloxan monohydrate (70 mg/kg i.v.) solution. After 48 hours, the animals showing serum glucose level above 200 mg/dl (diabetic) were selected for the study. All the animals had free access to tap water and pellet diet.

Collection of blood and determination of serum glucose

Blood samples from the experimental mice were collected by the retro orbital plexus technique using heparinised capillary glass tubes. The collected blood samples were analyzed for glucose levels by the glucose oxidase peroxidase (GOD/POD) method as described earlier (Abdel-Barry et al. 1997) and serum glucose levels were expressed in mg/dl.

Effect of PP-aqu with acarbose on serum glucose in alloxan induced diabetic mice

Diabetic swiss albino mice of either sex were fasted overnight and divided into four groups (n=6) viz; Group I - vehicle (distilled water, 10 ml/kg), Group II - acarbose (50 mg/kg), Group III - PP-aqu (500 mg/kg) and Group IV - PP-aqu (500 mg/kg) with acarbose (50 mg/kg). PP-aqu and acarbose were given orally.

The acute study involved estimation of serum glucose levels at 0, 2, 4, 6 and 24 h after PP-aqu and acarbose administration. The animals had free access to feed and water after 6 h.

The sub acute study involved repeated administration of PP-aqu and acarbose for 28 days (once a day) at a prefixed time and serum glucose levels were estimated in samples withdrawn after 2 h on day 7, 14, 21 and 28. (Badole et al. 2006a). The animals had free access to feed and water during this period. The data was represented as mean serum glucose level and standard error of mean (SEM).

Effect of PP-aqu with acarbose on body weight in diabetic mice

During the study period of 28 days the mice were weighed daily and their body weights were recorded. From this data, mean change in body weight and SEM were calculated and tabulated.

Oral glucose tolerance test (OGTT) in diabetic mice

The diabetic animals were fasted overnight before commencing the experiment. Diabetic mice were divided into four groups (n=6) viz; Group I - vehicle (distilled water, 10 ml/kg), Group II - acarbose (50 mg/kg), Group III - PP-aqu (500 mg/kg) and Group IV - PP-aqu (500 mg/kg) with acarbose (50 mg/kg).

The mice of all the groups were loaded with D-glucose (2.5 gm/kg p.o.) solution after half an hour of drug administration (Latha and Pari 2003, Badole et al. 2006a, b, 2007). Blood samples were withdrawn by the retro orbital plexus technique before drug administration and at 30, 60 and 120 minutes after glucose loading. The serum glucose was estimated immediately in the samples.

Statistical analysis

Data was expressed as mean ± SEM and statistical analysis was carried out by two-way ANOVA with *post hoc* Dunnett's test performed using GraphPad InStat version 3.00 for Windows 95, GraphPad Software, San Diego California USA, www.graphpad.com. The significance level was considered at $2\alpha=0.05$.

RESULTS

A single administration of PP-aqu (500 mg/kg) as well as acarbose (50 mg/kg) significantly reduced serum glucose level at 2, 4 and 6 h after administration. The reduction in serum glucose from basal value (before) at 6 h after acarbose, PP-aqu and their combination was 241.15, 213.05 and 214.92 mg/dl respectively. The onset of the antihyperglycaemic effect of PP-aqu and acarbose alone was at 2 h; the peak effect was at 6^{th} h but the effect waned at 24 h. The combination of PP-aqu with acarbose resulted in lowered serum glucose at 24 h. The significant ($P<0.001$) reduction in serum glucose from basal value (before) at 24^{th} h was 108.26 mg/dl (Table 1).

In the subacute study, repeated administration (once a day for 28 days) of acarbose, PP-aqu and their combination caused a significant reduction in the serum glucose level as compared to the vehicle treated group. On the 28^{th} day the reductions in serum glucose level of acarbose, PP-aqu and combination were 182.48, 169.97 and 214.71 mg/dl respectively (Table 2).

The body weight of vehicle treated diabetic mice decreased during the study period. Acarbose, PP-aqu and combination treatment prevented the decrease in body weight of diabetic mice. On the other hand, mice gained body weight which indicated a beneficial effect of combination (Table 3).

In the oral glucose tolerance test, administration of glucose load (2.5 g/kg) increased serum glucose levels significantly after 30 min in alloxan treated diabetic mice (Table 4). Acarbose (50 mg/kg) or PP-aqu treatment alone produced a significant ($P<0.001$) increase in the glucose threshold within 30 mins which was then reversed at 120 min after glucose loading. Combination of PP-aqu with acarbose significantly increased the glucose threshold at 120 min (Table 4).

DISCUSSION

Many mushroom varieties have been reported to possess hypoglycaemic activities in animals (Swanston-Flatt et al. 1989, Gray and Flatt 1998) as well as in diabetic patients (Konno et al. 2001). *Agaricus bisporus*, has been shown to retard the development of hyperglycaemia, hyperphagia, polydipsia, body weight loss, and glycated haemoglobin in streptozotocin treated mice by counteracting the reduction in plasma and pancreatic insulin concentration and by improving the hypoglycaemic effect of exogenous insulin (Swanston-Flatt et al. 1989). The antihyperglycaemic effect of PP-aqu alone was limited to 6 h (with onset effect at 2 h). But the

Table 1. **Effect of aqueous extract of *P. pulmonarius* and acarbose on serum glucose level of alloxan induced diabetic mice (Acute study)**

Treatment (mg/kg p.o.)	Mean fasting serum glucose level (mg/dl, SEM)				
	0 h	2 h	4 h	6 h	24 h
Vehicle (10 ml/kg)	431.79 ± 10.97	434.70 ±10.80	443.04 ± 13.16	452.43 ± 13.83	456.09 ± 14.67
Acarbose (50)	472.14 ± 19.87	365.73 ± 16.14***	261.79 ± 15.54***	231.89 ± 12.10***	433.28 ± 31.27
PP-aqu (500)	444.29 ± 13.05	348.22 ± 15.24***	231.24 ± 9.59***	212.10 ± 13.55***	445.09 ± 9.55
PP-aqu (500) + Acarbose (50)	462.99 ± 16.85	348.14 ± 17.50***	297.65 ± 13.34***	248.07 ± 9.48***	354.73 ± 19.87***

n=6, Data was analysed by two-way ANOVA followed by *post hoc* Dunnett's test.
***P<0.001, compared to vehicle treated group (distilled water, 10 ml/kg)

Table 2. **Effect of aqueous extract of *P. pulmonarius* and acarbose on serum glucose level of alloxan induced diabetic mice (Subacute study)**

Treatment (mg/kg p.o.)	Mean fasting serum glucose level (mg/dl, SEM)				
	Day 0	Day 7	Day 14	Day 21	Day 28
Vehicle (10 ml/kg)	431.79 ± 10.97	448.38±6.57	457.23 ± 4.88	460.95 ± 19.86	431.96 ± 18.47
Acarbose (50)	472.14 ± 19.87	358.39 ± 14.51***	334.56 ± 17.55***	282.18 ± 18.45***	289.66 ± 18.45***
PP-aqu (500)	444.29 ± 13.05	361.87 ± 14.64***	290.33 ± 15.46***	317.21 ± 14.83***	274.32±14.83***
PP-aqu (500) + Acarbose (50)	462.99 ± 16.85	354.73 ± 16.09***	303.29 ± 11.08***	273.50 ± 9.87***	247.28 ± 14.4***

n=6, Data was analysed by two-way ANOVA followed by *post hoc* Dunnetts test.
*** statistically significant as compared with vehicle treated group (distilled water, 10 ml/kg)

Table 3**: Effect of acute pretreatment of aqueous extract of** *P. pulmonarius* **and acarbose on body weight of alloxan induced diabetic mice**

Treatment (mg/kg, p.o.)	Mean body weight (g)				
	Day 0	Day 7	Day 14	Day 21	Day 28
Vehicle (10 ml/kg)	32.00 ± 1.41	26.33±0.75	24.33±0.66	22.33±0.66	17.83±0.60
Acarbose (50)	36.17 ± 1.33	34.37±0.36***	36.29±2.39***	36.33±2.38***	37.00±1.20***
PP-aqu (500)	31.17 ± 2.04	32.00±0.60***	33.00±0.70***	33.00±0.70***	33.10±0.56***
PP-aqu (500) + Acarbose (50)	34.10 ± 1.56	34.89±0.57***	33.17±0.87***	32.00±0.86***	31.57±0.87 ***

Symbols as in the table 1

Table 4: **Effect of oral glucose tolerance test of aqueous extract of *P. pulmonarius* and acarbose on serum glucose level of alloxan induced diabetic mice**

Treatment (mg/kg, p.o.)	Mean fasting serum glucose level (mg/dl, SEM)				
	Before glucose	0 min	30 min	60 min	120 min
Vehicle (10 ml/kg)	421.53±18.59	465.76±4.54	457.46±11.22	385.90±11.02	434.62±12.16
Acarbose (50)	497.56±20.85	567.75±6.47	465.07±5.13***	474.59±9.56***	532.60±27.28*
PP-aqu (500)	489.35±20.75	542.69±8.44	310.43±8.37***	326.69±10.29***	485.56±10.39
PP-aqu (500) + Acarbose (50)	470.99±12.78	541.70±11.25	479.90±15.90*	401.94±15.81***	378.35± 18.22***

Symbols as in the table 1

combination of PP-aqu and acarbose showed a sustained antihyperglycaemic effect at 24 h. (Table 1) suggesting the advantage of combination in longterm treatment. The more pronounced effect of the extract in alloxan-induced diabetic mice may possibly be due to the increased action of insulin which is normally limited or compromised in diabetic condition, and conversely a greater and more direct role of the antihyperglycaemic principle present in the extract. Several antihyperglycaemic principles from plant origin have been reported to have antihyperglycaemic effects up to 24 h. (Akhtar et al. 1985, Hikino et al. 1985, Takahasi et al. 1985). In the present study, the combination of PP-aqu with acarbose showed its peak effect at 6 h. It thus seems possible that more than one phytochemical constituent from PP-aqu may contribute to the anti-hyperglycaemic effect.

In the present study, PP-aqu alone or in combination with acarbose protected the weight loss induced by alloxan; similar findings are observed in other plant extracts (Swanston-Flatt et al. 1989, Badole et al. 2006a, b). These studies substantiate the usefulness of herb-drug combinations in the long-term treatment of diabetes.

Many varieties of mushrooms have been reported to possess antihyperglycaemic activity through various mechanisms like glucose/insulin metabolism and/or by enhancing peripheral insulin sensitivity (Talpur et al. 2002a, Talpur et al. 2002b) or by enhancing insulin release by Islets of Langerhans (Ewart et al. 1975, Gray and Flatt 1998). Insulin-releasing and insulin-like activity in *A. campestris* (a variety of mushroom) has been reported (Gray and Flatt 1998). Lectins from *Agaricus bisporus* and *Agaricus campestris* stimulate insulin and glucagon release from isolated rat islets in the presence of glucose and specific interaction between mushroom lectin and its receptors that facilitate exocytosis (leading to conformational changes in the structure of the membranes of the islet α_2- and ß-cells) has also been proposed (Ewart et al. 1975). The effects of water-soluble extract of the Maitake mushroom have been reported to have anti-hyperglycaemic activity by lowering of circulating glucose and insulin concentrations and it has been suggested that they work primarily by enhancing peripheral insulin sensitivity (Manohar et al. 2002).

Guanide, a known hypoglycaemic substance related to the biguanide class of oral antidiabetic drugs, has been detected in edible mushroom of the *Pleurotus* species (Windholz 1983) and might be responsible for the anti-diabetic effect. This phytochemical might be responsible for the synergistic action of PP-aqu with acarbose against alloxan induced diabetic mice as well as the OGTT that is observed in our study.

Acarbose is an alpha-glucosidase inhibitor which competitively inhibits the digestion of oligosaccharides to monosaccharides, so that glucose is slowly absorbed throughout the length of the small intestine, rather than rapidly in the proximal jejunum (Lebovitz 1998, Raptis and Dimitriadis 2001).

Mushrooms contain a variety of secondary metabolites, including various phenolic compounds, which have been said to act as excellent antioxidants (Ishikawa et al. 1984, Cheung and Lee 2000, Fu and Shieh 2002, Mau et al. 2002, Yang et al. 2002). Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense, is considered to be an important pathogenic factor in diabetes mellitus and its complications (Gumieniczek et al.2005). It has been postulated that enhanced generation of reactive oxygen species (ROS) may take part in a pathogenesis of diabetic microvascular complication – retinopathy (Siemianowicz et al. 2004). The relationship between the antioxidant potential of herbs and their antidiabetic activity have been shown many times (Sabu 2004, Ramkumar et al. 2004, Reddy et al. 2005). Niacin-bound chromium constituents from the Maitake mushroom (Talpur et al. 2002a, Talpur et al. 2003) and nicotinamide (Pan et al. 1995) are reported to ameliorate diabetes mellitus in laboratory animals as well as in the clinic. Therefore, the antioxidant components in PP-aqu (niacin and ascorbic acid that are present in remarkable proportion) might be an important contributory factor in the antihyperglycaemic effect of *P pulmonarius*.

Preliminary phytochemical analysis of the *P. pulmonarius* showed the presence of proteins, minerals, vitamins and carbohydrates (data not tabulated). Such constituents are confirmed also by the Food and Agriculture Organization of the United Nations (FAO 1968). Mushrooms contain approximately 20-35% proteins. The glycoprotein constituents have been shown to have had an antihyperglycaemic effect. (Kusano et al. 2001).

It is thus apparent from the results that PP-aqu (500 mg/kg) showed a significant antihyperglycaemic effect in alloxan induced diabetic mice. PP-aqu (500 mg/kg) in combination with acarbose (50 mg/kg) showed a synergistic antihyperglycaemic effect which may be due to increased insulin secretion or an increased glucose threshold.

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