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Biosynthesis of glycosidase inhibitors on wheat bread wastes hydrolysate medium by *Streptomyces sp.* 170

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Abstract. The aim of the present study is to investigate the potential effect of bread hydrolysate as a novel nutrient medium for cultivating *Streptomyces sp.* 170 (*S.*170). Moreover, it evaluates the productivity and inhibitory activity of pancreatic α-amylase inhibitors (PAAI). Bread hydrolysate medium (BHM) and corn starch hydrolysate medium (CHM) prepared with α-amylase enzyme concentrations (1.5 and 2.5 units g^{-1} bread) and (1.5 units g^{-1} corn starch), respectively were utilized in the study. The Seherde-Blair and modified Akulova methods were applied to evaluate the carbohydrates concentration and the inhibitory activity of the media respectively. Results of bread and corn media were compared to each other. Furthermore, the activity of PAAI synthesized by *S.*170 was compared to other *Streptomyces* species. The results showed a significant difference ($P < 0.05$) between the total simple sugars (glucose + maltose) concentration produced in CHM (27.5%) and BHM prepared with α-amylase 1.5 units (45.1%). Besides, BHM produced by α-amylase 2.5 units demonstrated the maximum total concentration of simple sugars (49.9%). In addition, 48 h of *S.*170 incubation were quite enough to exhibit the highest inhibitory activity (2,632 IU mL^{-1}) in BHM prepared with α-amylase 2.5 units. The analysis demonstrated a non-significant difference in the inhibitory activity of PAAI in CMH (1,300 IU mL^{-1}) and BMH with α-amylase 1.5 units (1,111 IU mL^{-1}). Also, compared to other *Streptomyces* species, *S.*170 conferred highly active PAAI. In conclusion, BHM showed its efficiency to a great extent in the cultivation of *S.*170 and production of PAAI with a notable high activity.

Key words: bread hydrolysate medium, corn starch medium, *Streptomyces sp.* 170, inhibitory activity, pancreatic α-amylase inhibitors.

INTRODUCTION

Glucosidase enzymes are a group of enzymes, which hydrolyse the complex carbohydrates as starch into simple sugars such as dextrin, maltose and glucose. The pancreatic α-amylase enzyme is considered as one of the glucosidase enzymes. It is

secreted by human pancreas for digesting starch into glucose which is absorbed into the bloodstream. This process elevates the postprandial glucose level in the blood (Selvaraj et al., 2012). α- amylase inhibitors aid blocking the carbohydrate digestion through inhibiting the activity of α- amylase enzymes in the small intestine. Thus, it can delay the digestion of carbohydrates and reduce the postprandial glucose level in blood. Several researchers stated that α-amylase inhibitors can be applied in the biomedical field for treating diabetes millets type 2 and obesity management, also in agriculture field for pests controlling and in the biotechnological field (Paloma et al., 2012; Sujatha et al., 2013; Elizabeth et al., 2017).

α- amylase inhibitors can be obtained from different sources such as medicinal plants, animal and microbial sources, also it can be synthesized chemically. Among all the sources, the microbial source was reported as the best source because of its plasticity for genetic manipulation and potential for economical bulk production. The principal producers for α-amylase inhibitors are some bacteria such as *Streptomyces, Bacillus, Stenotrophomonas maltrophilia* and *Actinoplanes sp. SE*-50, as well as some fungi (Sharova, 2015; Tayyaba et al., 2017; Van Bon et al., 2017). The growth conditions of *Streptomyces* species in liquid media are key factors for controlling the production of secondary metabolites. These metabolites can be antibiotics, antitumor, antifungals, pesticides and enzyme inhibitors (Ferial, 2015). Most of the secondary metabolites are synthesized in the stationary phase of *Streptomyces* growth (Lelia, 1998). The synthesis of secondary metabolites by *Streptomyces* differs quantitatively and qualitatively depending on the composition of liquid medium utilized during the cultivation. The main nutritional requirements for *Streptomyces* cultivation are nitrogen sources such as ammonium salts (ammonium lactate, ammonium nitrate or ammonium chloride) in combination with carbon source such as glucose, mannose, starch (corn or potato) or dextrin and mineral salts such as phosphorus salts (Robert & Hubert, 1954; Linda & Rabab, 2017). However, finding the most desirable liquid medium for cultivating *Streptomyces* is a hurdle, since it varies according to the purpose of their cultivation. The common types of liquid media employed Corn-Glucose broth, Tryptic Soy-Broth (TSB), R2YE and YEME media (Micah et al., 2010; English et al., 2017).

Industrial wheat bread wastes have been skyrocketing over the past decades. They represent 10% of the total production of wheat bread annually, which can provoke massive environmental and economic problems. These bread wastes come from unsold bread in retail stores and substandard produced bread from the industries (Yuji et al., 1997; Ahmet et al., 2016; Sükrü et al., 2017). Wheat bread wastes were reported to contain wide myriad of nutrients such as moisture content – 36.5%; protein – 17%; fat – 0.5%; carbohydrate – 46% (contains 80–82% starch); minerals approximately 1.68% (Ca, P, Mg, Fe) and vitamins (B_1, B_2, Niacin) (Abede et al., 1992; Mohammed & Mohsen, 2009; Shalaby et al., 2014).

In recent years, the biotechnological recycling of wheat bread wastes has been proposed as an interesting solution for managing the wastes of bread by using them as a raw material in preparing a novel liquid medium for the production of valuable secondary products. The main step in bread recycling is the hydrolysis using enzymes to produce hydrolysate media containing simple nutrients like glucose, free amino nitrogen and phosphate. The hydrolysate media can be used in cultivating different microorganisms to produce secondary products like bioethanol, methane, lactic acid, succinic acid, amylase, protease, anaerobic bio-hydrogen and some aroma compounds

(Daniel & Carol, 2013; Ahmet et al., 2016; Saima et al., 2016). Bread hydrolysis entails two main steps: 1 – liquefaction for hydrolysing starch into dextrin and small amounts of maltose and glucose using thermostable α-amylase enzyme; 2 – saccharification for hydrolysing dextrin and maltose into glucose using the glucoamylase enzyme (Fatemeh et al., 2008; Marijana et al., 2014). Many factors can influence the hydrolysis rate, quality of hydrolysed media and yield of hydrolysed nutrients in the media and consequently change the productivity of secondary products. Substrate quantity, substrate particle size, the temperature of hydrolysis, hydro-module, the viscosity of hydrolysed media, enzymes concentration, pH of hydrolysed media and others are the most influential factors (Helena et al., 2017; Sükrü et al., 2017).

Therefore, the objective of this research is to produce a novel nutrient medium by replacing the traditional carbon source of corn starch with bread starch through bread hydrolysis using different enzyme concentrations. Besides, this study evaluates the activity of pancreatic α-amylase inhibitors produced by *Streptomyces sp.* 170 in bread nutrient medium. In addition, it investigates the effect of different enzyme concentrations on the yield of hydrolysed nutrients, as well on the activity and the yield of pancreatic α-amylase inhibitors. The bread hydrolysis was performed using an only thermostable α-amylase enzyme, based on the fact that the *Streptomyces* species are able to produce the glucoamylase enzyme (Razieh, 1993).

MATERIAL AND METHOD

Materials

Enzymes preparations (Table 1) were obtained from Erbsloh Company, German.

Table 1. Enzymes preparations and their properties

Enzymes types	Preparation contents	Activity	Temperature range	pH range
Dystistim BA-T	Bacterial thermostable α-amylase produced from *B. licheniformis stearothermophilus*	950 units AC mL^{-1}	30 to 110 °C	4.5 to 8.0
Dystistim GL	Fungal xylanase produced from *Penicillium funiculosum* and some species of *Trichoderma reesei*	730 units KC mL^{-1}	30 to 90 °C	3.5 to 6.0

Streptomyces sp. 170 (*S.*170) was sourced from the collection VNIIPD – filial of FSFSE 'FSC of food systems of V. M. Gorbatov' RAS, Russia; and stored at low temperature (-12 °C) for 7 months, suspended in 15% glycerol solution.

Wheat bread 'Moskovskii Company, Russia' and corn starch 'Ibred'krakh Malpatoka, Russia' were purchased from local supermarkets. Soy flour was supplied by Partnior-M Company, Russia. Pancreatin preparation was received from Sigma Company, USA.

Methods

Preparation of wheat bread and its hydrolysis

Method of wheat bread preparation for its hydrolysis is presented in the following scheme of bread preparation (Fig. 1).

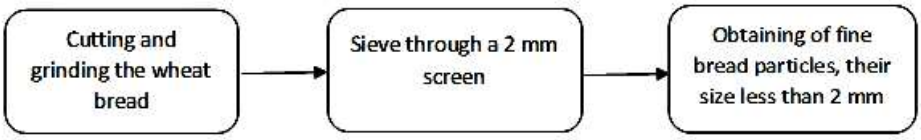

Figure 1. Scheme of wheat bread preparation for its hydrolysis.

The hydrolysis of bread was carried out using thermostable α-amylase enzyme with two different concentrations (2.5 or 1.5 units g^{-1} bread) and xylanase enzyme to produce bread hydrolysate medium (BHM). The technological steps of the bread hydrolysis process are depicted in Fig. 2.

Hydrolysis process of corn starch

Corn starch was hydrolysed using thermostable α-amylase enzyme with a concentration of 1.5 units g^{-1} corn starch and xylanase enzyme. The method of hydrolysis to produce corn starch hydrolysate medium (CHM) is the same as described above.

Physicochemical analysis of bread hydrolysate medium and corn starch hydrolysate medium

Individual analysis of carbohydrates concentration (glucose, maltose, and dextrin) of each medium were quantified using Seherde-Blair method which is a modification of Smirnov method (Tregubov & Kostenko, 1991), whereas the total dry matter concentration (°Brix) and the refractive index were measured with the aid of refractometer PTR46 Index Instruments (Lembe & Umezuruike, 2015).

Media modification and sterilization methods

Corn and bread hydrolysate media were modified, adding soy flour (5.0 g L^{-1}), NaCl (3.0 g L^{-1}), KH_2PO_4 (1.0 g L^{-1}), and $MgSO_4 \times 7H_2O$ (0.5 g L^{-1}), to allow growth of *Streptomyces sp.*170 (*S.*170) and production of pancreatic α-amylase inhibitors (PAAI). The pH of the media was adjusted to 7.0. The media were then sterilized using an autoclave (Tuttnauer, MK 2540, USA), at temperature 121 °C under atmospheric pressure 1 bar (15 psi) for 15 min.

Inoculum preparation

The frozen *Streptomyces sp.* 170 culture was prepared for inoculation by thawing it at temperature 37 °C for 3 min. The titre of the thawed bacterial culture was 10^7–10^8 CFU mL^{-1}.

Bacterial inoculation and its incubation

Periodical deep inoculation of *Streptomyces sp.*170 was carried out under aerobic sterilized conditions with cell titre 10^7–10^8 cells mL^{-1} culture medium. The incubation

was performed in a thermostatic shaker incubator (Multitron, INFORS Company, Switzerland), with speed 230 ± 20 rpm at temperature 29 ± 1 °C for 96 h (Pozdnjakova et al., 2009; Sharova et al., 2009).

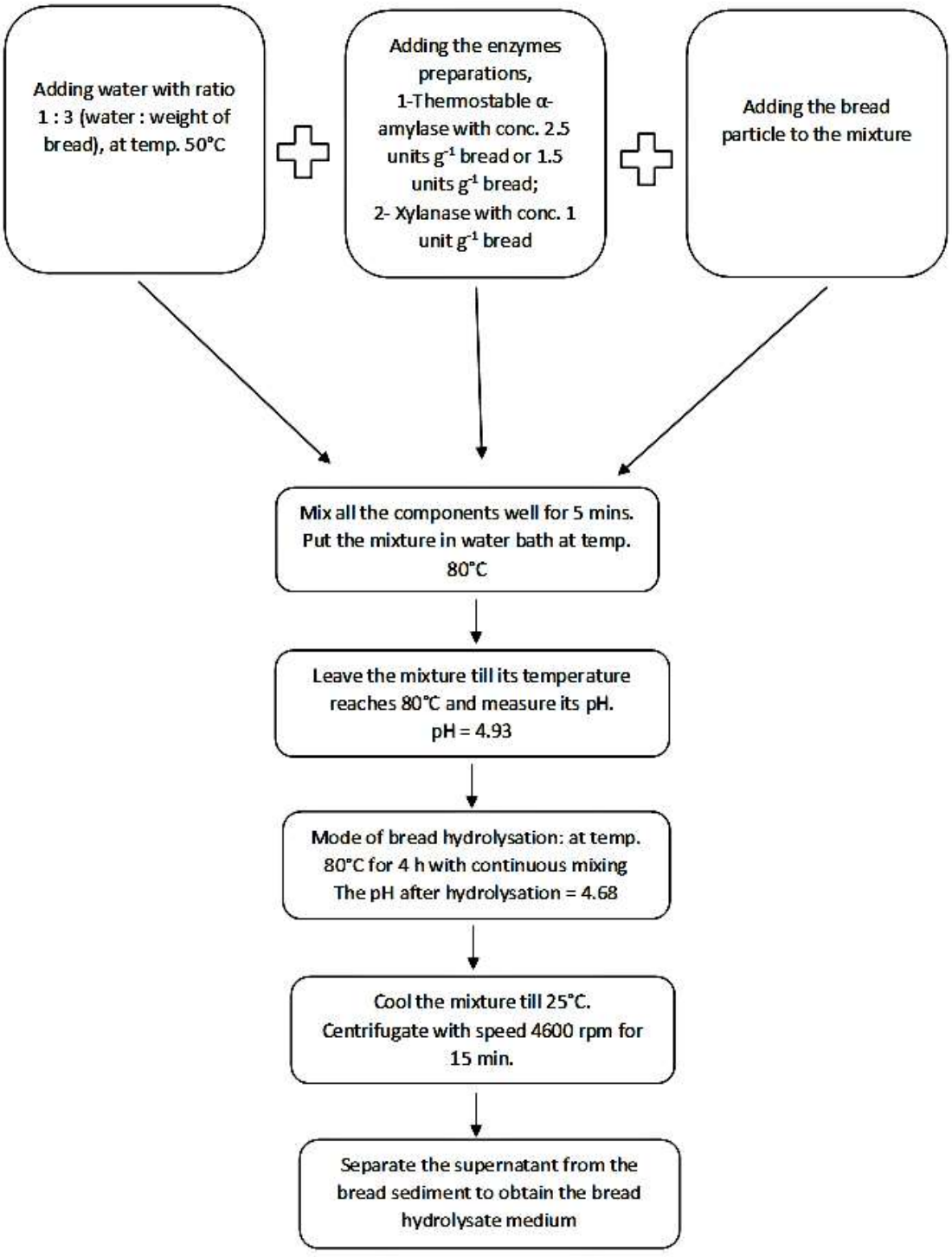

Figure 2. The technological flow chart of bread hydrolysis using thermostable α-amylase and xylanase enzymes.

Determination of inhibitors activity

Samples were taken after 24, 48, 72 and 96 h of incubation and biomass separated via filter element cartridge (Sartorius, Germany) with a polyethersulfone membrane (300 μm) at a pressure of 0.2 MPa and temperature 25 °C. The filtrate was further filtered through a membrane with pores size of 0.45/0.20 μm to remove residual bacterial cells.

The inhibitors activity (IA) was quantified with a spectrophotometer (CF-46, LOMO, Russia) at wavelength 660 nm using a modified Akulova method (Pozdnjakova et al., 2009; Sharova, 2015). Pancreatin preparation consists of pancreatic α-amylase (EC 3.2.1.1; 1,4-α-D-glucan glucanohydrolase) was utilized as the standard.

The inhibitory activity unit (IU) was expressed as IU mL^{-1}. This unit means the amount of inhibitor which can suppress the activity of 1 unit of pancreatic α-amylase by 50% for 10 min at 37 °C and pH 7.0.

The inhibitory activity was calculated by the following equation (1):

$$IA = \frac{D_{00.} - D_2 \cdot 100}{D_1 - D_2 \cdot 50} \cdot K \quad (1)$$

where D_{oo} – is the optical absorption of the experimental sample, nm; D_1 – is the optical absorption of the control sample 1, nm; D_2 – is the optical absorption of the control sample 2, nm; $\frac{D_{00.}-D_2}{D_1-D_2} \cdot 100$ – is the extent of inhibition, %; K – is the dilution factor of the experimental sample; and 50 – is the coefficient of the calculation of the inhibitory extent by 50%. The extent of inhibition should be in the range of 40–55% (Sharova, 2015).

Statistical analysis

All experimental measurements were performed in triplicate to avoid experimental error. The generated data were subjected to analysis of variance (ANOVA one-way) using Origin 61 statistical software with a significant difference at $P \leq 0.05$. The graphical analysis was performed using Microsoft Excel 2013.

RESULTS AND DISCUSSION

The physicochemical parameters of corn starch and bread hydrolysate media

The chemical analysis of corn starch and bread hydrolysate nutrient media shows the presence of glucose, maltose and dextrin with different concentrations according to the type of raw material.

The results analysis of both nutrient media are represented in Table 2 and significant difference ($P < 0.05$) was established between the total concentration of simple sugars (glucose + maltose) produced by corn starch or bread starch hydrolysis using 1.5 units of α-amylase enzyme. In corn starch hydrolysate media (CHM), it was found that the total concentration of simple sugars was 27.5 ± 5.0%. On the other side, the total concentration of simple sugars in bread hydrolysate media (BHM) prepared with α-amylase 1.5 units g^{-1} bread was 45.1 ± 8.2%.

The results could be ascribed to the starch hydrolysis process. Before starch liquefaction using an α-amylase enzyme, starch gelatinization must occur. Starch gelatinization means absorption of water by starch granules at high temperature, which

differs with respect to the type of grain. This can help in physical disruption of starch granules and its exposure to the enzymatic hydrolysis (Uthumporn et al., 2010). The corn gelatinization temperature is between 66–72 °C and the gelatinization temperature for wheat is between 52–66 °C (Marek et al., 2010; Ubwa et al., 2012). The difference in gelatinization temperature between corn and wheat can help the wheat bread begins its hydrolysis faster than the corn hydrolysis, consequently, the wheat bread hydrolysis produces more simple sugars in the hydrolysate nutrient media. This result agrees with the previous observations of Ubwa et al. (2012) which concern the rapid hydrolysis of cereal grains starch with low gelatinization temperature and its conversion into simple sugars.

The results of total dry matter concentration and refractive index presented in Table 2 prove the non-significant difference ($P > 0.05$) between CHM and BHM prepared with 1.5 units of α-amylase enzyme. Therefore, the variance in *Streptomyces sp*. 170 growth rate will depend on the difference of total simple sugars concentration more than the difference of total dry matter concentration in both hydrolysate media.

In addition, the chemical analysis of the bread hydrolysate medium (BHM) prepared with 2.5 units of α-amylase enzyme for each gram bread was evaluated and its results were presented in Table 2. The ANOVA analysis was established between the result of total simple sugars concentration in BHM prepared with 1.5 units of α-amylase enzyme (Table 2) and its result in BHM prepared with 2.5 units of α-amylase enzyme (Table 2), for studying the significant effect of α-amylase enzyme concentration utilized during the BHM preparation on the yield of total simple sugars.

Table 2. Physicochemical parameters of corn starch and bread hydrolysate media

Type of media	Simple sugars (glucose + maltose), %	Dextrin, %	DM, %	RI
CHM with α-amylase 1.5 units	27.5 ± 5.06	72.5 ± 7.39	12.0 ± 4.58	1.3560 ± 3.18
BHM with α-amylase 1.5 units	45.1 ± 8.25	54.8 ± 6.01	15.6 ± 4.72	1.3572 ± 3.47
BHM with α-amylase 2.5 units	49.9 ± 7.11	50.1 ± 4.18	16.0 ± 2.29	1.3576 ± 4.15

The statistical analysis indicates that there is no significant different ($P > 0.05$) between the results of total simple sugars concentration in both BHM prepared by two different concentrations of α-amylase enzyme. This result proves the non-significant effect of utilizing the α-amylase enzyme with different concentrations in BHM preparation on the yield of total simple sugars.

The concentration of total simple sugars in BHM prepared with α-amylase 1.5 units g^{-1} bread was 45.1 ± 8.25%, whereas in BHM prepared with α-amylase 2.5 units g^{-1} bread was 49.9 ± 7.11%. These results were in agreement with the previous work, that the effect of different α-amylase enzyme concentrations had no significant effect on glucose yield during the liquefaction step of bread hydrolysis. Moreover, without the addition of α-amylase enzyme, less glucose yield can be obtained, which demonstrates a synergistic action between α-amylase and glucoamylase enzymes (Sükrü et al., 2017).

A non-significant difference ($P > 0.05$) was observed between the results of total dry matter concentration and refractive index in both hydrolysate media. The non-significant difference ($P > 0.05$) in both concentrations of total simple sugars and total dry matter within hydrolysate media can indicate non-variation in the growth rate of *Streptomyces sp.* 170 and the productivity of secondary metabolites.

Inhibitory activity of pancreatic α-amylase inhibitors produced by *Streptomyces sp.* 170 in corn starch and bread hydrolysate media

The activity of pancreatic α-amylase inhibitors (PAAI) was represented in Fig. 3 and expressed by inhibitory unit per mL nutrient media (IU mL^{-1})

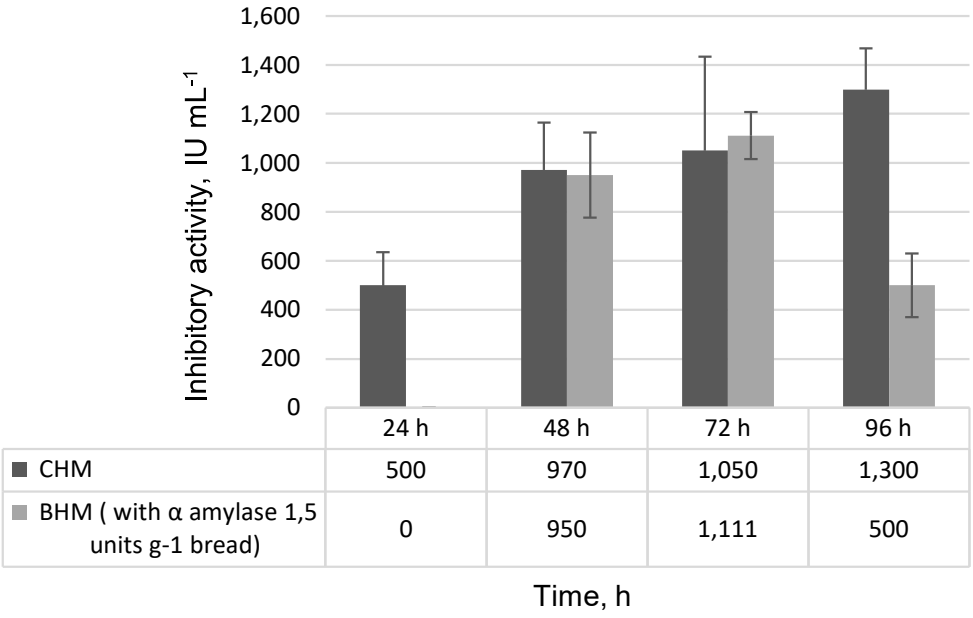

Figure 3. Inhibitory activity of pancreatic α-amylase inhibitors in CHM and BHM.

The results show that the difference between the maximum inhibitory activity in CHM (1,300 ± 100 IU mL^{-1}) and the maximum inhibitory activity in BHM produced with α-amylase enzyme 1.5 units g^{-1} bread (1,111 ± 50 IU mL^{-1}) is not significantly different ($P > 0.05$). Besides, the maximum inhibitory activity of PAAI was obtained after 96 h and 72 h of bacterial incubation in CHM and BHM respectively. According to literature, *Streptomyces* species can utilize glucose and maltose more than dextrin during their growth, thus can increase the production rate of secondary metabolites (Robert & Hubert, 1954; Sharova, 2015). The previous results of carbohydrates analysis revealed more glucose and maltose in BHM when compared to CHM, hence the reason for the rapid production of PAAI in BHM than in CHM. The same results were noticed previously that the highest glucose and maltose concentrations in hydrolysate media aid to rapid production of inhibitors by *Streptomyces* species (Pozdnjakova et al., 2009; Natalya, 2015).

Inhibitory activity of pancreatic α-amylase inhibitors produced by *Streptomyces sp.* 170 in bread hydrolysate media prepared with two different concentrations of α-amylase enzyme

Fig. 4 shows the inhibitory activity of pancreatic α-amylase inhibitors (PAAI) in BHM prepared with two different α-amylase enzyme concentrations (1.5 and 2.5 units g^{-1} bread).

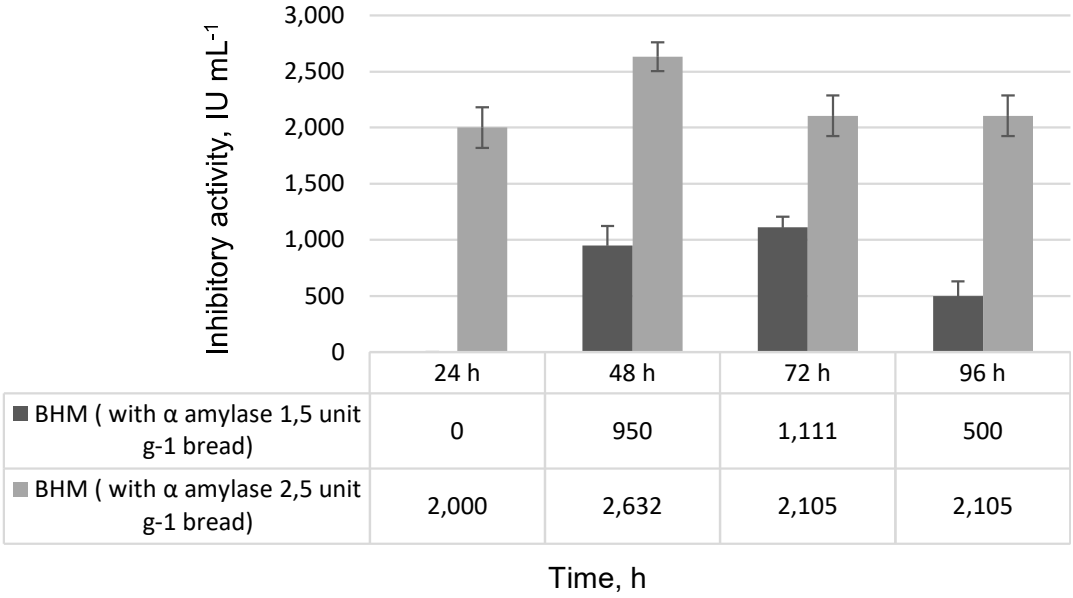

Figure 4. Inhibitory activity of pancreatic α-amylase inhibitors in BHM prepared with two different α-amylase enzyme concentrations.

The diagram shows a significant difference ($P > 0.05$) between the maximum inhibitory activity in BHM prepared with α-amylase 1.5 units g^{-1} bread (1,111 ± 50 IU mL^{-1}) and the maximum inhibitory activity in BHM prepared with α-amylase 2.5 units g^{-1} bread (2,632 ± 100 IU mL^{-1}). Furthermore, the maximum inhibitory activity was obtained after 72 h and 48 h of bacterial incubation in BHM prepared with α-amylase 1.5 unit g^{-1} bread and 2.5 unit g^{-1} bread respectively. The reason of these significant changes in the inhibitory activity can be justified by the slight increment of total simple sugars concentration in BHM prepared with α-amylase 2.5 units g^{-1} bread (49.9 ± 7.11%) than its concentration in BHM prepared with α-amylase 1.5 units g^{-1} bread (45.1 ± 8.25%). The prior investigation also showed a significant effect of glucose concentration in growth media on the productivity and activity of bacterial secondary metabolites (Bharathiraja et al., 2016). The same observation was established by Natalya (2015), which proved the significant effect of increment the α-amylase enzyme concentration during the hydrolysate media preparation to increase the activity of inhibitors produced by *Streptomyces sp.* 170.

The final result proves the ability of *Streptomyces sp.* 170 to produce PAAI with high activity (2,632 ± 100 IU mL^{-1}) in BHM prepared with α-amylase 2.5 unit g^{-1} bread. The inhibitory activity of PAAI produced by different *Streptomyces* species was compared in Table 3.

Table 3. Comparison of the inhibitory activity of pancreatic α-amylase inhibitors produced by different *Streptomyces* species

Bacterial species	Inhibitory activity in the initial media, IU mL^{-1}	Conditions of α-amylase inhibitors production	Reference
Streptomyces lucensis BKIIM Ac-1743**	1,600 ± 100	Starch hydrolysate medium, incubation at 32 °C for 120 h	(Sharova et al., 2018)
Streptomyces violaceus BKIIM Ac-1734**	2,400 ± 100	Starch hydrolysate medium, incubation at 32 °C for 120 h	(Sharova et al., 2018)
Streptomyces species *K*-20	3,200 ± 200	Potato starch hydrolysate medium, incubation at 29 °C for 120 h	(Kolodyaznaya et al., 2014)
Actinoplanaceen S/E 50/13	2,800 ± 280	Sucrose medium, incubation at 30 °C for 120 h	(Xiaolong et al., 2006)
Streptomyces dimorphogenes nov. sp. NR-320-*OM 7HB*	1,240 ± 120	Glucose medium, incubation at 30 °C for 120 h	(Natalya, 2015)
Streptomyces sp. 170	2,632 ± 100	Bread hydrolysate medium, incubation at 29 °C for 48 h	Current study

**: the storage temperature of *Streptomyces lucensis* and *Streptomyces violaceus* was at -12 °C.

CONCLUSION

This article shows that the wheat bread hydrolysate medium could replace the traditional corn starch hydrolysate medium in cultivating *Streptomyces sp.* 170. In addition, the bread hydrolysis could produce higher simple sugars concentration than in corn starch hydrolysis. The different enzyme concentrations had no significant effect on the simple sugars concentration. Nevertheless, a non-significant change in the simple sugars concentration using different enzyme concentrations had a significant effect on the inhibitory activity of pancreatic α-amylase inhibitors. The maximum inhibitory activity of pancreatic α-amylase inhibitors was obtained in bread hydrolysate medium prepared with α-amylase 2.5 units g^{-1} bread after 48 h of bacterial incubation. There was no significant difference between the inhibitory activity of pancreatic α-amylase inhibitors produced in corn starch and bread hydrolysate media. Furthermore, the inhibitory activity reached its peak in bread hydrolysate medium faster than in corn starch hydrolysate medium. Comparing literature data with the current study revealed that *Streptomyces sp.* 170 has the ability to produce pancreatic α-amylase inhibitors with high activity. Therefore, the bread hydrolysate could be employed as a rich nutrient media in cultivating *Streptomyces sp.* 170 for synthesizing pancreatic α-amylase inhibitors with high activity.

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