PRODUCTION OF VIOLACEIN NANOPARTICLES VIA SONICATION TECHNIQUE WITH THE AID OF SURFACTANTS AS STABILIZER

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DEDICATION

This thesis is dedicated to my beloved father and mother, Mohd Hamzah bin Hassan and Norimah binti Salatin who have been very supportive through thick and thin for this meaningful two years. Thanks for all the prayers, advices and guidance.

Special thanks to all my wonderful friends who brighten my life with all the joys, sadness, smiles and laughters. This friendship has been very great experience in my life.

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ABSTRACT

Violacein, a violet pigment produced from *Chromobacterium violaceum* UTM5, has gained interest due to its biodegradability and pharmacological properties. However, its high production cost and limited solubility in water have become the major stumbling blocks for the pigment to be applied in different industries. In this study, liquid pineapple waste was used as an alternative inexpensive growth medium for bacteria cultivation instead of expensive synthetic nutrient broth, thus reducing the production cost of this pigment. The cultivation of *C. violaceum* in 50 L bioreactor gave a crude yield of 11846 ± 925 mg L^{-1}, which was comparable to the yield obtained using commercial growth medium. The crude pigment was successfully extracted using ethyl acetate. The presence of violacein, the major active compound of the crude pigment, was confirmed using high performance liquid chromatography (HPLC), Fourier transform infrared spectroscopy (FTIR) and ultraviolet-visible spectrophotometry (UV-Vis). Thermal gravimetric analysis was used to determine crystallinity and thermal degradation while Zetasizer analyzer was used to identify the isoelectric point, stability at various pHs, and particle size of violacein. Violacein nanoparticles were produced via sonication technique, with the aid of surfactants (Tween 80, Triton X-100, sodium dodecyl sulfate and dodecyltrimethylammonium bromide) as solubilizing and stabilizing agent, to address the violacein's poor solubility in water. The violacein nanoparticles were characterized using UV-Vis spectrophotometry, FTIR, thermal analysis and Zetasizer analysis. Water soluble violacein nanoparticles were produced at surfactant concentration greater than its critical micelle concentration, as indicated by FTIR. Zetasizer analysis showed the smallest violacein nanoparticle, which was 131.5 ± 2.001 nm, with polydispersity index (PDI) of 0.180 ± 0.018, which indicated a monodispersed violacein nanoparticle distribution. The thermal analysis showed that violacein nanoparticles were in amorphous state and stable upon dispersion in water, with a zeta potential of -49.8 ± 3.49 mV. The violacein nanoparticles have better solubility than the crude violacein pigment. The solubilized violacein nanoparticles remained well-dispersed upon storage in 28 days at different temperatures. In addition, the violet color of the violacein nanoparticles was maintained at pH range of 3 to 11, temperatures of up to 60°C, and under dark condition, despite its nanoscale size. Higher degradation rate was observed at high temperature and upon light illumination, with $k = 6.51 \times 10^{-3}$ h^{-1}, $t_{1/2}$ = 148 h and $k = 6.75 \times 10^{-4}$ h^{-1}, $t_{1/2}$ = 1027 h, respectively, following the first-order kinetics. In conclusion, this study confirmed the feasibility of using liquid pineapple waste as cheap growth medium for cultivation of *C. violaceum* UTM5 in pilot scale (50-L bioreactor) while production of water-soluble violacein nanoparticles via sonication method with the aid of surfactants as stabilizers would increase its usefulness, especially in pharmaceutical industry.

ABSTRAK

Violasin, pigmen ungu yang terhasil daripada *Chromobacterium violaceum* UTM5, telah menarik banyak perhatian kerana sifat keterbiodegradan dan farmakologinya. Walau bagaimanapun, kos penghasilan yang tinggi dan keterlarutannya dalam air yang terhad menjadi penghalang utama untuk pigmen ini digunakan dalam pelbagai industri. Dalam kajian ini, sisa nenas cecair telah digunakan sebagai medium pertumbuhan alternatif yang murah bagi pemeliharaan bakteria untuk menggantikan kaldu nutrien sintetik yang mahal, seterusnya mengurangkan kos pengeluaran pigmen ini. Pemeliharaan *C. violaceum* di dalam bioreaktor bersaiz 50 L menghasilkan pigmen mentah sebanyak 11846 ± 925 mg L^{-1}, yang setanding dengan hasil yang diperoleh menggunakan medium pertumbuhan komersial. Pigmen mentah telah berjaya diekstrak menggunakan etil asetat. Kehadiran violasin, komponen aktif utama di dalam pigmen mentah, telah disahkan menggunakan kromatografi cecair berprestasi tinggi (HPLC), spektroskopi inframerah transformasi Fourier (FTIR) dan spektrofotometri ultra ungu-cahaya nampak (UV-Vis). Analisis gravimetri terma telah digunakan untuk menentukan kehabluran dan degradasi haba manakala penganalisis Zetasizer telah digunakan untuk mengenalpasti titik isoelektrik, kestabilan pada pelbagai pH, dan saiz zarah violasin. Nanopartikel violasin telah dihasilkan menggunakan teknik sonikasi, dengan bantuan beberapa surfaktan (Tween 80, Triton X-100, sodium dodekil sulfat dan dodekiltrimetilammonium bromida) sebagai agen pelarut dan penstabil untuk menangani keterlarutan violasin yang rendah dalam air. Nanopartikel violasin telah dicirikan menggunakan spektrofotometri UV-vis, FTIR, analisis terma dan analisis Zetasizer. Nanopartikel violasin yang mudah larut dalam air telah berjaya dihasilkan pada kepekatan surfaktan melebihi kepekatan kritikal misel, seperti yang ditunjukkan oleh FTIR. Analisis Zetasizer menunjukkan saiz nanopartikel violasin yang terkecil iaitu 131.5 ± 2.001 nm, dengan indeks kepoliserakan (PDI) 0.180 ± 0.018, yang menunjukkan taburan nanopartikel violasin yang sekata. Analisis terma menunjukkan nanopartikel violasin berada dalam keadaan amorfus dan stabil apabila terserak di dalam air dengan potensi zeta -49.8 ± 3.49 mV. Nanopartikel violasin mempunyai keterlarutan yang lebih baik berbanding pigmen violasin mentah. Nanopartikel violasin yang larut ini kekal terserak apabila disimpan selama 28 hari pada suhu yang berbeza. Tambahan pula, warna ungu nanopartikel violasin masih kekal pada julat pH antara 3 dengan 11, suhu sehingga 60°C, dan dalam keadaan gelap walaupun saiznya berskala nano. Kadar degradasi violasin yang lebih tinggi telah dilihat pada suhu tinggi dan apabila terdedah pada cahaya, masing-masing dengan $k = 6.51 \times 10^{-3}$ h^{-1}, $t_{1/2} = 148$ h dan $k = 6.75 \times 10^{-4}$ h^{-1}, $t_{1/2} = 1027$ h, mengikut kinetik tertib pertama. Kesimpulannya, kajian ini mengesahkan kebolehlaksanaan dalam menggunakan sisa nenas cecair sebagai medium pertumbuhan yang murah untuk pembiakan *C. violaceum* UTM5 pada skala perintis (50-L bioreaktor) manakala penghasilan nanopartikel violasin yang mudah larut dalam air menggunakan teknik sonikasi dengan bantuan surfaktan sebagai penstabil akan meningkatkan kegunaannya terutamanya dalam industri farmasi.

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LIST OF SYMBOLS AND ABBREVIATIONS

ATR-FTIR	: Attenuated Total Reflectance - Fourier Transform Infrared Spectroscopy
CMC	: Critical micelle concentration
HPLC	: High-performance liquid chromatography
LPW	: Liquid pineapple waste
MHA	: Muller-Hinton agar
MHB	: Muller-Hinton broth
NA	: Nutrient agar
NB	: Nutrient broth
PDI	: Polydispersity index
TLC	: Thin layer chromatography
UV-vis	: UV-visible spectroscopy
mg	: Milligram
mg L^{-1}	: Milligram per litre
°C	: Degree celcius
% w/v	: Percentage of weight in 100 mL of solvent/solution
% v/v	: Percentage of volume in 100 mL of total solvent/solution

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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

In 2010, tartrazine, quinoline yellow and carmoisine are the synthetic colorants that are banned in the United Kingdom and European Union as they trigger hyperactive behavior amongst children (Fusaro, 2010). Increase of awareness in regard to the danger of artificial (synthetic) colorants to human safety and environment leads to the increase in the use of natural colorants, known as biological colorants. These pigment, extracted from flora and fauna are found to be non-toxic, non-carcinogenic, and biodegradable (Venil *et al.*, 2013). On top of that, pharmacological properties exhibited by natural colorants have better advantages over synthetic pigments. For example, chlorophylls found in green plants exhibit anticancer properties as they can bind with cancer-causing chemicals to form complex structure, thus minimizing the absorption of potential carcinogens via gastrointestinal tract (İnanç, 2011).

Besides extracting the pigments from animals and plants, microbial pigments are also chosen due to their wide strain selection, shorter fermentation period, gene manipulability, lesser downstream processing (involves simple liquid-liquid extraction step) and cheaper growth medium availability (Venil *et al.*, 2013; Tuli *et al.*, 2015). Also, microorganisms can produce unique pigments such as violacein, prodigiosin and flexirubin, which are non-synthesizable by animals and plants. For example, bacterial strain of genus *Chromobacterium* is known for its ability to produce violacein pigment, with pharmacological properties as an antioxidant, and serves as antimicrobial, antiprotozoal, and antipyretic compound (Durán *et al.*, 2016). The multiresistant *S. aureus* (MRSA) poses a challenge in dealing with antibiotics due to multidrug resistance behavior. The use of violacein to treat MRSA has been reported by Aruldass *et al.* (2015). As a colorant, the intense violet exhibited by violacein, even at low concentration, this is useful to formulate solvent-based ink in plastic application (Venil *et al.*, 2017; Durán *et al.*, 2007). In addition, violacein has been tested and the findings show its application as food colorant in yogurt and jelly (Venil *et al.*, 2015).

However, the challenge in manufacturing bacterial pigments is the need to produce the pigments in a large quantity at low cost (Malik *et al.*, 2012). Nutrient-rich agricultural waste medium obtained from brown sugar, rice bran, pineapple and sugar cane are increasingly popular due to its availability, low cost, and renewability (Ahmad *et al.*, 2012). In addition, the use of agricultural waste residues in bioprocess helps to reduce environmental pollution. Pineapple waste is the choice for growth medium in this study due to its high glucose content and other nutrients such as esters, ketones, alcohols, aldehydes, and acids, which are required for bacterial growth (Hemalatha and Anbuselvi, 2013). The use of pineapple waste as growth medium for the production of *Lactobacilli* sp. has been demonstrated by Pyar *et al.* (2014).

Furthermore, like other natural pigments, violacein has poor solubility in water, thus limits its usage in industrial application. The common organic solvents for violacein are dimethyl sulfoxide (DMSO), acetone, methanol and ethyl acetate, which are harmful to health and environment upon emission. Thus, particle size reduction which includes mechanical nanosization can improve solubility and dissolution rate of violacein in water due to the increase of surface area to volume ratio (Khadka *et al.*, 2014). Besides, violacein nanoparticles allow better membrane penetration and increase its pharmacological activities in drug delivery. To achieve nanosization, sonication is one of the effective top-down particle size reduction approaches. Sonication employs non-interaction vibration energy to disagglomerate and overcome bonding forces in dispersing the nanomaterials.

Nevertheless, agglomeration is a common issue in nanoparticle production. Agglomeration occurs when substances prefer to interact with the same molecules instead of interacting with solvent molecules to lower the kinetic energy and achieve a more stable structure (Mohd Hamzah *et al.*, 2017). Thus, the presence of surfactants as stabilizing agent is important to prevent agglomeration by providing steric or electrostatic repulsion. For example, baicalein nanocrystals which have potent antioxidant, antitumor, and anticancer properties were stable in water with the aid of a surfactant (Zhang *et al.*, 2011). Besides, surfactants can act as solubilizing agent by increasing the solubility in both organic and aqueous solvents. Tehrani-Bagha, Singh and Holmberg (2013) reported the increase of synthetic pigments' solubility when added with surfactant above its critical micelle concentration (CMC).

In this study, crude violacein extracted from *Chromobacterium violaceum* UTM5 was downsized to nanoparticles via sonication, with surfactants as stabilizing agent. The aim was to improve the violacein solubility in aqueous system with small particle size, narrower particle size distribution (low polydispersity index) and high zeta potential (high stability), besides retaining its violet color at different pH, temperature, time and light illumination.

1.2 Problem Statement

The major challenge to commercialize microbial pigments is to achieve high yield with cost-effective production (Malik *et al.*, 2012). The synthetic growth medium is expensive, thus hamper the production of the pigments at industrial scale, leading to its low usage in any applications where people prefer to use synthetic pigments. As for violacein, although exhibiting many pharmacological activities, it has not been utilized in commercial applications. Besides the high cost of production, another issue is its limited solubility in water, but can dissolve in methanol and DMSO (Durán *et al.*, 2007). The organic solvents are toxic even at low dosage (Galvao *et al.*, 2014). To reduce the production cost of violacein, liquid pineapple waste was used as a cheaper alternative growth medium. On the other hand, the solubility of violacein in water can be increased by reducing its size into nanoscale, due to the increase of surface area to volume ratio. The high surface-to-volume ratio thus increases particle solubility in water system. This study focused on the use of sonication technique to produce the violacein nanoparticles. However, common issues with nanoparticles are poor solubility and dispersibility, this leads to aggregation and sedimentation process, which results in the loss of the bacterial pigment biological activities and reduces the pigment quality to be used as ink (Wu *et al.*, 2011). Thus, surface modification of the violacein nanoparticles with stabilizer molecules such as surfactants imparts the nanoparticles stability. The presence of surfactant as stabilizer acts as barrier, preventing agglomeration via two protection mechanisms, which are steric repulsion and electrostatic repulsion. In short, this research aims to produce a low cost and stable violacein nanoparticles with high dispersibility/solubility in aqueous system.

1.3 Objectives

1) To produce, extract and characterize crude violacein pigment from *C. violaceum* UTM5 using liquid pineapple waste as the growth medium.
2) To produce and characterize violacein nanoparticles via sonication technique with the aid of surfactants as stabilizers.
3) To test the solubility, stability and color performance of the violacein nanoparticles.

1.4 Scope of Study

The crude violacein used in this study was extracted from *C. violaceum* UTM5 strain and used without further purification. Liquid pineapple waste (LPW) and nutrient broth were used as growth medium for *C. violaceum* UTM5. The production of crude violacein was compared from using nutrient broth (NB), LPW (with and without L-tryptophan) as growth media. The bacteria was grown using continuous shaking condition and extracted via liquid-liquid extraction using ethyl acetate and acetone as the solvents.

The production of violacein nanoparticles was done using water as the medium. The effectiveness of the sonication technique was first compared with mechanical stirring method. By focusing on sonication technique, several parameters including surfactant concentration and violacein concentration, pulse and sonication time were further investigated. Several common industrial surfactants were used in this study such as Tween 80 and Triton X-100 (nonionic surfactant), sodium dodecyl sulfate (anionic surfactant) and dodecyl trimethylammonium bromide (cationic surfactant). The performance of each surfactant was analyzed in terms of particle size, polydispersity index, zeta potential value, and solubilizing power. Sonication parameters such as sonication time and pulse time was optimized to produce stable violacein nanoparticles. The violacein nanoparticles were characterized using attenuated total reflectance Fourier transform infrared, thermal and Zetasizer analyzer.

The dispersion stability of the violacein nanoparticles were tested as a function of time (28 days) and at different temperatures. The dispersion stability was measured via violet color intensity using UV-Vis spectroscopy for upper and lower portion of the violacein solution. The color stability of the violacein nanoparticles was tested as a function of time, pH and temperature and under light illumination using UV-Vis spectrophotometer and Colorflex color meter.

1.5 Significance of Study

The use of liquid pineapple waste as an alternative growth medium reduces the production cost of violacein. Besides that, the use of fruit wastes for the production of microbial pigments leads to lower waste generation, better waste management and fulfills the waste-to-wealth initiative as described in RMK-11. The development of violacein nanoparticles will improve the solubility of violacein in water, thus making them useful for various applications especially in pharmaceutical industry. The use of

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