UTILIZATION OF CASSAVA RESIDUE BY-PRODUCT AS A C/N SOURCE FOR EFFECTIVE PRODUCTION OF PRODIGIOSIN VIA MICROBIAL FERMENTATION

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SUMMARY

Recently, prodigiosin (PG), a red pigment compound produced mainly by Serratia marcescens, has been applied in various fields. Thus, this microbial pigment has been extensively studied for biosynthesis and potential biofuntions. This study aimed to utilize cassava residue by-product (CRBP) as a C/N source for the eco-friend production of PG via fermentation. PG was produced at the highest yield when *Serratia marcescens* TNU1 was grown in the medium containing 1.5% CRBP, 0.2% casein, 0.05% $MgSO_4$, 0.1% K_2HPO_4, with an initial pH of 7.0, and fermentation was performed at 27.5° C for two days. Additionally, PG scale-up bioproduction was investigated in a 14 L bioreactor system, and PG was produced at a high yield (6450 mg/L) in a short fermentation time (12h). This study suggests CRBP is a novel and potential C/N for the cost-effective bioproduction of PG.

Keywords: *Cassava residue by-product, prodigiosin, bioreactor, Serratia marcescens, fermentation.*

1. INTRODUCTION

Prodigiosin (PG), a red pigment, is a ring compound belonging to the prodigionine group with a pyrrolylpyrromethane skeleton. The structure and physicochemical properties of PG are presented in Figure 1 (Nguyen et al., 2020a; Rafael et al., 2022). This microbial pigment was biosynthesised from various microbial strains, including *Serratia marcescens, Serratia rubidaea, Alteromonas rubra, Janthinobacterium lividum BR01, Rugamonas rubra, Streptomyces longisporus ruber 100-19, Serratia coelicolor, Serratia spectabilis BCC 4785, Streptomyces fusant* NRCF69, *Streptomyces* sp., *Vibrio* sp. C1-TDSG02-1, *Vibrio* sp. KSJ45, *V. gazogenes, V. psychroerythrus, Pseudomonas magnesiorubra, Pseudomonas putida* KT2440*, Streptoverticillium* sp. 26-1, *Streptoverticillium rubrireticuli, Pseudoalteromonas* sp., *Pityriasis rubra, Actinomycetes,* and *Pseudomonas putida*. Among them, the main source of PG producing is *Serratia marcescens* (Wang et al., 2020). PG attracted a lot of research due to its potential bio-activities in many fields, such as medicine, agriculture, industry, food, and the environment (Wang et al., 2020). Furthermore, its safety has also proved in many reports (Suryawanshi et al., 2014; Nguyen et al., 2022a; Tomas & Vinas, 2010; Guryanova et al., 2013; Siew et al., 2016; Li et al., 2021).

The study on PG production has been occurring for years. However, almost previous reports investigated the PG biosynthesis on minor scales of various Erlenmeyer flasks, and commercial substrates such as nutrient broth were used as C/N sources for cultivation by different strains of *S. marcescens* (Nguyen et al., 2022b). On the contrary, in this report, we used cassava residue by-product as C/N for fermentation, and a 14L bioreactor system was applied to scale up PG production in this report.

For lower-cost production of PG, several nontraditional media such as sesame oil, sesame seed, peanut oil, cassava, crude glycerol, corn steep, peanut seed, copra seed, coconut oil, and the complexes of mannitol/cassava, and steep were conducted for fermentation (Nguyen et al., 2020a). Some wastes and processed by-products were also utilized for cultivation to produce PG (Wang et al., 2020). Cassava powder and cassava wastewater were also previously used for fermentation to produce this pigment. However, it has not been reported that the cassava residue byproduct (CRBP) being used for PG production via fermentation (Tran et al., 2021).

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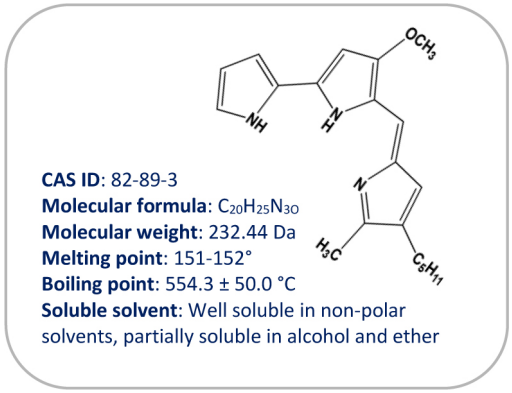


Figure 1. The structure and physicochemical properties of prodigiosin

Cassava (*Manihot esculenta Crantz*), a drought-tolerant crop plant, can be grown in unfavorable conditions even with poor soil quality and unpredictable rainfall (FAO, 2013). Cassava is one of the main staple crops in sub-Saharan Africa and a high-value industrial crop in Asian countries (Nguyen et al., 2020a). Of these, Vietnam was ranked as the top 8th country by cassava production (Rafael et al., 2022). The cassava processing industry generates a large amount of wastes/residues that are rich in organic components that can be good carbon/nitrogen sources for the production of some valuable products by fermentation (Wang et al., 2020; Suryawanshi et al., 2014) for the production of biogases, biosurfactants, biofuels, organic acids, volatile fatty acids, and some aroma components (Wang et al., 2020; Nguyen et al., 2022a; Tomas & Vinas, 2010; Guryanova et al., 2013). In this work, we investigated the potential use of CRBP as a C/N source for microbial fermentation for the eco-friendly production of PG in mass. This green strategy for PG production was summarised in Scheme 1.

2. STUDY CONTENT, MATERIALS AND METHODS

2.1. Study contents

- Establishment of the fermentation process for the production of prodigiosin in flask.

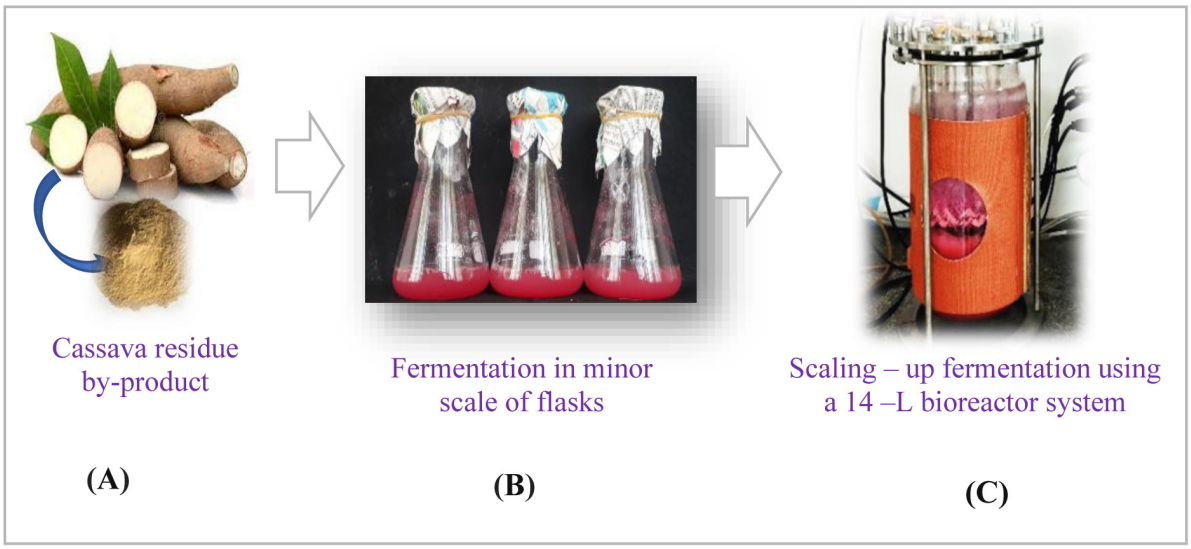
- Scale-up of PG production in a bioreactor system.

2.2. Materials

Cassava wastewater was collected from Buon Ma Thuot City, Dak Lak, Vietnam. Bacterial strains such as *S. marcescens* TKU011, TNU01, TNU02 and CC17 were required from earlier works (Nguyen et al., 2020b; Liang et al., 2013; Nguyen et al., 2019a). Silicagel (Geduran® Si 60, size: 0.040-0.063 mm) was obtained from Merck Sigma Chemical Co. (St. Louis City, MO, USA).

2.3. Methodology

2.3.1. Prodigiosin production via microbial fermentation in a minor scale of flasks



Skim 1. The green strategy for prodigiosin production via fermentation.

The cassava residue by- product was used as C/N sourced for fermentation (A). The cultivation was conducted in the minor scale flasks for determination of suitable fermentation condition (B), then prodigiosin was further investigated for scaling-up production using a 14 – L bioreactor system.

Screening of the suitable PG-producing bacterial strain: the total 4 strains of *S. marcescens* (TUK011, TNU01, TNU02, and CC17) obtained from the previous works (Nguyen et al., 2020b; Wang et al., 2012; Nguyen et al., 2019a) were conducted for fermentation of cassava residue by-product (CRBP). 1.5% CRBP, free protein (0.5% casein), 0.02% K_2SO_4, 0.025% $Ca_3(PO_4)_2$, with

initial pH7.0 was used for cultivated by above 4 bacterial strains at 28°C for 48 h (this fermentation process was denoted by *). The most active strain TNU02 was chosen for further tests.

The effect of casein supplemented in the culture medium on PG yield: casein at different concentrations (0, 0.1, 0.2, 0.3, 0.5, 0.6, and 0.7 %) was supplemented into the culture medium containing 0.02% K_2SO_4, 0.025% $Ca_3(PO_4)_2$, with initial pH7.0. This designed medium was cultivated by TNU02 with the fermentation process presented above (*). 0.2% casein was found as the suitable added concentration for PG biosynthesis, as such was selected for further tests.

The effect of phosphate and sulfate salts added to media on PG yield: some phosphate salts (KH_2PO_4, $Ca_3(PO_4)_2$, Na_2HPO_4, K_2HPO_4, and NaH_2PO_4) were added at their concentration of 0.03% into culture media, while, some sulfate salts (K_2SO_4, $(NH_4)_2SO_4$, $CaSO_4$, $MgSO_4$, $ZnSO_4$, and $FeSO_4$) were added at their concentration of 0.05% into culture media to explore their effect on PG production by *S. Marcescens* TNU02. The most suitable salts were further added in the medium at various concentrations in the range of (0-0.125%) to investigate their most suitable concentration.

2.3.2. Scaling-up production of PG in a 14 L-bio-reactor system

600 ml of *S. marcescens* TNU02 were pre-cultured in a 1 L flask at 27.5°C for 36 h and then injected into the bioreactor system containing 5.4 L of medium containing 1.75% C/N (CRBP/casein in the ratio of 8/2), 0.05% $MgSO_4$, 0.1% K_2HPO_4, with an initial pH of 7.0, and the fermentation process was carried out at an initial pH of 7, and fermentation was carried out at 27.5°C in 12 h of cultivation time. Sampling and detection of the PG yield were performed every 2 h.

2.3.3. Statistical Analysis

The experimental results were analysed using simple variance (ANOVA) then Duncan′s multiple range tests (when the experiment contains more than 5 items that need to be compared) and Fisher's LSD tests (when the experiment contains less than 6 items that need to be compared) were evaluated at p = 0.01. Statistical Analysis Software (SAS-9.4) purchased from SAS Institute Taiwan Ltd (Taipei, Taiwan) was used for statistical analysis.

3. RESULT AND DISCUSSION

3.1. Prodigiosin production by different strains of S. marcescens

For screening the PG-producing bacteria, 4 strains (TKU011, TNU01, TNU02 and CC17) of *S. marcescens* were conducted for the fermentation of medium containing CRBP. The result in Figure 1A indicated that *S. marcescens* TNU01 produced PG with the highest content (4.1 mg/ml), and therefore this strain was selected for further study.

In our previous work, TUK011 was found as the most active strain to convert squid pens into PG (Nguyen et al., 2019a), TNU02 effectively fermented crab shell (Nguyen et al., 2020a), shrimp shell (Nguyen et al., 2021a), and peanut oil cake (Nguyen et al., 2022b) to produce PG, while the CC17 strain demonstrated as a potential PG producer from Shrimp head (Nguyen et al., 2021b). Recently, *S. marcescens* TNU01 was also found a good strain to effective produce PG from medium containing Cassava wastewater, casein, $MgSO_4$, and K_2HPO_4 (Tran et al., 2021). These data contributed to the potential use of S. marcescens TNU01 to produce PG from CRBP.

3.2. The effect of casein supplemented into culture medium on PG production by TNU01

Casein was reported as a suitable free protein source supplemented into the culture medium for effective PG biosynthesis (Nguyen et al., 2020a; Nguyen et al., 2022a; Nguyen et al., 2020b). Thus, casein was also used for adding into the media for PG production in this work. As shown in Figure 1B, casein at a concentration of 0.2-0.5% significantly increased PG yield via fermentation by TNU01. Regarding the ecofriendly and effective bioproduction of PG, casein at 0.2 % was chosen for addition to the media in further tests.

PG has been biosynthesised from various organic wastes such as squid pens, crab shells, shrimp shells, peanut oil cake, brown sugar, fertilizer waste (Nguyen et al., 2022a). Recently, PG was reported being produced from cassava wastewater supplemented with 0.25% casein, however, few available data reported the utilization of CRBP for PG production via microbial fermentation (Wang et al., 2012).

3.3. The effect of phosphate and sulphate salts on PG production by TNU01

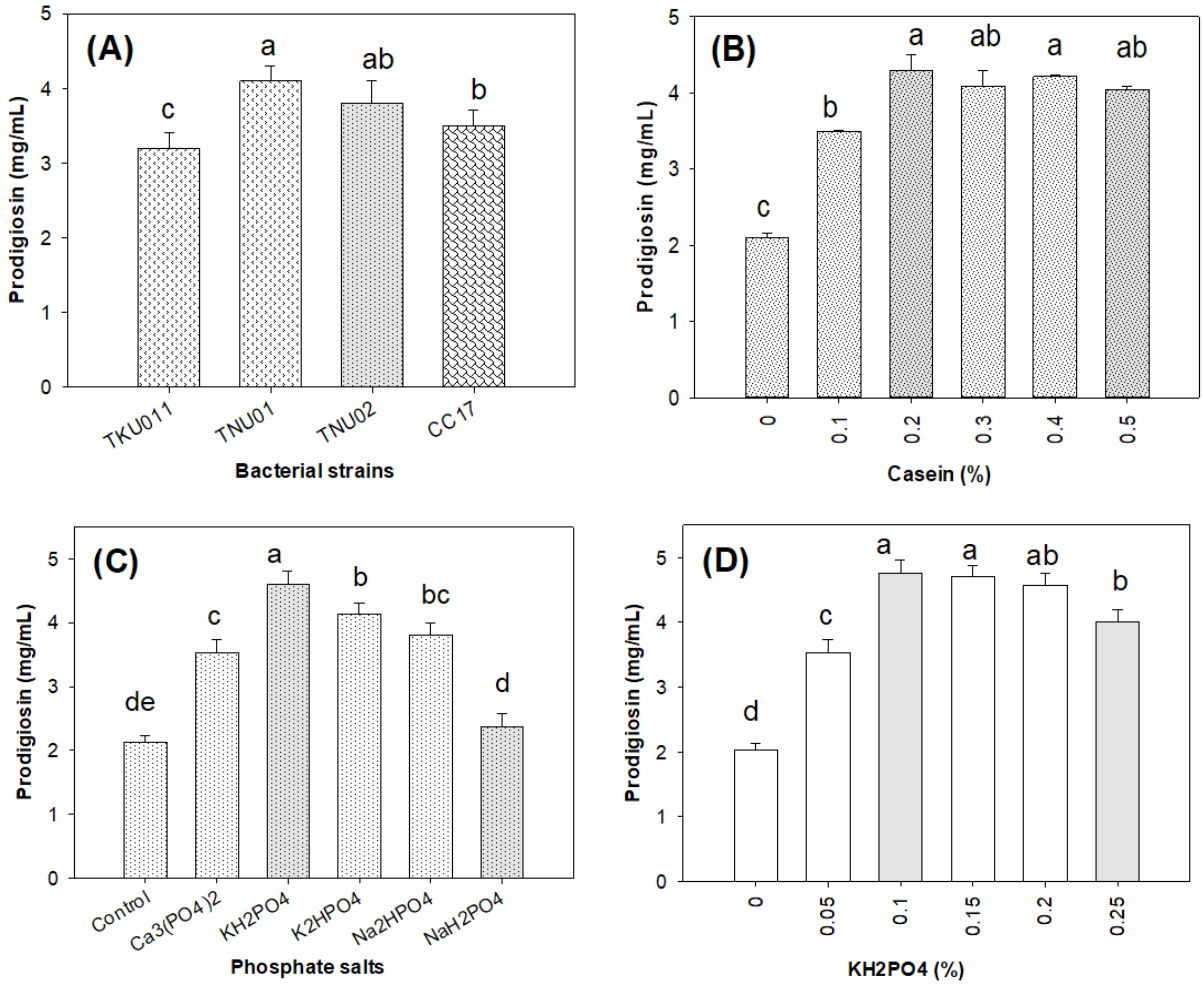
Phosphate and sulphate salts were evidenced as enhanced factors of PG production in *S. marcescens* fermentation (Nguyen et al., 2020a; Wang et al., 2020; Nguyen et al., 2022a; Nguyen et al., 2020b; Wang et al., 2012). Thus, various types of these salts were supplemented into culture media to enhance PG yield. As shown in Figure 1 C, KH_2PO_4 was found to be a suitable phosphate source and its optimal added concentration for the

highest PG production (4.75 mg/ml) was found at 0.1% (Figure 1 D). The experimental results (Figure 1E & F) revealed that PG was produced at high-level yield (5.4 mg/ml) when $MgSO_4$ was added to a cultivated medium at the concentration of 0.075%. Although phosphate and sulphate salts have been widely reported to significantly improve the yield of PG biosynthesized by fermentation of *S. marcescens* fermentation in numerous studies, the mechanisms of action of this positive effect of these salts are mot clear (Tran et al., 2021).

3.4. Scaling-up bioproduction of PG using a 14 L-bioreactor system

Reactor systems are valuable equipment that can be applied for the production of bioactive compounds on a large scale with high-level yield in a short cultivation time (Nguyen et al., 2022b). Therefore, to scale up PG production, a 14 L-bioreactor system was installed for fermentation in this work. The result presented in Figure 2 indicated that PG was biosynthesized by *S. marcescens* TNU01 in the significant amount from 8 h of cultivation and the PG was found produced at the highest yield (6.45 mg/ml) at 12 h of fermentation. Thus, compared to fermentation on a minor scale (in flasks), the utilization of a 14 L-bioreactor system in fermentation resulted in the biosynthesis of PG on a much larger scale with higher yield and a much shorter fermentation time.

For the production of PG in mass from by-products, some studies approached using bioreactor systems for fermentation (Nguyen et al., 2020a; Nguyen et al., 2019a; Nguyen et al., 2020c; Nguyen et al., 2021a; Nguyen et al., 2021b; Qi et al., 2019; Vijayalakshmi et al., 2016; Tao et al., 2005; Aruldass et al., 2014). As summarised in Table 1, various reactor scales (1.5-50L) were applied for fermentation to obtain PG yield in the range of 583-8109 mg/L. Especially, the utilization of bioreactors for fermentation significantly reduced fermentation time compared to use of flasks. Furthermore, the PG yield also increased significantly by 1.2-1.3 folds and even highly increased up to 34.2 and 76.7 folds in some reports by Aruldass et al 2014 (Aruldass e t al., 2014) and Qi et al. 2019 (Qi et al., 2019), respectively.



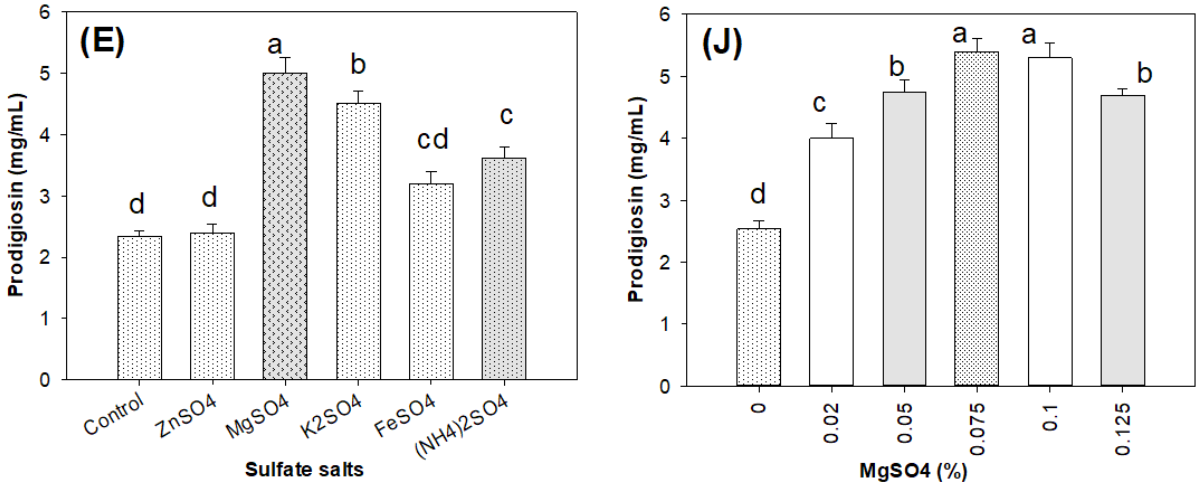


Figure 1. The effect of *S. marcescens* strains and medium compositions on the production of prodigiosin via fermentation.

The effect of different S. marcescens strains (A), casein concentration (B), the sources of phosphate salts (C), KH_2PO_4 concentration (D), the sources of sulphate salts (E), and $MgSO_4$ concentration supplemented into the media (J) on prodigiosin yield production by S. marcescens TNU1. Phosphate and sulphate salts were not added to the control medium (C and E). Values in the same figure with the different letters are significantly different. Standard errors (SE) are shown as error bars.

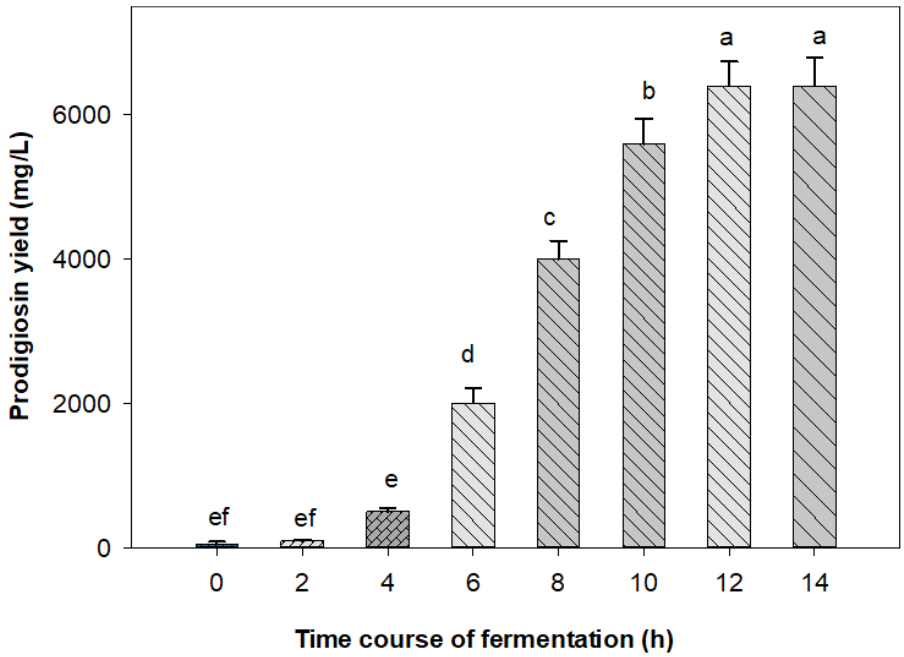


Figure 2. Scale-up prodigiosin bioproduction by S. marcescens TNU1 using a 14L bioreactor system. Values in the same figure with the different letters are significantly different. Standard errors (SE) are shown as error bars.

Table 2. Prodigiosin production in a large-scale reported by various studies.

***S. marcescens* Strains**	**Substrates**	**Maximum PG yield (mg/L) in cultivation time (hours)**		**Culture volume (L) /Bioreactor (L)**	**Enhancing yield (folds)**	**Re.**
		In flasks	**Bioreactors**			
S. marcescens TNU01	cassava residue by-product, casein	5400 (48h)	6450 (12h)	6 L (14L)	1.2	This study
S. marcescens TUN02	Peanut oil cake	5380 (48h)	6886 (10h)	4L (14L)	1.3	Nguyen et al., 2022b
S. marcescens TNU01	Squid pens powder	3790 (48h)	3450 (12h)	3L (10L)	-	Nguyen et al., 2022c
S. marcescens TNU01	Cassava wastewater, casein	5202 (48h)	6150 (8h)	7L (14L)	1.2	Nguyen et al., 2019a
S. marcescens TUN02	Shrimp shell powder, casein,	5910 (36h)	6200 (8h)	5L (15L)	1.18	Nguyen et al., 2021a
S. marcescens TUN02	Crab shell powder, casein,	4514 (36h)	5100 (8h)	4.5L (15L)	1.3	Nguyen et al., 2020a
S. marcescens CC17	Shrimp head powder, casein	5355 (60h)	6310 (8h)	6.75L (12L)	1.2	Nguyen et al., 2021b
S. marcescens NS-17	Maltose, peptone, Tween-80, soybean oil,	60.5 (56h)	4644.6 (56h)	47.8L (50L)	76.7	Qi et al., 2019
S. marcescens	Peanut oil cake	40.9 (30h)	50 (30h)	1.5L (3L)	1.22	Vijayalakshmi & Jagathy, 2016
S. marcescens B6	Two-step feeding strategy with glycerol	ND	583 (30h)	2.5L (5L)	ND	Tao et al., 2005
S. marcescens UTM1	Brown sugar	237 (24h)	8109 (24h)	5L (5L)	34.2	Aruldass et al., 2014

ND: No determined.

4. CONCLUSIONS

Serratia marcescens TNU1 was screened as a potent strain for PG production. A newly designed medium consisting of 1.5% CRBP, 0.2% casein, 0.05% $MgSO_4$, and 0.1% K_2HPO_4, with an initial pH of 7.0 were found for cost-effective production of PG. This pigment compound was further successfully produced on a large scale with high-level yield of 6450 mg/L in a short fermentation time (12 h) using a 14-L bioreactor system. The results of this work demonstrated the potential use of cassava residue by-product as a C/N source for the effective production of PG via microbial fermentation.

5. FUNDING

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ỨNG DỤNG PHỤ PHẨM BÃ SẮN LÀM NGUỒN C/N CHO QUÁ TRÌNH LÊN MEN TỔNG HỢP HOẠT CHẤT PRODIGIOSIN

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TÓM TẮT

Hiện tại, prodigiosin (PG), một hợp chất màu đỏ thu nhận chủ yếu từ vi khuẩn *Serratia marcescens* được ứng dụng trong nhiều lĩnh vực. Do đó, hợp chất này thu hút nhiều nghiên cứu về sinh tổng hợp và khảo sát tiềm năng hoạt tính sinh học. Mục tiêu của nghiên cứu này là tận dụng phụ phẩm bã sắn làm nguồn cơ chất cho lên men tổng hợp PG. Hoạt chất PG đã được tổng hợp với hàm lượng cao bởi vi khuẩn *Serratia marcescens* TNU1 với thành phần môi trường 1,5% phụ phẩm bã sắn, bổ sung 0,2% casein, 0,05% $MgSO_4$, 0,1% K_2HPO_4, pH ban đầu của môi trường là 7,0, lên men trong 2 ngày ở 27,5°C. PG tiếp tục được được nghiên cứu tăng cường sinh tổng hợp thông qua sử dụng hệ thống lên men lỏng tự động (bioreactor loại 14 lít), kết quả cho thấy PG được tổng hợp với sản lượng cao (6.450 mg/L) với thời gian lên men ngắn (12h). Nghiên cứu này cho thấy phụ phẩm bã sắn là nguồn cơ chất mới, tiềm năng cho quá trình lên men sinh tổng hợp hoạt chất PG.

Từ khóa: *Phụ phẩm bã sắn, prodigiosin, bioreactor, Serratia marcescens, lên men.*

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