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HYPOGLYCEMIC ACTIVITY OF FRUITING BODY EXTRACTS FROM *Pycnoporus sanguineus* (L.: Fr.) Murrill MUSHROOM

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ABSTRACT

Alpha-amylase and α-glucosidase are two main enzymes involved in carbohydrate metabolism. Inhibition of α-amylase and α-glucosidase can be said as an effective treatment for delaying the absorption of glucose after meals in people with diabetes mellitus. The objective of the this study is to provide an *in vitro* evidence for the potential hypoglycemic activity via inhibitory activity of the ethanolic and aqueous extracts from fruiting bodies of *Pycnoporus sanguineus* mushroom on α-amylase and α-glucosidase enzymes. Alpha-amylase and α-glucosidase inhibitory activities of ethanolic and aqueous extracts from *P. sanguineus* fruiting body were examined in a dose-response manner. Acarbose was used as a positive control and the results showed that the ethanolic extract of *P. sanguineus* possessed strong inhibitory activity on α-amylase and α-glucosidase with IC_{50} values of 97.08 and 92.60 μg/mL, respectively. The aqueous extract also exhibited moderate activity against α-amylase and α-glucosidase with IC_{50} values of 150.15 and 102.29 μg/mL, respectively. Which was significantly lower than that of acarbose with IC_{50} values of 85.12 and 68.36 μg/mL, respectively. The degree of α-amylase and α-glucosidase inhibition was correlated with the dose of inhibitors. From these results *Pycnoporus sanguineus* possesses high potential in lowering blood glucose level, reduced insulin resistance and the risk of diabetic-related complications.

Keywords: *Pycnoporus sanguineus*, alpha-amylase, alpha-glucosidase, diabetes mellitus, hypoglycemic activity, inhibitory activity.

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INTRODUCTION

Pycnoporus sanguineus (L.: Fr.) Murrill (Syn. *Trametes sanguinea* (L.) Lloyd, accession number: MH225776.1) mushroom has been considered as one of the 25 major medicinal macrofungi worldwide (Boa, 2004). This mushroom is known to be rich in various bioactive substances like anti-bacterial, anti-fungal, anti-viral, antiparasitic, anti-oxidant, anti-inflammatory, anti-proliferative, anti-cancer, anti-tumour, cytotoxic, anti-HIV, hypocholesterolemic, anti-diabetic, anti-coagulant, hepatoprotective, and more others activities (Wasser & Weis, 1999; Ajith & Janardhanan, 2007).

Diabetes mellitus (DM) is a chronic metabolic disorder of the endocrine system. It is now considered the third-ranked dangerous disease of the humans following cardiovascular disease and cancer. DM is characterized by chronic hyperglycemia and metabolic disorders (carbohydrate, fat and protein metabolism disturbances) caused by defects of insulin secretion (type 1 DM), due to increased cellular resistance to insulin (type 2 DM) or by both causes. Type 2 DM is more common in diabetic populations. The consequence of this is characterized by an abnormally high level of blood glucose or known as hyperglycemia that leads to serious damage of various body organs.

When there is not enough insulin, body tissues, in particular, the liver, muscle and adipose tissues fail to take up and utilize glucose from the blood circulation. Although genetic factor is a main risk factor in the development of DM, it is possible to modify DM via lifestyle and food diet in combating the disease (Okada, 2011).

DM is rapidly increasing in the whole world and currently become the third "killer" of human health. The prevalence of type 2 DM has been estimated to increase from 50 million now, to 225 million by 2020 and is expected to increase to 300 million by 2025 (Maggi et al., 2013). Uncontrolled DM disease leads to the development of both acute and long-term chronic complications such as retinopathy, neuropathy, amputation, organ dysfunction involving the eyes, kidneys, nervous system, heart and damage of vascular systems thereby increase the risk of cardiovascular diseases (Genuth et al., 2003). Untreated complications resulted from this disease can lead to death (Ortiz et al., 2010).

In Vietnam, the prevalence of diabetes is growing at alarming rates and has almost doubled within the past 10 years. Currently, it's estimated that one in every 20 Vietnamese adults has diabetes. In addition, the number of people with a prediabetic condition is three times higher than those with diabetes. Severe complications, such as feet ulcers, gangrene and resulting amputations, cardiovascular diseases, blindness and kidney failures are common in diabetic patients. These complications are the main causes of death and disability for people with diabetes. In 2015, it is estimated that 53,458 people died because of diabetes in Vietnam. The treatment costs, along with travel costs to hospitals as well as the loss of productivity due to illness and prolonged hospitalization can debilitate a whole family and drain funds for basic subsistence. According to the International Diabetes Federation, the diabetes-related expenditures in Vietnam are on average 162.7 USD per patient per year in 2015. This was more than the average monthly salary of 150 USD in Vietnam (WHO in Vietnam, 2016).

Currently, many kinds of anti-diabetic medicines are available in the market such as sulfonylureas, biguanides, glinides, tolbutamide, troglitazone, rosigitazone and repaglinide. However, most of them are too toxic, costly, and they give rise to negative effects to the patients and significantly fail to alter the course of diabetic complications. Furthermore, the major focus of current anti-diabetic research is the development of hypoglycemic agents that are safe and free of negative side effects such as nausea, diarrhoea, liver problems and weight gain (Malviya et al., 2010). Recently, many researchers are working on an alternative therapeutic approach 2 for combating DM by decreasing postprandial hyperglycemia via delaying the absorption of carbohydrates through the inhibition of carbohydrate hydrolysing enzymes, α-amylase and α-glucosidase enzymes in the digestive tract using compound from natural sources such as polysaccharides, proteins, steroids terpenoids and alkaloids (Etxeberria et al., 2012). These compounds are originated from medicinal mushrooms in which *Pycnoporus sanguineus* mushroom is a typification. The present study is the first on evaluation of hypoglycemic activity of this mushroom via *in vitro* α-amylase and α-glucosidase inhibition.

MATERIALS AND METHODS

Materials

Ethanolic and aqueous extracts from fruiting bodies of the mushroom *Pycnoporus sanguineus* (this mushroom was planted on the formula of compost consisting of 50% corn cobs and 50% rubber sawdust).

Chemicals and reagents

Alpha-amylase from porcine pancreas (A3176-500KU), α-glucosidase from *Saccharomyces cerevisiae* (G5003-100UN) and p-Nitrophenyl-α-D-glucopyranoside (p-NPG) were the products of Sigma-Adrich Co., USA; Other reagents are acarbose (Bayer Pharma AG, Germany); Na_2CO_3 0.2 M; Phosphate buffer pH 7.0; HCl 1 N; Iodine 0.1 N; Starch soluble (Extra pure); DMSO buffer (Prolabo, France).

Qualitative phytochemical analysis

Phytochemical compositions of fruiting body extracts from *P. sanguineus* were determined using the methods variously

described by Harborne (1973), Trease & Evans (1989), Sofowora (1993), Njoku & Obi (2009).

Test for flavonoids

1 mL of ethanolic/aqueous extract from fruiting bodies of *P. sanguineus* was added to 1.0 mL of $Pb(OAc)_4$ (10%). The formation of a yellow precipitate is taken as a positive test for flavonoids.

Test for saponins (Foam Test)

Approximately 5 mL of the ethanolic/aqueous extract from fruiting bodies of the *P. sanguineus* was mixed with 5 mL of distilled water in a test tube warmed, and shaken vigorously for 1 min. The formation of stable foam is taken as an indication for the presence of saponins.

Test for tannins

2 mL of the ethanolic/aqueous extract from fruiting bodies of the *P. sanguineus* were mixed with 2 mL of distilled water and few drops of $FeCl_3$ (5%) and stirred. The formation of a green precipitate is an indication for the presence of tannins.

Test for terpenoids

About 1 mL of the ethanolic/aqueous extract from fruiting bodies of the *P. sanguineus* was added to 2 mL chloroform. Then 3 mL of concentrated sulphuric acid was added carefully to form a layer. A reddish-brown coloration of the interface indicates the presence of terpenoids.

Determination of alpha-amylase inhibitory activity

This assay was carried out using a modified procedure of Kusano et al. (2011) and Hanh et al. (2014). One hundred µL each of the inhibitors with various concentrations (20, 40, 80, 120 and 160 µg/mL) were placed in tubes and 100 µL of phosphate buffer (0.05 M, pH 7.0) containing 50 µL α-amylase solution (0.5 U/mL) was added, mixed, and incubated at 37°C for 10 min. Next, 250 µL of starch solution (0.25 mg/mL) was added at timed intervals and then incubated further at 37℃ for 10 min. Finally, the reaction was stopped by adding 200 µL of HCl (1 N), and then the solution was reacted with 300 µL of iodine solution (0.1 N) for 30 min at room temperature to determine the remaining starch content based on the characteristic blue color of "starch-iodine". A control was prepared using the same procedure replacing the extracts and α-amylase with 250 µL of phosphate buffer (pH 7.0). The absorbance was measured at 660 nm using a microplate reader (Thermo Spectronic Genesys 10 UV Vis Spectrophotometer, Thermo Electron Corporation, USA). Acarbose was used as a positive control for this assay. The experiment was arranged with three replications. Percentage inhibition is calculated as:

Efficiency of starch metabolism (%) = $[(Abs_{control} - Abs_{extracts/acarbose})/Abs_{control}] \times 100$

Inhibitory activity (%) = 100 – %Efficiency of starch metabolism

Notes: $Abs_{control}$: The optical density values of negative control (samples do not contain the extracts and α-amylase).

$Abs_{extracts/acarbose}$: The optical density values of test samples.

Concentrations of the extracts resulting in 50% inhibition of enzyme activity (IC_{50}) were determined graphically.

Determination of alpha-glucosidase inhibitory activity

Alpha-glucosidase inhibitory assay was performed as previously described by Kim et al. (2011) with modification as follows. The substrate solution p-Nitrophenyl-α-D-glucopyranoside (p-NPG) and α-glucosidase was prepared in phosphate buffer (pH 7.0). 100 µL of α-glucosidase solution (0.23 U/mL) was preincubated with 50 µL of various concentrations of the inhibitors (10, 20, 60, 100, 120, 140 and 160 µg/mL) at 37℃ for 10 min. Then, 50 µL of p-NPG substrate solution (4 mM) was added to start the reaction. The reaction mixture was incubated at 37℃ for 20 min and the reaction was stopped by adding 1 mL of Na_2CO_3 (0.2 M). A control was prepared using the same procedure replacing the extracts with 50 µL of DMSO. p-Nitrophenol absorption was measured at 405 nm using a microplate reader (Thermo Spectronic Genesys 10 UV Vis Spectrophotometer). Acarbose was used as a positive control for this assay. The experiment was arranged with three replications. Percentage inhibition is calculated as:

Inhibitory activity (%) = $[(Abs_{control} - Abs_{extracts/acarbose})/Abs_{control}] \times 100$

Notes: $Abs_{control}$: The optical density values of negative control.

$Abs_{extracts/acarbose}$: The optical density values of the extracts/acarbose samples.

Concentrations of the extracts resulting in 50% inhibition of enzyme activity (IC_{50}) were determined graphically.

Statistical analysis

The data were statistically analyzed by one-way analysis of variance (ANOVA) of the SPSS Statistics 22.0 software. Statistical differences at p-values under 0.05 were considered significant and subsequently compared using the Tukey's test with 95% confidence intervals.

RESULTS AND DISCUSSION

Qualitative phytochemical

The results indicated that both ethanolic and aqueous extracts from fruiting bodies of the *P. sanguineus* contain flavonoids, saponins, tannins and terpenoids (Table 1).

Table 1. Qualitative phytochemical analysis of the ethanolic and aqueous extracts from fruiting bodies of the *P. sanguineus*

Class of compounds	Phenomena	Ethanolic extract	Aqueous extract
Flavonoid	yellow precipitate	+	+
Saponins	stable foam	+	+
Tannins	green precipitate	+	+
Terpenoids	reddish brown	+	+

Notes: (+): present; (−): not detected

Alpha-amylase inhibitory activity

As shown in figure 1, acarbose, ethanolic and aqueous extracts from fruiting bodies of the *P. sanguineus* showed α-amylase inhibitory effects in a dose-dependent manner. Inhibition at various concentrations are significantly different ($p < 0.05$) (Fig. 1).

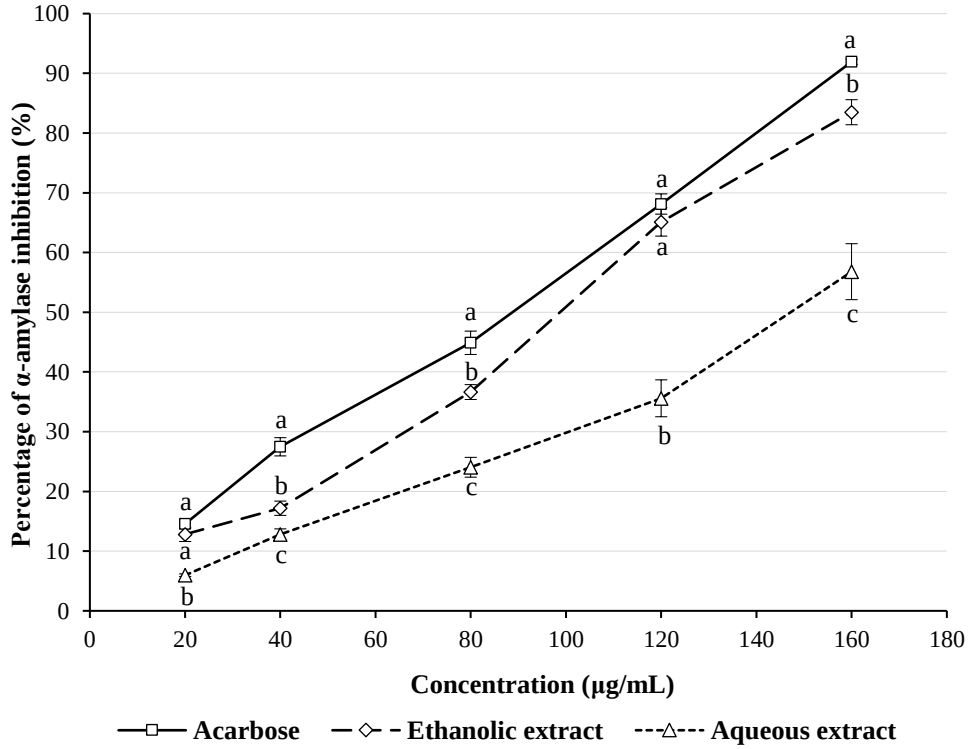

Figure 1. Alpha-amylase inhibitory activity of acarbose (positive control), ethanolic and aqueous extracts from fruiting bodies of the *P. sanguineus* at various concentrations. The values are expressed as the mean ± standard deviation of three replicates (one-way ANOVA followed by Tukey's test). Means not sharing a common letter at the same concentration were significantly different ($p < 0.05$)

The highest α-amylase inhibitory activity at the concentration of 160 µg/mL of each inhibitors was observed from acarbose (91.93%), ethanolic extract (83.49%) and aqueous extract (56.79%) from fruiting bodies of the *P. sanguineus*. IC_{50} values of each inhibitors were 85.12 µg/mL, 97.08 µg/mL and 150.15 µg/mL, respectively (Tabe 2). This result is in agreement with previous report of Geetika et al. (2013).

Tabe 2. IC_{50} values of inhibitors (acarbose, ethanolic and aqueous extracts from fruiting bodies of the *P. sanguineus*) against α-amylase and α-glucosidase with linear regression equation and correlation coefficient

Inhibitors	**IC_{50} values of α-amylase (µg/mL)**	**Linear regression equation and correlation coefficient**	**IC_{50} values of α-glucosidase (µg/mL)**	**Linear regression equation and correlation coefficient**
Acarbose	85.12	y = 0.5426x + 3.8136 R^2 = 0.997	68.36	y = 0.533x + 13.566 R^2 = 0.9924
Ethanolic extract	97.08	y = 0.531x - 1.5512 R^2 = 0.9873	92.60	y = 0.5944x - 5.0432 R^2 = 0.9836
Aqueous extract	150.15	y = 0.3472x - 2.1331 R^2 = 0.9802	102.29	y = 0.5472x - 5.9721 R^2 = 0.9908

The results showed that the ethanolic extract of mushroom had high inhibitory activity, whereas the aqueous extract exhibited moderate activity at the concentrations examined. However, this inhibitory activity of aqueous extract was significantly lower than that of acarbose (positive control). The α-amylase inhibitory activity of the ethanolic extract was significantly higher than that of aqueous extract in the concentrations range of 20–160 µg/mL ($p < 0.05$) (Fig. 1).

Alpha-glucosidase inhibitory activity

Similar to the results of α-amylase inhibition activity, acarbose, ethanolic and aqueous extracts from fruiting bodies of the *P. sanguineus* showed α-glucosidase inhibitory effects in a dose-dependent manner at the concentrations examined. Inhibition at various concentrations are significantly different ($p < 0.05$) (Fig. 2).

The highest α-glucosidase inhibitory activity (at the concentration of 160 µg/mL) was observed from the acarbose (94.72%), ethanolic extract (89.02%) and aqueous extract (82.17%) from fruiting bodies of the *P. sanguineus* with IC_{50} values were 68.36 µg/mL, 92.60 µg/mL and 102.29 µg/mL, respectively (Tabe 2). Alpha-glucosidase inhibition of extracts from fruiting bodies of the *P. sanguineus* in this study is higher than that of the extracts of *Abutilon indicum* leaves (IC_{50} value at 137.61 µg/mL) reported by Geetika et al. (2013). The results showed that both ethanolic and aqueous extracts of mushroom had good α-glucosidase inhibitory activity at all the concentrations examined. However, this inhibitory activity of ethanolic and aqueous extracts was significantly lower than that of acarbose (positive control). The α-glucosidase inhibitory activity of the ethanolic extract was significantly higher than aqueous extract in the concentrations range of 120–160 µg/mL ($p < 0.05$) (Fig. 2).

In this study, inhibitory effects of ethanolic and aqueous extracts of the fruiting bodies of *P. sanguineus* on α-amylase and α-glucosidase activities were evaluated. The both extracts showed potent inhibition on α-amylase and α-glucosidase activities with the superior inhibitory activity in ethanolic extract. These inhibitory actions might be due to the presence of several phytochemicals such as flavonoids, saponins, and tannins. Previous studies revealed that several flavonoids isolated from medicinal plants have inhibitory activity against α-amylase and α-glucosidase (Kwon et al., 2007; Geetika et al., 2013). According to the previous study of Su et al. (2013), six medicinal mushrooms (*Grifola frondosa*, *Hericium erinaceum*, *Agaricus blazei*, *Ganoderma lucidum*, *Coriolus versicolor* and *Phellinus linteus*) from Nantou, Taiwan showed α-amylase inhibitory activities with IC_{50} values of 2,790 µg/mL, 3,350 µg/mL, 6,900 µg/mL, 2,080 µg/mL, 1,200 µg/mL, and 4,080 µg/mL, respectively, which were weaker than that of acarbose (IC_{50} of 39 µg/mL).

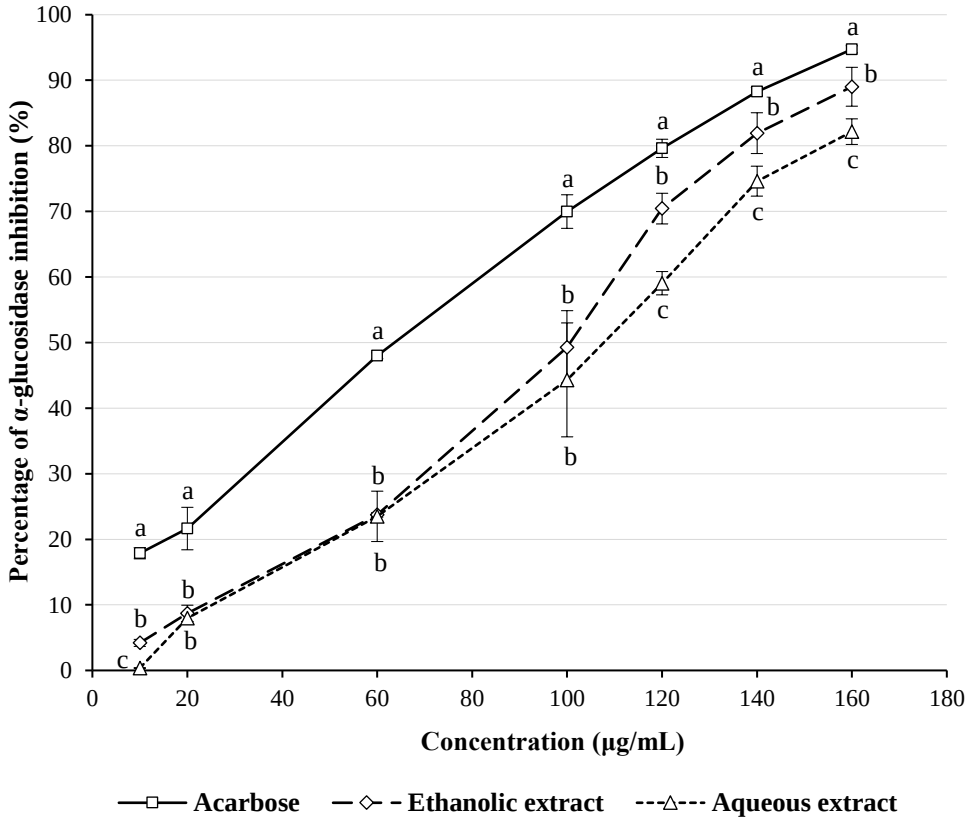

Figure 2. Alpha-glucosidase inhibitory activity of acarbose (positive control), ethanolic andaqueous extracts from fruiting bodies of the *P. sanguineus* at various concentrations. The values are expressed as the mean ± standard deviation of three replicates (one-way ANOVA followed by Tukey's test). Means not sharing a common letter at the same concentration were significantly different ($p < 0.05$)

Inhibition of pancreatic α-amylase is assumed to mitigate the breakdown of carbohydrates and absorption of glucose in the small intestine. Thus, the postprandial blood glucose level in people suffering from diabetes can be controlled to some extent via inhibition of pancreatic α-amylase. This is one of the many strategies approved for the treatment of diabetes mellitus (Sales et al., 2012). This is also an attempt to search for alternative drugs from medicinal plants with increased potency and lesser adverse effects than existing drugs (Matsui et al., 2006; Ogunwande, 2007). In the market, many α-amylase inhibitory drugs, such as acarbose, metformin and others are available, but most of them have adverse side effects (Gyemant et al., 2003; Kwon et al., 2008). For example, acarbose has side effects such as abdominal distention, flatulence, meteorism and possibly diarrhea (Apostolidis & Lee, 2010). Thus, search for novel α-amylase and α-glucosidase inhibitors from natural sources is on desire. Most of the herbal plants and its parts as well as medicinal mushrooms have the tendency to reduce the blood glucose level by their bioactive components such as tannins, terpenoids and flavonoids (Osadebe et al., 2010). Tannins and flavonoids have potential inhibitory effects on α-amylase and α-glucosidase (Poongunran et al., 2015). Alpha-amylase inhibitory effects of tannins were due to its ability to bind with carbohydrates and proteins. The earlier studies proved that, the secondary metabolites like flavonoids, tannins and terpenoids were effectively inhibit α-amylase and α-glucosidase (Osadebe et al., 2010; Ng et al., 2015). In the present study, the ethanolic and aqueous extracts from the fruiting

bodies of *P. sanguineus* significantly inhibits α-amylase with IC_{50} values (97.08 µg/mL, 150.15 µg/mL) and α-glucosidase (92.60 µg/mL, 102.29 µg/mL), respectively. The results also demonstrated that α-amylase and α-glucosidase inhibitory activities of ethanolic extract were higher than aqueous extract, although the inhibitory activities of both extracts were lower than that of acarbose. The present study confirmed the α-amylase and α-glucosidase inhibitory effects of ethanolic and aqueous extracts of *P. sanguineus* suggesting the presence of flavonoids, saponins, tannins and terpenoids. Further studies are required for the identification of anti-diabetic compounds in *P. sanguineus*.

CONCLUSION

Ethanolic and aqueous extracts from fruiting bodies of the *Pycnoporus sanguineus(Trametes sanguinea)* displayed the inhibitory effects on alpha-amylase and alpha-glucosidase with the predominant inhibitory activity in ethanolic extract. It is necessary to conduct further study to isolate the active components which is responsible for these activities of *P. sanguineus* mushroom.

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